Mathematical Biology

Lecture notes for MATH 4333
(formerly MATH 365)

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Preface

What follows are my lecture notes for Math 4333: Mathematical Biology, taught at the Hong Kong University of Science and Technology. This applied mathematics course is primarily for final year mathematics major and minor students. Other students are also welcome to enroll, but must have the necessary mathematical skills.

My main emphasis is on mathematical modeling, with biology the sole application area. I assume that students have no knowledge of biology, but I hope that they will learn a substantial amount during the course. Students are required to know differential equations and linear algebra, and this usually means having taken two courses in these subjects. I also touch on topics in stochastic modeling, which requires some knowledge of probability. A full course on probability, however, is not a prerequisite though it might be helpful.

Biology, as is usually taught, requires memorizing a wide selection of facts and remembering them for exams, sometimes forgetting them soon after. For students exposed to biology in secondary school, my course may seem like a different subject. The ability to model problems using mathematics requires almost no rote memorization, but it does require a deep understanding of basic principles and a wide range of mathematical techniques. Biology offers a rich variety of topics that are amenable to mathematical modeling, and I have chosen specific topics that I have found to be the most interesting.

If, as a UST student, you have not yet decided if you will take my course, please browse these lecture notes to see if you are interested in these topics. Other web surfers are welcome to download these notes from http://www.math.ust.hk/~machas/mathematical-biology.pdf and to use them freely for teaching and learning. I welcome any comments, suggestions, or corrections sent to me by email (jeffrey.chasnov@ust.hk). Although most of the material in my notes can be found elsewhere, I hope that some of it will be considered to be original.

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Chapter 1

Population Dynamics

Populations grow in size when the birth rate exceeds the death rate. Thomas Malthus, in *An Essay on the Principle of Population* (1798), used unchecked population growth to famously predict a global famine unless governments regulated family size—an idea later echoed by Mainland China’s one-child policy. The reading of Malthus is said by Charles Darwin in his autobiography to have inspired his discovery of what is now the cornerstone of modern biology: the principle of evolution by natural selection.

The Malthusian growth model is the granddaddy of all population models, and we begin this chapter with a simple derivation of the famous exponential growth law. Unchecked exponential growth obviously does not occur in nature, and population growth rates may be regulated by limited food or other environmental resources, and by competition among individuals within a species or across species. We will develop models for three types of regulation. The first model is the well-known logistic equation, a model that will also make an appearance in subsequent chapters. The second model is an extension of the logistic model to species competition. And the third model is the famous Lotka-Volterra predator-prey equations. Because all these mathematical models are nonlinear differential equations, mathematical methods to analyze such equations will be developed.

1.1 The Malthusian growth model

Let $N(t)$ be the number of individuals in a population at time $t$, and let $b$ and $d$ be the average per capita birth rate and death rate, respectively. In a short time $\Delta t$, the number of births in the population is $b\Delta t N$, and the number of deaths is $d\Delta t N$. An equation for $N$ at time $t + \Delta t$ is then determined to be

$$N(t + \Delta t) = N(t) + b\Delta t N(t) - d\Delta t N(t),$$

which can be rearranged to

$$\frac{N(t + \Delta t) - N(t)}{\Delta t} = (b - d)N(t);$$

and as $\Delta t \to 0$,

$$\frac{dN}{dt} = (b - d)N.$$
CHAPTER 1. POPULATION DYNAMICS

With an initial population size of \(N_0\), and with \(r = b - d\) positive, the solution for \(N = N(t)\) grows exponentially:

\[ N(t) = N_0 e^{rt}. \]

With population size replaced by the amount of money in a bank, the exponential growth law also describes the growth of an account under continuous compounding with interest rate \(r\).

1.2 The Logistic equation

The exponential growth law for population size is unrealistic over long times. Eventually, growth will be checked by the over-consumption of resources. We assume that the environment has an intrinsic carrying capacity \(K\), and populations larger than this size experience heightened death rates.

To model population growth with an environmental carrying capacity \(K\), we look for a nonlinear equation of the form

\[ \frac{dN}{dt} = rN F(N), \]

where \(F(N)\) provides a model for environmental regulation. This function should satisfy \(F(0) = 1\) (the population grows exponentially with growth rate \(r\) when \(N\) is small), \(F(K) = 0\) (the population stops growing at the carrying capacity), and \(F(N) < 0\) when \(N > K\) (the population decays when it is larger than the carrying capacity). The simplest function \(F(N)\) satisfying these conditions is linear and given by \(F(N) = 1 - N/K\). The resulting model is the well-known logistic equation,

\[ \frac{dN}{dt} = rN(1 - N/K), \quad (1.1) \]

an important model for many processes besides bounded population growth.

Although (1.1) is a nonlinear equation, an analytical solution can be found by separating the variables. Before we embark on this algebra, we first illustrate some basic concepts used in analyzing nonlinear differential equations.

Fixed points, also called equilibria, of a differential equation such as (1.1) are defined as the values of \(N\) where \(\dot{N} = 0\). Here, we see that the fixed points of (1.1) are \(N = 0\) and \(N = K\). If the initial value of \(N\) is at one of these fixed points, then \(N\) will remain fixed there for all time. Fixed points, however, can be stable or unstable. A fixed point is stable if a small perturbation from the fixed point decays to zero so that the solution returns to the fixed point. Likewise, a fixed point is unstable if a small perturbation grows exponentially so that the solution moves away from the fixed point. Calculation of stability by means of small perturbations is called linear stability analysis. For example, consider the general one-dimensional differential equation

\[ \dot{x} = f(x), \quad (1.2) \]

with \(x_*\) a fixed point of the equation, that is \(f(x_*) = 0\). To determine analytically if \(x_*\) is a stable or unstable fixed point, we perturb the solution. Let us write our solution \(x = x(t)\) in the form

\[ x(t) = x_* + \epsilon(t), \quad (1.3) \]
1.2. THE LOGISTIC EQUATION

where initially $\epsilon(0)$ is small but different from zero. Substituting (1.3) into (1.2), we obtain

$$\dot{\epsilon} = f(x_\ast + \epsilon) = f(x_\ast) + \epsilon f'(x_\ast) + \ldots = \epsilon f'(x_\ast) + \ldots,$$

where the second equality uses a Taylor series expansion of $f(x)$ about $x_\ast$ and the third equality uses $f(x_\ast) = 0$. If $f'(x_\ast) \neq 0$, we can neglect higher-order terms in $\epsilon$ for small times, and integrating we have

$$\epsilon(t) = \epsilon(0)e^{f'(x_\ast)t}.$$

The perturbation $\epsilon(t)$ to the fixed point $x_\ast$ goes to zero as $t \to \infty$ provided $f'(x_\ast) < 0$. Therefore, the stability condition on $x_\ast$ is

$$x_\ast \text{ is } \begin{cases} \text{a stable fixed point if } & f'(x_\ast) < 0, \\ \text{an unstable fixed point if } & f'(x_\ast) > 0. \end{cases}$$

Another equivalent but sometimes simpler approach to analyzing the stability of the fixed points of a one-dimensional nonlinear equation such as (1.2) is to plot $f(x)$ versus $x$. We show a generic example in Fig. 1.1. The fixed points are the x-intercepts of the graph. Directional arrows on the x-axis can be drawn based on the sign of $f(x)$. If $f(x) < 0$, then the arrow points to the left; if $f(x) > 0$, then the arrow points to the right. The arrows show the direction of motion for a particle at position $x$ satisfying $\dot{x} = f(x)$. As illustrated in Fig. 1.1, fixed points with arrows on both sides pointing in are stable, and fixed points with arrows on both sides pointing out are unstable.

In the logistic equation (1.1), the fixed points are $N_\ast = 0, K$. A sketch of $F(N) = rN(1 - N/K)$ versus $N$, with $r, K > 0$ in Fig. 1.2 immediately shows that $N_\ast = 0$ is an unstable fixed point and $N_\ast = K$ is a stable fixed point. The

Figure 1.1: Determining one-dimensional stability using a graphical approach.
analytical approach computes \( F'(N) = r(1 - 2N/K) \), so that \( F'(0) = r > 0 \) and \( F'(K) = -r < 0 \). Again we conclude that \( N^* = 0 \) is unstable and \( N^* = K \) is stable.

We now solve the logistic equation analytically. Although this relatively simple equation can be solved as is, we first nondimensionalize to illustrate this very important technique that will later prove to be most useful. Perhaps here one can guess the appropriate unit of time to be \( 1/r \) and the appropriate unit of population size to be \( K \). However, we prefer to demonstrate a more general technique that may be useful for equations that are difficult to guess. We begin by nondimensionalizing time and population size:

\[
\tau = t/t^*, \quad \eta = N/N^*,
\]

where \( t^* \) and \( N^* \) are unknown dimensional units. The derivative \( \dot{N} \) is computed as

\[
\frac{dN}{dt} = \frac{d(N\eta)}{d\tau} \frac{d\tau}{dt} = \frac{N^*}{t^*} \frac{d\eta}{d\tau}.
\]

Therefore, the logistic equation (1.1) becomes

\[
\frac{d\eta}{d\tau} = rt^*\eta \left(1 - \frac{N^*\eta}{K}\right),
\]

which assumes the simplest form with the choices \( t^* = 1/r \) and \( N^* = K \). Therefore, our dimensionless variables are

\[
\tau = rt, \quad \eta = N/K,
\]

and the logistic equation, in dimensionless form, becomes

\[
\frac{d\eta}{d\tau} = \eta (1 - \eta),
\]

(1.4)
1.2. THE LOGISTIC EQUATION

with the dimensionless initial condition $\eta(0) = \eta_0 = N_0/K$, where $N_0$ is the initial population size. Note that the dimensionless logistic equation (1.4) has no free parameters, while the dimensional form of the equation (1.1) contains $r$ and $K$. Reduction in the number of free parameters (here, two: $r$ and $K$) by the number of independent units (here, also two: time and population size) is a general feature of nondimensionalization. The theoretical result is known as the Buckingham Pi Theorem. Reducing the number of free parameters in a problem to the absolute minimum is especially important before proceeding to a numerical solution. The parameter space that must be explored may be substantially reduced.

Solving the dimensionless logistic equation (1.4) can proceed by separating the variables. Separating and integrating from $\tau = 0$ to $\tau$ and $\eta_0$ to $\eta$ yields

$$\int_{\eta_0}^{\eta} \frac{d\eta'}{\eta'(1-\eta')} = \int_0^\tau d\tau'. $$

The integral on the left-hand-side can be performed using the method of partial fractions:

$$\frac{1}{\eta(1-\eta)} = \frac{A}{\eta} + \frac{B}{1-\eta} = \frac{A + (B-A)\eta}{\eta(1-\eta)};$$

and by equating the coefficients of the numerators proportional to $\eta^0$ and $\eta^1$, we find that $A = 1$ and $B = 1$. Therefore,

$$\int_{\eta_0}^{\eta} \frac{d\eta}{\eta(1-\eta)} = \int_{\eta_0}^{\eta} \frac{d\eta}{\eta} + \int_{\eta_0}^{\eta} \frac{d\eta}{(1-\eta)} = \ln \frac{\eta}{\eta_0} - \ln \frac{1-\eta}{1-\eta_0} = \ln \frac{\eta(1-\eta_0)}{\eta_0(1-\eta)} = \tau.$$ 

Solving for $\eta$, we first exponentiate both sides and then isolate $\eta$:

$$\frac{\eta(1-\eta_0)}{\eta_0(1-\eta)} = e^\tau, \text{ or } \eta(1-\eta_0) = \eta_0 e^\tau - \eta_0 e^\tau,$$

or $\eta(1-\eta_0 + \eta_0 e^\tau) = \eta_0 e^\tau$, or $\eta = \frac{\eta_0}{\eta_0 + (1-\eta_0) e^{-\tau}}$.

Returning to the dimensional variables, we finally have

$$N(t) = \frac{N_0}{N_0/K + (1-N_0/K)e^{-rt}}. \quad (1.5)$$

There are many ways to write (1.5) so please examine my carefully considered choice. The aesthetic consideration in writing the final result is an important element of mathematical technique that students all too often neglect. In deciding how to write (1.5), I considered if it was easy to observe the following limiting results: (1) $N(0) = N_0$; (2) $\lim_{t \to \infty} N(t) = K$; (3) $\lim_{K \to \infty} N(t) = N_0 \exp(rt)$. 

1.3 A model of species competition

Suppose that two species compete for the same resources. To build a model, we can start with logistic equations for both species. Different species would have different growth rates and different carrying capacities. If we let $N_1$ and $N_2$ be the number of individuals of species one and species two, then

\[
\frac{dN_1}{dt} = r_1 N_1 (1 - N_1 / K_1), \\
\frac{dN_2}{dt} = r_2 N_2 (1 - N_2 / K_2).
\]

These are uncoupled equations so that asymptotically, $N_1 \to K_1$ and $N_2 \to K_2$. How do we model the competition between species? If $N_1$ is much smaller than $K_1$, and $N_2$ much smaller than $K_2$, then resources are plentiful and populations

---

Figure 1.3: Solutions of the nondimensional logistic equation.

In Fig. 1.3, we plot the solution to the nondimensional logistic equation for initial conditions $\eta_0 = 0.02, 0.2, 0.5, 0.8, 1.0, \text{ and } 1.2$. The lowest curve is the characteristic ‘S-shape’ usually associated with the solution of the logistic equation. This sigmoidal curve appears in many other types of models. The MATLAB script to produce Fig. 1.3 is shown below.

\[
\text{eta0} = [0.02, 0.2, 0.5, 0.8, 1.0, 1.2]; \\
\text{tau} = \text{linspace}(0, 8); \\
\text{for } i = 1 : \text{length(eta0)} \\
\text{ \ \ \ \ eta} = \text{eta0}(i) / (\text{eta0}(i) + (1 - \text{eta0}(i)) \times \text{exp}(-\text{tau})); \\
\text{ \ \ \ \ plot(tau, eta); hold on} \\
\text{end} \\
\text{axis([0 8 0 1.25]);} \\
\text{xlabel('t'); ylabel('\eta'); title('Logistic Equation');}
\]
1.4. **THE LOTKA-VOLTERRA PREDATOR-PREY MODEL**

grow exponentially with growth rates $r_1$ and $r_2$. If species one and two compete, then the growth of species one reduces resources available to species two, and vice-versa. Since we do not know the impact species one and two have on each other, we introduce two additional parameters to model the competition. A reasonable modification that couples the two logistic equations is

\[
\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{N_1 + \alpha_{12} N_2}{K_1}\right),
\]

\[
\frac{dN_2}{dt} = r_2 N_2 \left(1 - \frac{\alpha_{21} N_1 + N_2}{K_2}\right),
\]

where $\alpha_{12}$ and $\alpha_{21}$ are dimensionless parameters that model the consumption of species one’s resources by species two, and vice-versa. For example, suppose that both species eat exactly the same food, but species two consumes twice as much as species one. Since one individual of species two consumes the equivalent of two individuals of species one, the correct model is $\alpha_{12} = 2$ and $\alpha_{21} = 1/2$.

Another example supposes that species one and two occupy the same niche, consume resources at the same rate, but may have different growth rates and carrying capacities. Can the species coexist, or does one species eventually drive the other to extinction? It is possible to answer this question without actually solving the differential equations. With $\alpha_{12} = \alpha_{21} = 1$ as appropriate for this example, the coupled logistic equations (1.7) become

\[
\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{N_1 + N_2}{K_1}\right),
\]

\[
\frac{dN_2}{dt} = r_2 N_2 \left(1 - \frac{N_1 + N_2}{K_2}\right).
\]

For sake of argument, we assume that $K_1 > K_2$. The only fixed points other than the trivial one $(N_1, N_2) = (0, 0)$ are $(N_1, N_2) = (K_1, 0)$ and $(N_1, N_2) = (0, K_2)$. Stability can be computed analytically by a two-dimensional Taylor-series expansion, but here a simpler argument can suffice. We first consider $(N_1, N_2) = (K_1, \epsilon)$, with $\epsilon$ small. Since $K_1 > K_2$, observe from (1.7) that $N_2 < 0$ so that species two goes extinct. Therefore $(N_1, N_2) = (K_1, 0)$ is a stable fixed point. Now consider $(N_1, N_2) = (\epsilon, K_2)$, with $\epsilon$ small. Again, since $K_1 > K_2$, observe from (1.7) that $N_1 > 0$ and species one increases in number. Therefore, $(N_1, N_2) = (0, K_2)$ is an unstable fixed point. We have thus found that, within our coupled logistic model, species that occupy the same niche and consume resources at the same rate cannot coexist and that the species with the largest carrying capacity will survive and drive the other species to extinction. This is the so-called principle of competitive exclusion, also called $K$-selection since the species with the largest carrying capacity wins. In fact, ecologists also talk about $r$-selection; that is, the species with the largest growth rate wins. Our coupled logistic model does not model $r$-selection, demonstrating the potential limitations of a too simple mathematical model.

For some values of $\alpha_{12}$ and $\alpha_{21}$, our model admits a stable equilibrium solution where two species coexist. The calculation of the fixed points and their stability is more complicated than the calculation just done, and I present only the results. The stable coexistence of two species within our model is possible only if $\alpha_{12} K_2 < K_1$ and $\alpha_{21} K_1 < K_2$. 
1.4 The Lotka-Volterra predator-prey model

Pelt-trading records (Fig. 1.4) of the Hudson Bay company from over almost a century display a near-periodic oscillation in the number of trapped snowshoe hares and lynxes. With the reasonable assumption that the recorded number of trapped animals is proportional to the animal population, these records suggest that predator-prey populations—as typified by the hare and the lynx—can oscillate over time. Lotka and Volterra independently proposed in the 1920s a mathematical model for the population dynamics of a predator and prey, and these Lotka-Volterra predator-prey equations have since become an iconic model of mathematical biology.

To develop these equations, suppose that a predator population feeds on a prey population. We assume that the number of prey grow exponentially in the absence of predators (there is unlimited food available to the prey), and that the number of predators decay exponentially in the absence of prey (predators must eat prey or starve). Contact between predators and prey increases the number of predators and decreases the number of prey.

Let $U(t)$ and $V(t)$ be the number of prey and predators at time $t$. To develop a coupled differential equation model, we consider population sizes at time $t + \Delta t$. Exponential growth of prey in the absence of predators and exponential decay of predators in the absence of prey can be modeled by the usual linear terms. The coupling between prey and predator must be modeled with two additional parameters. We write the population sizes at time $t + \Delta t$ as

\[
U(t + \Delta t) = U(t) + \alpha \Delta t U(t) - \gamma \Delta t U(t) V(t),
\]
\[
V(t + \Delta t) = V(t) + e\gamma \Delta t U(t) V(t) - \beta \Delta t V(t).
\]

The parameters $\alpha$ and $\beta$ are the average per capita birthrate of the prey and the deathrate of the predators, in the absence of the other species. The coupling
1.4. THE LOTKA-VOLterra PREDATOR-PREY MODEL

terms model contact between predators and prey. The parameter $\gamma$ is the fraction of prey caught per predator per unit time; the total number of prey caught by predators during time $\Delta t$ is $\gamma \Delta t U V$. The prey eaten is then converted into newborn predators (view this as a conversion of biomass), with conversion factor $e$, so that the number of predators during time $\Delta t$ increases by $e \gamma \Delta t U V$.

We convert these equations into differential equations by letting $\Delta t \to 0$.

We obtain the well-known Lotka-Volterra predator-prey equations:

$$
\frac{dU}{dt} = \alpha U - \gamma U V, \quad \frac{dV}{dt} = e \gamma U V - \beta V.
$$

Before analyzing the Lotka-Volterra equations, we first review fixed point and linear stability analysis applied to what is called an autonomous system of differential equations. For simplicity, we consider a system of only two differential equations of the form

$$
\frac{dx}{dt} = f(x, y), \quad \frac{dy}{dt} = g(x, y),
$$

though our results can be generalized to larger systems. The system given by (1.9) is said to be autonomous since $f$ and $g$ do not depend explicitly on the independent variable $t$. Fixed points of this system are determined by setting $\dot{x} = \dot{y} = 0$ and solving for $x$ and $y$. Suppose that one fixed point is $(x^*, y^*)$.

To determine its linear stability, we consider initial conditions for $(x, y)$ near the fixed point with small independent perturbations in both directions, i.e., $x(0) = x^* + \epsilon(0), \ y(0) = y^* + \delta(0)$. If the initial perturbation grows in time, we say that the fixed point is unstable; if it decays, we say that the fixed point is stable. Accordingly, we let

$$
x(t) = x^* + \epsilon(t), \quad y(t) = y^* + \delta(t),
$$

and substitute (1.10) into (1.9) to determine the time-dependence of $\epsilon$ and $\delta$.

Since $x^*$ and $y^*$ are constants, we have

$$
\frac{d\epsilon}{dt} = f(x^* + \epsilon, y^* + \delta), \quad \frac{d\delta}{dt} = g(x^* + \epsilon, y^* + \delta).
$$

The linear stability analysis proceeds by assuming that the initial perturbations $\epsilon(0)$ and $\delta(0)$ are small enough to truncate the two-dimensional Taylor-series expansion of $f$ and $g$ about $\epsilon = \delta = 0$ at first-order in $\epsilon$ and $\delta$. Note that in general, the two-dimensional Taylor series of a function $F(x, y)$ about the origin is given by

$$
F(x, y) = F(0, 0) + x F_x(0, 0) + y F_y(0, 0) + \frac{1}{2} \left[ x^2 F_{xx}(0, 0) + 2 x y F_{xy}(0, 0) + y^2 F_{yy}(0, 0) \right] + \ldots,
$$

where the terms in the expansion can be remembered by requiring that all of the partial derivatives of the series agree with that of $F(x, y)$ at the origin. We now Taylor-series expand $f(x^* + \epsilon, y^* + \delta)$ and $g(x^* + \epsilon, y^* + \delta)$ about $(\epsilon, \delta) = (0, 0)$. The constant terms vanish since $(x^*, y^*)$ is a fixed point, and we neglect all terms with higher orders than $\epsilon$ and $\delta$. Therefore,

$$
\frac{d\epsilon}{dt} = \epsilon f_x(x^*, y^*) + \delta f_y(x^*, y^*), \quad \frac{d\delta}{dt} = \epsilon g_x(x^*, y^*) + \delta g_y(x^*, y^*),
$$

which may be written in matrix form as
\[
\frac{d}{dt} \begin{pmatrix} \epsilon \\ \delta \end{pmatrix} = \begin{pmatrix} f_x^* \\ g_y^* \end{pmatrix} \begin{pmatrix} \epsilon \\ \delta \end{pmatrix},
\]
(1.11)
where \( f_x^* = f_x(x, y) \), etc. Equation (1.11) is a system of linear ode’s, and its solution proceeds by assuming the form
\[
\begin{pmatrix} \epsilon \\ \delta \end{pmatrix} = e^{\lambda t} \mathbf{v}.
\]
(1.12)
Upon substitution of (1.12) into (1.11), and canceling \( e^{\lambda t} \), we obtain the linear algebra eigenvalue problem
\[
J^* \mathbf{v} = \lambda \mathbf{v},
\]
where \( \lambda \) is the eigenvalue, \( \mathbf{v} \) the corresponding eigenvector, and \( J^* \) the Jacobian matrix evaluated at the fixed point. The eigenvalue is determined from the characteristic equation
\[
\det (J^* - \lambda I) = 0,
\]
which for a two-by-two Jacobian matrix results in a quadratic equation for \( \lambda \). From the form of the solution (1.12), the fixed point is stable if for all eigenvalues \( \lambda \), Re\{\lambda\} < 0, and unstable if for at least one \( \lambda \), Re\{\lambda\} > 0. Here Re\{\lambda\} means the real part of the (possibly) complex eigenvalue \( \lambda \).

We now reconsider the Lotka-Volterra equations (1.8). Fixed point solutions are found by solving \( \dot{U} = \dot{V} = 0 \), and the two solutions are
\[
(U_*, V_*) = (0, 0) \text{ or } \left( \frac{\beta}{e^\gamma}, \frac{\alpha}{\gamma} \right).
\]
The trivial fixed point \( (0, 0) \) is unstable since the prey population grows exponentially if it is initially small. To determine the stability of the second fixed point, we write the Lotka-Volterra equation in the form
\[
\frac{dU}{dt} = F(U, V), \quad \frac{dV}{dt} = G(U, V),
\]
with
\[
F(U, V) = \alpha U - \gamma UV, \quad G(U, V) = e^\gamma UV - \beta V.
\]
The partial derivatives are then computed to be
\[
F_U = \alpha - \gamma V, \quad F_V = -\gamma U \\
G_U = e^\gamma V, \quad G_V = e^\gamma U - \beta.
\]
The Jacobian at the fixed point \( (U_*, V_*) = (\beta/e^\gamma, \alpha/\gamma) \) is
\[
J^* = \begin{pmatrix} 0 & -\beta/e^\gamma \\ \alpha & 0 \end{pmatrix},
\]
and
\[
\det(J^* - \lambda I) = \begin{vmatrix} -\lambda & -\beta/e^\gamma \\ \alpha & -\lambda \end{vmatrix} = \lambda^2 + \alpha \beta = 0
\]
1.4. THE LOTKA-VOLTERRA PREDATOR-PREY MODEL

has the solutions $\lambda_{\pm} = \pm i \sqrt{\alpha \beta}$, which are pure imaginary. When the eigenvalues of the two-by-two Jacobian are pure imaginary, the fixed point is called a center and the perturbation neither grows nor decays, but oscillates. Here, the angular frequency of oscillation is $\omega = \sqrt{\alpha \beta}$, and the period of the oscillation is $2\pi / \omega$.

We plot $U$ and $V$ versus $t$ (time series plot), and $V$ versus $U$ (phase space diagram) to see how the solutions behave. For a nonlinear system of equations such as (1.5), a numerical solution is required. The Lotka-Volterra system has four free parameters $\alpha$, $\beta$, $\gamma$ and $\epsilon$. The relevant units here are time, the number of prey, and the number of predators. The Buckingham Pi Theorem predicts that nondimensionalizing the equations can reduce the number of free parameters by three to a manageable single dimensionless grouping of parameters. We choose to nondimensionalize time using the angular frequency of oscillation and the number of prey and predators using their fixed point values. With carets denoting the dimensionless variables, we let

$$
\hat{t} = \sqrt{\alpha \beta} t, \quad \hat{U} = U/U_*, \quad \hat{V} = V/V_* = \frac{\gamma}{\alpha} \hat{V}.
$$

Substitution of (1.13) into the Lotka-Volterra equations (1.8) results in the dimensionless equations

$$
\frac{d\hat{U}}{dt} = r(\hat{U} - \hat{U} \hat{V}), \quad \frac{d\hat{V}}{dt} = \frac{1}{r}(\hat{U} \hat{V} - \hat{V}),
$$

with single dimensionless grouping $r = \sqrt{\alpha / \beta}$. A numerical solution uses MATLAB’s ode45.m built-in function to integrate the differential equations. The code below produces Fig. 1.5. Notice how the predator population lags the prey population: an increase in prey numbers results in a delayed increase in predator numbers as the predators eat more prey. The phase space diagrams clearly show the periodicity of the oscillation. Note that the curves move counterclockwise: prey numbers increase when predator numbers are minimal, and prey numbers decrease when predator numbers are maximal.
function lotka_volterra
% plots time series and phase space diagrams
clear all; close all;
t0=0; tf=6*pi; eps=0.1; delta=0;
r=[1/2, 1, 2];
options = odeset('RelTol',1e-6,'AbsTol',[1e-6 1e-6]);
%time series plots
for i=1:length(r);
    [t,UV]=ode45(@lv_eq,[t0,tf],[1+eps 1+delta],options,r(i));
    U=UV(:,1); V=UV(:,2);
    subplot(3,1,i); plot(t,U,t,V,'--');
    axis([0 6*pi,0.8 1.25]); ylabel('predator,prey');
    text(3,1.15,['r=',num2str(r(i))]);
end
xlabel('t');
subplot(3,1,1); legend('prey', 'predator');
%phase space plot
xpos=[2.5 2.5 2.5]; ypos=[3.5 3.5 3.5];%for annotating graph
for i=1:length(r);
    for eps=0.1:0.1:1.0;
        [t,UV]=ode45(@lv_eq,[t0,tf],[1+eps 1+eps],options,r(i));
        U=UV(:,1); V=UV(:,2);
        figure(2);subplot(1,3,i); plot(U,V); hold on;
    end
    axis equal; axis([0 4 0 4]);
    text(xpos(i),ypos(i),['r=',num2str(r(i))]);
    if i==1; ylabel('predator'); end;
    xlabel('prey');
end
Figure 1.5: Solutions of the nondimensional Lotka-Volterra equations. Upper plots: time-series solutions; lower plots: phase space diagrams.
Chapter 2

Age-structured Populations

Determining the age-structure of a population helps governments plan economic development. Age-structure theory can also help evolutionary biologists better understand a species’s life-history. An age-structured population occurs because offspring are born to mothers at different ages. If average per capita birth and death rates at different ages are constant, then a stable age-structure arises. However, a rapid change in birth or death rates can cause the age-structure to shift distributions. In this section, we develop the theory of age-structured populations using both discrete- and continuous-time models. We also present two interesting applications: (1) modeling age-structure changes in China and other countries as these populations age, and; (2) modeling the life cycle of a hermaphroditic worm. We begin this section, however, with one of the oldest problems in mathematical biology: Fibonacci’s rabbits. This will lead us to a brief digression about the golden mean, rational approximations and flower development, before returning to our main topic.

2.1 Fibonacci’s rabbits

In 1202, Fibonacci proposed the following puzzle, which we paraphrase here:

A man put a male-female pair of newly born rabbits in a field. Rabbits take a month to mature before mating. One month after mating, females give birth to one male-female pair and then mate again. Assume no rabbits die. How many rabbit pairs are there after one year?

Let \( a_n \) be the number of rabbit pairs at the start of the \( n \)th month, counted after the birth of any new rabbits. There are twelve months in a year, so the number of rabbits at the start of the 13th month will be the solution to Fibonacci’s puzzle. Now \( a_1 = 1 \) because the population consists of the initial newborn rabbit pair at the start of the first month; \( a_2 = 1 \) because the population still consists of the initial rabbit pair, now mature; and \( a_3 = a_2 + a_1 \) because the population consists of \( a_2 \) rabbit pairs present in the previous month (here equal to one), and \( a_1 \) newborn rabbit pairs born to the \( a_1 \) female rabbits that are now old enough to give birth (here, also equal to one). In general

\[
a_{n+1} = a_n + a_{n-1}.
\]
For only 12 months we can simply count using (2.1) and $a_1 = a_2 = 1$, so the Fibonacci numbers are

$$1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, 144, 233, \ldots$$

where $a_{13} = 233$ is the solution to Fibonacci’s puzzle.

Let us solve (2.1) for all the $a_n$’s. This equation is a second-order linear difference equation, and to solve it, we look for a solution of the form $a_n = \lambda^n$. Substitution into (2.1) yields

$$\lambda^{n+1} = \lambda^n + \lambda^{n-1},$$

or after division by $\lambda^{n-1}$:

$$\lambda^2 - \lambda - 1 = 0,$$

with solution

$$\lambda_{\pm} = \frac{1 \pm \sqrt{5}}{2}.$$  

Define

$$\Phi = \frac{1 + \sqrt{5}}{2} = 1.61803\ldots,$$

and

$$\phi = \frac{\sqrt{5} - 1}{2} = \Phi - 1 = 0.61803\ldots.$$ 

Then $\lambda_+ = \Phi$ and $\lambda_- = -\phi$. Also, notice that since $\Phi^2 - \Phi - 1 = 0$, division by $\Phi$ yields $1/\Phi = \Phi - 1$, so that

$$\phi = \frac{1}{\Phi}.$$ 

As in the solution of linear homogeneous differential equations, the two values of $\lambda$ can be used to construct a general solution to the linear difference equation using the principle of linear superposition:

$$a_n = c_1 \Phi^n + c_2 (-1)^n \phi^n.$$ 

Extending the Fibonacci sequence to $a_0 = 0$ (since $a_0 = a_2 - a_1$), we satisfy the conditions $a_0 = 0$ and $a_1 = 1$:

$$c_1 + c_2 = 0,$$
$$c_1 \Phi - c_2 \phi = 1.$$ 

Therefore, $c_2 = -c_1$, and $c_1 (\Phi + \phi) = 1$, or $c_1 = 1/\sqrt{5}$, $c_2 = -1/\sqrt{5}$. We can rewrite the solution as

$$a_n = \frac{1}{\sqrt{5}} \Phi^n [1 + (-1)^{n+1} \Phi^{-2n}].$$  \hspace{1cm} (2.2)$$

In this form, we see that, as $n \to \infty$, $a_n \to \Phi^n / \sqrt{5}$, and $a_{n+1}/a_n \to \Phi$. 
2.1. FIBONACCI’S RABBITS

2.1.1 The golden ratio \( \Phi \)

The number \( \Phi \) is known as the golden ratio. Two positive numbers \( x \) and \( y \), with \( x > y \), are said to be in the golden ratio if the ratio between the sum of those numbers and the larger one is the same as the ratio between the larger one and the smaller; that is,

\[
\frac{x + y}{x} = \frac{x}{y}.
\]

Solution of (2.3) yields \( x/y = \Phi \). In some well-defined way, \( \Phi \) can also be called the most irrational of the irrational numbers.

To understand why \( \Phi \) has this distinction as the most irrational number, we need first to understand an algorithm—continued fraction expansions—for approximating irrational numbers by rational numbers. Let \( n_i \) be positive integers. To construct a continued fraction expansion to the positive irrational number \( x \), we choose the largest possible \( n_i \)'s that satisfy the following inequalities:

\[
x > c_1 = n_1,
\]
\[
x < c_2 = n_1 + \frac{1}{n_2},
\]
\[
x > c_3 = n_1 + \frac{1}{n_2 + \frac{1}{n_3}},
\]
\[
x < c_4 = n_1 + \frac{1}{n_2 + \frac{1}{n_3 + \frac{1}{n_4}}},\text{ etc.}
\]

There is a simple algorithm for calculating the \( n_i \)'s. Firstly, \( c_1 = n_1 \) is the integer part of \( x \). One computes the remainder, \( x - c_1 \), and takes its reciprocal \( 1/(x - c_1) \). The integer part of this inverse is \( n_2 \). One then takes the remainder \( 1/(x - c_1) - n_2 \), and its reciprocal. The integer part of this inverse is \( n_3 \). We follow this algorithm to find successively better rational approximations of \( \pi = 3.141592654\ldots \):

<table>
<thead>
<tr>
<th>( c )'s</th>
<th>remainder</th>
<th>( 1/\text{remainder} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( c_1 = 3 )</td>
<td>0.14159265</td>
<td>7.06251329</td>
</tr>
<tr>
<td>( c_2 = 3 + \frac{1}{7} )</td>
<td>0.06251329</td>
<td>15.99659848</td>
</tr>
<tr>
<td>( c_3 = 3 + \frac{1}{7 + \frac{1}{15}} )</td>
<td>0.99659848</td>
<td>1.00341313</td>
</tr>
<tr>
<td>( c_4 = 3 + \frac{1}{7 + \frac{1}{15 + \frac{1}{7}}} )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Follow how this works. The first rational approximation of \( \pi \) is \( c_1 = 3 \), which is less than \( \pi \). The remainder is 0.14159265. The remainder’s reciprocal is
CHAPTER 2. AGE-STRUCTURED POPULATIONS

7.06251329. The integer part of this reciprocal is 7, so our next rational approximation of \( \pi \) is \( c_2 = 3 + 1/7 \), which is larger than \( \pi \) since \( 1/7 \) is greater than \( 0.141592654 \). The next remainder is \( 7.06251329 - 7 = 0.06251329 \), and its reciprocal is 15.99659848. Therefore, our next rational approximation is \( c_3 = 3 + 1/(7 + (1/15)) \), and since 1/15 is greater than 0.06251329, \( c_3 \) is less than \( \pi \). Rationalizing the continued fractions gives us the following successive rational number approximation of \( \pi \): \{3, 22/7, 333/106, 355/113, \ldots \}, or in decimal form: \{3, 3.1428 \ldots , 3.141509 \ldots , 3.14159292 \ldots \}.

Now consider a rational approximation for \( \Phi = 1.61803399 \ldots \):

\[
dfrac{c's}{remainder} \quad \dfrac{1/remainder}{1/1^{\infty}}
\]

\[
c_1 = 1 \quad \phi \quad \Phi
\]

\[
c_2 = 1 + \dfrac{1}{\phi} \quad \phi \quad \Phi
\]

and so on. All the \( n_i \)'s are one, and the sequence results in the slowest possible convergence for the \( c_i \)'s. Formerly, the limiting expression for \( \Phi \) is

\[
\Phi = \dfrac{1}{1 + \dfrac{1}{1^{\infty}}}
\]

Another derivation of the continued fraction expansion for \( \Phi \) can be obtained from \( \Phi^2 - \Phi - 1 = 0 \), written as \( \Phi = 1 + 1/\Phi \). Then inserting this expression for \( \Phi \) back into the right-hand-side gives \( \Phi = 1 + 1/(1 + 1/\Phi) \), and iterating infinitum shows that all the \( n_i \)'s are one. (As a side note, another interesting expression for \( \Phi \) comes from iterating \( \Phi = \sqrt{1 + \Phi} \).

The sequence of rational approximations just constructed for \( \Phi \) is 1, 2, 3/2, 5/3, 8/5, 13/8, etc., which are just the ratios of consecutive Fibonacci numbers. We have already shown that this ratio converges to \( \Phi \).

Because the golden ratio is the most irrational number, it has a way of appearing unexpectedly in nature. One well-known example is in the structure of flower petals. In class, I will show you how to see \( \Phi \) in a sunflower. Now let us begin our discussion of age-structured populations.

2.2 Rabbits are an age-structured population

Fibonacci’s rabbits form an age-structured population and we can use this simple case to illustrate the more general approach. Fibonacci’s rabbits can be categorized into two meaningful age classes: juveniles and adults. Here, juveniles are the newborn rabbits that can not yet mate; adults are those rabbits at least one month old. Beginning with a newborn pair at the beginning of the first month, we census the population at the beginning of each subsequent month after mated females have given birth. At the start of the \( n \)th month, let \( u_{1,n} \) be the number of newborn rabbit pairs, and let \( u_{2,n} \) be the number of rabbit pairs at least one month old. Since each adult pair gives birth to a juvenile pair, the number of juvenile pairs at the start of the \( (n + 1) \)-st month is equal to the number of adult pairs at the start of the \( n \)-th month. And since the number of
2.2. RABBITS ARE AN AGE-STRUCTURED POPULATION

Adult pairs at the start of the \((n + 1)\)-st month is equal to the sum of adult and juvenile pairs at the start of the \(n\)-th month, we have

\[
\begin{align*}
    u_{1,n+1} &= u_{2,n}, \\
    u_{2,n+1} &= u_{1,n} + u_{2,n};
\end{align*}
\]

or written in matrix form

\[
\begin{pmatrix}
    u_{1,n+1} \\
    u_{2,n+1}
\end{pmatrix} =
\begin{pmatrix}
    0 & 1 \\
    1 & 1
\end{pmatrix}
\begin{pmatrix}
    u_{1,n} \\
    u_{2,n}
\end{pmatrix}.
\]

(2.4)

Rewritten in vector form, we have

\[
    \mathbf{u}_{n+1} = L \mathbf{u}_n,
\]

(2.5)

where the definitions of the vector \(\mathbf{u}_n\) and the matrix \(L\) are obvious. The initial conditions, with one juvenile pair and no adults, are given by

\[
\begin{pmatrix}
    u_{1,1} \\
    u_{2,1}
\end{pmatrix} = \begin{pmatrix} 1 \\ 0 \end{pmatrix}.
\]

The solution of the system of coupled first-order linear difference equations, \((2.5)\), proceeds similarly to that of coupled first-order differential equations. With the ansatz, \(\mathbf{u}_n = \lambda^n \mathbf{v}\), we obtain upon substitution into \((2.5)\) the eigenvalue problem

\[
L \mathbf{v} = \lambda \mathbf{v},
\]

whose solution yields two eigenvalues \(\lambda_1\) and \(\lambda_2\), with corresponding eigenvectors \(\mathbf{v}_1\) and \(\mathbf{v}_2\). The general solution to \((2.5)\) is then

\[
\mathbf{u}_n = c_1 \lambda_1^n \mathbf{v}_1 + c_2 \lambda_2^n \mathbf{v}_2,
\]

(2.6)

with \(c_1\) and \(c_2\) determined from the initial conditions. Now suppose that \(|\lambda_1| > |\lambda_2|\). If we rewrite \((2.6)\) in the form

\[
\mathbf{u}_n = \lambda_1^n \left( c_1 \mathbf{v}_1 + c_2 \left( \frac{\lambda_2}{\lambda_1} \right)^n \mathbf{v}_2 \right),
\]

then because \(|\lambda_2/\lambda_1| < 1\), \(\mathbf{u}_n \to c_1 \lambda_1^n \mathbf{v}_1\) as \(n \to \infty\). The long-time asymptotics of the population, therefore, depends only on \(\lambda_1\) and the corresponding eigenvector \(\mathbf{v}_1\). For our Fibonacci’s rabbits, the eigenvalues are obtained by solving \(\det (L - \lambda I) = 0\), and we find

\[
\begin{pmatrix}
    -\lambda & 1 \\
    1 & -\lambda
\end{pmatrix} = -\lambda(1 - \lambda) - 1
\]

\[
= 0,
\]

or \(\lambda^2 - \lambda - 1 = 0\), with solutions \(\Phi\) and \(-\phi\). Since \(\Phi > \phi\), the eigenvalue \(\Phi\) and its corresponding eigenvector determine the long-time asymptotic population age-structure. The eigenvector may be found by solving

\[
(L - \Phi I) \mathbf{v}_1 = 0,
\]
| $u_{i,n}$ | number of females in age class $i$ at census $n$ |
| $s_i$ | fraction of females surviving from age class $i-1$ to $i$ |
| $m_i$ | expected number of female offspring from a female in age class $i$ |
| $l_i = s_1 \cdot s_i$ | fraction of females surviving from birth to age class $i$ |
| $f_i = m_i/l_i$ | |
| $R_0 = \sum_i f_i$ | basic reproductive ratio |

Table 2.1: Definitions needed in an age-structured, discrete-time population model

or

$$
\begin{pmatrix}
-\Phi & 1 \\
1 & 1 - \Phi
\end{pmatrix}
\begin{pmatrix}
v_{11} \\
v_{12}
\end{pmatrix}
= 
\begin{pmatrix}
0 \\
0
\end{pmatrix}.
$$

The first equation is just $-\Phi$ times the second equation (use $\Phi^2 - \Phi - 1 = 0$), so that $v_{12} = \Phi v_{11}$. Taking $v_{11} = 1$, we have

$$v_1 = \begin{pmatrix} 1 \\ \Phi \end{pmatrix}.$$

The asymptotic age-structure obtained from $v_1$ shows that the ratio of adults to juveniles approaches the golden mean; that is,

$$
\lim_{n \to \infty} \frac{u_{2,n}}{u_{1,n}} = v_{12}/v_{11}
= \Phi.
$$

2.3 Discrete age-structured populations

In a discrete model, population censuses occur at discrete times and individuals are assigned to age classes, spanning a range of ages. For model simplicity, we assume that the time between censuses is equal to the age span of all age classes. An example is a country that censuses its population every five years, and assigns individuals to age classes spanning five years (e.g., 0-4 years old, 5-9 years old, etc.). Although country censuses commonly count both females and males separately, we will only count females and ignore males.

There are several new definitions in this Section and I place these in Table 2.1 for easy reference. We define $u_{i,n}$ to be the number of females in age class $i$ at census $n$. We assume that $i = 1$ represents the first age class and $i = \omega$ the last. No female survives past the last age class. We also assume that the first census takes place when $n = 1$. We define $s_i$ as the fraction of females that survive from age class $i-1$ to age class $i$ (with $s_1$ the fraction of newborns that survive to their first census), and define $m_i$ as the expected number of female births per female in age class $i$.

We construct difference equations for $\{u_{i,n+1}\}$ in terms of $\{u_{i,n}\}$. First, newborns at census $n + 1$ were born between census $n$ and $n + 1$ to different aged females, with differing fertilities. Also, only a faction of these newborns survive to their first census. Second, only a fraction of females in age class $i$ that were counted in census $n$ survive to be counted in age class $i + 1$ in census $n + 1$. 

Putting these two ideas together with the appropriately defined parameters, the difference equations for \( \{u_{i,n+1}\} \) are determined to be

\[
\begin{align*}
    u_{1,n+1} &= s_1 (m_1 u_{1,n} + m_2 u_{2,n} + \cdots + m_{\omega} u_{\omega,n}), \\
    u_{2,n+1} &= s_2 u_{1,n}, \\
    u_{3,n+1} &= s_3 u_{2,n}, \\
    & \vdots \\
    u_{\omega,n+1} &= s_\omega u_{\omega-1,n},
\end{align*}
\]

which can be rewritten as the matrix equation

\[
\begin{pmatrix}
    u_{1,n+1} \\
    u_{2,n+1} \\
    u_{3,n+1} \\
    \vdots \\
    u_{\omega,n+1}
\end{pmatrix} =
\begin{pmatrix}
    s_1 m_1 & s_1 m_2 & \ldots & s_1 m_{\omega-1} & s_1 m_{\omega} \\
    s_2 & 0 & \ldots & 0 & 0 \\
    0 & s_3 & \ldots & 0 & 0 \\
    \vdots & \vdots & \vdots & \vdots & \vdots \\
    0 & 0 & \ldots & s_\omega & 0
\end{pmatrix}
\begin{pmatrix}
    u_{1,n} \\
    u_{2,n} \\
    u_{3,n} \\
    \vdots \\
    u_{\omega,n}
\end{pmatrix},
\]

or in compact vector form as

\[
u_{n+1} = L u_n, \tag{2.7}\]

where \( L \) is called the Leslie Matrix.

This system of linear equations can be solved by determining the eigenvalues and associated eigenvectors of the Leslie Matrix. One can solve directly the characteristic equation, \( \det (L - \lambda I) = 0 \), or reduce the system of first-order difference equations (2.7) to a single high-order equation for the number of females in the first age class. Following the latter approach, and beginning with the second row of (2.7), we have

\[
\begin{align*}
    u_{2,n+1} &= s_2 u_{1,n}, \\
    u_{3,n+1} &= s_3 u_{2,n} \\
    &= s_3 s_2 u_{1,n-1}, \\
    & \vdots \\
    u_{\omega,n+1} &= s_\omega u_{\omega-1,n} \\
    &= s_\omega s_{\omega-1} u_{\omega-2,n-1} \\
    & \vdots \\
    &= s_\omega s_{\omega-1} \cdots s_2 u_{1,n-\omega+2}.
\end{align*}
\]

If we define \( l_i = s_1 s_2 \cdots s_i \) to be the fraction of females that survive from birth to age class \( i \), and \( f_i = m_i l_i \), then the first row of (2.7) becomes

\[
u_{1,n+1} = f_1 u_{1,n} + f_2 u_{1,n-1} + f_3 u_{1,n-2} + \cdots + f_\omega u_{1,n-\omega+1}. \tag{2.8}\]

Here, we have made the simplifying assumption that \( n \geq \omega \) so that all the females counted in the \( n + 1 \) census were born after the first census.
CHAPTER 2. AGE-STRUCTURED POPULATIONS

The high-order linear difference equation \(2.8\) may be solved using the ansatz \(u_{1,n} = \lambda^n\). Direct substitution and division by \(\lambda^{n+1}\) results in the discrete Euler-Lotka equation

\[
\sum_{j=1}^{\omega} f_j \lambda^{-j} = 1,
\]

which may have both real and complex-conjugate roots.

Once an eigenvalue \(\lambda\) is determined from \(2.9\), the corresponding eigenvector \(v\) can be computed using the Leslie matrix. We have

\[
\begin{pmatrix}
    s_1 m_1 - \lambda & s_1 m_2 & \cdots & s_1 m_{\omega-1} & s_1 m_\omega \\
    s_2 & -\lambda & \cdots & 0 & 0 \\
    0 & s_3 & \cdots & 0 & 0 \\
    \vdots & \vdots & \ddots & \vdots & \vdots \\
    0 & 0 & \cdots & s_\omega & -\lambda
\end{pmatrix}
\begin{pmatrix}
    v_1 \\
    v_2 \\
    v_3 \\
    \vdots \\
    v_\omega
\end{pmatrix}
= \begin{pmatrix}
    0 \\
    0 \\
    0 \\
    \vdots \\
    0
\end{pmatrix}.
\]

Taking \(v_\omega = l_\omega / \lambda^\omega\), and beginning with the last row and working backwards, we have:

\[
v_{\omega-1} = l_{\omega-1} / \lambda^{\omega-1},
\]
\[
v_{\omega-2} = l_{\omega-2} / \lambda^{\omega-2},
\]
\[
\vdots
\]
\[
v_1 = l_1 / \lambda,
\]
so that

\[
v_i = l_i / \lambda^i, \quad \text{for } i = 1, 2, \ldots, \omega.
\]

We can obtain an interesting implication of this result by forming the ratio of two consecutive age classes. If \(\lambda\) is the dominant eigenvalue (and is real and positive, as is the case for human populations), then asymptotically,

\[
u_{i+1,n}/u_{i,n} \sim v_{i+1}/v_i = s_{i+1}/\lambda.
\]

With the survival fractions \(\{s_i\}\) fixed, a smaller positive \(\lambda\) implies a larger ratio: a slower growing (or decreasing) population has relatively more older people than a faster growing population. In fact, we are now living through a time when developed countries, particularly Japan and those in Western Europe, as well as Hong Kong and Singapore, have substantially lowered their population growth rates and are increasing the average age of their citizens.

If we want to simply determine if a population grows or decays, we can calculate the basic reproduction ratio \(R_0\), defined as the net expectation of female offspring to a newborn female. Stasis is obtained if the female only replaces herself before dying. If \(R_0 > 1\), then the population grows, and if \(R_0 < 1\) then the population decays. \(R_0\) is equal to the number of female offspring expected from a newborn when she is in age class \(i\), summed over all age classes, or

\[
R_0 = \sum_{i=1}^{\omega} f_i.
\]
For a population with approximately equal numbers of males and females, 
\( R_0 = 1 \) means a newborn female must produce on average two children over 
her lifetime. News stories in the western press frequently state that for zero 
population growth, women need to have 2.1 children. The term \( \text{women} \) used 
in these stories presumably means women of child-bearing age. Since girls who 
die young have no children, the statistic of 2.1 children implies that 0.1/2.1, or 
about 5% of children die before reaching adulthood.

A useful application of the mathematical model developed in this Section 
is to predict the future age structure within various countries. This can be 
important for economic planning—for instance, determining the tax revenues 
that can pay for the rising costs of health care as a population ages. For accurate 
predictions on the future age-structure of a given country, immigration and 
migration must also be modeled. An interesting website to browse is at 

This website, created by the US census bureau, provides access to the Interna-
tional Data Base (IDB), a computerized source of demographic and socio-
ceconomic statistics for 227 countries and areas of the world. In class, we will 
look at and discuss the dynamic output of some of the population pyramids, 
including those for Hong Kong and China.

### 2.4 Continuous age-structured populations

We can derive a continuous-time model by considering the discrete model in 
the limit as the age span \( \Delta a \) of an age class (also equal to the time between 
censuses) goes to zero. For \( n > \omega \), (2.8) can be rewritten as

\[
 u_{1,n} = \sum_{i=1}^{\omega} f_i u_{1,n-i}. \tag{2.10}
\]

The first age class in the discrete model consists of females born between two 
consecutive censuses. The corresponding function in the continuous model is 
the female birth rate of the population as a whole, \( B(t) \), satisfying

\[
 u_{1,n} = B(t_n) \Delta a.
\]

If we assume that the \( n \)th census takes place at a time \( t_n = n\Delta a \), we also have

\[
 u_{1,n-i} = B(t_{n-i}) \Delta a = B(t_n - t_i) \Delta a.
\]

To determine the continuous analogue of the parameter \( f_i = m_i l_i \), we define 
the age-specific survival function \( l(a) \) to be the fraction of newborn females that 
survive to age \( a \), and define the age-specific maternity function \( m(a) \), multiplied 
by \( \Delta a \), to be the average number of females born to a female between the ages 
of \( a \) and \( a + \Delta a \). With the definition of the age-specific net maternity function, 
\( f(a) = m(a) l(a) \), and \( a_i = i \Delta a \), we have

\[
 f_i = f(a_i) \Delta a.
\]
With these new definitions, (2.10) becomes

\[ B(t_n)\Delta a = \sum_{i=1}^\omega f(a_i)B(t_n - t_i)(\Delta a)^2. \]

Canceling one factor of \( \Delta a \), and using \( t_i = a_i \), the right-hand side becomes a Riemann sum. Taking \( t_n = t \) and assigning \( f(a) = 0 \) when \( a \) is greater than the maximum age of female fertility, the limit \( \Delta a \to 0 \) transforms (2.10) to

\[ B(t) = \int_0^\infty B(t - a)f(a)da. \]

(2.11)

Equation (2.11) states that the population-wide female birth rate at time \( t \) has contributions from females of all ages, and that the contribution to this birth rate from females between the ages of \( a \) and \( a + da \) is determined from the population-wide female birth rate at the earlier time \( t - a \) times the fraction of females that survive to age \( a \) times the number of female births to females between the ages of \( a \) and \( a + da \). Equation (2.11) is a linear homogeneous integral equation, valid for \( t \) greater than the maximum age of female fertility. A more complete but inhomogeneous equation valid for smaller \( t \) can also be derived.

Equation (2.11) can be solved by the ansatz \( B(t) = e^{rt} \). Direct substitution yields

\[ e^{rt} = \int_0^\infty f(a)e^{r(t-a)}da, \]

which upon canceling \( e^{rt} \) results in the continuous Euler-Lotka equation

\[ \int_0^\infty f(a)e^{-ra}da = 1. \]

(2.12)

Equation (2.12) is an integral equation for \( r \) given the age-specific net maternity function \( f(a) \). It is possible to prove that for \( f(a) \) a continuous non-negative function, (2.13) has exactly one real root \( r^*_s \), and that the population grows \( (r_s > 0) \) or decays \( (r_s < 0) \) asymptotically as \( e^{r_*t} \). The population growth rate \( r_s \) has been called the intrinsic rate of increase, the intrinsic growth rate, or the Malthusian parameter. Typically, (2.12) must be solved for \( r_s \) using Newton’s method.

We briefly digress here to explain Newton’s method, which is an efficient root-finding algorithm that solves \( F(x) = 0 \) for \( x \). Newton’s method can be derived graphically by plotting \( F(x) \) versus \( x \), approximating \( F(x) \) by the tangential line at \( x = x_n \) with slope \( F'(x_n) \), and letting \( x_{n+1} \) be the intercept of the tangential line with the x-axis. An alternative derivation starts with the Taylor series \( F(x_{n+1}) = F(x_n) + (x_{n+1} - x_n)F'(x_n) + \ldots \). We set \( F(x_{n+1}) = 0 \), drop higher-order terms in the Taylor series, and solve for \( x_{n+1} \):

\[ x_{n+1} = x_n - \frac{F(x_n)}{F'(x_n)}, \]

which is to be solved iteratively, starting with a wise choice of initial guess \( x_0 \), until convergence.
Solution of (2.12) by Newton’s method requires defining

\[ F(r) = \int_0^\infty f(a)e^{-ra}da - 1, \quad (2.13) \]

from which one derives

\[ F'(r) = -\int_0^\infty af(a)e^{-ra}da. \]

Newton’s method then begins with an initial guess \( r_0 \) and computes the iteration

\[ r_{n+1} = r_n + \frac{\int_0^\infty f(a)e^{-r_n a}da - 1}{\int_0^\infty af(a)e^{-r_n a}da} \]

until \( r_n \) converges sufficiently close to \( r^*_n \).

After asymptotically attaining a stable age structure, the population grows like \( e^{r^*_n t} \), and our previous discussion of the Malthusian growth model suggests that \( r^*_n \) may be found from the constant per capita birth rate \( b \) and death rate \( d \). By determining expressions for \( b \) and \( d \), we will indeed show that \( r^*_n = b - d \).

Because females that have survived to age \( a \) at time \( t \) were born earlier at time \( t - a \), \( B(t - a)l(a)da \) represents the number of females at time \( t \) that are between the ages of \( a \) and \( a + da \). The total number of females \( N(t) \) at time \( t \) is therefore given by

\[ N(t) = \int_0^\infty B(t - a)l(a)da. \quad (2.14) \]

The per capita birth rate \( b(t) \) equals the population-wide birth rate \( B(t) \) divided by the population size \( N(t) \), and using (2.11) and (2.14),

\[ b(t) = \frac{B(t)}{N(t)} = \frac{\int_0^\infty B(t - a)f(a)da}{\int_0^\infty B(t - a)l(a)da} \]

Similarly, the per capita death rate \( d(t) \) equals the population-wide death rate \( D(t) \) divided by \( N(t) \). To derive \( D(t) \), we first define the age-specific mortality function \( \mu(a) \), multiplied by \( \Delta a \), to be the probability that a female of age \( a \) dies before attaining the age \( a + \Delta a \). The relationship between the age-specific mortality function \( \mu(a) \) and the age-specific survival function \( l(a) \) may be obtained by computing the probability of a female surviving to age \( a + \Delta a \). This probability is equal to the probability of a female surviving to age \( a \) times the probability \( 1 - \mu(a)\Delta a \) of not dying in the next small interval of time \( \Delta a \); that is,

\[ l(a + \Delta a) = l(a)(1 - \mu(a)\Delta a), \]

or

\[ \frac{l(a + \Delta a) - l(a)}{\Delta a} = -\mu(a)l(a); \]

and as \( \Delta a \to 0 \),

\[ l'(a) = -\mu(a)l(a). \quad (2.15) \]

The age-specific mortality function \( \mu(a) \) is analogous to the age-specific maternity function \( m(a) \), and we define the age-specific net mortality function \( g(a) = \)
\[ \mu(a)l(a) \] in analogy to the age-specific net maternity function \( f(a) = m(a)l(a) \).

The population-wide birth rate \( B(t) \) is determined from \( f(a) \) using (2.11), and in analogy, the population-wide death rate \( D(t) \) is determined from \( g(a) \) using

\[ D(t) = \int_0^\infty B(t-a)g(a)\,da, \tag{2.16} \]

where the integrand represents the contribution to the death rate from females that die between the ages of \( a \) and \( a + da \). The per capita death rate is therefore

\[ d(t) = D(t)/N(t) = \frac{\int_0^\infty B(t-a)g(a)\,da}{\int_0^\infty B(t-a)l(a)\,da}; \]

and the difference between the per capita birth and death rates is calculated from

\[ b(t) - d(t) = \frac{\int_0^\infty B(t-a)[f(a) - g(a)]\,da}{\int_0^\infty B(t-a)l(a)\,da}. \tag{2.17} \]

Asymptotically, a stable age structure is established and the population-wide birth rate grows as \( B(t) \sim e^{r_*t} \). Substitution of this expression for \( B(t) \) into (2.17) and cancelation of \( e^{r_*t} \) results in

\[ b - d = \frac{\int_0^\infty [f(a) - g(a)]e^{-r_*a}da}{\int_0^\infty l(a)e^{-r_*a}da} = 1 + \frac{\int_0^\infty l'(a)e^{-r_*a}da}{\int_0^\infty l(a)e^{-r_*a}da}, \]

where use has been made of (2.12) and (2.15). Simplifying the numerator using integration by parts,

\[ \int_0^\infty l'(a)e^{-r_*a}da = l(a)e^{-r_*a}\bigg|_0^\infty + r_* \int_0^\infty l(a)e^{-r_*a}da \]

\[ = -1 + r_* \int_0^\infty l(a)e^{-r_*a}da, \]

provides the desired result,

\[ r_* = b - d. \]

It is usually supposed that evolution by natural selection will result in populations with the largest value of the Malthusian parameter \( r_* \), and that natural selection would favor those females that constitute such a population. We will exploit this idea in the next section to compute the brood size of the self-fertilizing hermaphroditic worm of the species \textit{Caenorhabditis elegans}.

### 2.5 The brood size of a hermaphroditic worm

\textit{Caenorhabditis elegans}, a soil-dwelling nematode worm about 1 mm in length, is a widely studied model organism in biology. With a body made up of approximately 1000 cells, it is one of the simplest multicellular organisms under study. Advances in understanding the development of this multicellular organism led
2.5. THE BROOD SIZE OF A HERMAPHRODITIC WORM

Figure 2.1: *Caenorhabditis elegans*, a nematode worm used by biologists as a simple animal model of a multicellular organism. (Photo by Amy Pasquinelli.)

![Figure 2.1 Diagram](image)

Figure 2.2: A simplified timeline of a hermaphrodite’s life.

to the awarding of the 2002 Nobel prize in Physiology or Medicine to the three *C. elegans* biologists Sydney Brenner, H. Robert Horvitz and John E. Sulston.

The worm *C. elegans* has two sexes: hermaphrodites, which are essentially females that can produce internal sperm and self-fertilize their own eggs, and males, which must mate with hermaphrodites to produce offspring. In laboratory cultures, males are rare and worms generally propagate by self-fertilization. Typically, a hermaphrodite lays about 250-350 self-fertilized eggs before becoming infertile. It is reasonable to assume that the forces of natural selection have shaped the life-history of *C. elegans*, and that the number of offspring produced by a selling hermaphrodite must be in some sense optimal. Here, we show how an age-structured model applied to *C. elegans* yields theoretical insights into the brood size of a selling hermaphrodite.

To develop a mathematical model for *C. elegans*, we need to know some details of its life history. As a first approximation (Barker, 1992), a simplified timeline of a hermaphrodite’s life is shown in Fig. 2.2. The fertilized egg is laid at time $t = 0$. During a juvenile growth period, the immature worm develops through four larval stages (L1-L4). Towards the end of L4 and for a short while after its final molt to adulthood, the hermaphrodite produces sperm, which is then stored for later use. Then the hermaphrodite produces eggs, self-fertilizes them using her internally stored sperm, and lays them. In the absence of males, egg production ceases after all the sperm are utilized. We assume that the juvenile growth period occurs during $0 < t < g$, spermatogenesis occurs during $g < t < g+s$, and egg-production, self-fertilization, and egg laying occurs during...
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<table>
<thead>
<tr>
<th>g</th>
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<th>72 h</th>
</tr>
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<td>s</td>
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</tr>
<tr>
<td>e</td>
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<td>65 h</td>
</tr>
<tr>
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<td>sperm production rate</td>
<td>24 h$^{-1}$</td>
</tr>
<tr>
<td>m</td>
<td>egg production rate</td>
<td>4.4 h$^{-1}$</td>
</tr>
<tr>
<td>B</td>
<td>brood size</td>
<td>286</td>
</tr>
</tbody>
</table>

Table 2.2: Parameters in a life-history model of *C. elegans*, with experimental estimates.

$g + s < t < g + s + e$.

Here, we want to understand why hermaphrodites limit their sperm production. Biologists define males and females from the size and metabolic cost of their gametes: sperm are cheap and eggs are expensive. So on first look, it is puzzling why the total number of offspring produced by a hermaphrodite is limited by the number of sperm produced, rather than by the number of eggs. There must be a hidden cost to the hermaphrodite of producing additional sperm other than metabolic. To understand the basic biology, it is instructive to consider two limiting cases: (1) no sperm production; (2) infinite sperm production. In both cases, the hermaphrodite produces no offspring—in the first case because there are no sperm, and in the second case because there are no eggs. The number of sperm produced by a hermaphrodite before laying eggs is therefore a compromise; although more sperm means more offspring, more sperm also means delayed egg production.

Our main theoretical assumption is that natural selection will favor worms with the ability to establish populations with the largest Malthusian parameter $r$. Worms containing a genetic mutation resulting in a larger value for $r$ will eventually outnumber all other worms.

The parameters we need for our mathematical model are listed in Table 2.2 together with estimated experimental values (Cutter, 2004). In addition to the growth period $g$, sperm production period $s$, and egg production period $e$ (all in units of hours), we need the sperm production rate $p$ and the egg production rate $m$ (both in units of inverse hours). We also define the brood size $B$ as the total number of fertilized eggs laid by a selfing hermaphrodite. The brood size is equal to the number of sperm produced, and also equal to the number of eggs laid, so that

$$B = ps = me.$$  (2.18)

We may use (2.18) to eliminate $s$ and $e$ in favor of $B$:

$$s = B/m, \quad e = B/p.$$  (2.19)

The continuous Euler-Lotka equation (2.12) for $r$ requires a model for $f(a) = m(a)/l(a)$, where $m(a)$ is the age-specific maternity function and $l(a)$ is the age-specific survival function. The function $l(a)$ satisfies the differential equation (2.15), and here we make the simplifying assumption that the age-specific mortality function $\mu(a) = d$, where $d$ is the age-independent per capita death rate. Implicitly, we are assuming that worms do not die of old age during egg-laying, but rather die of predation, starvation, disease, or other age-independent causes. Such an assumption is reasonable since worms can live in the laboratory for
2.5. THE BROOD SIZE OF A HERMAPHRODITIC WORM

several weeks after sperm-depletion. Solving (2.15) with the initial condition
\( l(0) = 1 \) results in
\[
\begin{align*}
\frac{dl}{da} &= -d \cdot a. \\
\int (a) &= \exp (-d \cdot a). 
\end{align*}
\]

The age-specific maternity function \( m(a) \) is defined such that \( m(a) \Delta a \) is the
expected number of offspring produced over the age interval \( \Delta a \). We assume that
a hermaphrodite lays eggs at a constant rate \( m \) over the ages
\( g+s < a < g+s+e \); therefore,
\[
m(a) = \begin{cases} 
  m & \text{for } g + s < a < g + s + e, \\
  0 & \text{otherwise.}
\end{cases}
\] (2.20)

Using (2.19), (2.20) and (2.21), the continuous Euler-Lotka equation (2.12)
for the Malthusian parameter \( r \) becomes
\[
\int_{g+B/p}^{g+B/p+B/m} m \exp \left\{ -(r + d)a \right\} da = 1. 
\] (2.22)

Integrating,
\[
1 = \int_{g+B/p}^{g+B/p+B/m} m \exp \left\{ -(r + d)a \right\} da \\
= \frac{m}{r + d} \left\{ \exp \{-(g + B/p)(r + d)\} - \exp \{-(g + B/p + B/m)(r + d)\} \right\} \\
= \frac{m}{r + d} \exp \{-(g + B/p)(r + d)\} \left\{ 1 - \exp \{-(B/m)(r + d)\} \right\},
\]
which may be rewritten as
\[
(r + d) \exp \{(g + B/p)(r + d)\} = m \left\{ 1 - \exp \{-(B/m)(r + d)\} \right\}. 
\] (2.23)

With the parameters \( d, g, p, \) and \( m \) fixed, the integrated Euler-Lotka equation (2.23)
is an implicit equation for \( r = r(B) \).

To demonstrate that \( r = r(B) \) has a maximum at some value of \( B \), we numerically solve (2.23) for \( r \) with the parameter values of \( g, p \) and \( m \) obtained from Table 2.2. Since \( r + d \) is maximum at the same value of \( B \) that \( r \) is
maximum, and \( d \) only enters (2.23) in the form \( r + d \), without loss of generality we can take \( d = 0 \). To solve (2.23), it is best to make use of Newton’s method. We let
\[
F(r) = (r + d) \exp \{(g + B/p)(r + d)\} - m \left\{ 1 - \exp \{-(B/m)(r + d)\} \right\},
\]
differentiate with respect to \( r \) to obtain
\[
F'(r) = [1 + (g + B/p)(r + d)] \exp \{(g + B/p)(r + d)\} - B \frac{m}{m} \exp \{-(B/m)(r + d)\}.
\]

For a given \( B \), we then solve \( F(r) = 0 \) by iterating
\[
r_{n+1} = r_n - \frac{F(r_n)}{F'(r_n)}.
\]

Using appropriate starting values for \( r \), the function \( r = r(B) \) can be computed and is presented in Fig. 2.3. Evidently, \( r \) is maximum near the value \( B = 152 \), which is 53% of the value shown in Table 2.2.
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Figure 2.3: A plot of $r = r(B)$, which demonstrates that the Malthusian growth rate $r$ is maximum near a brood size of $B = 152$.

We can also directly determine a single equation for the value of $B$ at which $r$ is maximum. We implicitly differentiate (2.23) with respect to $B$—with $r$ the only parameter that depends on $B$—and apply the condition $dr/dB = 0$. We find

$$(r + d) \exp \left[ (g + B/p)(r + d) \right] = p \exp \left[ -(B/m)(r + d) \right].$$  \hspace{1cm} (2.24)

Taking the ratio of (2.23) to (2.24) results in

$$1 = \frac{m}{p} (\exp ((B/m)(r + d)) - 1),$$  \hspace{1cm} (2.25)

from which we can find

$$r + d = \frac{m}{B} \ln (1 + p/m).$$  \hspace{1cm} (2.26)

Substituting (2.26) back into either (2.23) or (2.24) results in

$$\frac{m}{B} \left( 1 + \frac{p}{m} \right)^{\frac{x}{m} + \frac{y}{m}} \ln \left( 1 + \frac{p}{m} \right) = \frac{pm}{p + m}.$$  \hspace{1cm} (2.27)

Equation (2.27) contains the four parameters $p$, $m$, $g$ and $B$, which can be further reduced to three parameters by dimensional analysis. The brood size $B$ is already dimensionless. The rate at which eggs are produced and laid $m$ may be multiplied by the sperm production period $s = B/p$ to form the dimensionless parameter $x = mB/p$. The parameter $x$ represents the number of eggs forgone because of the adult sperm production period and is a measure of the cost of producing sperm. Similarly, $m$ may be multiplied by the larval growth period $g$ to form the dimensionless parameter $y = mg$. The parameter $y$ represents the number of eggs forgone because of the juvenile growth period and is a measure of the cost of development. With $B$, $x$ and $y$ as our three
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Figure 2.4: Solution curve of $y$ versus $x$ with brood size $B = 286$, obtained by solving (2.28). Values for $B, m, p$ and $g$ are taken from Table 2.2. The cross, crossed open circle and open circle correspond to $y = mg$ and $x = mfB/p$ with $f = 1, 1/3$ and $1/8$, respectively.

Given values for two of the three dimensionless parameters $x, y$ and $B$, (2.28) may be solved for the remaining parameter, either explicitly for the case of $y = y(x, B)$, or by Newton’s method.

The values of $x$ and $y$ obtained from Table 2.2 are $x = 52.5$ and $y = 317$. With $B = 286$, the solution $y = y(x)$ is shown in Fig. 2.4 with the experimental value of $(x, y)$ plotted as a cross.

The seemingly large disagreement between the theoretical result and the experimental data leads us to question the underlying assumptions of the model. Indeed, Cutter (2004) first suggested that the sperm produced precociously as a juvenile does not delay egg production and should be considered cost free. One possibility is to fix the absolute number of sperm produced precociously and to optimize the number of sperm produced as an adult. Another possibility is to fix the fraction of sperm produced precociously and to optimize the total number of sperm produced. This latter assumption was made by Cutter (2004) and seems to best improve the model agreement with the experimental data.

We therefore split the total sperm production period $s$ into juvenile and adult sperm production periods $s_J$ and $s_A$, with $s = s_J + s_A$. The revised timeline of the hermaphrodite’s life is now shown in Fig. 2.5. With the fraction of sperm produced as an adult denoted by $f$, and the fraction produced as a juvenile by $1 - f$, we have

$$s_J = (1 - f)s, \quad s_A = fs.$$  

(2.29)
Figure 2.5: A more refined timeline of a hermaphrodite’s life.

Equation (2.21) for the age-specific maternity function becomes

\[ m(a) = \begin{cases} 
  m & \text{for } g + s_A < a < g + s_A + e, \\
  0 & \text{otherwise}. 
\end{cases} \]  

(2.30)

with

\[ s_A = fB/p. \]  

(2.31)

The Euler-Lotka equation (2.22) is then changed by the substitution \( p \to p/f \). Following this substitution to the final result given by (2.28) shows that this equation still holds (which is in fact equivalent to (12) of Chasnov (2011)), but with the now changed definition

\[ x = mBf/p. \]  

(2.32)

A close examination of the results shown in Fig. 2.4 demonstrates that near-perfect agreement can be made between the results of the theoretical model and the experimental data if \( f = 1/8 \) (shown as the open circle in Fig. 2.4). Cutter (2004) suggested the value of \( f = 1/3 \), and this result is shown as a crossed open circle in Fig. 2.4 still in much better agreement with the experimental data than the open circle corresponding to \( f = 1 \). The added modeling of precocious sperm production through the parameter \( f \) thus seems to improve the verisimilitude of the model to the underlying biology.

**References**


Chapter 3

Stochastic Modeling of Population Growth

Our derivation of the Malthusian growth model implicitly assumed a large population size. Smaller populations exhibit stochastic effects and these can considerably complicate the modeling. Since in general, modeling stochastic processes in biology is an important yet difficult topic, we will spend some time here analyzing the simplest model of births in finite populations.

3.1 A stochastic model of population growth

The size of the population \( N \) is now considered to be a discrete random variable. We define the time-dependent probability mass function \( p_N(t) \) of \( N \) to be the probability that the population is of size \( N \) at time \( t \). Since \( N \) must take on one of the values from zero to infinity, we have

\[
\sum_{N=0}^{\infty} p_N(t) = 1,
\]

for all \( t \geq 0 \). Again, let \( b \) be the average per capita birth rate. We make the simplifying approximations that all births are singlets, and that the probability of an individual giving birth is independent of past birthing history. We can then interpret \( b \) probabilistically by supposing that as \( \Delta t \to 0 \), the probability that an individual gives birth during the time \( \Delta t \) is given by \( b\Delta t \). For example, if the average per capita birthrate is one offspring every 365-day year, then the probability that a given individual gives birth on a given day is \( 1/365 \). As we will be considering the limit as \( \Delta t \to 0 \), we neglect probabilities of more than one birth in the population in the time interval \( \Delta t \) since they are of order \( (\Delta t)^2 \) or higher. Furthermore, we will suppose that at \( t = 0 \), the population size is known to be \( N_0 \), so that \( p_{N_0}(0) = 1 \), with all other \( p_N \)’s at \( t = 0 \) equal to zero.

We can determine a system of differential equations for the probability mass function \( p_N(t) \) as follows. For a population to be of size \( N > 0 \) at a time \( t + \Delta t \), either it was of size \( N - 1 \) at time \( t \) and one birth occured, or it was of size \( N \) at time \( t \) and there were no births; that is

\[
p_N(t + \Delta t) = p_{N-1}(t)b(N - 1)\Delta t + p_N(t)(1 - bN\Delta t).
\]
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Subtracting $p_N(t)$ from both sides, dividing by $\Delta t$, and taking the limit $\Delta t \to 0$ results in the forward Kolmogorov differential equations:

$$\frac{dp_N}{dt} = b[(N-1)p_{N-1} - Np_N], \quad N = 1, 2, \ldots \quad (3.1)$$

where $p_0(t) = p_0(0)$ since a population of zero size remains zero. This system of coupled first-order linear differential equations can be solved iteratively.

We first review how to solve a first-order linear differential equation of the form

$$\frac{dy}{dt} + ay = g(t), \quad y(0) = y_0 \quad (3.2)$$

where $y = y(t)$ and $a$ is constant. First, we look for an integrating factor $\mu$ such that

$$\frac{d(\mu y)}{dt} = \mu \left( \frac{dy}{dt} + ay \right).$$

Differentiating the left-hand-side and multiplying out the right-hand-side results in

$$\frac{d\mu}{dt} y + \frac{dy}{dt} \mu = \mu \frac{dy}{dt} + a\mu y;$$

and cancelling terms yields

$$\frac{d\mu}{dt} = a\mu.$$

We may integrate this equation with an arbitrary initial condition, so for simplicity we take $\mu(0) = 1$. Therefore, $\mu(t) = e^{at}$. Hence,

$$\frac{d}{dt} (e^{at} y) = e^{at} g(t).$$

Integrating this equation from 0 to $t$ yields

$$e^{at} y(t) - y(0) = \int_0^t e^{as} g(s) ds.$$ 

Therefore, the solution is

$$y(t) = e^{-at} \left( y(0) + \int_0^t e^{as} g(s) ds \right). \quad (3.3)$$

The forward Kolmogorov differential equation $[3.1]$ is of the form Eq. $[3.2]$ with $a = bN$ and $g(t) = b(N - 1)p_{N-1}$. With the population size known to be $N_0$ at $t = 0$, the initial conditions can be written succinctly as $p_N(0) = \delta_{N,N_0}$, where $\delta_{ij}$ is the Kronecker delta, defined as

$$\delta_{ij} = \begin{cases} 0 & \text{for } i \neq j, \\ 1 & i = j. \end{cases}$$

Therefore, formal integration of $[3.1]$ using Eq. $[3.3]$ results in

$$p_N(t) = e^{-bNt} \left[ \delta_{N,N_0} + b(N - 1) \int_0^t e^{bNs} p_{N-1}(s) ds \right]. \quad (3.4)$$
The first few solutions of (3.4) can now be obtained by successive integrations:

\[
p_N(t) = \begin{cases} 
0 & \text{if } N < N_0, \\
e^{-bN_0 t} & \text{if } N = N_0, \\
N_0 e^{-bN_0 t}[1 - e^{-bt}] & \text{if } N = N_0 + 1, \\
\frac{1}{2}N_0(N_0 + 1)e^{-bN_0 t}[1 - e^{-bt}]^2 & \text{if } N = N_0 + 2, \\
& \ldots 
\end{cases}
\]

Although we will not need this, for completeness I give the complete solution. By defining the binomial coefficient as the number of ways one can select \( k \) objects from a set of \( n \) identical objects, where the order of selection is immaterial, we have

\[
\binom{n}{k} = \frac{n!}{k!(n-k)!},
\]

(read as “\( n \) choose \( k \)”). The general solution for \( p_N(t) \), \( N \geq N_0 \), is known to be

\[
p_N(t) = \binom{N-1}{N_0-1} e^{-bN_0 t}[1 - e^{-bt}]^{N-N_0},
\]

which statisticians call a “shifted negative binomial distribution.” Determining the time-evolution of the probability mass function of \( N \) completely solves the stochastic problem.

Of usual main interest is the mean and variance of the population size, and although both could in principle be computed from the probability mass function, we will compute them directly from the differential equation for \( p_N \). The definitions of the mean population size \( \langle N \rangle \) and its variance \( \sigma^2 \) are

\[
\langle N \rangle = \sum_{N=0}^{\infty} N p_N, \quad \sigma^2 = \sum_{N=0}^{\infty} (N - \langle N \rangle)^2 p_N,
\]

and we will make use of the equality

\[
\sigma^2 = \langle N^2 \rangle - \langle N \rangle^2.
\]

Multiplying the differential equation (3.1) by the constant \( N \), summing over \( N \), and using \( p_N = 0 \) for \( N < N_0 \), we obtain

\[
\frac{d\langle N \rangle}{dt} = b \left[ \sum_{N=N_0+1}^{\infty} N(N-1)p_{N-1} - \sum_{N=N_0}^{\infty} N^2 p_N \right].
\]

Now \( N(N-1) = (N-1)^2 + (N-1) \), so that the first term on the right-hand-side is

\[
\sum_{N=N_0+1}^{\infty} N(N-1)p_{N-1} = \sum_{N=N_0+1}^{\infty} (N-1)^2 p_{N-1} + \sum_{N=N_0+1}^{\infty} (N-1) p_{N-1} \\
= \sum_{N=N_0}^{\infty} N^2 p_N + \sum_{N=N_0}^{\infty} N p_N,
\]
where the second equality was obtained by shifting the summation index downward by one. Therefore, we find the familiar equation
\[ \frac{d\langle N \rangle}{dt} = b\langle N \rangle. \]
Together with the initial condition \( \langle N \rangle(0) = N_0 \), we have the solution \( \langle N \rangle(t) = N_0 \exp(bt) \). We proceed similarly to find \( \sigma^2 \) by first determining the differential equation for \( \langle N^2 \rangle \). Multiplying the differential equation for \( p_N \), Eq. (3.1), by \( N^2 \) and summing over \( N \) results in
\[ \frac{d\langle N^2 \rangle}{dt} = b \left( \sum_{N=N_0+1}^{\infty} N^2(N-1)p_{N-1} - \sum_{N=N_0}^{\infty} N^3p_N \right). \]
Here, we use the equality \( N^2(N-1) = (N-1)^3 + 2(N-1)^2 + (N-1) \). Proceeding in the same way as above by shifting the index downward, we obtain
\[ \frac{d\langle N^2 \rangle}{dt} - 2b\langle N^2 \rangle = b\langle N \rangle, \]
which is a first-order linear inhomogeneous equation for \( \langle N^2 \rangle \) since \( \langle N \rangle \) is known, and can be solved using an integrating factor. The solution obtained using Eq. (3.3) is
\[ \langle N^2 \rangle = e^{2bt} \left( N_0^2 + \int_0^t e^{-2bs}b\langle N \rangle(s)ds \right), \]
with \( \langle N \rangle(t) = N_0e^{bt} \). Performing the integration, we obtain
\[ \langle N^2 \rangle = e^{2bt} \left[ N_0^2 + N_0(1 - e^{-bt}) \right]. \]
Finally, using \( \sigma^2 = \langle N^2 \rangle - \langle N \rangle^2 \), we obtain the variance. Thus we arrive at our final result for the population mean and variance:
\[ \langle N \rangle = N_0e^{bt}, \quad \sigma^2 = N_0e^{2bt}(1 - e^{-bt}). \quad (3.7) \]

### 3.2 Asymptotics of large initial populations

Here, we determine the limiting form of the probability distribution when the initial population size is large. Our goal is to solve for an expansion of the distribution in powers of \( 1/N_0 \) to leading-orders; notice that \( 1/N_0 \) is small if \( N_0 \) is large. To zeroth-order, that is in the limit \( N_0 \to \infty \), we show that the deterministic model of population growth is recovered. To first-order in \( 1/N_0 \), we show that the probability distribution is normal. The latter result will be shown to be a consequence of the well-known Central Limit Theorem in probability theory.

We develop our expansion by working directly with the differential equation for \( p_N(t) \). Now, when the population size \( N \) is a discrete random variable (taking only the nonnegative integer values of 0, 1, 2, \ldots), \( p_N(t) \) is the probability mass function for \( N \). If \( N_0 \) is large, then the discrete nature of \( N \) is inconsequential, and it is preferable to work with a continuous random variable and its probability density function. Accordingly, we define the random variable \( x = N/N_0 \), and
treat $x$ as a continuous random variable, with $0 \leq x < \infty$. Now, $p_N(t)$ is the probability that the population is of size $N$ at time $t$, and the probability density function of $x$, $P(x, t)$, is defined such that $\int_a^b P(x, t)dx$ is the probability that $a \leq x \leq b$. The relationship between $p$ and $P$ can be determined by considering how to approximate a discrete probability distribution by a continuous distribution, that is, by defining $P$ such that

$$p_N(t) = \int_{(N - \frac{1}{2})/N_0}^{(N + \frac{1}{2})/N_0} P(x, t)dx$$

$$= P(\frac{N}{N_0}, t)/N_0$$

where the last equality becomes exact as $N_0 \rightarrow \infty$. Therefore, the appropriate definition for $P(x, t)$ is given by

$$P(x, t) = N_0p_N(t), \quad x = \frac{N}{N_0},$$

(3.8)

which satisfies

$$\int_0^\infty P(x, t)dx = \sum_{N=0}^\infty P(\frac{N}{N_0}, t)(1/N_0)$$

$$= \sum_{N=0}^\infty p_N(t)$$

$$= 1,$$

the first equality (exact only when $N_0 \rightarrow \infty$) being a Reimann sum approximation of the integral.

We now transform the infinite set of ordinary differential equations (3.1) for $p_N(t)$ into a single partial differential equation for $P(x, t)$. We multiply (3.1) by $N_0$ and substitute $N = N_0x$, $p_N(t) = P(x, t)/N_0$, and $p_{N-1}(t) = P(x - \frac{1}{N_0}, t)/N_0$ to obtain

$$\frac{\partial P(x, t)}{\partial t} = b \left[ (N_0x - 1)P(x - \frac{1}{N_0}, t) - N_0xP(x, t) \right].$$

(3.9)

We next Taylor series expand $P(x - 1/N_0, t)$ around $x$, treating $1/N_0$ as a small parameter. That is, we make use of

$$P(x - \frac{1}{N_0}, t) = P(x, t) - \frac{1}{N_0}P_x(x, t) + \frac{1}{2N_0^2}P_{xx}(x, t) - \ldots$$

$$= \sum_{n=0}^\infty \frac{(-1)^n}{n!N_0^n} \frac{\partial^n P}{\partial x^n}.$$

The two leading terms proportional to $N_0$ on the right-hand-side of (3.9) cancel exactly, and if we group the remaining terms in powers of $1/N_0$, we obtain for the first three leading terms in the expansion

$$P_t = -b \left[ (xP_x + P) - \frac{1}{N_0} \left( \frac{xP_{xx}}{2!} + \frac{P_x}{1!} \right) + \frac{1}{N_0^2} \left( \frac{xP_{xxx}}{3!} + \frac{P_{xx}}{2!} \right) - \ldots \right]$$

$$= -b \left[ (xP)_x - \frac{1}{N_02!}(xP)_{xx} + \frac{1}{N_03!}(xP)_{xxx} - \ldots \right].$$

(3.10)
and higher-order terms can be obtained by following the evident pattern.

Equation (3.10) may be further analyzed by a perturbation expansion of the probability density function in powers of $1/N_0$:

$$P(x, t) = P^{(0)}(x, t) + \frac{1}{N_0} P^{(1)}(x, t) + \frac{1}{N_0^2} P^{(2)}(x, t) + \ldots$$

(3.11)

Here, the unknown functions $P^{(0)}(x, t)$, $P^{(1)}(x, t)$, $P^{(2)}(x, t)$, etc. are to be determined by substituting the expansion (3.11) into (3.10) and equating coefficients of powers of $1/N_0$. We thus obtain for the coefficients of $(1/N_0)^0$ and $(1/N_0)^1$,

$$P_t^{(0)} = -b \left( xP^{(0)} \right)_x$$

(3.12)

$$P_t^{(1)} = -b \left[ (xP^{(1)})_x - \frac{1}{2} \left( xP^{(0)} \right)_{xx} \right].$$

(3.13)

### 3.2.1 Derivation of the deterministic model

The zeroth-order term in the perturbation expansion (3.11),

$$P^{(0)}(x, t) = \lim_{N_0 \to \infty} P(x, t),$$

satisfies (3.12). Equation (3.12) is a first-order linear partial differential equation with a variable coefficient. One way to solve this equation is to try the ansatz

$$P^{(0)}(x, t) = h(t)f(r), \quad r = r(x, t),$$

(3.14)

together with the initial condition

$$P^{(0)}(x, 0) = f(x),$$

since at $t = 0$, the probability distribution is assumed to be a known function. This initial condition imposes further useful constraints on the functions $h(t)$ and $r(x, t)$:

$$h(0) = 1, \quad r(x, 0) = x.$$

The partial derivatives of Eq. (3.14) are

$$P_t^{(0)} = h'f + hr_t f', \quad P_x^{(0)} = hr_x f',$$

which after substitution into Eq. (3.12) results in

$$(h' + bh) f + (r_t + bxr_x) hf' = 0.$$  

This equation can be satisfied for any $f$ provided that $h(t)$ and $r(x, t)$ satisfy

$$h' + bh = 0, \quad r_t + bxr_x = 0.$$  

(3.15)

The first equation for $h(t)$, together with the initial condition $h(0) = 1$, is easily solved to yield

$$h(t) = e^{-bt}.$$  

(3.16)
To determine a solution for $r(x, t)$, we try the technique of separation of variables. We write $r(x, t) = X(x)T(t)$, and upon substitution into the differential equation for $r(x, t)$, we obtain
\[ XT' + bxX'T = 0; \]
and division by $XT$ and separation yields
\[ \frac{T'}{T} = -\frac{bxX'}{X}. \]  
(3.17)

Since the left-hand-side is independent of $x$, and the right-hand-side is independent of $t$, both the left-hand-side and right-hand-side must be constant, independent of both $x$ and $t$. Now, our initial condition is $r(x, 0) = x$, so that $X(x)T(0) = x$. Without lose of generality, we can take $T(0) = 1$, so that $X(x) = x$. The right-hand-side of (3.17) is therefore equal to the constant $-b$, and we obtain the differential equation and initial condition
\[ T' + bT = 0, \quad T(0) = 1, \]  
(3.18)

By putting our solutions (3.16) and (3.18) together into our ansatz (3.14), we have obtained the general solution to the pde:
\[ P(0)(x, t) = e^{-bt}f(xe^{-bt}). \]  
(3.19)

To determine $f$, we apply the initial condition of the probability mass function, $p_N(0) = \delta_{N,N_0}$. From Eq. (3.8), the corresponding initial condition on the probability distribution function is
\[ P(x, 0) = \begin{cases} N_0 & \text{if } 1 - \frac{1}{2N_0} \leq x \leq 1 + \frac{1}{2N_0}, \\ 0 & \text{otherwise}. \end{cases} \]

In the limit $N_0 \to \infty$, $P(x, 0) \to P^{(0)}(x, 0) = \delta(x - 1)$, where $\delta(x - 1)$ is the Dirac delta-function, centered around 1. The delta-function is widely used in quantum physics and was introduced by Dirac for that purpose. It now finds many uses in applied mathematics. It can be defined by requiring that, for any function $g(x)$,
\[ \int_{-\infty}^{+\infty} g(x)\delta(x)dx = g(0). \]

The usual view of the delta-function $\delta(x - a)$ is that it is zero everywhere except at $x = a$ at which it is infinite, and its integral is one. It is not really a function, but it is what mathematicians call a distribution.

Now, since $P^{(0)}(x, 0) = f(x) = \delta(x - 1)$, our solution becomes
\[ P^{(0)}(x, t) = e^{-bt}\delta(xe^{-bt} - 1). \]  
(3.19)

This can be rewritten by noting that (letting $y = ax - c$),
\[ \int_{-\infty}^{+\infty} g(x)\delta(ax - c)dx = \frac{1}{a} \int_{-\infty}^{+\infty} g((y + c)/a)\delta(y)dy = \frac{1}{a} g(c/a), \]
yielding the identity
\[ \delta(ax - c) = \frac{1}{a} \delta(x - \frac{c}{a}). \]
From this, we can rewrite our solution (3.19) in the more intuitive form
\[ P^{(0)}(x, t) = \delta(x - e^{bt}). \]  
(3.20)

Using (3.20), the zeroth-order expected value of \( x \) is
\[ \langle x_0 \rangle = \int_0^\infty x P^{(0)}(x, t) dx \]
\[ = \int_0^\infty x \delta(x - e^{bt}) dx \]
\[ = e^{bt}; \]
while the zeroth-order variance is
\[ \sigma^2_{x_0} = \langle x^2_0 \rangle - \langle x_0 \rangle^2 \]
\[ = \int_0^\infty x^2 P^{(0)}(x, t) dx - e^{2bt} \]
\[ = \int_0^\infty x^2 \delta(x - e^{bt}) dx - e^{2bt} \]
\[ = e^{2bt} - e^{2bt} \]
\[ = 0. \]
Thus, in the infinite population limit, the random variable \( x \) has zero variance, and is therefore no longer random, but follows \( x = e^{bt} \) deterministically. We say that the probability distribution of \( x \) becomes sharp in the limit of large population sizes. The general principle of modeling large populations deterministically can simplify mathematical models when stochastic effects are unimportant.

3.2.2 Derivation of the normal probability distribution

We now consider the first-order term in the perturbation expansion (3.11), which satisfies (3.13). We do not know how to solve (3.13) directly, so we will attempt to find a solution following a more circuitous route. First, we proceed by computing the moments of the probability distribution. We have
\[ \langle x^n \rangle = \int_0^\infty x^n P(x, t) dx \]
\[ = \int_0^\infty x^n P^{(0)}(x, t) dx + \frac{1}{N_0} \int_0^\infty x^n P^{(1)}(x, t) dx + \ldots \]
\[ = \langle x^n_0 \rangle + \frac{1}{N_0} \langle x^n_1 \rangle + \ldots, \]
where the last equality defines \( \langle x^n_i \rangle \), etc. Now, using (3.20),
\[ \langle x^n_0 \rangle = \int_0^\infty x^n \delta(x - e^{bt}) dx \]
\[ = e^{nbt}. \]  
(3.21)
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To determine \( \langle x^n \rangle \), we need to start with the pde (3.13). Multiplying by \( x^n \) and integrating, we have

\[
\frac{d\langle x^n \rangle}{dt} = -b \left[ \int_0^\infty x^n \left( xP^{(1)} \right)_x \, dx - \frac{1}{2} \int_0^\infty x^n \left( xP^{(0)} \right)_{xx} \, dx \right]. \tag{3.22}
\]

We integrate by parts to remove the derivatives of \( xP \), assuming that \( xP \) and all its derivatives vanish on the boundaries of integration, where \( x \) is equal to zero or infinity. For example

\[
\int_0^\infty x^n \left( xP^{(1)} \right)_x \, dx = -\int_0^\infty nx^n P^{(1)} \, dx = -n \langle x^n \rangle,
\]

and

\[
\frac{1}{2} \int_0^\infty x^n \left( xP^{(0)} \right)_{xx} \, dx = -\frac{n}{2} \int_0^\infty x^{n-1} \left( xP^{(0)} \right)_x \, dx = -\frac{n(n-1)}{2} \int_0^\infty x^{n-1} P^{(0)} \, dx = -\frac{n(n-1)}{2} \langle x^{n-1} \rangle.
\]

Therefore, after integration by parts, (3.22) becomes

\[
\frac{d\langle x^n \rangle}{dt} = -b \left[ n \langle x^n \rangle + \frac{n(n-1)}{2} \langle x^{n-1} \rangle \right]. \tag{3.23}
\]

Equation (3.23) is a first-order linear inhomogeneous differential equation and can be solved using an integrating factor (see (3.3) and the preceding discussion). Solving this differential equation using (3.21) and the initial condition \( \langle x^n \rangle(0) = 0 \), we obtain

\[
\langle x^n \rangle = \frac{n(n-1)}{2} e^{nbt} \left( 1 - e^{-bt} \right). \tag{3.24}
\]

The probability distribution function, accurate to order \( 1/N_0 \), may be obtained by making use of the so-called moment generating function \( \Psi(s) \), defined as

\[
\Psi(s) = \langle e^{sx} \rangle = 1 + s\langle x \rangle + \frac{s^2}{2!} \langle x^2 \rangle + \frac{s^3}{3!} \langle x^3 \rangle + \ldots = \sum_{n=0}^{\infty} \frac{s^n \langle x^n \rangle}{n!}.
\]

To order \( 1/N_0 \), we have

\[
\Psi(s) = \sum_{n=0}^{\infty} \frac{s^n \langle x^n \rangle}{n!} + \frac{1}{N_0} \sum_{n=0}^{\infty} \frac{s^n \langle x^n \rangle}{n!} + O(1/N_0^2). \tag{3.25}
\]

Now, using (3.21),

\[
\sum_{n=0}^{\infty} \frac{s^n \langle x^n \rangle}{n!} = \sum_{n=0}^{\infty} \frac{(se^{bt})^n}{n!} = e^{se^{bt}},
\]

where

\[
\langle x^n \rangle = \frac{n(n-1)}{2} e^{nbt} \left( 1 - e^{-bt} \right). \tag{3.24}
\]
and using (3.24),
\[ \sum_{n=0}^{\infty} \frac{s^n (x_1^n)}{n!} = \frac{1}{2} \left( 1 - e^{-bt} \right) \sum_{n=0}^{\infty} \frac{n(n-1)}{n!} (se^{bt})^n \]
\[ = \frac{1}{2} \left( 1 - e^{-bt} \right) s^2 e^{2bt} \sum_{n=0}^{\infty} \frac{1}{n!} n(n-1) (se^{bt})^{n-2} \]
\[ = \frac{1}{2} \left( 1 - e^{-bt} \right) s^2 \sum_{n=0}^{\infty} \frac{1}{n!} \frac{\partial^2}{\partial s^2} (se^{bt})^n \]
\[ = \frac{1}{2} \left( 1 - e^{-bt} \right) s^2 \frac{\partial^2}{\partial s^2} \sum_{n=0}^{\infty} \frac{(se^{bt})^n}{n!} \]
\[ = \frac{1}{2} \left( 1 - e^{-bt} \right) s^2 \frac{\partial^2}{\partial s^2} \left( e^{se^{bt}} \right) \]
\[ = \frac{1}{2} \left( 1 - e^{-bt} \right) s^2 e^{2bt} e^{se^{bt}}. \]

Therefore,
\[ \Psi(s) = e^{se^{bt}} \left( 1 + \frac{1}{2N_0} \left( 1 - e^{-bt} \right) s^2 e^{2bt} + \ldots \right). \quad (3.26) \]

We can recognize the parenthetical term of (3.26) as a Taylor-series expansion of an exponential function truncated to first-order, i.e.,
\[ \exp \left( \frac{1}{2N_0} \left( 1 - e^{-bt} \right) s^2 e^{2bt} \right) = 1 + \frac{1}{2N_0} \left( 1 - e^{-bt} \right) s^2 e^{2bt} + O(1/N_0^2). \]

Therefore, to first-order in $1/N_0$, we have
\[ \Psi(s) = \exp \left( se^{bt} + \frac{1}{2N_0} \left( 1 - e^{-bt} \right) s^2 e^{2bt} \right) + O(1/N_0^2). \quad (3.27) \]

Standard books on probability theory (e.g., A first course in probability by Sheldon Ross, pg. 365) detail the derivation of the moment generating function of a normal random variable:
\[ \Psi(s) = \exp \left( \langle x \rangle s + \frac{1}{2} \sigma_x^2 s^2 \right), \quad \text{for a normal random variable;} \quad (3.28) \]

and comparing (3.28) with (3.27) shows us that the probability distribution $P(x,t)$ to first-order in $1/N_0$ is normal with the mean and variance given by
\[ \langle x \rangle = e^{bt}, \quad \sigma_x^2 = \frac{1}{N_0} e^{2bt} \left( 1 - e^{-bt} \right). \quad (3.29) \]

The mean and variance of $x = N/N_0$ is equivalent to those derived for $N$ in (3.7), but now we learn that $N$ is approximately normal for large populations.

The appearance of a normal probability distribution (also called a Gaussian probability distribution) in a first-order expansion is in fact a particular case of the Central Limit Theorem, one of the most important and useful theorems in probability and statistics. We state here a simple version of this theorem without proof:
3.3 SIMULATION OF POPULATION GROWTH

Central Limit Theorem: Suppose that $X_1, X_2, \ldots, X_n$ are independent and identically distributed (iid) random variables with mean $\langle X \rangle$ and variance $\sigma^2_X$. Then for sufficiently large $n$, the probability distribution of the average of the $X_i$'s, denoted as the random variable $Z = \frac{1}{n} \sum_{i=1}^{n} X_i$, is well approximated by a Gaussian with mean $\langle X \rangle$ and variance $\sigma^2 = \sigma^2_X/n$.

The central limit theorem can be applied directly to our problem. Consider that our population consists of $N_0$ founders. If $m_i(t)$ denotes the number of individuals descendant from founder $i$ at time $t$ (including the still living founder), then the total number of individuals at time $t$ is $N(t) = \sum_{i=1}^{N_0} m_i(t)$; and the average number of descendents of a single founder is $x(t) = N(t)/N_0$. If the mean number of descendents of a single founder is $\langle m \rangle$, with variance $\sigma^2_m$, then by applying the central limit theorem for large $N_0$, the probability distribution function of $x$ is well approximated by a Gaussian with mean $\langle x \rangle = \langle m \rangle$ and variance $\sigma^2_x = \sigma^2_m/N_0$. Comparing with our results (3.29), we find $\langle m \rangle = e^{bt}$ and $\sigma^2_m = e^{2bt}(1 - e^{-bt})$.

3.3 Simulation of population growth

As we have seen, stochastic modeling is significantly more complicated than deterministic modeling. As the modeling becomes more detailed, it may become necessary to solve a stochastic model numerically. Here, for illustration, we show how to simulate individual realizations of population growth.

A straightforward approach would make use of the birth rate $b$ directly. During the time $\Delta t$, each individual of a population has probability $b\Delta t$ of giving birth, accurate to order $\Delta t$. If we have $N$ individuals at time $t$, we can compute the number of individuals at time $t + \Delta t$ by computing $N$ random deviates (random numbers between zero and unity) and calculating the number of new births by the number of random deviates less than $b\Delta t$. In principle, this approach will be accurate provided that $\Delta t$ is sufficiently small.

There is, however, a more efficient way to simulate population growth. We first determine the probability density function of the interevent time $\tau$, defined as the time required for the population to grow from size $N$ to size $N+1$ because of a single birth. A simulation from population size $N_0$ to size $N_f$ would then simply require computing $N_f - N_0$ different random values of $\tau$, a relatively easy and quick computation.

Let $P(\tau)d\tau$ be the probability that the interevent time for a population of size $N$ lies in the interval $(\tau, \tau + d\tau)$, $F(\tau) = \int_0^\tau P(\tau')d\tau'$ the probability that the interevent time is less than $\tau$, and $G(\tau) = 1 - F(\tau)$ the probability that the interevent time is greater than $\tau$. $P(\tau)$ is called the probability density function of $\tau$, and $F(\tau)$ the cumulative distribution function of $\tau$. They satisfy the relation $P(\tau) = F'(\tau)$. Since the probability that the interevent time is greater than $\tau + \Delta \tau$ is given by the probability that it is greater than $\tau$ times the probability that no new births occur in the time interval $(\tau, \tau + \Delta \tau)$, the distribution $G(\tau + \Delta \tau)$ is given for small $\Delta \tau$ by

$$G(\tau + \Delta \tau) = G(\tau)(1 - bN\Delta \tau).$$
CHAPTER 3. STOCHASTIC POPULATION GROWTH

Figure 3.1: How to generate a random number with a given probability density function.

Differencing $G$ and taking the limit $\Delta \tau \to 0$ yields the differential equation

$$\frac{dG}{d\tau} = -bNG,$$

which can be integrated using the initial condition $G(0) = 1$ to further yield

$$G(\tau) = e^{-bN\tau}.$$

Therefore,

$$F(\tau) = 1 - e^{-bN\tau}, \quad P(\tau) = bNe^{-bN\tau}; \quad (3.30)$$

$P(\tau)$ has the form of an exponential distribution.

We now compute random values for $\tau$ using its known cumulative distribution function $F(\tau)$. We do this in reference to Figure 3.1 where we plot $y = F(\tau)$ versus $\tau$. The range $y$ of $F(\tau)$ is $[0, 1)$, and for each $y$, we can compute $\tau$ by inverting $y(\tau) = 1 - \exp(-bN\tau)$; that is,

$$\tau(y) = -\frac{\ln(1 - y)}{bN}.$$

Our claim is that with $y$ a random number sampled uniformly on $(0, 1)$, the random numbers $\tau(y)$ have probability density function $P(\tau)$.

Now, the fraction of random numbers $y$ in the interval $(y_1, y_2)$ is equal to the corresponding fraction of random numbers $\tau$ in the interval $(\tau_1, \tau_2)$, where $\tau_1 = \tau(y_1)$ and $\tau_2 = \tau(y_2)$; and for $y$ sampled uniformly on $(0, 1)$, this fraction is equal to $y_2 - y_1$. We thus have the following string of equalities: (the fraction of random numbers in $(y_1, y_2)$) = (the fraction of random numbers in $(\tau_1, \tau_2)$) = $y_2 - y_1 = F(\tau_2) - F(\tau_1) = \int_{\tau_1}^{\tau_2} P(\tau) \, d\tau$. Therefore, (the fraction of random numbers in $(\tau_1, \tau_2)$) = $\int_{\tau_1}^{\tau_2} P(\tau) \, d\tau$. This is exactly the definition of $\tau$ having probability density function $P(\tau)$. 
3.3. SIMULATION OF POPULATION GROWTH

Below, we illustrate a simple MATLAB function that simulates one realization of population growth from initial size $N_0$ to final size $N_f$, with birth rate $b$.

```matlab
function [t, N] = population_growth_simulation(b,N0,Nf)
% simulates population growth from NO to NF with birth rate b
N=N0:Nf; t=0*N;
y=rand(1,Nf-N0);
tau=-log(1-y)./(b*N(1:Nf-N0)); % interevent times
 t=[0 cumsum(tau)]; % cumulative sum of interevent times
```

The function `population_growth_simulation.m` can be driven by a MATLAB script to compute realizations of population growth. For instance, the following script computes 100 realizations for a population growth from 10 to 100 with $b = 1$ and plots all the realizations:

```matlab
% calculate nreal realizations and plot
b=1; N0=10; Nf=100;
nreal=100;
for i=1:nreal
    [t,N]=population_growth_simulation(b,N0,Nf);
    plot(t,N); hold on;
end
xlabel('t'); ylabel('N');
```

Figure 3.2 presents three graphs, showing 25 realizations of population growth starting with population sizes of 10, 100, and 1000, and ending with population sizes a factor of 10 larger. Observe that the variance, relative to the initial population size, decreases as the initial population size increases, following our analytical result (3.29).
Figure 3.2: Twenty-five realizations of population growth with initial population sizes of 10, 100, and 1000, in (a), (b), and (c), respectively.
Chapter 4

Infectious Disease Modeling

In the late 1320’s, an outbreak of the bubonic plague occurred in China. The disease is caused by the bacteria *Yersinia pestis* and is transmitted from rats to humans by fleas. The outbreak in China spread west, and the first major outbreak in Europe occurred in 1347. During a five year period, 25 million people in Europe, approximately 1/3 of the population, died of the black death. Other more recent epidemics include the influenza pandemic known as the Spanish flu killing 50-100 million people worldwide during the year 1918-1919, and the present AIDS epidemic, originating in Africa and first recognized in the USA in 1981, killing more than 25 million people. For comparison, the SARS epidemic for which Hong Kong was the global epicenter resulted in 8096 known SARS cases and 774 deaths. Yet, we know well that this relatively small epidemic caused social and economic turmoil, locally.

Here, we introduce the most basic mathematical models of infectious disease epidemics and endemics. These models form the basis of the necessarily more detailed models currently used by world health organizations, both to predict the future spread of a disease and to develop strategies for containment and eradication.

4.1 The SI model

The simplest model of an infectious disease categorizes people as either susceptible or infective (*SI*). One can imagine that susceptible people are healthy and infective people are sick. A susceptible person can become infective by contact with an infective. Here, and in all subsequent models, we assume that the population under study is well mixed so that every person has equal probability of coming into contact with every other person. This is a major approximation. For example, while the population of Amoy Gardens could be considered well mixed during the SARS epidemic because of shared water pipes and elevators, the population of Hong Kong as a whole could not because of the larger geographical distances, and the limited travel of many people outside the neighborhoods where they live.

We derive the governing differential equation for the SI model by considering the number of people that become infective during time $\Delta t$. Let $\beta \Delta t$ be the probability that a random infective person infects a random susceptible
person during time $\Delta t$. Then with $S$ susceptible and $I$ infective people, the expected number of newly infected people in the total population during time $\Delta t$ is $\beta \Delta t S I$. Thus,

$$I(t + \Delta t) = I(t) + \beta \Delta t S(t)I(t),$$

and in the limit $\Delta t \to 0$,

$$\frac{dI}{dt} = \beta SI.$$  \hspace{1cm} (4.1)

We diagram (4.1) as $S \xrightarrow{\beta SI} I$.

Later, diagrams will make it easier to construct more complicated systems of equations. We now assume a constant population size $N$, neglecting births and deaths, so that $S + I = N$. We can eliminate $S$ from (4.1) and rewrite the equation as

$$\frac{dI}{dt} = \beta NI \left(1 - \frac{I}{N}\right),$$

which can be recognized as a logistic equation, with growth rate $\beta N$ and carrying capacity $N$. Therefore $I \to N$ as $t \to \infty$ and the entire population will become infective.

### 4.2 The SIS model

The SI model may be extended to the SIS model, where an infective can recover and become susceptible again. We assume that the probability that an infective recovers during time $\Delta t$ is given by $\gamma \Delta t$. Then the total number of infective people that recover during time $\Delta t$ is given by $I \times \gamma \Delta t$, and

$$I(t + \Delta t) = I(t) + \beta \Delta t S(t)I(t) - \gamma \Delta t I(t),$$

or as $\Delta t \to 0$,

$$\frac{dI}{dt} = \beta SI - \gamma I,$$  \hspace{1cm} (4.2)

which we diagram as $S \xrightarrow{\beta SI} I \xrightarrow{\gamma I} S$.

Using $S + I = N$, we eliminate $S$ from (4.2) and define the basic reproductive ratio as

$$R_0 = \frac{\beta N}{\gamma}.$$  \hspace{1cm} (4.3)

Equation (4.2) may then be rewritten as

$$\frac{dI}{dt} = \gamma (R_0 - 1) I \left(1 - \frac{I}{N(1-1/R_0)}\right),$$

which is again a logistic equation, but now with growth rate $\gamma (R_0 - 1)$ and carrying capacity $N(1 - 1/R_0)$. The disease will disappear if the growth rate is negative, that is, $R_0 < 1$, and it will become endemic if the growth rate is positive, that is, $R_0 > 1$. For an endemic disease with $R_0 > 1$, the number of infected people approaches the carrying capacity: $I \to N(1 - 1/R_0)$ as $t \to \infty$. 
We can give a biological interpretation to the basic reproductive ratio $R_0$. Let $l(t)$ be the probability that an individual initially infected at $t = 0$ is still infective at time $t$. Since the probability of being infective at time $t + \Delta t$ is equal to the probability of being infective at time $t$ multiplied by the probability of not recovering during time $\Delta t$, we have

$$l(t + \Delta t) = l(t)(1 - \gamma \Delta t),$$

or as $\Delta t \to 0$,

$$\frac{dl}{dt} = -\gamma l.$$

With initial condition $l(0) = 1$,

$$l(t) = e^{-\gamma t}. \quad (4.4)$$

Now, the expected number of secondary infections produced by a single primary infective over the time period $(t, t + dt)$ is given by the probability that the primary infective is still infectious at time $t$ multiplied by the expected number of secondary infections produced by a single infective during time $dt$, that is, $l(t) \times S(t)\beta dt$. We assume that the total number of secondary infections from a single infective individual is small relative to the population size $N$. Therefore, the expected number of secondary infectives produced by a single primary infective introduced into a completely susceptible population is

$$\int_0^\infty \beta l(t)S(t)dt \approx \beta N \int_0^\infty l(t)dt = \beta N \int_0^\infty e^{-\gamma t}dt = \frac{\beta N}{\gamma} = \mathcal{R}_0,$$

where we have approximated $S(t) \approx N$ during the time period in which the infective remains infectious. If a single infected individual introduced into a completely susceptible population produces more than one secondary infection before recovering, then $\mathcal{R}_0 > 1$ and the disease becomes endemic.

We have seen previously two other analogous calculations with results similar to $(4.4)$: the first when computing the probability distribution of the interevent time between births ($\S 3.3$); the second when computing the probability distribution of a worm’s lifetime ($\S 2.5$). We have also seen an analogous definition of the basic reproductive ratio in our previous discussion of age-structured populations ($\S 2.3$). There, the basic reproductive ratio was the number of female offspring expected from a new born female over her lifetime; the population size would grow if this value was greater than unity. Both $l(t)$ and the basic reproductive ratio are good examples of how the same mathematical concept can be applied to seemingly unrelated biological problems.

### 4.3 The SIR epidemic disease model

The SIR model, first published by Kermack and McKendrick in 1927, is undoubtedly the most famous mathematical model for the spread of an infectious
disease. Here, people are characterized into three classes: susceptible $S$, infective $I$ and removed $R$. Removed individuals are no longer susceptible nor infective for whatever reason; for example, they have recovered from the disease and are now immune, or they have been vaccinated, or they have been isolated from the rest of the population, or perhaps they have died from the disease. As in the SIS model, we assume that infectives leave the $I$ class with constant rate $\gamma$, but in the SIR model they move directly into the $R$ class. The model may be diagrammed as

$$S \xrightarrow{\beta S I} I \xrightarrow{\gamma I} R,$$

and the corresponding coupled differential equations are

$$\frac{dS}{dt} = -\beta SI, \quad \frac{dI}{dt} = \beta SI - \gamma I, \quad \frac{dR}{dt} = \gamma I,$$

with the constant population constraint $S + I + R = N$. For convenience, we nondimensionalize (4.5) using $N$ for population size and $\gamma^{-1}$ for time; that is, let

$$\hat{S} = S/N, \quad \hat{I} = I/N, \quad \hat{R} = R/N, \quad \hat{t} = \gamma t,$$

and define the basic reproductive ratio $R_0 = \frac{\beta N}{\gamma}$.

The nondimensional SIR equations are

$$\frac{d\hat{S}}{d\hat{t}} = -R_0 \hat{S}\hat{I}, \quad \frac{d\hat{I}}{d\hat{t}} = R_0 \hat{S}\hat{I} - \hat{I}, \quad \frac{d\hat{R}}{d\hat{t}} = \hat{I},$$

with nondimensional constraint $\hat{S} + \hat{I} + \hat{R} = 1$.

We will use the SIR model to address two fundamental questions: (1) Under what condition does an epidemic occur? (2) If an epidemic occurs, what fraction of the population gets sick?

Let $(\hat{S}_*, \hat{I}_*, \hat{R}_*)$ be the fixed points of (4.7). Setting $d\hat{S}/d\hat{t} = d\hat{I}/d\hat{t} = d\hat{R}/d\hat{t} = 0$, we immediately observe from the equation for $d\hat{R}/d\hat{t}$ that $\hat{I} = 0$, and this value forces all the time-derivatives to vanish for any $\hat{S}$ and $\hat{R}$. Since with $\hat{I} = 0$, we have $\hat{R} = 1 - \hat{S}$, evidently all the fixed points of (4.7) are given by the one parameter family $(\hat{S}_*, \hat{I}_*, \hat{R}_*) = (\hat{S}_*, 0, 1 - \hat{S}_*)$.

An epidemic occurs when a small number of infectives introduced into a susceptible population results in an increasing number of infectives. We can assume an initial population at a fixed point of (4.7), perturb this fixed point by introducing a small number of infectives, and determine the fixed point’s stability. An epidemic occurs when the fixed point is unstable. The linear stability problem may be solved by considering only the equation for $d\hat{I}/d\hat{t}$ in (4.7). With $\hat{I} << 1$ and $\hat{S} \approx \hat{S}_0$, we have

$$\frac{d\hat{I}}{d\hat{t}} = \left(R_0 \hat{S}_0 - 1\right) \hat{I},$$

so that an epidemic occurs if $R_0 \hat{S}_0 - 1 > 0$. With the basic reproductive ratio given by (4.6), and $\hat{S}_0 = S_0/N$, where $S_0$ is the number of initial susceptible individuals, an epidemic occurs if

$$R_0 \hat{S}_0 = \frac{\beta S_0}{\gamma} > 1,$$
which could have been guessed. An epidemic occurs if an infective individual introduced into a population of $S_0$ susceptible individuals infects on average more than one other person.

We now address the second question: If an epidemic occurs, what fraction of the population gets sick? For simplicity, we assume that the entire initial population is susceptible to the disease, so that $\hat{S}_0 = 1$. We expect the solution of the governing equations \((4.7)\) to approach a fixed point asymptotically in time (so that the final number of infectives will be zero), and we define this fixed point to be $(\hat{S}, \hat{I}, \hat{R}) = (1 - \hat{R}_\infty, 0, \hat{R}_\infty)$, with $\hat{R}_\infty$ equal to the fraction of the population that gets sick. To compute $\hat{R}_\infty$, it is simpler to work with a transformed version of \((4.7)\). By the chain rule, $d\hat{S}/d\hat{R} = (d\hat{S}/d\hat{R})(d\hat{R}/d\hat{t})$, so that

$$
\frac{d\hat{S}}{d\hat{R}} = \frac{d\hat{S}}{d\hat{t}} \frac{d\hat{R}}{d\hat{t}} = -R_0 \hat{S},
$$

which is separable. Separating and integrating from the initial to final conditions,

$$
\int_1^{1-R_\infty} \frac{d\hat{S}}{\hat{S}} = -R_0 \int_0^{R_\infty} d\hat{R},
$$

which upon integration and simplification, results in the following transcendental equation for $R_\infty$:

$$
1 - \hat{R}_\infty - e^{-R_0 \hat{R}_\infty} = 0,
\quad (4.9)
$$

an equation that can be solved numerically using Newton’s method. We have

$$
F(\hat{R}_\infty) = 1 - \hat{R}_\infty - e^{-R_0 \hat{R}_\infty},
$$

$$
F'(\hat{R}_\infty) = -1 + R_0 e^{-R_0 \hat{R}_\infty},
$$
and Newton’s method for solving \( F(\hat{R}_\infty) = 0 \) iterates

\[
\hat{R}_\infty^{(n+1)} = \hat{R}_\infty^{(n)} - \frac{F(\hat{R}_\infty^{(n)})}{F'(\hat{R}_\infty^{(n)})}
\]

for fixed \( R_0 \) and a suitable initial condition for \( R_\infty^{(0)} \), which we take to be unity. My code for computing \( R_\infty \) as a function of \( R_0 \) is given below, and the result is shown in Fig. 4.1. There is an explosion in the number of infections as \( R_0 \) increases from unity, and this rapid increase is a classic example of what is known more generally as a threshold phenomenon.

```matlab
function [R0, R_inf] = sir_rinf
% computes solution of R_inf using Newton's method from SIR model
nmax=10; numpts=1000;
R0 = linspace(0,2,numpts); R_inf = ones(1,numpts);
for i=1:nmax
    R_inf = R_inf - F(R_inf,R0)./Fp(R_inf,R0);
end
plot(R0,R_inf); axis([0 2 -0.02 0.8])
xlabel('R_0'); ylabel('R_\infty'); title('fraction of population that get sick')
%subfunctions
function y = F(R_inf,R0)
y = 1 - R_inf - exp(-R0.*R_inf);
function y = Fp(R_inf,R0)
y = -1 + R0.*exp(-R0.*R_inf);
```

### 4.4 The SIR endemic disease model

A disease that is constantly present in a population is said to be endemic. For example, malaria is endemic to Sub-Saharan Africa, where about 90% of malaria-related deaths occur. Endemic diseases prevail over long time scales: babies are born, old people die. Let \( b \) be the birth rate and \( d \) the disease-unrelated death rate. We separately define \( c \) to be the disease-related death rate; \( R \) is now the immune class. We may diagram a SIR model of an endemic disease as

\[
\begin{align*}
\text{S} & \quad \xrightarrow{bN} \quad \beta SI \\
\downarrow dS & \quad \text{I} & \quad \gamma I \\
\text{I} & \quad \xrightarrow{dI} \quad \text{R} & \quad \xrightarrow{dR}
\end{align*}
\]

and the governing differential equations are

\[
\frac{dS}{dt} = bN - \beta SI - dS, \quad \frac{dI}{dt} = \beta SI - (c + d + \gamma)I, \quad \frac{dR}{dt} = \gamma I - dR, \quad (4.10)
\]
4.4. THE SIR ENDEMIC DISEASE MODEL

with $N = S + I + R$. In our endemic disease model, $N$ separately satisfies the differential equation

$$\frac{dN}{dt} = (b - d)N - cI,$$  \hfill (4.11)

and is not necessarily constant.

We model two simplified situations for which equilibrium solutions exist. First, we assume that there are no disease-related deaths ($c = 0$) and equal birth and death rates ($b = d$); the population size $N$ will then be constant and the equations will admit an equilibrium solution. Second, we explore whether disease-related deaths can stabilize a disease-free growing population in which $b > d$.

In our first model, with $c = 0$, $b = d$ and $S + I + R = N$ constant, the governing equations simplify to

$$\frac{dS}{dt} = d(I + R) - \beta SI, \quad \frac{dI}{dt} = \beta SI - (\gamma + d)I, \quad \frac{dR}{dt} = \gamma I - dR.$$  

Fixed points are obtained from $\dot{S} = \dot{I} = \dot{R} = 0$. To solve, we first consider $\dot{I} = 0$. The solution is either $I_* = 0$ or $S_* = (\gamma + d)/\beta$. For $I_* = 0$, the equation $\dot{R} = 0$ yields $R_* = 0$, and the constraint $S + I + R = N$ yields $S_* = N$. Hence, one fixed point is $(S_*, I_*, R_*) = (N, 0, 0)$, corresponding to a disease-free population. The other fixed point corresponds to an endemic disease. We eliminate $R_*$ from the equation $\dot{R} = 0$ using $R_* = N - S_* - I_*$, and we substitute $S_* = (\gamma + d)/\beta$ to obtain

$$\gamma I_* - d \left( N - \frac{\gamma + d}{\beta} - I_* \right) = 0,$$

which can be solved for $I_*$. We then determine $R_*$ using $R_* = (\gamma/d)I_*$. After some simple algebraic manipulation, the endemic disease equilibrium solution is determined to be

$$S_* = \frac{(\gamma + d)/\beta}{1 - \frac{\gamma + d}{\beta N}}, \quad I_* = \frac{\frac{dN}{\gamma + d} \left( 1 - \frac{\gamma + d}{\beta N} \right)}{\gamma + d}, \quad R_* = \frac{\gamma N}{\gamma + d} \left( 1 - \frac{\gamma + d}{\beta N} \right).$$  \hfill (4.12), (4.13), (4.14)

Clearly, this solution only exists if $\beta N/(\gamma + d) \equiv R_0 > 1$, defining the basic reproductive ratio $R_0$ for this model. (Note that the probability that an infective leaves class $I$ during time $\Delta t$ is given by $(\gamma + d)\Delta t$, since the infective can either recover or die a natural death.) It can be shown that the disease-free state is unstable and the endemic disease state is stable when $R_0 > 1$.

In our second model, we consider the full system of equations (4.10)-(4.11), assume that $b > d$, and look for an equilibrium solution with $N = N_*$ constant. From $\dot{N} = 0$, we have

$$I_* = \frac{b - d}{c} N_*;$$

from $\dot{I} = 0$, we have

$$S_* = \frac{\gamma + d + c}{\beta};$$
and from $\dot{R} = 0$, we have
\[ R_* = \frac{\gamma(b - d)}{dc} N_* . \]

Using $N_* = S_* + I_* + R_*$, we obtain
\[ N_* = \left( \frac{\gamma + d + c}{\beta} \right) \left( \frac{1}{1 - \left( 1 + \frac{\gamma}{d} \right) \left( \frac{b - d}{c} \right)} \right) . \]

The condition $N_* > 0$, implies that
\[ \left( 1 + \frac{\gamma}{d} \right) \left( \frac{b - d}{c} \right) < 1 , \]

or
\[ c > (b - d) \left( 1 + \frac{\gamma}{d} \right) . \quad (4.15) \]

When the disease-related death rate satisfies $(4.15)$, then the population size, in equilibrium, is constant. To interpret $(4.15)$, we use $\gamma/d = R_*/I_*$ and rewrite $(4.15)$ as
\[ \frac{cI_*}{I_* + R_*} > (b - d) . \]

The extra factor $I_*/(I_* + R_*)$ must occur because only infectious but not recovered people can die from the disease.

### 4.5 Vaccination

Table [4.1] lists the diseases for which vaccines exist and are widely administered to children. Health care authorities must determine the fraction of a population that must be vaccinated to prevent epidemics.

We address this problem within the SIR epidemic disease model. Let $p$ be the fraction of the population that is vaccinated and $p_*$ the minimum fraction required to prevent an epidemic. When $p > p_*$, an epidemic cannot occur. Since even non-vaccinated people are protected by the absence of epidemics, we say that the population has acquired herd immunity.

We assume that individuals are susceptible unless vaccinated, and vaccinated individuals are in the removed class. The initial population is then modeled as $(S, I, R) = (1 - p, 0, p)$. We have already determined the stability of this fixed point to perturbation by a small number of infectives. The condition for an epidemic to occur is given by $(4.8)$, and with $S_0 = 1 - p$, an epidemic occurs if
\[ R_0(1 - p) > 1 . \]

Therefore, the minimum fraction of the population that must be vaccinated to prevent an epidemic is
\[ p_* = 1 - \frac{1}{R_0} . \]

Diseases with smaller values of $R_0$ are easier to eradicate than diseases with larger values $R_0$ since a population can acquire herd immunity with a smaller fraction of the population vaccinated. For example, smallpox with $R_0 \approx 4$ has been eradicated throughout the world whereas measles with $R_0 \approx 17$ still has occasional outbreaks.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
<th>Symptoms</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>A bacterial respiratory disease</td>
<td>Sore throat and low-grade fever</td>
<td>Airway obstruction, coma, and death</td>
</tr>
<tr>
<td>Haemophilus influenzae type b (Hib)</td>
<td>A bacterial infection occurring primarily in infants</td>
<td>Skin and throat infections, meningitis, pneumonia, sepsis, and arthritis</td>
<td>Death in one out of 20 children, and permanent brain damage in 10% - 30% of the survivors</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>A viral liver disease</td>
<td>Potentially none; yellow skin or eyes, tiredness, stomach ache, loss of appetite, or nausea</td>
<td>Usually none</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Same as Hepatitis A</td>
<td>Same as Hepatitis A</td>
<td>Life-long liver problems, such as scarring of the liver and liver cancer</td>
</tr>
<tr>
<td>Measles</td>
<td>A viral respiratory disease</td>
<td>Rash, high fever, cough, runny nose, and red, watery eyes</td>
<td>Diarrhea, ear infections, pneumonia, encephalitis, seizures, and death</td>
</tr>
<tr>
<td>Mumps</td>
<td>A viral lymph node disease</td>
<td>Fever, headache, muscle ache, and swelling of the lymph nodes close to the jaw</td>
<td>Meningitis, inflammation of the testicles or ovaries, inflammation of the pancreas and deafness</td>
</tr>
<tr>
<td>Pertussis (whooping cough)</td>
<td>A bacterial respiratory disease</td>
<td>Severe spasms of coughing</td>
<td>Pneumonia, encephalitis, and death, especially in infants</td>
</tr>
<tr>
<td>Pneumococcal disease</td>
<td>A bacterial disease</td>
<td>High fever, cough, and stabbing chest pains, bacteremia, and meningitis</td>
<td>Death</td>
</tr>
<tr>
<td>Polio</td>
<td>A viral lymphatic and nervous system disease</td>
<td>Fever, sore throat, nausea, headaches, stomach aches, stiffness in the neck, back, and legs</td>
<td>Paralysis that can lead to permanent disability and death</td>
</tr>
<tr>
<td>Rubella (German measles)</td>
<td>A viral respiratory disease</td>
<td>Rash and fever for two to three days</td>
<td>Birth defects if acquired by a pregnant woman</td>
</tr>
<tr>
<td>Tetanus (lockjaw)</td>
<td>A bacterial nervous system disease</td>
<td>Lockjaw, stiffness in the neck and abdomen, and difficulty swallowing</td>
<td>Death in one third of the cases, especially people over age 50</td>
</tr>
<tr>
<td>Varicella (chickenpox)</td>
<td>A viral disease in the Herpes family</td>
<td>A skin rash of blister-like lesions</td>
<td>Bacterial infection of the skin, swelling of the brain, and pneumonia</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>A viral skin and mucous membrane disease</td>
<td>Warts, cervical cancer</td>
<td>The 5-year survival rate from all diagnoses of cervical cancer is 72%</td>
</tr>
</tbody>
</table>

Table 4.1: Previously common diseases for which vaccines have been developed.
4.6 Evolution of virulence

Microorganisms continuously evolve due to selection pressures in their environments. Antibiotics are a common source of selection pressure on pathogenic bacteria, and the development of antibiotic-resistant strains presents a major health challenge to medical science. Viruses also compete directly with each other for reproductive success resulting in the evolution of virulence. Here, using the SIR endemic disease model, we study how virulence may evolve.

We assume that a population is initially in equilibrium with an endemic disease caused by a wildtype virus. Now suppose that a virus mutates by a random, undirected process that occurs naturally. We want to determine the conditions under which the mutant virus will replace the wildtype virus in the population. In mathematical terms, we want to determine the linear stability of the endemic disease equilibrium to the introduction of a mutant viral strain.

We assume that the original wildtype virus has infection rate \( \beta \), removal rate \( \gamma \), and disease-related death rate \( c \), and that the mutant virus has corresponding rates \( \beta' \), \( \gamma' \) and \( c' \). We further assume that an individual infected with either a wildtype or mutant virus gains immunity to subsequent infection from both wildtype and mutant viral forms. Our model thus has a single susceptible class \( S \), two distinct infective classes \( I \) and \( I' \) depending on which virus causes the infection, and a single recovered class \( R \). The appropriate diagram is

\[
\begin{align*}
&\text{\( S \)} \quad \text{\( I \)} \quad \text{\( I' \)} \quad \text{\( R \)} \\
&\text{\( bN \)} \quad \text{\( \beta SI \)} \quad \gamma I \quad \beta' SI' \quad \gamma'I' \quad \text{\( dR \)} \\
&\text{\( dS \)} \quad \gamma I \quad \gamma'I' \quad \text{\( dR \)} \\
&\text{\( \beta SI' \)} \\
\end{align*}
\]

with corresponding differential equations

\[
\begin{align*}
\frac{dS}{dt} &= bN - dS - S(\beta I + \beta' I'), \\
\frac{dI}{dt} &= \beta SI - (\gamma + d + c)I, \\
\frac{dI'}{dt} &= \beta' SI' - (\gamma' + d + c')I', \\
\frac{dR}{dt} &= \gamma I + \gamma'I' - dR.
\end{align*}
\]

If the population is in equilibrium with the wildtype virus, then \( \dot{I} = 0 \), \( I \neq 0 \), and the equilibrium value for \( S \) is

\[
S_* = \frac{\gamma + d + c}{\beta}.
\]  

(4.16)
We perturb this endemic disease equilibrium by introducing a small number of infectives carrying the mutated virus, that is, by letting $I'$ be small. Rather than solve the stability problem by means of a Jacobian analysis, we can directly examine the equation for $dI'/dt$. Here, with $S = S_*$ given by (4.16), we have

$$
\frac{dI'}{dt} = \left[ \frac{\beta'(\gamma + d + c)}{\beta} - (\gamma' + d + c') \right] I',
$$

and $I'$ increases exponentially if

$$
\frac{\beta'(\gamma + d + c)}{\beta} - (\gamma' + d + c') > 0,
$$

or after some elementary algebra:

$$
\frac{\beta'}{\gamma' + d + c'} > \frac{\beta}{\gamma + d + c}. \quad (4.17)
$$

Our result suggests that endemic viruses (or other microorganisms) will tend to evolve (i) to be more easily transmitted between people ($\beta' > \beta$); (ii) to make people sick longer ($\gamma' < \gamma$), and; (iii) to be less deadly ($c' < c$). In other words, viruses evolve to increase their basic reproductive ratios. For instance, our model suggests that viruses evolve to be less deadly because the dead do not spread disease. Our result would not be applicable, however, if the dead in fact did spread disease, a possibility if disposal of the dead was not done with sufficient care, perhaps because of certain cultural traditions such as family washing of the dead body.
Chapter 5

Population Genetics

Deoxyribonucleic acid, or DNA—a large double-stranded, helical molecule, with rungs made from the four base pairs adenine (A), cytosine (C), thymine (T) and guanine (G)—carries inherited genetic information. The ordering of the base pairs A, C, T and G determines the DNA sequence. A gene is a particular DNA sequence that is the fundamental unit of heredity for a particular trait. Some species develop as diploids, carrying two copies of every gene, one from each parent, and some species develop as haploids with only one copy. There are even species that develop as both diploids and haploids. When we say there is a gene for pea color, say, we mean there is a particular DNA sequence that may vary in a pea plant population, and that there are at least two subtypes, called alleles, where plants with two copies of the yellow-color allele have yellow peas, those with two copies of the green-color allele, green peas. A plant with two copies of the same allele is homozygous for that particular gene (or a homozygote), while a plant carrying two different alleles is heterozygous (or a heterozygote). For the pea color gene, a plant carrying both a yellow- and green-color allele has yellow peas. We say that the green color is a recessive trait (or the green-color allele is recessive), and the yellow color is a dominant trait (or the yellow-color allele is dominant). The combination of alleles carried by the plant is called its genotype, while the actual trait (green or yellow peas) is called its phenotype. A gene that has more than one allele in a population is called polymorphic, and we say the population has a polymorphism for that particular gene.

Population genetics can be defined as the mathematical modeling of the evolution and maintenance of polymorphism in a population. Population genetics together with Charles Darwin’s theory of evolution by natural selection and Gregor Mendel’s theory of biological inheritance forms the modern evolutionary synthesis (sometimes called the modern synthesis, the evolutionary synthesis, the neo-Darwinian synthesis, or neo-Darwinism). The primary founders in the early twentieth century of population genetics were Sewall Wright, J. B. S. Haldane and Ronald Fisher.

Allele frequencies in a population can change due to the influence of four primary evolutionary forces: natural selection, genetic drift, mutation, and migration. Here, we mainly focus on natural selection and mutation. Genetic drift is the study of stochastic effects, and it is important in small populations. Migration requires consideration of the spatial distribution of a population, and it is usually modeled mathematically by partial differential equations.
Table 5.1: Haploid genetics using population size, absolute viability, and fertility fitnesses.

<table>
<thead>
<tr>
<th>genotype</th>
<th>A</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>number</td>
<td>$n_A$</td>
<td>$n_a$</td>
</tr>
<tr>
<td>viability fitness</td>
<td>$g_A$</td>
<td>$g_a$</td>
</tr>
<tr>
<td>fertility fitness</td>
<td>$f_A$</td>
<td>$f_a$</td>
</tr>
</tbody>
</table>

The simplified models we will consider assume infinite population sizes (neglecting stochastic effects except in §5.5), well-mixed populations (neglecting any spatial distribution), and discrete generations (neglecting any age-structure). Our main purpose is to illustrate the fundamental ways that a genetic polymorphism can be maintained in a population.

5.1 Haploid genetics

We first consider the modeling of selection in a population of haploid organisms. Selection is modeled by fitness coefficients, with different genotypes having different fitnesses. We begin with a simple model that counts the number of individuals in the next generation, and then show how this model can be reformulated in terms of allele frequencies and relative fitness coefficients.

Table 5.1 formulates the basic model. We assume that there are two alleles $A$ and $a$ for a particular haploid gene. These alleles are carried in the population by $n_A$ and $n_a$ individuals, respectively. A fraction $g_A$ ($g_a$) of individuals carrying allele $A$ ($a$) is assumed to survive to reproduction age, and those that survive contribute $f_A$ ($f_a$) offspring to the next generation. These are of course average values, but under the assumption of an infinite population, our model is deterministic. Accordingly, with $n_A^{(i)}$ ($n_a^{(i)}$) representing the number of individuals carrying allele $A$ ($a$) in the $i$th generation, and formulating a discrete generation model, we have

$$n_A^{(i+1)} = f_A g_A n_A^{(i)}, \quad n_a^{(i+1)} = f_a g_a n_a^{(i)}.$$  \hspace{1cm} (5.1)

It is mathematically easier and more transparent to work with allele frequencies rather than individual numbers. We denote the frequency (or more accurately, proportion) of allele $A$ ($a$) in the $i$th generation by $p_i$ ($q_i$); that is,

$$p_i = \frac{n_A^{(i)}}{n_A^{(i)} + n_a^{(i)}}, \quad q_i = \frac{n_a^{(i)}}{n_A^{(i)} + n_a^{(i)}},$$

where evidently $p_i + q_i = 1$. Now, from (5.1),

$$n_A^{(i+1)} + n_a^{(i+1)} = f_A g_A n_A^{(i)} + f_a g_a n_a^{(i)},$$  \hspace{1cm} (5.2)
5.1. HAPLOID GENETICS

<table>
<thead>
<tr>
<th>genotype</th>
<th>( A )</th>
<th>( a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>freq. of gamete</td>
<td>( p )</td>
<td>( q )</td>
</tr>
<tr>
<td>relative fitness</td>
<td>( 1 + s )</td>
<td>1</td>
</tr>
<tr>
<td>freq after selection</td>
<td>( (1 + s)p/w )</td>
<td>( q/w )</td>
</tr>
<tr>
<td>normalization</td>
<td>( w = (1 + s)p + q )</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.2: Haploid genetic model of the spread of a favored allele.

so that dividing the first equation in (5.1) by (5.2) yields

\[
p_{i+1} = \frac{f_{AAGA}n_A^{(i)}}{f_{AAGA}n_A^{(i)} + f_{aa}n_a^{(i)}} = \frac{f_{AAGA}p_i}{f_{AAGA}p_i + f_{aa}q_i} = \frac{p_i + \left(\frac{f_{aa}}{f_{AAGA}}\right)q_i}{p_i + \left(\frac{f_{aa}}{f_{AAGA}}\right)q_i},
\]

(5.3)

where the second equality comes from dividing the numerator and denominator by \( n_A^{(i)} + n_a^{(i)} \), and the third equality from dividing the numerator and denominator by \( f_{AAGA} \). Similarly,

\[
q_{i+1} = \frac{\left(\frac{f_{aa}}{f_{AAGA}}\right)q_i}{p_i + \left(\frac{f_{aa}}{f_{AAGA}}\right)q_i},
\]

(5.4)

which could also be derived using \( q_{i+1} = 1 - p_{i+1} \). We observe from the evolution equations for the allele frequencies, (5.3) and (5.4), that only the relative fitness \( f_{aa}/f_{AAGA} \) of the alleles matters. Accordingly, in our models, we will consider only relative fitnesses, and we will arbitrarily set one fitness to unity to simplify the algebra and make the final result more transparent.

5.1.1 Spread of a favored allele

We consider a simple model for the spread of a favored allele in Table 5.2 with \( s > 0 \). Denoting \( p' \) by the frequency of \( A \) in the next generation (not the derivative of \( p' \)), the model equation is given by

\[
p' = \frac{(1 + s)p}{w} = \frac{(1 + s)p}{1 + sp},
\]

(5.5)

where we have used \( (1 + s)p + q = 1 + sp \), since \( p + q = 1 \). Note that (5.5) is the same as (5.3) with \( p' = p_{i+1}, p = p_i, \) and \( f_{AAGA}/f_{aa} = 1 + s \). Fixed points of (5.5) are determined from \( p' = p \). We find two fixed points: \( p_\ast = 0 \), corresponding to a population in which allele \( A \) is absent; and \( p_\ast = 1 \), corresponding to a population in which allele \( A \) is fixed. Intuitively, \( p_\ast = 0 \) is unstable while \( p_\ast = 1 \) is stable.
To illustrate how a stability analysis is performed analytically for a difference equation (instead of a differential equation), consider the general difference equation
\[ p' = f(p). \] (5.6)

With \( p = p_\star \) a fixed point such that \( p_\star = f(p_\star) \), we write \( p = p_\star + \epsilon \), and (5.6) becomes
\[ p_\star + \epsilon' = f(p_\star + \epsilon) = f(p_\star) + \epsilon f'(p_\star) + \ldots = p_\star + \epsilon f'(p_\star) + \ldots, \]
where \( f'(p_\star) \) denotes the derivative of \( f \) evaluated at \( p_\star \). Therefore, to leading-order in \( \epsilon \)
\[ |\epsilon'/\epsilon| = |f'(p_\star)|, \]
and the fixed point is stable provided that \( |f'(p_\star)| < 1 \). For our haploid model,
\[ f(p) = \frac{(1 + s)p}{1 + sp}, \quad f'(p) = \frac{1 + s}{(1 + sp)^2}, \]
so that \( f'(p_\star = 0) = 1 + s > 1 \), and \( f'(p_\star = 1) = 1/(1 + s) < 1 \), confirming that \( p_\star = 0 \) is unstable and \( p_\star = 1 \) is stable.

If the selection coefficient \( s \) is small, the model equation (5.5) simplifies further. We have
\[ p' = \frac{(1 + s)p}{1 + sp}, \]
\[ = (1 + s)(1 - sp + O(s^2)) \]
\[ = p + (p - p^2)s + O(s^2), \]
so that to leading-order in \( s \),
\[ p' - p = sp(1 - p). \]

If \( p' - p << 1 \), which is valid for \( s << 1 \), we can approximate this difference equation by the differential equation
\[ dp/dn = sp(1 - p), \]
which shows that the frequency of allele \( A \) satisfies the now very familiar logistic equation.

Although a polymorphism for this gene exists in the population as the new allele spreads, eventually \( A \) becomes fixed in the population and the polymorphism is lost. In the next section, we consider how a polymorphism can be maintained in a haploid population by the balance between mutation and selection.

5.1.2 Mutation-selection balance
We consider a gene with two alleles: a wildtype allele \( A \) and a mutant allele \( a \). We view the mutant allele as a defective genotype, which confers on the
carrier a lowered fitness $1 - s$ relative to the wildtype. Although all mutant alleles may not have identical DNA sequences, we assume that they share in common the same phenotype of reduced fitness. We model the opposing effects of two evolutionary forces: natural selection, which favors the wildtype allele $A$ over the mutant allele $a$, and mutation, which confers a small probability $u$ that allele $A$ mutates to allele $a$ in each newborn individual. Schematically,

$$A \xrightarrow{u/s} a,$$

where $u$ represents mutation and $s$ represents selection. The model is shown in Table 5.3. The equations for $p$ and $q$ in the next generation are

$$p' = \frac{(1-u)p}{w} = \frac{(1-u)p}{1-s(1-p)}, \quad (5.7)$$

and

$$q' = \frac{(1-s)q + up}{w} = \frac{(1-s-u)q + u}{1-sq}, \quad (5.8)$$

where we have used $p + q = 1$ to eliminate $q$ from the equation for $p'$ and $p$ from the equation for $q'$. The equations for $p'$ and $q'$ are linearly dependent since $p' + q' = 1$, and we need solve only one of them.

Considering (5.7), the fixed points determined from $p' = p$ are $p_* = 0$, for which the mutant allele $a$ is fixed in the population and there is no polymorphism, and the solution to

$$1 - s(1-p_*) = 1 - u,$$

which is $p_* = 1 - u/s$, and there is a polymorphism. The stability of these two fixed points is determined by considering $p' = f(p)$, with $f(p)$ given by the right-hand-side of (5.7). Taking the derivative of $f$,

$$f'(p) = \frac{(1-u)(1-s)}{(1-s(1-p))^2},$$

so that

$$f'(p_0 = 0) = \frac{1-u}{1-s}, \quad f'(p_* = 1 - u/s) = \frac{1-s}{1-u}.$$
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<table>
<thead>
<tr>
<th>genotype</th>
<th>AA referred to as</th>
<th>Aa</th>
<th>aa referred to as</th>
</tr>
</thead>
<tbody>
<tr>
<td>frequency</td>
<td>P</td>
<td>Q</td>
<td>R</td>
</tr>
</tbody>
</table>

Table 5.4: The terminology of diploidy.

Applying the criterion $|f'(p_*)| < 1$ for stability, $p_* = 0$ is stable for $s < u$ and $p_* = 1 - u/s$ is stable for $s > u$. A polymorphism is therefore possible under mutation-selection balance when $s > u > 0$.

5.2 Diploid genetics

Most sexually reproducing species are diploid. In particular, our species *Homo sapiens* is diploid with two exceptions: we are haploid at the gamete stage (sperm and unfertilized egg); and males are haploid for most genes on the unmatched X and Y sex chromosomes (females are XX and diploid). This latter seemingly innocent fact is of great significance to males suffering from genetic diseases due to an X-linked recessive mutation inherited from their mother. Females inheriting this mutation are most probably disease-free because of the functional gene inherited from their father.

A polymorphic gene with alleles $A$ and $a$ can appear in a diploid gene as three distinct genotypes: $AA$, $Aa$ and $aa$. Conventionally, we denote $A$ to be the wildtype allele and $a$ the mutant allele. Table 5.4 presents the terminology of diploidy.

As for haploid genetics, we will determine evolution equations for allele and/or genotype frequencies. To develop the appropriate definitions and relations, we initially assume a population of size $N$ (which we will later take to be infinite), and assume that the number of individuals with genotypes $AA$, $Aa$ and $aa$ are $N_{AA}$, $N_{Aa}$ and $N_{aa}$. Now, $N = N_{AA} + N_{Aa} + N_{aa}$. Define genotype frequencies $P$, $Q$ and $R$ as

$$P = \frac{N_{AA}}{N}, \quad Q = \frac{N_{Aa}}{N}, \quad R = \frac{N_{aa}}{N},$$

so that $P + Q + R = 1$. It will also be useful to define allele frequencies. Let $n_A$ and $n_a$ be the number of alleles $A$ and $a$ in the population, with $n = n_A + n_a$ the total number of alleles. Since the population is of size $N$ and diploidy, $n = 2N$; and since each homozygote contains two identical alleles, and each heterozygote contains one of each allele, $n_A = 2N_{AA} + N_{Aa}$ and $n_a = 2N_{aa} + N_{Aa}$. Defining the allele frequencies $p$ and $q$ as previously,

$$p = \frac{n_A}{n} = \frac{2N_{AA} + N_{Aa}}{2N} = P + \frac{1}{2}Q;$$
and similarly,

\[ q = \frac{n_a}{n} \]
\[ = \frac{2N_{aa} + N_{Aa}}{2N} \]
\[ = R + \frac{1}{2}Q. \]

With five frequencies, \( P, Q, R, p, q \), and four constraints \( P + Q + R = 1, \ p + q = 1, \ p = P + Q/2, \ q = R + Q/2 \), how many independent frequencies are there? In fact, there are two because one of the four constraints is linearly dependent. We may choose any two frequencies other than the choice \( \{p, q\} \) as our linearly independent set. For instance, one choice is \( \{P, p\} \); then,

\[ q = 1 - p, \quad Q = 2(p - P), \quad R = 1 + P - 2p. \]

Similarly, another choice is \( \{P, Q\} \); then

\[ R = 1 - P - Q \quad p = P + \frac{1}{2}Q, \quad q = 1 - P - \frac{1}{2}Q. \]

5.2.1 Sexual reproduction

Diploid reproduction may be sexual or asexual, and sexual reproduction may be of varying types (e.g., random mating, selfing, brother-sister mating, and various other types of assortative mating). The two simplest types to model exactly are random mating and selfing. These mating systems are useful for contrasting the biology of both outbreeding and inbreeding.

Random mating

The simplest type of sexual reproduction to model mathematically is random mating. Here, we assume a well-mixed population of individuals that have equal probability of mating with every other individual. We will determine the genotype frequencies of the zygotes (fertilized eggs) in terms of the allele frequencies using two approaches: (1) the gene pool approach, and (2) the mating table approach.

The gene pool approach models sexual reproduction by assuming that males and females release their gametes into pools. Offspring genotypes are determined by randomly combining one gamete from the male pool and one gamete from the female pool. As the probability of a random gamete containing allele \( A \) or \( a \) is equal to the allele’s population frequency \( p \) or \( q \), respectively, the probability of an offspring being \( AA \) is \( p^2 \), of being \( Aa \) is \( 2pq \) (male \( A \) female \( a \) + female \( A \) male \( a \)), and of being \( aa \) is \( q^2 \). Therefore, after a single generation of random mating, the genotype frequencies can be given in terms of the allele frequencies by

\[ P = p^2, \quad Q = 2pq, \quad R = q^2. \]

This is the celebrated Hardy-Weinberg law. Notice that under the assumption of random mating, there is now only a single independent frequency, greatly simplifying the mathematical modeling. For example, if \( p \) is taken as the independent frequency, then

\[ q = 1 - p, \quad P = p^2, \quad Q = 2p(1 - p), \quad R = (1 - p)^2. \]
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The second approach uses a mating table (see Table 5.5). This approach to modeling sexual reproduction is more general and can be applied to other mating systems. We explain this approach by considering the mating $AA \times Aa$. The genotypes $AA$ and $Aa$ have frequencies $P$ and $Q$, respectively. The frequency of $AA$ males mating with $Aa$ females is $PQ$ and is the same as $AA$ females mating with $Aa$ males, so the sum is $2PQ$. Half of the offspring will be $AA$ and half $Aa$, and the frequencies $PQ$ are denoted under progeny frequency. The sums of all the progeny frequencies are given in the Totals row, and the random mating results are recovered upon use of the relationship between the genotype and allele frequencies.

Table 5.5: Random mating table.

<table>
<thead>
<tr>
<th>mating</th>
<th>frequency</th>
<th>progeny frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AA \times AA$</td>
<td>$P^2$</td>
<td>$AA$</td>
</tr>
<tr>
<td>$AA \times Aa$</td>
<td>$2PQ$</td>
<td>$PQ$</td>
</tr>
<tr>
<td>$AA \times aa$</td>
<td>$2PR$</td>
<td>$0$</td>
</tr>
<tr>
<td>$Aa \times Aa$</td>
<td>$Q^2$</td>
<td>$\frac{1}{4}Q^2$</td>
</tr>
<tr>
<td>$Aa \times aa$</td>
<td>$2QR$</td>
<td>$0$</td>
</tr>
<tr>
<td>$aa \times aa$</td>
<td>$R^2$</td>
<td>$0$</td>
</tr>
</tbody>
</table>

Table 5.6: Selfing mating table.

<table>
<thead>
<tr>
<th>mating</th>
<th>frequency</th>
<th>progeny frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AA \otimes$</td>
<td>$P$</td>
<td>$AA$</td>
</tr>
<tr>
<td>$Aa \otimes$</td>
<td>$Q$</td>
<td>$\frac{1}{2}Q$</td>
</tr>
<tr>
<td>$aa \otimes$</td>
<td>$R$</td>
<td>$0$</td>
</tr>
<tr>
<td>Totals</td>
<td>$1$</td>
<td>$P + \frac{1}{2}Q$</td>
</tr>
</tbody>
</table>

Most modeling is done assuming random mating unless the biology under study is influenced by inbreeding.

The second approach uses a mating table (see Table 5.5). This approach to modeling sexual reproduction is more general and can be applied to other mating systems. We explain this approach by considering the mating $AA \times Aa$. The genotypes $AA$ and $Aa$ have frequencies $P$ and $Q$, respectively. The frequency of $AA$ males mating with $Aa$ females is $PQ$ and is the same as $AA$ females mating with $Aa$ males, so the sum is $2PQ$. Half of the offspring will be $AA$ and half $Aa$, and the frequencies $PQ$ are denoted under progeny frequency. The sums of all the progeny frequencies are given in the Totals row, and the random mating results are recovered upon use of the relationship between the genotype and allele frequencies.

Selfing

Perhaps the next simplest type of mating system is self-fertilization, or selfing. Here, an individual reproduces sexually (passing through a haploid gamete stage in its life-cycle), but provides both of the gametes. For example, the nematode worm *C. elegans* can reproduce by selfing. The mating table for selfing is given in Table 5.6. The selfing frequency of a particular genotype is just the frequency of the genotype itself. For a selfing population, disregarding selection or any other evolutionary forces, the genotype frequencies evolve as

$$P' = P + \frac{1}{4}Q, \quad Q' = \frac{1}{2}Q, \quad R' = R + \frac{1}{4}Q. \quad (5.9)$$

Assuming an initially heterozygous population, we solve (5.9) with the initial conditions $Q_0 = 1$ and $P_0 = R_0 = 0$. In the worm lab, this type of initial
population is commonly created by crossing wildtype homozygous *C. elegans* males with mutant homozygous *C. elegans* hermaphrodites, where the mutant allele is recessive. Wildtype hermaphrodite offspring, which are necessarily heterozygous, are then picked to separate worm plates and allowed to self-fertilize. (Do you see why the experiment is not done with wildtype hermaphrodites and mutant males?) From the equation for $Q'$ in (5.9), we have $Q_n = (1/2)^n$, and from symmetry, $P_n = R_n$. Then, since $P_n + Q_n + R_n = 1$, we obtain the complete solution

$$P_n = \frac{1}{2} \left( 1 - \left( \frac{1}{2} \right)^n \right), \quad Q_n = \left( \frac{1}{2} \right)^n, \quad R_n = \frac{1}{2} \left( 1 - \left( \frac{1}{2} \right)^n \right).$$

The main result to be emphasized here is that the heterozygosity of the population decreases by a factor of two in each generation. Selfing populations rapidly become homozygous. For homework, I will ask you to determine the genotype frequencies for an initially random mating population that transitions to selfing.

**Constancy of allele frequencies**

Mating by itself does not change allele frequencies in a population, but only reshuffles alleles into different genotypes. We can show this directly for random mating and selfing. For random mating,

$$p' = p' + \frac{1}{2} Q'$$

$$= p^2 + \frac{1}{2} (2pq)$$

$$= p(p + q)$$

$$= p;$$

and for selfing,

$$p' = p' + \frac{1}{2} Q'$$

$$= \left( p + \frac{1}{4} Q \right) + \frac{1}{2} \left( \frac{1}{2} Q \right)$$

$$= p + \frac{1}{2} \frac{1}{2} Q$$

$$= p.$$

The conservation of allele frequency by mating is an important element of neo-Darwinism. In Darwin’s time, most biologists believed in *blending inheritance*, where the genetic material from parents with different traits actually blended in their offspring, rather like the mixing of paints of different colors. If blending inheritance occurred, then genetic variation, or polymorphism, would eventually be lost over several generations as the “genetic paints” became well-mixed. Mendel’s work on peas, published in 1866, suggested a particulate theory of inheritance, where the genetic material, later called genes, maintain their integrity across generations. Sadly, Mendel’s paper was not read by Darwin (who published *The Origin of Species* in 1859 and died in 1882) or other influential biologists during Mendel’s lifetime (Mendel died in 1884). After being rediscovered in 1900, Mendel and his work eventually became widely celebrated.
5.2.2 Spread of a favored allele

We consider the spread of a favored allele in a diploid population. The classic example – widely repeated in biology textbooks as a modern example of natural selection – is the change in the frequencies of the dark and light phenotypes of the peppered moth during England’s industrial revolution. The evolutionary story begins with the observation that pollution killed the light colored lichen on trees during industrialization of the cities. Light colored peppered moths camouflage well on light colored lichens, but are exposed to birds on plain tree bark. On the other hand, dark colored peppered moths camouflage well on plain tree bark, but are exposed on light colored lichens (see Fig. 5.1). Natural selection therefore favored the light-colored allele in preindustrialized England and the dark-colored allele during industrialization. The dark-colored allele, presumably kept at low frequency by mutation-selection balance in pre-industrialized England, increased rapidly under natural selection in industrializing England.

We present our model in Table 5.7. Here, we consider $aa$ as the wildtype genotype and normalize its fitness to unity. The allele $A$ is the mutant whose frequency increases in the population. In our example of the peppered moth, the $aa$ phenotype is light colored and the $AA$ phenotype is dark colored. The color of the $Aa$ phenotype depends on the relative dominance of $A$ and $a$. Usually, no pigment results in light color and is a consequence of nonfunctioning pigment-producing genes. One functioning pigment-producing allele is usually sufficient to result in a dark-colored moth. With $A$ a functioning pigment-producing allele and $a$ the mutated nonfunctioning allele, $a$ is most likely recessive, $A$ is most likely dominant, and the phenotype of $Aa$ is most likely dark, so $h \approx 1$. For the moment, though, we leave $h$ as a free parameter.

We assume random mating, and this simplification is used to write the genotype frequencies as $P = p^2$, $Q = 2pq$, and $R = q^2$. Since $q = 1 - p$, we reduce our problem to determining an equation for $p'$ in terms of $p$. Using $p' = P_s + (1/2)Q_s$, where $p'$ is the $A$ allele frequency in the next generation’s zygotes, and $P_s$ and $Q_s$ are the $AA$ and $Aa$ genotype frequencies, respectively, in the present generation.
5.2. DIPLOID GENETICS

<table>
<thead>
<tr>
<th>genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>freq. of zygote</td>
<td>$p^2$</td>
<td>$2pq$</td>
<td>$q^2$</td>
</tr>
<tr>
<td>relative fitness</td>
<td>$1 + s$</td>
<td>$1 + sh$</td>
<td>1</td>
</tr>
<tr>
<td>freq after selection</td>
<td>$(1 + s)p^2/w$</td>
<td>$2(1 + sh)pq/w$</td>
<td>$q^2/w$</td>
</tr>
<tr>
<td>normalization</td>
<td>$w = (1 + s)p^2 + 2(1 + sh)pq + q^2$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.7: A diploid genetic model of the spread of a favored allele assuming random mating.

After selection, $$p' = \frac{(1 + s)p^2 + (1 + sh)pq}{w},$$

where $q = 1 - p$, and

$$w = (1 + s)p^2 + 2(1 + sh)pq + q^2 = 1 + s(p^2 + 2hpq).$$

After some algebra, the final evolution equation written solely in terms of $p$ is

$$p' = \frac{(1 + sh)p + s(1 - h)p^2}{1 + 2shp + s(1 - 2h)p^2}.$$  \hspace{1cm} (5.10)

The expected fixed points of this equation are $p^* = 0$ (unstable) and $p^* = 1$ (stable), where our assignment of stability assumes positive selection coefficients.

The evolution equation (5.10) in this form is not particularly illuminating. In general, a numerical solution would require specifying numerical values for $s$ and $h$, as well as an initial value for $p$. Here, we investigate analytically the increase of a favored allele $A$ assuming the selection coefficient $s \ll 1$, to determine how the spread of $A$ depends on the dominance coefficient $h$. We Taylor-series expand the right-hand-side of (5.10) in powers of $s$, keeping terms to order $s^2$:

$$p' = \frac{(1 + sh)p + s(1 - h)p^2}{1 + 2shp + s(1 - 2h)p^2}.$$  \hspace{1cm} (5.11)

If $s \ll 1$, we expect a small change in allele frequency in each generation, so we can approximate $p' - p \approx \frac{dp}{dn}$, where $n$ denotes the generation number, and $p = p(n)$. The approximate differential equation obtained from (5.11) is

$$\frac{dp}{dn} = sp \left( h + (1 - 3h)p - (1 - 2h)p^2 \right).$$  \hspace{1cm} (5.12)

If $A$ is partially dominant so that $h \neq 0$ (e.g., the heterozygous moth is darker than the homozygous mutant moth), then the solution to (5.12) behaves similarly to the solution of a logistic equation: $p$ initially grows exponentially as $p(n) = p_0 \exp(shn)$, and asymptotes to one for large $n$. If $A$ is recessive so
CHAPTER 5. POPULATION GENETICS

<table>
<thead>
<tr>
<th>disease</th>
<th>mutation</th>
<th>symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassemia</td>
<td>haemoglobin</td>
<td>anemia</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>haemoglobin</td>
<td>anemia</td>
</tr>
<tr>
<td>Haemophilia</td>
<td>blood clotting factor</td>
<td>uncontrolled bleeding</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>chloride ion channel</td>
<td>thick lung mucous</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>Hexosaminidase A enzyme</td>
<td>nerve cell damage</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>FMR1 gene</td>
<td>mental retardation</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>HD gene</td>
<td>brain degeneration</td>
</tr>
</tbody>
</table>

Table 5.8: Seven common monogenic diseases.

that \( h = 0 \) (e.g., the heterozygous moth is as light-colored as the homozygous mutant moth), then (5.12) reduces to

\[
\frac{dp}{dn} = sp^2 (1 - p), \quad \text{for } h = 0. \tag{5.13}
\]

Of main interest is the initial growth of \( p \) when \( p(0) = p_0 << 1 \), so that \( dp/dn \approx sp^2 \). This differential equation may be integrated by separating variables to yield

\[
p(n) = \frac{p_0}{1 - sp_0 n}
\approx p_0 (1 + sp_0 n).
\]

The frequency of a recessive favored allele increases only linearly across generations, a consequence of the heterozygote being hidden from natural selection. Most likely, the peppered-moth heterozygote is significantly darker than the light-colored homozygote since the dark colored moth rapidly increased in frequency over a short period of time.

As a final comment, linear growth in the frequency of \( A \) when \( h = 0 \) is sensitive to our assumption of random mating. If selfing occurred, or another type of close family mating, then a recessive favored allele may still increase exponentially. In this circumstance, the production of homozygous offspring from more frequent heterozygote pairings allows selection to act more effectively.

5.2.3 Mutation-selection balance

By virtue of self-knowledge, the species with the most known mutant phenotypes is *Homo sapiens*. There are thousands of known genetic diseases in humans, many of them caused by mutation of a single gene (called a monogenic disease). For an easy-to-read overview of genetic disease in humans, see the website [http://www.who.int/genomics/public/geneticdiseases](http://www.who.int/genomics/public/geneticdiseases).

Table 5.8 lists seven common monogenic diseases. The first two diseases are maintained at significant frequencies in some human populations by heterosis. We will discuss in §5.2.4 the maintenance of a polymorphism by heterosis, for which the heterozygote has higher fitness than either homozygote. It is postulated that Tay-Sachs disease, prevalent among ancestors of Eastern European Jews, and cystic fibrosis may also have been maintained by heterosis acting in the past. (Note that the cystic fibrosis gene was identified in 1989 by a Toronto
5.2. DIPLOID GENETICS

<table>
<thead>
<tr>
<th>genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
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<tr>
<td>freq. of zygote</td>
<td>(p^2)</td>
<td>(2pq)</td>
<td>(q^2)</td>
</tr>
<tr>
<td>relative fitness</td>
<td>1</td>
<td>(1 - sh)</td>
<td>(1 - s)</td>
</tr>
<tr>
<td>freq after selection</td>
<td>(p^2/w)</td>
<td>(2(1 - sh)pq/w)</td>
<td>((1 - s)q^2/w)</td>
</tr>
<tr>
<td>normalization</td>
<td>(w = p^2 + 2(1 - sh)pq + (1 - s)q^2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.9: A diploid genetic model of mutation-selection balance assuming random mating.

The other disease genes listed may be maintained by mutation-selection balance. (The group led by Lap Chee Tsui, who later became President of the University of Hong Kong.)

Our model for diploid mutation selection-balance is given in Table 5.9. We further assume that mutations of type \(A \rightarrow a\) occur in gamete production with frequency \(u\). Back-mutation is neglected. The gametic frequency of \(A\) and \(a\) after selection but before mutation is given by \(\hat{p} = \frac{Ps + Qs}{2}\) and \(\hat{q} = \frac{Rs + Qs}{2}\), and the gametic frequency of \(a\) after mutation is given by \(q' = u\hat{p} + \hat{q}\). Therefore,

\[
q' = \left\{ u[p^2 + (1 - sh)pq] + [(1 - s)q^2 + (1 - sh)pq] \right\} / w,
\]

where

\[
w = p^2 + 2(1 - sh)pq + (1 - s)q^2
= 1 - sq(2hp + q).
\]

Using \(p = 1 - q\), we write the evolution equation for \(q'\) in terms of \(q\) alone. After some algebra that could be facilitated using a computer algebra software such as Mathematica, we obtain

\[
q' = \frac{u + [1 - u - sh(1 + u)]q - s[1 - h(1 + u)]q^2}{1 - 2shq - s(1 - 2h)q^2}.
\] (5.14)

To determine the equilibrium solutions of (5.14), we set \(q_* \equiv q' = q\) to obtain a cubic equation for \(q_*\). One solution readily found is \(q_* = 1\), in which all the \(A\) alleles have mutated to \(a\). This is a solution because of the neglect of back mutation in our model. The \(q_* = 1\) solution may be factored out of the cubic equation resulting in a quadratic equation, with two solutions. Rather than show the exact result here, we determine equilibrium solutions under two approximations: (i) \(0 < u << h, s\), and; (ii) \(0 = h < u < s\).

First, when \(0 < u << h, s\), we look for a solution of the form \(q_* = au + O(u^2)\), with \(a\) constant, and Taylor series expand in \(u\) (assuming \(s, h = O(u^0)\)). If such a solution exists, then (5.14) will determine the unknown coefficient \(a\). We have

\[
au + O(u^2) = \frac{u + (1 - sh)au + O(u^2)}{1 - 2shau + O(u^2)}
= (1 + a - sha)u + O(u^2);
\]

and equating powers of \(u\), \(a = 1 + a - sha\), or \(a = 1/sh\). Therefore,

\[
q_* = u/sh + O(u^2), \quad \text{for } 0 < u << h, s.
\]
Table 5.10: Equilibrium frequencies of the genotypes at the diploid mutation-selection balance.

<table>
<thead>
<tr>
<th>genotype</th>
<th>freq: $0 &lt; u &lt;&lt; s, h$</th>
<th>freq: $0 = h &lt; u &lt; s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>$1 + O(u)$</td>
<td>$1 + O(\sqrt{u})$</td>
</tr>
<tr>
<td>Aa</td>
<td>$2u/sh + O(u^2)$</td>
<td>$2\sqrt{u}/s + O(u)$</td>
</tr>
<tr>
<td>aa</td>
<td>$u^2/(sh)^2 + O(u^2)$</td>
<td>$u/s$</td>
</tr>
</tbody>
</table>

Table 5.10 summarizes our results for the equilibrium frequencies of the genotypes at mutation-selection balance. The first row of frequencies, $0 < u << s, h$, corresponds to a dominant ($h = 1$) or partially-dominant ($u << h < 1$) mutation, where the heterozygote is of reduced fitness and shows symptoms of the genetic disease. The second row of frequencies, $0 = h < u < s$, corresponds to a recessive mutation, where the heterozygote is symptom-free. Notice that individuals carrying a dominant mutation are twice as prevalent in the population as individuals homozygous for a recessive mutation (with the same $u$ and $s$).

A heterozygote carrying a dominant mutation most commonly arises either de novo (by direct mutation of allele $A$) or by the mating of a heterozygote with a wildtype. The latter is more common for $s << 1$, while the former must occur for $s = 1$ (a heterozygote with an $s = h = 1$ mutation by definition does not reproduce). One of the most common autosomal dominant genetic diseases is Huntington’s disease, resulting in brain deterioration during middle age. Because individuals with Huntington’s disease have children before disease symptoms appear, $s$ is small and the disease is usually passed to offspring by the mating of a (heterozygote) with a wildtype homozygote. For a recessive mutation, a mutant homozygote usually occurs by the mating of two heterozygotes. If both parents carry a single recessive disease allele, then their child has a $1/4$ chance of getting the disease.

5.2.4 Heterosis

Heterosis, also called overdominance or heterozygote advantage, occurs when the heterozygote has higher fitness than either homozygote. The best-known examples are sickle-cell anemia and thalassemia, diseases that both affect hemoglobin,
5.3. FREQUENCY-DEPENDENT SELECTION

<table>
<thead>
<tr>
<th>genotype</th>
<th>AA</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>freq. of zygote</td>
<td>$p^2$</td>
<td>$2pq$</td>
<td>$q^2$</td>
</tr>
<tr>
<td>relative fitness</td>
<td>$1 - s$</td>
<td>1</td>
<td>$1 - t$</td>
</tr>
<tr>
<td>freq after selection</td>
<td>$(1 - s)p^2/w$</td>
<td>$2pq/w$</td>
<td>$(1 - t)q^2/w$</td>
</tr>
<tr>
<td>normalization</td>
<td>$w = (1 - s)p^2 + 2pq + (1 - t)q^2$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.11: A diploid genetic model of heterosis assuming random mating.

the oxygen-carrier protein of red blood cells. The sickle-cell mutations are most common in people of West African descent, while the thalassemia mutations are most common in people from the Mediterranean and Asia. In Hong Kong, the television stations occasionally play public service announcements concerning thalassemia. The heterozygote carrier of the sickle-cell or thalassemia gene is healthy and resistant to malaria; the wildtype homozygote is healthy, but susceptible to malaria; the mutant homozygote is sick with anemia. In class, we will watch the short video, A Mutation Story, about the sickle cell gene, which you can also view at your convenience:


Table 5.11 presents our model of heterosis. Both homozygotes are of lower fitness than the heterozygote, whose relative fitness we arbitrarily set to unity. Writing the equation for $p'$, we have

$$p' = \frac{(1 - s)p^2 + pq}{1 - sp^2 - tq^2} = \frac{p - sp^2}{1 - t + 2tp - (s + t)p^2}.$$

At equilibrium, $p_* = p'$, and we obtain a cubic equation for $p_*$:

$$(s + t)p_*^3 - (s + 2t)p_*^2 + tp_* = 0. \quad (5.15)$$

Evidently, $p_* = 0$ and $p_* = 1$ are fixed points, and (5.15) can be factored as

$$p(1 - p)(t - (s + t)p) = 0.$$

The polymorphic solution is therefore

$$p_* = \frac{t}{s + t}, \quad q_* = \frac{s}{s + t},$$

valid when $s, t > 0$. Since the value of $q_*$ can be large, recessive mutations that cause disease, yet are highly prevalent in a population, are suspected to provide some benefit to the heterozygote. However, only a few genes are unequivocally known to exhibit heterosis.

5.3 Frequency-dependent selection

A polymorphism may also result from frequency-dependent selection. A well-known model of frequency-dependent selection is the Hawk-Dove game. Most
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<table>
<thead>
<tr>
<th>player \ opponent</th>
<th>H</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>$E_{HH} = -2$</td>
<td>$E_{HD} = 2$</td>
</tr>
<tr>
<td>D</td>
<td>$E_{DH} = 0$</td>
<td>$E_{DD} = 1$</td>
</tr>
</tbody>
</table>

Table 5.12: General payoff matrix for the Hawk-Dove game, and the usually assumed values. The payoffs are paid to the player (first column) when playing against the opponent (first row).

<table>
<thead>
<tr>
<th>genotype</th>
<th>H</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>freq of zygote</td>
<td>p</td>
<td>q</td>
</tr>
<tr>
<td>relative fitness</td>
<td>$K + pE_{HH} + qE_{HD}$</td>
<td>$K + pE_{DH} + qE_{DD}$</td>
</tr>
<tr>
<td>freq after selection</td>
<td>$(K + pE_{HH} + qE_{HD})p/w$</td>
<td>$(K + pE_{DH} + qE_{DD})q/w$</td>
</tr>
<tr>
<td>normalization</td>
<td>$w = (K + pE_{HH} + qE_{HD})p + (K + pE_{DH} + qE_{DD})q$</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.13: Haploid genetic model for frequency-selection in the Hawk-Dove game

commonly, frequency-dependent selection is studied using game theory, and following John Maynard Smith, one looks for an evolutionarily stable strategy (ESS). Here, we study frequency-dependent selection using a population-genetics model.

We consider two phenotypes: Hawk and Dove, with no mating between different phenotypes (for example, different phenotypes may correspond to different species, such as hawks and doves). We describe the Hawk-Dove game as follows: (i) when Hawk meets Dove, Hawk gets the resource and Dove retreats before injury; (ii) when two Hawks meet, they engage in an escalating fight, seriously risking injury, and; (iii) when two Doves meet, they share the resource. The Hawk-Dove game is modeled by a payoff matrix, as shown in Table 5.12. The player in the first column receives the payoff when playing the opponent in the first row. For instance, Hawk playing Dove gets the payoff $E_{HD}$. The numerical values are commonly chosen such that $E_{HH} < E_{DH} < E_{DD} < E_{HD}$, that is, Hawk playing Dove does better than Dove playing Dove does better than Dove playing Hawk does better than Hawk playing Hawk.

Frequency-dependent selection occurs because the fitness of Hawk or Dove depends on the frequency of Hawks and Doves in the population. For example, a Hawk in a population of Doves does well, but a Hawk in a population of Hawks does poorly. We model the Hawk-Dove game using a haploid genetic model, with $p$ and $q$ the population frequencies of Hawks and Doves, respectively. We assume that the times a player phenotype plays an opponent phenotype is proportional to the population frequency of the opponent phenotype. For example, if the population is composed of 1/4 Hawks and 3/4 Doves, then Hawk or Dove plays Hawk 1/4 of the time and Dove 3/4 of the time. Our haploid genetic model assuming frequency-dependent selection is formulated in Table 5.13. The fitness parameter $K$ is arbitrary, but assumed to be large and positive so that the fitness of Hawk or Dove is always positive. A negative fitness in our haploid model has no meaning (see §5.1).

From Table 5.13, the equation for $p'$ is

$$p' = (K + pE_{HH} + qE_{HD})p/w,$$

(5.16)
with
\[ w = (K + pE_{HH} + qE_{HD})p + (K + pE_{DH} + qE_{DD})q. \] (5.17)
Both \( p_* = 0 \) and \( p_* = 1 \) are fixed points; a stable polymorphism exists when
both these fixed points are unstable.

First, consider the fixed point \( p_* = 0 \). With perturbation \( p \ll 1 \) and \( q = 1 - p \), to leading-order in \( p \)
\[ p' = \left( \frac{K + E_{HD}}{K + E_{DD}} \right) p. \]
Therefore, \( p_* = 0 \) is an unstable fixed point when \( E_{HD} > E_{DD} \)—a population of
Doves is unstable if Hawk playing Dove does better than Dove playing Dove. By symmetry,
\( p_* = 1 \) is an unstable fixed point when \( E_{DH} > E_{HH} \)—a population of
Hawks is unstable if Dove playing Hawk does better than Hawk playing Hawk.

Both homogeneous populations of either all Hawks or all Doves are unstable for
the numerical values shown in Table 5.12.

The polymorphic solution may be determined from (5.16) and (5.17). Assuming
\( p_* \equiv p^* = p, q_* = 1 - p_* \), and \( p_*, q_\neq 0 \), we have
\[ (K + p_*E_{HH} + q_*E_{HD})p^* + (K + p_*E_{DH} + q_*E_{DD})q_* = K + p_*E_{HH} + q_*E_{HD}; \]
and solving for \( p_* \), we have
\[ p_* = \frac{E_{HD} - E_{DD}}{(E_{HH} - E_{DD}) + (E_{DH} - E_{HH})}. \]
Since we have assumed \( E_{HD} > E_{DD} \) and \( E_{DH} > E_{HH} \), the polymorphic solution satisfies \( 0 < p_* < 1 \). With the numerical values in Table 5.12
\[ p_* = \frac{2 - 1}{(2 - 1) + (0 + 2)} = 1/3; \]
the stable polymorphic population, maintained by frequency-dependent selection,
consists of 1/3 Hawks and 2/3 Doves.

5.4 Recombination and the approach to linkage equilibrium

When considering a polymorphism at a single genetic loci, we assumed two
distinct alleles, \( A \) and \( a \). The diploid then occurs as one of three types: \( AA \),
\( Aa \) and \( aa \). We now consider a polymorphism at two genetic loci, each with
those at the second \( B \) and \( b \), then four distinct haploid gametes are possible,
\( AB \), \( Ab \), \( aB \) and \( ab \). Ten distinct diplotypes are possible, obtained by
forming pairs of all possible haplotypes. We can write these ten diplotypes as
\( AB/AB \), \( AB/Ab \), \( AB/aB \), \( AB/ab \), \( Ab/Ab \), \( Ab/Ab \), \( Ab/aB \), \( aB/aB \), \( aB/ab \), and \( ab/ab \), where the numerator represents the haplotype from one parent,
the denominator represents the haplotype from the other parent. We do not
distinguish here which haplotype came from which parent.
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To proceed further, we define the allelic and gametic frequencies for our two loci problem in Table 5.14. If the probability that a gamete contains allele $A$ or $a$ does not depend on whether the gamete contains allele $B$ or $b$, then the two loci are said to be independent. Under the assumption of independence, the gametic frequencies are the products of the allelic frequencies, i.e., $p_{AB} = p_A p_B$, $p_{Ab} = p_A p_b$, etc.

Often, the two loci are not independent. This can be due to epistatic selection, or *epistasis*. As an example, suppose that two loci in humans influence height, and that the most fit genotype is the one resulting in an average height. Selection that favors the average population value of a trait is called normalizing or stabilizing. Suppose that $A$ and $B$ are hypothetical tall alleles, $a$ and $b$ are short alleles, and a person with two tall and two short alleles obtains average height. Then selection may favor the specific genotypes $AB/ab$, $Ab/Ab$, $Ab/aB$, and $aB/aB$. Selection may act against both the genotypes yielding above average heights, $AB/AB$, $AB/Ab$, and $AB/aB$, and those yielding below average heights, $Ab/ab$, $aB/ab$ and $ab/ab$. Epistatic selection occurs because the fitness of the $A,a$ loci depends on which alleles are present at the $B,b$ loci. Here, $A$ has higher fitness when paired with $b$ than when paired with $B$.

The two loci may also not be independent because of a finite population size (i.e., stochastic effects). For instance, suppose a mutation $a \rightarrow A$ occurs only once in a finite population (in an infinite population, any possible mutation occurs an infinite number of times), and that $A$ is strongly favored by natural selection. The frequency of $A$ may then increase. If a nearby polymorphic locus on the same chromosome as $A$ happens to be $B$ (say, with a polymorphism $b$ in the population), then $AB$ gametes may substantially increase in frequency, with $Ab$ absent. We say that the allele $B$ hitchhikes with the favored allele $A$.

When the two loci are not independent, we say that the loci are in gametic phase disequilibrium, or more commonly *linkage disequilibrium*, sometimes abbreviated as LD. When the loci are independent, we say they are in *linkage equilibrium*. Here, we will model how two loci, initially in linkage disequilibrium, approach linkage equilibrium through the process of recombination.

To begin, we need a rudimentary understanding of *meiosis*. During meiosis, a diploid cell’s DNA, arranged in very long molecules called chromosomes, is replicated once and separated twice, producing four haploid cells, each containing half of the original cell’s chromosomes. Sexual reproduction results in *syngamy*, the fusing of a haploid egg and sperm cell to form a diploid zygote cell.

Fig. 5.2 presents a schematic of meiosis and the process of crossing-over resulting in recombination. In a diploid, each chromosome has a corresponding sister chromosome, one chromosome originating from the egg, one from the sperm. These sibling chromosomes have the same genes, but possibly different alleles. In Fig. 5.2, we schematically show alleles $a,b,c$ on the light chromosome, $A,B,C$ on its sister’s dark chromosome. In the first step of meiosis, each

<table>
<thead>
<tr>
<th>allele or gamete genotype</th>
<th>$A$</th>
<th>$a$</th>
<th>$B$</th>
<th>$b$</th>
<th>$AB$</th>
<th>$Ab$</th>
<th>$aB$</th>
<th>$ab$</th>
<th>frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p_A$</td>
<td></td>
<td></td>
<td>$p_B$</td>
<td></td>
<td>$p_{AB}$</td>
<td>$p_{Ab}$</td>
<td>$p_{aB}$</td>
<td>$p_{ab}$</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.14: Definitions of allelic and gametic frequencies for two genetic loci each with two alleles.
chromosome replicates itself exactly. In the second step, sister chromosomes exchange genetic material by the process of crossing-over. All four chromosomes then separate into haploid cells. Notice from the schematic that the process of crossing-over can result in genetic recombination. Suppose that the schematic of Fig. 5.2 represents the production of a sperm by a male. If the chromosome from the male’s father contains the alleles \( ABC \) and that from the male’s mother \( abc \), recombination can result in the sperm containing a chromosome with alleles \( ABc \) (the third gamete in Fig. 5.2). We say this chromosome is a recombinant; it contains alleles from both its paternal grandfather and paternal grandmother. It is likely that the precise combination of alleles on this recombinant chromosome has never existed before in a single person. Recombination is the reason why everybody, with the exception of identical twins, is genetically unique.

Genes that occur on the same chromosome are said to be linked. The closer the genes are to each other on the chromosome, the tighter the linkage, and the less likely recombination will separate them. Tightly linked genes are likely to be inherited from the same grandparent. Genes on different chromosomes are by definition unlinked; independent assortment of chromosomes results in a 50% chance of a gamete receiving either grandparents’ genes.

To define and model the evolution of linkage disequilibrium, we first obtain allele frequencies from gametic frequencies by

\[
\begin{align*}
p_A &= p_{AB} + p_{Ab}, \\
p_a &= p_{aB} + p_{ab}, \\
p_B &= p_{AB} + p_{aB}, \\
p_b &= p_{AB} + p_{ab}.
\end{align*}
\]

(5.18)

Since the frequencies sum to unity,

\[
\begin{align*}
p_A + p_a &= 1, \\
p_B + p_b &= 1, \\
p_{AB} + p_{Ab} + p_{aB} + p_{ab} &= 1.
\end{align*}
\]

(5.19)
There are three independent gametic frequencies and only two independent allelic frequencies, so in general it is not possible to obtain the gametic frequencies from the allelic frequencies without assuming an additional constraint such as linkage equilibrium. We can, however, introduce an additional variable $D$, called the coefficient of linkage disequilibrium, and define $D$ to be the difference between the gametic frequency $p_{AB}$ and what this gametic frequency would be if the loci were in linkage equilibrium:

$$p_{AB} = p_A p_B + D. \quad (5.20a)$$

Using $p_{AB} + p_{Ab} = p_A$,

$$p_{Ab} = p_A p_b - D; \quad (5.20b)$$

and using $p_{aB} + p_{ab} = p_a$,

$$p_{aB} = p_a p_B - D; \quad (5.20c)$$

we have used (5.20) to obtain the third equality. The change in $D$ is therefore equal to the change in frequency of the $AB$ gametes,

$$D' - D = p'_{AB} - p_{AB}. \quad (5.22)$$

To understand why gametic frequencies change across generations, we should first recognize when they do not change. Without genetic recombination, chromosomes maintain their exact identity across generations. Chromosome frequencies without recombination are therefore constant, and for genetic loci with, say, alleles $A,a$ and $B,b$ on the same chromosome, $p'_{AB} = p_{AB}$. In an infinite population without selection or mutation, gametic frequencies change only for genetic loci in linkage disequilibrium on different chromosomes, or for genetic loci in linkage disequilibrium on the same chromosome subjected to genetic recombination.
5.4. LINKAGE EQUILIBRIUM

Table 5.15: Computation of gamete frequencies.

<table>
<thead>
<tr>
<th>diploid</th>
<th>dip freq</th>
<th>AB</th>
<th>Ab</th>
<th>aB</th>
<th>ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AB/AB$</td>
<td>$p_{AB}'$</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$AB/Ab$</td>
<td>$p_{AB}p_{ab}$</td>
<td>$1/2$</td>
<td>1/2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$AB/aB$</td>
<td>$p_{AB}p_{aB}$</td>
<td>1/2</td>
<td>0</td>
<td>$1/2$</td>
<td>0</td>
</tr>
<tr>
<td>$AB/ab$</td>
<td>$(1-r)/2$</td>
<td>0</td>
<td>1</td>
<td>$r/2$</td>
<td>$(1-r)/2$</td>
</tr>
<tr>
<td>$Ab/Ab$</td>
<td>$p_{Ab}'$</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$Ab/aB$</td>
<td>$p_{Ab}p_{aB}$</td>
<td>$r/2$</td>
<td>$1-r/2$</td>
<td>$(1-r)/2$</td>
<td>$r/2$</td>
</tr>
<tr>
<td>$Ab/ab$</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>$1/2$</td>
<td>$1/2$</td>
</tr>
<tr>
<td>$aB/aB$</td>
<td>$p_{aB}'$</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>$aB/ab$</td>
<td>0</td>
<td>0</td>
<td>1/2</td>
<td>$1/2$</td>
<td>0</td>
</tr>
<tr>
<td>$ab/ab$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

We will compute the frequency $p_{AB}'$ of $AB$ gametes in the next generation, given the frequency $p_{AB}$ of $AB$ gametes in the present generation, using two different methods. The first method uses a ‘mating’ table (see Table 5.15). The first column is the parent diploid genotype before meiosis. The second column is the diploid genotype frequency assuming random mating. The next four columns are the haploid genotype frequencies (normalized by the corresponding diploid frequencies to simplify the table presentation). Here, we define $r$ to be the frequency at which the gamete arises from a combination of grandmother and grandfather genes. If the A,a and B,b loci occur on the same chromosome, then $r$ is the recombination frequency due to crossing-over. If the A,a and B,b loci occur on different chromosomes, then because of the independent assortment of chromosomes there is an equal probability that the gamete contains all grandfather or grandmother genes, or contains a combination of grandmother and grandfather genes, so that $r = 1/2$. Notice that crossing-over or independent assortment is of importance only if the grandfather’s and grandmother’s contribution to the diploid genotype share no common alleles (i.e., $AB/ab$ and $Ab/aB$ genotypes). The frequency $p_{AB}'$ in the next generation is given by the sum of the $AB$ column (after multiplication by the diploid frequencies). Therefore,

\[
p_{AB}' = p_{AB}^2 + p_{AB}p_{ab} + p_{AB}p_{aB} + (1-r)p_{AB}p_{ab} + rp_{Ab}p_{aB} - rD,
\]

where the final equality makes use of (5.19) and (5.21).

The second method for computing $p_{AB}'$ is more direct. An $AB$ haplotype can arise from a diploid of general type $AB/XX$ without recombination, or a diploid of type $AX/XB$ with recombination. Therefore,

\[
p_{AB}' = (1-r)p_{AB} + rp_{APB},
\]

where the first term is from non-recombinants and the second term from recombinants. With $p_{APB} = p_{AB} - D$, we have

\[
p_{AB}' = (1-r)p_{AB} + r(p_{AB} - D) = p_{AB} - rD,
\]
CHAPTER 5. POPULATION GENETICS

the same result as that obtained using the mating table.

Using (5.22), we derive

\[ D' = (1 - r)D, \]

with the solution

\[ D_n = D_0(1 - r)^n. \]

Recombination decreases linkage disequilibrium in each generation by a factor of \((1 - r)\). Tightly linked genes on the same chromosome have small values of \(r\); unlinked genes on different chromosomes have \(r = 1/2\). For unlinked genes, linkage disequilibrium decreases by a factor of two in each generation. We conclude that very strong selection is required to maintain linkage disequilibrium for genes on different chromosomes, while weak selection can maintain linkage disequilibrium for tightly linked genes.

5.5 Random genetic drift

Up to now, our simplified genetic models have all assumed an infinite population, neglecting stochastic effects. Now, we consider the random drift of allelic frequencies in a finite population.

We develop a simple genetic model incorporating random drift by assuming a fixed-sized population of \(N\) individuals, and modeling the evolution of a single two-allele haploid genetic locus. Let \(n\) denote the number of individuals in the population with allele \(A\); \(N - n\) the number of individuals with allele \(a\).

There are two widely used genetic models for finite populations: The Wright-Fisher model and the Moran model. The Wright-Fisher model is most similar to our infinite-population discrete-generation model. In this model, \(N\) adult individuals release a very large number of gametes into a gene pool; the next generation is formed from \(N\) random gametes independently chosen from the gene pool. The Moran model takes a different approach. In this model, a single evolution step consists of one random individual in the population reproducing, and another independent random individual dying, maintaining the population at a fixed size \(N\). A total of \(N\) evolution steps in the Moran model is comparable, although not exactly identical, to a single discrete generation in the Wright-Fisher model. For our purposes, the Moran model is mathematically more tractable and we adopt it here.

We develop our model analogously to the stochastic population growth model derived in §1.2. With \(n = 0, 1, 2, \ldots, N\) a discrete random variable, the probability mass function \(p_n(g)\) denotes the probability of \(n\) individuals carrying allele \(A\) at evolution step \(g\). The probability at each evolution step of an individual carrying allele \(A\) reproducing or dying when there are \(n\) such individuals in the population is given by \(s_n = n/N\); the corresponding probabilities for \(a\) is \(1 - s_n\).

There are three ways to obtain a population of \(n\) individuals with allele \(A\) at evolution step \(g + 1\). First, there were \(n\) individuals with allele \(A\) at evolution step \(g\), and the individual reproducing carried the same allele as the individual dying. Second, there were \(n - 1\) individuals with allele \(A\) at evolution step \(g\), and the individual reproducing carried the same allele as the individual dying. Second, there were \(n + 1\) individuals with allele \(A\) at evolution step \(g\), and the individual reproducing carried \(A\) and the individual dying carried \(a\). And third, there were \(n + 1\) individuals with allele \(A\) at evolution step \(g\), and the individual reproducing carried \(a\) and the individual dying carried \(A\).
Multiplying the probabilities and summing the three cases results in

\[ p_n(g + 1) = \left( s_n^2 + (1 - s_n)^2 \right) p_n(g) + s_{n-1}(1 - s_{n-1})p_{n-1}(g) + s_{n+1}(1 - s_{n+1})p_{n+1}(g). \] (5.23)

Note that this equation is valid for \( 0 < n < N \), and that the equations at the boundaries—representing the probabilities that one of the alleles is fixed—are

\[ p_0(g + 1) = p_0(g) + s_1(1 - s_1)p_1(g) \] (5.24a)
\[ p_N(g + 1) = p_N(g) + s_{N-1}(1 - s_{N-1})p_{N-1}(g). \] (5.24b)

Once an allele becomes fixed, there is no further change in allele frequencies: The boundaries are called absorbing and the probability of fixation of an allele monotonically increases with each birth and death.

We illustrate the solution of (5.23)-(5.24) in Fig. 5.3 for a small population of size \( N = 20 \), and where the number of individuals carrying \( A \) is precisely known in the founding generation, with either (a) \( p_{10}(0) = 1 \), or; (b) \( p_{13}(0) = 1 \). We plot the probability mass density of the number of \( A \) individuals every \( N \) evolution steps, up to \( 7N \) steps, corresponding to approximately 7 discrete generations of evolution in the Wright-Fisher model. Notice how the probability distribution diffuses away from its initial values, and how the probabilities eventually concentrate on the boundaries, with both \( p_0 \) and \( p_{20} \) monotonically increasing.

To better understand this numerical solution, we consider the limit of large (but not infinite) populations by expanding in powers of \( 1/N \). We first rewrite (5.23) as

\[ p_n(g + 1) - p_n(g) = s_{n+1}(1 - s_{n+1})p_{n+1}(g) - 2s_n(1 - s_n)p_n(g) + s_{n-1}(1 - s_{n-1})p_{n-1}(g). \] (5.25)

We then introduce the continuous random variable \( x = n/N \), with \( 0 \leq x \leq 1 \), and the continuous time \( t = g/N \). A unit of time corresponds to approximately a single discrete generation in the Wright-Fisher model (i.e., \( N \) evolution steps in the Moran model). The probability density function is defined by

\[ P(x, t) = N p_n(g), \quad \text{with} \ x = n/N, \quad t = g/N. \]

Furthermore,

\[ s_n = n/N = x \equiv S(x); \]

and similarly, \( s_{n+1} = S(x + \Delta x), s_{n-1} = S(x - \Delta x) \), where \( \Delta x = 1/N \). Then, with \( \Delta t = 1/N \), (5.25) transforms into

\[ P(x, t + \Delta t) - P(x, t) = S(x + \Delta x)(1 - S(x + \Delta x))P(x + \Delta x, t) - 2S(x)(1 - S(x))P(x, t) + S(x - \Delta x)(1 - S(x - \Delta x))P(x - \Delta x, t). \] (5.26)

To simplify further, we use the well-known central-difference approximation to the second-derivative of a function \( f(x) \),

\[ f''(x) = \frac{f(x + \Delta x) - 2f(x) + f(x - \Delta x)}{\Delta x^2} + O(\Delta x^2), \]
Figure 5.3: $p_n$ versus $n$ with $N = 20$. Evolution steps plotted correspond to $g = 0, N, 2N, \ldots, 7N$. (a) Initial number of $A$ individuals is $n = 10$. (b) Initial number of $A$ individuals is $n = 13$. 
and recognize the right-hand side of (5.26) to be the numerator of a second-
derivative. With $\Delta x = \Delta t = 1/N \to 0$, and $S(x) = x$, we derive to leading-order in $1/N$ the partial differential equation

$$
\frac{\partial P(x, t)}{\partial t} = \frac{\partial^2}{\partial x^2} \{V(x)P(x, t)\},
$$

(5.27)

with

$$
V(x) = \frac{x(1-x)}{N}.
$$

The function $V(x)$ can be interpreted using a result from probability theory. For $n$ independent trials, each with probability of success $p$ and probability of failure $1-p$, the number of successes, denoted by $X$, is a binomial random variable with parameters $(n, p)$. Well-known results are $E[X] = np$ and $\text{Var}[X] = np(1-p)$, where $E[\ldots]$ is the expected value, and $\text{Var}[\ldots]$ is the variance. The number of $A$ individuals chosen when forming the next Wright-Fisher generation is a binomial random variable $n'$ with parameters $(N, n/N)$. Therefore, $E(n') = n$ and $\text{Var}(n') = n(1-n/N)$. With $x' = n'/N$ and $x = n/N$, we have $E(x') = x$, and $\text{Var}(x') = x(1-x)/N$. The function $V(x)$ can therefore be interpreted as the variance of $x$ over a single Wright-Fisher generation.

Equation (5.27) is a diffusion equation for the probability distribution. Referring again to Fig. 5.3 we observe that after many generations, $p_n$ becomes nearly independent of $n$ at the interior points. Accordingly, we look for a solution to (5.27) with $P(x, t) = P(t)$, independent of $x$, for $0 < x < 1$. Equation (5.27) becomes

$$
\frac{dP(t)}{dt} = V''(x)P(t), \text{ where } V''(x) = -2/N.
$$

(5.28)

The solution of (5.28) is

$$
P(t) = ce^{-2t/N}.
$$

(5.29)

Now, the probability of an allele being fixed is determined from the unknown boundary values $P(0, t)$ and $P(1, t)$ for which (5.29) is not a valid solution. Since $\int_0^1 P(x, t) = 1$, the fixation probability missing from (5.29) can be found from

$$
1 - \int_0^1 ce^{-2t/N} dx = 1 - ce^{-2t/N}.
$$

An allele is therefore likely to become fixed over a number of Wright-Fisher generations that is much larger than the population size, i.e., $e^{-2t/N} \ll 1$.

A problem of interest, with a particularly simple solution, is the following. Suppose that, within a population of $N$ individuals homogeneous for $A$, a single neutral mutation occurs so that one individual now carries allele $a$. What is the probability that allele $a$ eventually becomes fixed? We can, in fact, answer this question without any calculation. Intuitively, after a sufficient number of generations has passed, all living individuals should be descendant from a single ancestral individual living at the time the single mutation occurred. The probability that that single individual carries the $a$ allele is $1/N$—since only one out of $N$ individuals carries the $a$ mutation—and this is the probability of the fixation of $a$. 

Biochemical Reactions

Biochemistry is the study of the chemistry of life. It can be considered a branch of molecular biology, perhaps more focused on specific molecules and their reactions, or a branch of chemistry focused on the complex chemical reactions occurring in living organisms. Perhaps the first application of biochemistry happened about 5000 years ago when bread was made using yeast.

Modern biochemistry, however, had a relatively slow start among the sciences, as did modern biology. Isaac Newton’s publication of *Principia Mathematica* in 1687 preceded Darwin’s *Origin of Species* in 1859 by almost 200 years. I find this amazing because the ideas of Darwin are in many ways simpler and easier to understand than the mathematical theory of Newton. Most of the delay must be attributed to a fundamental conflict between science and religion. The physical sciences experienced this conflict early—witness the famous prosecution of Galileo by the Catholic Church in 1633, during which Galileo was forced to recant his heliocentric view—but the conflict of religion with evolutionary biology continues even to this day. Advances in biochemistry were initially delayed because it was long believed that life was not subject to the laws of science the way nonlife was, and that only living things could produce the molecules of life. Certainly, this was more a religious conviction than a scientific one. Then Friedrich Wöhler in 1828 published his landmark paper on the synthesis of urea (a waste product neutralizing toxic ammonia before excretion in the urine), demonstrating for the first time that organic compounds can be created artificially.

Here, we present mathematical models for some important biochemical reactions. We begin by introducing a useful model for a chemical reaction: the *law of mass action*. We then model what may be the most important biochemical reactions, namely those catalyzed by enzymes. Using the mathematical model of enzyme kinetics, we consider three fundamental enzymatic properties: *competitive inhibition*, *allosteric inhibition*, and *cooperativity*.

### 6.1 The law of mass action

The law of mass action describes the rate at which chemicals interact in reactions. It is assumed that different chemical molecules come into contact by collision before reacting, and that the collision rate is directly proportional to
the number of molecules of each reacting species. Suppose that two chemicals $A$ and $B$ react to form a product chemical $C$, written as

$$A + B \overset{k}{\rightarrow} C,$$

with $k$ the rate constant of the reaction. For simplicity, we will use the same symbol $C$, say, to refer to both the chemical $C$ and its concentration. The law of mass action says that $dC/dt$ is proportional to the product of the concentrations $A$ and $B$, with proportionality constant $k$. That is,

$$\frac{dC}{dt} = kAB.$$  \hspace{1cm} (6.1)

Similarly, the law of mass action enables us to write equations for the time-derivatives of the reactant concentrations $A$ and $B$:

$$\frac{dA}{dt} = -kAB, \quad \frac{dB}{dt} = -kAB.$$  \hspace{1cm} (6.2)

Notice that when using the law of mass action to find the rate-of-change of a concentration, the chemical that the arrow points towards is increasing in concentration (positive sign), the chemical that the arrow points away from is decreasing in concentration (negative sign). The product of concentrations on the right-hand-side is always that of the reactants from which the arrow points away, multiplied by the rate constant that is on top of the arrow.

Equation (6.1) can be solved analytically using conservation laws. Each reactant, original and converted to product, is conserved since one molecule of each reactant gets converted into one molecule of product. Therefore,

$$\frac{d}{dt}(A + C) = 0 \quad \Rightarrow \quad A + C = A_0,$$

$$\frac{d}{dt}(B + C) = 0 \quad \Rightarrow \quad B + C = B_0,$$

where $A_0$ and $B_0$ are the initial concentrations of the reactants, and no product is present initially. Using the conservation laws, (6.1) becomes

$$\frac{dC}{dt} = k(A_0 - C)(B_0 - C), \text{ with } C(0) = 0,$$

which may be integrated by separating variables. After some algebra, the solution is determined to be

$$C(t) = A_0B_0 \frac{e^{(B_0 - A_0)kt} - 1}{B_0e^{(B_0 - A_0)kt} - A_0},$$

which is a complicated expression with the simple limits

$$\lim_{t \to \infty} C(t) = \begin{cases} A_0 & \text{if } A_0 < B_0, \\ B_0 & \text{if } B_0 < A_0. \end{cases}$$  \hspace{1cm} (6.3)

The reaction stops after one of the reactants is depleted; and the final concentration of the product is equal to the initial concentration of the depleted reactant.
6.1. THE LAW OF MASS ACTION

If we also include the reverse reaction,

\[ A + B \xrightleftharpoons[k_+]{k_-} C, \]

then the time-derivative of the product is given by

\[ \frac{dC}{dt} = k_+ AB - k_- C. \]

Notice that \( k_+ \) and \( k_- \) have different units. At equilibrium, \( \dot{C} = 0 \), and using the conservation laws \( A + C = A_0, B + C = B_0 \), we obtain

\[ (A_0 - C)(B_0 - C) - \frac{k_-}{k_+} C = 0 \]

from which we define the equilibrium constant \( K_{eq} \) by

\[ K_{eq} = \frac{k_-}{k_+}, \]

which has units of concentration. Therefore, at equilibrium, the concentration of the product is given by the solution of the quadratic equation

\[ C^2 - (A_0 + B_0 + K_{eq})C + A_0 B_0 = 0, \]

with the extra condition that \( 0 < C < \min(A_0, B_0) \). For instance, if \( A_0 = B_0 \equiv R_0 \), then, at equilibrium,

\[ C = R_0 - \frac{1}{2} K_{eq} \left[ \sqrt{1 + 4 R_0 / K_{eq}} - 1 \right]. \]

If \( K_{eq} \ll R_0 \), then \( A \) and \( B \) have a high affinity, and the reaction proceeds mainly to \( C \), with \( C \to R_0 \).

Below are two interesting reactions. In reaction (ii), \( A \) is assumed to be held at a constant concentration.

(i)

\[ A + X \xrightleftharpoons[k_-]{k_+} 2X \]

(ii)

\[ A + X \xrightarrow{k_1} 2X, \quad X + Y \xrightarrow{k_2} 2Y, \quad Y \xrightarrow{k_3} B \]

Can you write down the equations for \( \dot{X} \) in reaction (i), and \( \dot{X} \) and \( \dot{Y} \) in reaction (ii)? When normalized properly, the equations from reaction (ii) reduce to the Lotka-Volterra predator-prey equations introduced in §1.4. The chemical concentrations \( X \) and \( Y \), therefore, oscillate in time like predators and their prey.
6.2 Enzyme kinetics

Enzymes are catalysts, usually proteins, that help convert other molecules called substrates into products, but are themselves unchanged by the reaction. Each enzyme has high specificity for at least one reaction, and it can accelerate this reaction by millions of times. Without enzymes, most biochemical reactions are too slow for life to be possible. Enzymes are so important to our lives that a single amino acid mutation in one enzyme out of the more than 2000 enzymes in our bodies can result in a severe or lethal genetic disease. Enzymes do not follow the law of mass action directly: with $S$ substrate, $P$ product, and $E$ enzyme, the reaction

$$S + E \xrightarrow{k_2} P + E,$$

is a poor model since the reaction velocity $dP/dt$ is known to attain a finite limit with increasing substrate concentration. Rather, Michaelis and Menten (1913) proposed the following reaction scheme with an intermediate molecule:

$$S + E \overset{k_1}{\underset{k_-1}{\rightleftharpoons}} C \xrightarrow{k_2} P + E,$$

where $C$ is a complex formed by the enzyme and the substrate. A cartoon of the Michaelis-Menten reaction with an enzyme catalyzing a reaction between two substrates is shown in Fig. 6.1.

The complete set of differential equations representing the reaction of an enzyme catalyzing the conversion of a single substrate to a product is obtained from the law of mass action:

$$\begin{align*}
\frac{dS}{dt} &= -k_1 C - k_1 SE, \\
\frac{dE}{dt} &= (k_-1 + k_2)C - k_1 SE, \\
\frac{dC}{dt} &= k_1 SE - (k_-1 + k_2)C, \\
\frac{dP}{dt} &= k_2 C.
\end{align*}$$

Commonly, substrate is continuously provided to the reaction and product is continuously removed. The removal of product has been modeled by neglecting the reverse reaction $P + E \rightarrow C$. Because substrate is continuously provided,
biochemists usually want to determine the reaction velocity \( dP/dt \) in terms of the substrate concentration \( S \) and the total enzyme concentration \( E_0 \). We can eliminate \( E \) in favor of \( E_0 \) from the conservation law that the enzyme, free and bound, is conserved; that is

\[
\frac{d(E + C)}{dt} = 0 \quad \Rightarrow \quad E + C = E_0 \quad \Rightarrow \quad E = E_0 - C.
\]

We rewrite the equation for \( dC/dt \) eliminating \( E \):

\[
\frac{dC}{dt} = k_1 S (E_0 - C) - (k_{-1} + k_2)C
= k_1 E_0 S - (k_{-1} + k_2 + k_1 S)C.
\] (6.4)

We can solve (6.4) for \( C \) under the so-called quasi-steady-state approximation, where we assume that the complex \( C \) is in equilibrium with the rate of formation equal to the rate of dissociation. Accordingly, with \( \dot{C} = 0 \) in (6.4), we have

\[
C = \frac{k_1 E_0 S}{k_{-1} + k_2 + k_1 S}.
\]

The reaction velocity is then given by

\[
\frac{dP}{dt} = k_2 C
= \frac{k_1 k_2 E_0 S}{k_{-1} + k_2 + k_1 S}
= \frac{V_m S}{K_m + S},
\] (6.5)

where two fundamental constants are defined:

\[
K_m = \frac{(k_{-1} + k_2)}{k_1}, \quad V_m = k_2 E_0.
\] (6.6)

The Michaelis-Menten constant or the Michaelis constant \( K_m \) has units of concentration, and the maximum reaction velocity \( V_m \) has units of concentration divided by time. The interpretation of these constants is obtained by considering the following limits:

\[
as S \to \infty, \quad C \to E_0 \quad \text{and} \quad dP/dt \to V_m, \\
if S = K_m, \quad C = \frac{1}{2} E_0 \quad \text{and} \quad dP/dt = \frac{1}{2} V_m.
\]

Therefore, \( V_m \) is the limiting reaction velocity obtained by saturating the reaction with substrate so that every enzyme is bound; and \( K_m \) is the concentration of \( S \) at which only one-half of the enzymes are bound and the reaction proceeds at one-half maximum velocity.

### 6.3 Competitive inhibition

Competitive inhibition occurs when inhibitor molecules compete with substrate molecules for binding to the same enzyme’s active site. When an inhibitor
is bound to the enzyme, no product is produced so competitive inhibition will reduce the velocity of the reaction. A cartoon of this process is shown in Fig. 6.2.

To model competitive inhibition, we introduce an additional reaction associated with the inhibitor-enzyme binding:

\[
S + E \xrightleftharpoons[k_{-1}]{k_1} C_1 \xrightarrow{k_2} P + E, \\
I + E \xrightleftharpoons[k_{-3}]{k_3} C_2.
\]

With more complicated enzymatic reactions, the reaction schematic becomes difficult to interpret. Perhaps an easier way to visualize the reaction is from the following redrawn schematic:

Here, the substrate \( S \) and inhibitor \( I \) are combined with the relevant rate constants, rather than treated separately. It is immediately obvious from this redrawn schematic that inhibition is accomplished by sequestering enzyme in the
form of \( C_2 \) and preventing its participation in the catalysis of \( S \) to \( P \).

Our goal is to determine the reaction velocity \( \dot{P} \) in terms of the substrate and inhibitor concentrations, and the total concentration of the enzyme (free and bound). The law of mass action applied to the complex concentrations and the product results in

\[
\begin{align*}
\frac{dC_1}{dt} &= k_1 SE - (k_{-1} + k_2)C_1, \\
\frac{dC_2}{dt} &= k_3 IE - k_{-3}C_2, \\
\frac{dP}{dt} &= k_2 C_1.
\end{align*}
\]

The enzyme, free and bound, is conserved so that

\[
\frac{d}{dt}(E + C_1 + C_2) = 0 \implies E + C_1 + C_2 = E_0 \implies E = E_0 - C_1 - C_2.
\]

Under the quasi-equilibrium approximation, \( \dot{C}_1 = \dot{C}_2 = 0 \), so that

\[
\begin{align*}
k_1 S(E_0 - C_1 - C_2) - (k_{-1} + k_2)C_1 &= 0, \\
k_3 I(E_0 - C_1 - C_2) - k_{-3}C_2 &= 0,
\end{align*}
\]

which results in the following system of two linear equations and two unknowns \( (C_1 \text{ and } C_2) \):

\[
\begin{align*}
(k_{-1} + k_2 + k_1 S)C_1 + k_1 SC_2 &= k_1 E_0 S, \quad (6.7) \\
k_3 IC_1 + (k_{-3} + k_3 I)C_2 &= k_3 E_0 I. \quad (6.8)
\end{align*}
\]

We define the Michaelis-Menten constant \( K_m \) as before, and an additional constant \( K_i \) associated with the inhibitor reaction:

\[
K_m = \frac{k_{-1} + k_2}{k_1}, \quad K_i = \frac{k_{-3}}{k_3}.
\]

Dividing (6.7) by \( k_1 \) and (6.8) by \( k_3 \) yields

\[
\begin{align*}
(K_m + S)C_1 + SC_2 &= E_0 S, \quad (6.9) \\
k_3 IC_1 + (K_i + I)C_2 &= E_0 I. \quad (6.10)
\end{align*}
\]

Since our goal is to obtain the velocity of the reaction, which requires determining \( C_1 \), we multiply (6.9) by \( (K_i + I) \) and (6.10) by \( S \), and subtract:

\[
\begin{align*}
(K_m + S)(K_i + I)C_1 + S(K_i + I)C_2 &= E_0 (K_i + I) S \\
- SIC_1 + S(K_i + I)C_2 &= E_0 SI
\end{align*}
\]

\[
[(K_m + S)(K_i + I) - SI]C_1 = K_i E_0 S;
\]

or after cancelation and rearrangement

\[
C_1 = \frac{K_i E_0 S}{K_m K_i + K_i S + K_m I} = \frac{E_0 S}{K_m (1 + I/K_i) + S}.
\]
Therefore, the reaction velocity is given by

\[ \frac{dP}{dt} = \frac{(k_2 E_0)S}{K_m(1 + I/K_i)} + S = \frac{V_m S}{K'_m + S}, \tag{6.11} \]

where

\[ V_m = k_2 E_0, \quad K'_m = K_m(1 + I/K_i). \tag{6.12} \]

By comparing the inhibited reaction velocity (6.11) and (6.12) with the uninhibited reaction velocity (6.5) and (6.6), we observe that inhibition increases the Michaelis-Menten constant of the reaction, but leaves unchanged the maximum reaction velocity. Since the Michaelis-Menten constant is defined as the substrate concentration required to attain one-half of the maximum reaction velocity, addition of an inhibitor with a fixed substrate concentration acts to decrease the reaction velocity. However, a reaction saturated with substrate still attains the uninhibited maximum reaction velocity.

### 6.4 Allosteric inhibition

The term allostery comes from the Greek word *allos*, meaning different, and *stereos*, meaning solid, and refers to an enzyme with a regulatory binding site separate from its active binding site. In our model of *allosteric inhibition*, an inhibitor molecule is assumed to bind to its own regulatory site on the enzyme, resulting in either a lowered binding affinity of the substrate to the enzyme, or a lowered conversion rate of substrate to product. A cartoon of allosteric inhibition due to a lowered binding affinity is shown in Fig. 6.3.

In general, we need to define three complexes: \( C_1 \) is the complex formed from substrate and enzyme; \( C_2 \) from inhibitor and enzyme, and; \( C_3 \) from substrate, inhibitor, and enzyme. We write the chemical reactions as follows:
6.4. ALLOSTERIC INHIBITION

The general model for allosteric inhibition with ten independent rate constants appears too complicated to analyze. We will simplify this general model to one with fewer rate constants that still exhibits the unique features of allosteric inhibition. One possible but uninteresting simplification assumes that if \( I \) binds to \( E \), then \( S \) does not; however, this reduces allosteric inhibition to competitive inhibition and loses the essence of allostery. Instead, we simplify by allowing both \( I \) and \( S \) to simultaneously bind to \( E \), but we assume that the binding of \( I \) prevents substrate conversion to product. With this simplification, \( k'_2 = 0 \). To further reduce the number of independent rate constants, we assume that the binding of \( S \) to \( E \) is unaffected by the bound presence of \( I \), and the binding of \( I \) to \( E \) is unaffected by the bound presence of \( S \). These approximations imply that all the primed rate constants equal the corresponding unprimed rate constants, e.g., \( k'_1 = k_1 \), etc. With these simplifications, the schematic of the chemical reaction simplifies to

\[
\begin{align*}
E & \xrightleftharpoons[k_{-1}]{k_1 S} C_1 \xrightarrow{k_2} P + E \\
k_3 I & \downarrow \quad \downarrow k_{-3} \quad \downarrow k'_3 I \quad \downarrow k'_{-3} \\
C_2 \quad \downarrow k'_1 S \quad \downarrow k'_2 \quad \downarrow P + C_2 \\
\end{align*}
\]

and now there are only five independent rate constants. We write the equations for the complexes using the law of mass action:

\[
\begin{align*}
\frac{dC_1}{dt} &= k_1 SE + k_{-3} C_3 - (k_{-1} + k_2 + k_3 I) C_1, \quad (6.13) \\
\frac{dC_2}{dt} &= k_3 IE + k_{-1} C_3 - (k_{-3} + k_1 S) C_2, \quad (6.14) \\
\frac{dC_3}{dt} &= k_3 IC_1 + k_1 SC_2 - (k_{-1} + k_{-3}) C_3, \quad (6.15)
\end{align*}
\]
while the reaction velocity is given by

$$\frac{dP}{dt} = k_2 C_1.$$  \hfill (6.16)

Again, both free and bound enzyme is conserved, so that $E = E_0 - C_1 - C_2 - C_3$. With the quasi-equilibrium approximation $\dot{C}_1 = \dot{C}_2 = \dot{C}_3 = 0$, we obtain a system of three equations and three unknowns: $C_1$, $C_2$ and $C_3$. Despite our simplifications, the analytical solution for the reaction velocity remains messy (see Keener & Sneyd, referenced at the chapter’s end) and not especially illuminating. We omit the complete analytical result here and determine only the maximum reaction velocity.

The maximum reaction velocity $V'_m$ for the allosteric-inhibited reaction is defined as the time-derivative of the product concentration when the reaction is saturated with substrate; that is,

$$V'_m = \lim_{S \to \infty} \frac{dP}{dt} = k_2 \lim_{S \to \infty} C_1.$$

With substrate saturation, every enzyme will have its substrate binding site occupied. Enzymes are either bound with only substrate in the complex $C_1$, or bound together with substrate and inhibitor in the complex $C_3$. Accordingly, the schematic of the chemical reaction with substrate saturation simplifies to

![Chemical Reaction Schematic](image)

The equations for $C_1$ and $C_3$ with substrate saturation are thus given by

$$\frac{dC_1}{dt} = k_{-3} C_3 - k_3 I C_1,$$
$$\frac{dC_3}{dt} = k_3 I C_1 - k_{-3} C_3,$$  \hfill (6.17)  \hfill (6.18)

and the quasi-equilibrium approximation yields the single independent equation

$$C_3 = \frac{(k_3/k_{-3}) I C_1}{(1/K_i) C_1},$$  \hfill (6.19)

with $K_i = k_{-3}/k_3$ as before. The equation expressing the conservation of enzyme is given by $E_0 = C_1 + C_3$. This conservation law, together with (6.19), permits us to solve for $C_1$:

$$C_1 = \frac{E_0}{1 + I/K_i}.$$
Therefore, the maximum reaction velocity for the allosteric-inhibited reaction is given by

\[
V_m' = \frac{k_2E_0}{1 + I/K_i} = \frac{V_m}{1 + I/K_i},
\]

where \(V_m\) is the maximum reaction velocity of both the uninhibited and the competitive inhibited reaction. The allosteric inhibitor is thus seen to reduce the maximum velocity of the uninhibited reaction by the factor \((1 + I/K_i)\), which may be large if the concentration of allosteric inhibitor is substantial.

### 6.5 Cooperativity

Enzymes and other protein complexes may have multiple binding sites, and when a substrate binds to one of these sites, the other sites may become more active. A well-studied example is the binding of the oxygen molecule to the hemoglobin protein. Hemoglobin can bind four molecules of \(O_2\), and when three molecules are bound, the fourth molecule has an increased affinity for binding. We call this cooperativity.

We will model cooperativity by assuming that an enzyme has two separated but indistinguishable binding sites for a substrate \(S\). For example, the enzyme may be a protein dimer, composed of two identical subproteins with identical binding sites for \(S\). A cartoon of this enzyme is shown in Fig. 6.4. Because the two binding sites are indistinguishable, we need consider only two complexes: \(C_1\) and \(C_2\), with enzyme bound to one or two substrate molecules, respectively. When the enzyme exhibits cooperativity, the binding of the second substrate molecule has a greater rate constant than the binding of the first. We therefore consider the following reaction:
CHAPTER 6. BIOCHEMICAL REACTIONS

\[
\begin{align*}
E & \xrightleftharpoons[k_1]{k_2} C_1 \\
   & \xrightleftharpoons[k_{-3}]{k_3S} C_2 \\
   & \xrightarrow[k_4]{C_1} P + C_1
\end{align*}
\]

where cooperativity supposes that \( k_1 << k_3 \). Application of the law of mass action results in

\[ \frac{dC_1}{dt} = k_1SE + (k_{-3} + k_4)C_2 - (k_{-1} + k_2 + k_3S)C_1, \]
\[ \frac{dC_2}{dt} = k_3SC_1 - (k_{-3} + k_4)C_2. \]

Applying the quasi-equilibrium approximation \( \dot{C}_1 = \dot{C}_2 = 0 \) and the conservation law \( E_0 = E + C_1 + C_2 \) results in the following system of two equations and two unknowns:

\[
\begin{align*}
(k_{-1} + k_2 + (k_1 + k_3)S)C_1 - (k_{-3} + k_4 - k_1S)C_2 &= k_1E_0S, \\
k_3SC_1 - (k_{-3} + k_4)C_2 &= 0.
\end{align*}
\]

We divide (6.20) by \( k_1 \) and (6.21) by \( k_3 \) and define

\[
K_1 = \frac{k_{-1} + k_2}{k_1}, \quad K_2 = \frac{k_{-3} + k_4}{k_3}, \quad \epsilon = k_1/k_3
\]

to obtain

\[
\begin{align*}
(\epsilon K_1 + (1 + \epsilon)S) C_1 - (K_2 - \epsilon S) C_2 &= \epsilon E_0 S, \\
SC_1 - K_2 C_2 &= 0.
\end{align*}
\]

We can subtract (6.23) from (6.22) and cancel \( \epsilon \) to obtain

\[ (K_1 + S) C_1 + SC_2 = E_0 S. \]

Equations (6.23) and (6.24) can be solved for \( C_1 \) and \( C_2 \):

\[
\begin{align*}
C_1 &= \frac{K_2E_0}{S^2 + K_2S + K_1 K_2}, \\
C_2 &= \frac{E_0 S^2}{S^2 + K_2 S + K_1 K_2},
\end{align*}
\]

so that the reaction velocity is given by

\[
\begin{align*}
\frac{dP}{dt} &= k_2C_1 + k_4C_2 \\
&= \frac{(k_2 K_2 + k_4S) E_0 S}{S^2 + K_2 S + K_1 K_2}.
\end{align*}
\]
6.5. **COOPERATIVITY**

To illuminate this result, we consider two limiting cases: (i) the active sites act independently so that each protein dimer, say, can be considered as two independent protein monomers; (ii) the enzyme exhibits extreme cooperativity so that the binding of the second substrate has a much greater rate constant than the binding of the first.

**Independent active sites**

The free enzyme $E$ has two independent binding sites while $C_1$ has only a single binding site. Consulting the reaction schematic: $k_1$ is the rate constant for the binding of $S$ to two independent binding sites; $k_{-1}$ and $k_2$ are the rate constants for the dissociation and conversion of a single $S$ from the enzyme; $k_3$ is the rate constant for the binding of $S$ to a single free binding site, and; $k_{-3}$ and $k_4$ are the rate constants for the dissociation and conversion of one of two independent $S$’s from the enzyme. Accounting for these factors of two and assuming independence of active sites, we have

$$k_1 = 2k_3, \quad k_{-3} = 2k_{-1}, \quad k_4 = 2k_2.$$  

We define the Michaelis-Menten constant $K_M$ that is representative of the protein monomer with one binding site; that is,

$$K_M = \frac{k_{-1} + k_2}{k_3} = 2K_1 = \frac{1}{2}K_2.$$  

Therefore, for independent active sites, the reaction velocity becomes

$$\frac{dP}{dt} = \frac{(2k_2K_M + 2k_2S)E_0S}{S^2 + 2K_M S + K_M^2} = \frac{2k_2E_0S}{S + K_m}.$$  

The reaction velocity for a dimer protein enzyme composed of independent identical monomers is simply double that of a monomer protein enzyme, an intuitively obvious result.

**High cooperativity**

We now assume that after the first substrate binds to the enzyme, the second substrate binds much more easily, so that $k_1 << k_3$. The number of enzymes bound to a single substrate molecule should consequently be much less than the number bound to two substrate molecules, resulting in $C_1 << C_2$. Dividing (6.25) by (6.26), this inequality becomes

$$\frac{C_1}{C_2} = \frac{K_2}{S} << 1.$$  

Dividing the numerator and denominator of (6.27) by $S^2$, we have

$$\frac{dP}{dt} = \frac{(k_2K_M + k_4)E_0}{1 + \frac{k_2}{S} + \frac{k_4}{S^2}}.$$
To take the limit of this expression as $K_2/S \to 0$, we set $K_2/S = 0$ everywhere except in the last term in the denominator, since $K_1/S$ is inversely proportional to $k_1$ and may go to infinity in this limit. Taking the limit and multiplying the numerator and denominator by $S^2$,

$$
\frac{dP}{dt} = \frac{k_4 E_0 S^2}{S^2 + K_1 K_2}.
$$

Here, the maximum reaction velocity is $V_m = k_4 E_0$, and the modified Michaelis-Menten constant is $K_M = \sqrt{K_1 K_2}$, so that

$$
\frac{dP}{dt} = \frac{V_m S^2}{S^2 + K_M^2}.
$$

In biochemistry, this reaction velocity is generalized to

$$
\frac{dP}{dt} = \frac{V_m S^n}{S^n + K_M^n},
$$

known as the Hill equation, and by varying $n$ is used to fit experimental data.

References

Chapter 7

Sequence Alignment

The software program BLAST (Basic Local Alignment Search Tool) uses sequence alignment algorithms to compare a query sequence against a database to identify other known sequences similar to the query sequence. Often, the annotations attached to the already known sequences yield important biological information about the query sequence. Almost all biologists use BLAST, making sequence alignment one of the most important algorithms of bioinformatics.

The sequence under study can be composed of nucleotides (from the nucleic acids DNA or RNA) or amino acids (from proteins). Nucleic acids chain together four different nucleotides: A,C,T,G for DNA and A,C,U,G for RNA; proteins chain together twenty different amino acids. The sequence of a DNA molecule or of a protein is the linear order of nucleotides or amino acids in a specified direction, defined by the chemistry of the molecule. There is no need for us to know the exact details of the chemistry; it is sufficient to know that a protein has distinguishable ends called the N-terminus and the C-terminus, and that the usual convention is to read the amino acid sequence from the N-terminus to the C-terminus. Specification of the direction is more complicated for a DNA molecule than for a protein molecule because of the double helix structure of DNA, and this will be explained in Section 7.1.

The basic sequence alignment algorithm aligns two or more sequences to highlight their similarity, inserting a small number of gaps into each sequence (usually denoted by dashes) to align wherever possible identical or similar characters. For instance, Fig 7.1 presents an alignment using the software tool ClustalW of the hemoglobin beta-chain from a human, a chimpanzee, a rat, and a zebrafish. The human and chimpanzee sequences are identical, a consequence of our very close evolutionary relationship. The rat sequence differs from human/chimpanzee at only 27 out of 146 amino acids; we are all mammals. The zebrafish sequence, though clearly related, diverges significantly. Notice the insertion of a gap in each of the mammal sequences at the zebrafish amino acid position 122. This permits the subsequent zebrafish sequence to better align with the mammal sequences, and implies either an insertion of a new amino acid in fish, or a deletion of an amino acid in mammals. The insertion or deletion of a character in a sequence is called an indel. Mismatches in sequence, such as that occurring between zebrafish and mammals at amino acid positions 2 and 3 is called a mutation. Clustal W places a ‘*’ on the last line to denote exact amino acid matches across all sequences, and a ‘:’ and ‘.’ to
CLUSTAL W (1.83) multiple sequence alignment

<table>
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<tr>
<th>Species</th>
<th>Sequence</th>
<th>Position</th>
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<tbody>
<tr>
<td>Human</td>
<td>VHLTPEEKSLWGVKIDVEGVGEALGRLLVYYPWTRRFESFGDLSLTPDAVGMPFKV</td>
<td>60</td>
</tr>
<tr>
<td>Chimpanzee</td>
<td>VHLTDEKAVVFLGKIDVEGVGEALGRLLVYYPWTRRFESFGDLSLTPDAVGMPFKV</td>
<td>60</td>
</tr>
<tr>
<td>Rat</td>
<td>VHLTDAEKAVVFLGKIDVEGVGEALGRLLVYYPWTRRFESFGDLSLTPDAVGMPFKV</td>
<td>60</td>
</tr>
<tr>
<td>Zebrafish</td>
<td>VEWTDVKETAIAGLVGKIDVEGVGEALGRLLVYYPWTRRFESFGDLSLTPDAVGMPFKV</td>
<td>60</td>
</tr>
</tbody>
</table>

<table>
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<th>Species</th>
<th>Sequence</th>
<th>Position</th>
</tr>
</thead>
<tbody>
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<td>KAHGKKVLGAFGDIHLNKLGFTATASLICLKVHDPVENFRLLGHLVCLAHMPFKV</td>
<td>120</td>
</tr>
<tr>
<td>Chimpanzee</td>
<td>KAHGKKVLGAFGDIHLNKLGFTATASLICLKVHDPVENFRLLGHLVCLAHMPFKV</td>
<td>120</td>
</tr>
<tr>
<td>Rat</td>
<td>KAHGKKVLGAFGDIHLNKLGFTATASLICLKVHDPVENFRLLGHLVCLAHMPFKV</td>
<td>120</td>
</tr>
<tr>
<td>Zebrafish</td>
<td>AAHGRTVRNGELRAIKNDQVRSNYALTDDKLVHDPVFLNDFDRLLADCVCAAMKFGQV</td>
<td>120</td>
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<table>
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<th>Position</th>
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<td>Rat</td>
<td>E-FTPPVQAAYQKVYAGVNALAHKYH</td>
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</tr>
<tr>
<td>Zebrafish</td>
<td>AGFNAEVEAQQKFLAVVSLACQHYN</td>
<td>147</td>
</tr>
</tbody>
</table>

Figure 7.1: Multiple alignment of the hemoglobin beta-chain for Human, Chimpanzee, Rat and Zebrafish, obtained using ClustalW.

denote chemically similar amino acids across all sequences (each amino acid has characteristic chemical properties, and amino acids can be grouped according to similar properties). In this chapter, we detail the algorithms used to align sequences.

### 7.1 The minimum you need to know about DNA chemistry and the genetic code

In one of the most important scientific papers ever published, James Watson and Francis Crick, pictured in Fig. 7.2, determined the structure of DNA using a three-dimensional molecular model that makes plain the chemical basis of heredity. The DNA molecule consists of two strands wound around each other to form the now famous double helix. Arbitrarily, one strand is labeled by the sequencing group to be the positive strand, and the other the negative strand. The two strands of the DNA molecule bind to each other by base pairing: the bases of one strand pair with the bases of the other strand. Adenine (A) always pairs with thymine (T), and guanine (G) always pairs with cytosine (C): A with T, G with C. For RNA, T is replaced by uracil (U). When reading the sequence of nucleotides from a single strand, the direction of reading must be specified, and this is possible by referring to the chemical bonds of the DNA backbone. There are of course only two possible directions to read a linear sequence of bases, and these are denoted as 5’-to-3’ and 3’-to-5’. Importantly, the two separate strands of the DNA molecule are oriented in opposite directions. Below is the beginning of the DNA coding sequence for the human hemoglobin beta chain protein discussed earlier:

```
5’-GTGCACCTGACTCCTGAGGAGAAGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTG-3’
3’-CACGTGGACTGAGGACTCCTCTTCAGACGGCAATGACGGGACACCCCGTTCCACTTGCAC-5’
```
7.2. BRUTE FORCE ALIGNMENT

Figure 7.2: James Watson and Francis Crick posing in front of their DNA model. The original photograph was taken in 1953, the year of discovery, and was recreated in 2003, fifty years later. Francis Crick, the man on the right, died in 2004.

It is important to realize that there are two unique DNA sequences here, and either one, or even both, can be coding. Reading from 5'-to-3', the upper sequence begins ‘GTGCACCTG...’, while the lower sequence ends ‘...CAGGT-GCAC’. Here, only the upper sequence codes for the human hemoglobin beta chain, and the lower sequence is non-coding.

How is the DNA code read? Enzymes separate the two strands of DNA, and transcription occurs as the DNA sequence is copied into messenger RNA (mRNA). If the upper strand is the coding sequence, then the complementary lower strand serves as the template for constructing the mRNA sequence. The ACUG nucleotides of the mRNA bind to the lower sequence and construct a single stranded mRNA molecule containing the sequence ‘GUGCACCUG...’, which exactly matches the sequence of the upper, coding strand, but with T replaced by U. This mRNA is subsequently translated in the ribosome of the cell, where each nucleotide triplet codes for a single amino acid. The triplet coding of nucleotides for amino acids is the famous genetic code, shown in Fig. 7.3. Here, the translation to amino acid sequence is ‘VHL...’, where we have used the genetic code ‘GUG’ = V, ‘CAC’=H, ‘CUG’=L. The three out of the twenty amino acids used here are V = Valine, H = Histidine, and L = Leucine.

7.2 Sequence alignment by brute force

One (bad) approach to sequence alignment is to align the two sequences in all possible ways, score the alignments with an assumed scoring system, and determine the highest scoring alignment. The problem with this brute-force approach is that the number of possible alignments grows exponentially with sequence length; and for sequences of reasonable length, the computation is already impossible. For example, the number of ways to align two sequences of 50 characters each—a rather small alignment problem—is about $1.5 \times 10^{37}$, already an astonishingly large number. It is informative to count the number
CHAPTER 7. SEQUENCE ALIGNMENT

Figure 7.3: The genetic code.

of possible alignments between two sequences since a similar algorithm is used for sequence alignment.

Suppose we want to align two sequences. Gaps in either sequence are allowed but a gap can not be aligned with a gap. By way of illustration, we demonstrate the three ways that the first character of the upper-case alphabet and the lower-case alphabet may align:

A -A A-
1, 11, 11
a a= -a

and the five ways in which the first two characters of the upper-case alphabet can align with the first character of the lower-case alphabet:

AB AB AB= A-B -AB
11, 11, 111, 111, 111
a a= --a --a= a--

A recursion relation for the total number of possible alignments of a sequence of \( i \) characters with a sequence of \( j \) characters may be derived by considering the alignment of the last character. There are three possibilities that we illustrate by assuming the \( i \)th character is ‘F’ and the \( j \)th character is ‘d’:

1) \( i-1 \) characters of the first sequence are already aligned with \( j-1 \) characters of the second sequence, and the \( i \)th character of the first sequence aligns exactly with the \( j \)th character of the second sequence:

...F
1111
...d
7.2. BRUTE FORCE ALIGNMENT

(2) \( i - 1 \) characters of the first sequence are aligned with \( j \) characters of the second sequence and the \( i \)th character of the first sequence aligns with a gap in the second sequence:

\[
\begin{array}{c}
\ldots F \\
\ldots \quad \ldots \\
\ldots \quad \ldots \\
\end{array}
\]

(3) \( i \) characters of the first sequence are aligned with \( j - 1 \) characters of the second sequence and a gap in the first sequence aligns with the \( j \)th character of the second sequence:

\[
\begin{array}{c}
\ldots - \\
\ldots \quad \ldots \\
\ldots \quad \ldots \\
\end{array}
\]

If \( C(i, j) \) is the number of ways to align an \( i \) character sequence with a \( j \) character sequence, then, from our counting,

\[
C(i, j) = C(i - 1, j - 1) + C(i - 1, j) + C(i, j - 1).
\]  
(7.1)

This recursion relation requires boundary conditions. Because there is only one way to align an \( i > 0 \) character sequence against a zero character sequence (i.e., \( i \) characters against \( i \) gaps) the boundary conditions are \( C(0, j) = C(i, 0) = 1 \) for all \( i, j > 0 \). We may also add the additional boundary condition \( C(0, 0) = 1 \), obtained from the known result \( C(1, 1) = 3 \).

Using the recursion relation (7.1), we can construct the following dynamic matrix to count the number of ways to align the two five-character sequences \( a_1a_2a_3a_4a_5 \) and \( b_1b_2b_3b_4b_5 \):

\[
\begin{array}{c|c|c|c|c|c}
 & b_1 & b_2 & b_3 & b_4 & b_5 \\
\hline
- & 1 & 1 & 1 & 1 & 1 \\
a_1 & 1 & 3 & 5 & 7 & 9 \\
a_2 & 1 & 5 & 13 & 25 & 41 \\
a_3 & 1 & 7 & 25 & 63 & 129 \\
a_4 & 1 & 9 & 41 & 129 & 321 \\
a_5 & 1 & 11 & 61 & 231 & 681 \\
\end{array}
\]

The size of this dynamic matrix is \( 6 \times 6 \), and for convenience we label the rows and columns starting from zero (i.e., row 0, row 1, \ldots, row 5). This matrix was constructed by first writing \(-a_1a_2a_3a_4a_5\) to the left of the matrix and \(-b_1b_2b_3b_4b_5\) above the matrix, then filling in ones across the zeroth row and down the zeroth column to satisfy the boundary conditions, and finally applying the recursion relation directly by going across the first row from left-to-right, the second row from left-to-right, etc. To demonstrate the filling in of the matrix, we have across the first row: \( 1 + 1 + 1 = 3 \), \( 1 + 1 + 3 = 5 \), \( 1 + 1 + 5 = 7 \), etc, and across the second row: \( 1 + 3 + 1 = 5 \), \( 3 + 5 + 5 = 13 \), \( 5 + 7 + 13 = 25 \), etc. Finally, the last element entered gives the number of ways to align two five character sequences: 1683, already a remarkably large number.

It is possible to solve analytically the recursion relation (7.1) for \( C(i, j) \) using generating functions. Although the solution method is interesting—and in fact was shown to me by a student—the final analytical result is messy and we omit it here. In general, computation of \( C(i, j) \) is best done numerically by constructing the dynamic matrix.
7.3 Sequence alignment by dynamic programming

Two reasonably sized sequences cannot be aligned by brute force. Luckily, there is another algorithm borrowed from computer science, *dynamic programming*, that uses a dynamic matrix.

First, a scoring system is required to judge the quality of an alignment. The goal is to find the alignment that has the maximum score. We assume that the alignment of character $a_i$ with character $b_j$ has the score $S(a_i, b_j)$. For example, when aligning two DNA sequences, a match (A-A, C-C, T-T, G-G) may be scored as +2, and a mismatch (A-C, A-T, A-G, etc.) scored as $-1$. We also assume that an indel (a nucleotide aligned with a gap) is scored as $g$, with a typical value for DNA alignment being $g = -2$. In the next section, we develop a better and more widely used model for indel scoring that distinguishes gap openings from gap extensions.

Now, let $T(i, j)$ denote the maximum score for aligning a sequence of length $i$ with a sequence of length $j$. We can compute $T(i, j)$ provided we know $T(i - 1, j - 1)$, $T(i - 1, j)$ and $T(i, j - 1)$. Indeed, our logic is similar to that used when counting the total number of alignments. There are again three ways to compute $T(i, j)$: (1) $i - 1$ characters of the first sequence are already aligned with $j - 1$ characters of the second sequence with maximum score $T(i - 1, j - 1)$. The $i$th character of the first sequence then aligns with the $j$th character of the second sequence with updated maximum score $T(i - 1, j - 1) + S(a_i, b_j)$; (2) $i - 1$ characters of the first sequence are aligned with $j$ characters of the second sequence with maximum score $T(i - 1, j)$, and the $i$th character of the first sequence aligns with a gap in the second sequence with updated maximum score $T(i - 1, j) + g$ or; (3) $i$ characters of the first sequence are aligned with $j - 1$ characters of the second sequence with maximum score $T(i, j - 1)$, and a gap in the first sequence aligns with the $j$th character of the second sequence with updated maximum score $T(i, j - 1) + g$. We then compare these three scores and assign $T(i, j)$ to be the maximum; that is,

$$T(i, j) = \max \begin{cases} T(i - 1, j - 1) + S(a_i, b_j), \\ T(i - 1, j) + g, \\ T(i, j - 1) + g. \end{cases}$$ (7.2)

Boundary conditions give the score of aligning a sequence with a null sequence of gaps, so that

$$T(i, 0) = T(0, i) = ig, \quad i > 0,$$

with $T(0, 0) = 0$.

The recursion (7.2), together with the boundary conditions, can be used to fill in a dynamic matrix. The score of the best alignment is then given by the last filled-in element of the matrix, which for aligning a sequence of length $n$ with a sequence of length $m$ is $T(n, m)$. Besides this score, however, we also want to determine the alignment itself. This is obtained by tracing back the path in the dynamic matrix followed to compute $T(i, j)$ for each matrix element. There could be more than one path, and the best alignment can be degenerate.

Sequence alignment is always done using computers and there are excellent software tools freely available on the web (see §7.6). Just to illustrate the
dynamic programming algorithm, we compute by hand the dynamic matrix for aligning two short DNA sequences GGAT and GAATT, scoring a match as +2, a mismatch as $-1$ and an indel as $-2$:

-   G   A   A   T   T
-  0   -2   -4   -6   -8   -10
G -2   2   0   -2   -4   -6
G -4   0   1   -1   -3   -5
A -6   -2   2   3   1   -1
T -8   -4   0   1   5   3

In our hand calculation, the two sequences to be aligned go to the left and above the dynamic matrix, leading with a gap character ‘-’. Row 0 and column 0 are then filled in with the boundary conditions, starting with 0 in position $(0,0)$ and incrementing by the gap penalty $-2$ across row 0 and down column 0. The recursion relation (7.2) is then used to fill in the dynamic matrix one row at a time moving from left-to-right and top-to-bottom. To determine the $(i,j)$ matrix element, three numbers must be compared and the maximum taken: (1) inspect the nucleotides to the left of row $i$ and above column $j$ and add +2 for a match or -1 for a mismatch to the $(i-1,j-1)$ matrix element; (2) add $-2$ to the $(i-1,j)$ matrix element; (3) add $-2$ to the $(i,j-1)$ matrix element. For example, the first computed matrix element 2 at position $(1,1)$ was determined by taking the maximum of (1) $0+2 = 2$, since G-G is a match; (2) $-2 - 2 = -4$; (3) $-2 - 2 = -4$. You can test your understanding of dynamic programming by computing the other matrix elements.

After the matrix is constructed, the traceback algorithm that finds the best alignment starts at the bottom-right element of the matrix, here the $(4,5)$ matrix element with entry 3. The matrix element used to compute 3 was either at $(4,4)$ (horizontal move) or at $(3,4)$ (diagonal move). Having two possibilities implies that the best alignment is degenerate. For now, we arbitrarily choose the diagonal move. We build the alignment from end to beginning with GGAT on top and GAATT on bottom:

```
T
|TT
```

We illustrate our current position in the dynamic matrix by eliminating all the elements that are not on the traceback path and are no longer accessible:

-   G   A   A   T   T
-  0   -2   -4   -6   -8
G -2   2   0   -2   -4
G -4   0   1   -1   -3
A -6   -2   2   3   1
T -8   -4   0   1   5   3

We start again from the 1 entry at $(3,4)$. This value came from the 3 entry at $(3,3)$ by a horizontal move. Therefore, the alignment is extended to

```
-T
|TT
```
where a gap is inserted in the bottom sequence for a horizontal move. (A gap is inserted in the top sequence for a vertical move.) The dynamic matrix now looks like

\[
\begin{array}{cccc}
- & G & A & A & T & T \\
0 & -2 & -4 & -6 \\
G & -2 & 2 & 0 & -2 \\
G & -4 & 0 & 1 & -1 \\
A & -6 & -2 & 2 & 3 & 1 \\
T & & & & & 3 \\
\end{array}
\]

Starting again from the 3 entry at (3, 3), this value came from the 1 entry at (2, 2) in a diagonal move, extending the alignment to

A-T
|||
ATT

The dynamic matrix now looks like

\[
\begin{array}{cccc}
- & G & A & A & T & T \\
0 & -2 & -4 \\
G & -2 & 2 & 0 \\
G & -4 & 0 & 1 \\
3 & 1 \\
T & & & & & 3 \\
\end{array}
\]

Continuing in this fashion (try to do this), the final alignment is

GGA-T
:::
GAATT

where it is customary to represent a matching character with a colon ‘:’. The traceback path in the dynamic matrix is

\[
\begin{array}{cccc}
- & G & A & A & T & T \\
0 & 2 \\
G & 1 \\
A & 3 & 1 \\
T & & & & & 3 \\
\end{array}
\]

If the other degenerate path was initially taken, the final alignment would be

GGAT-
:::
GAATT

and the traceback path would be

\[
\begin{array}{cccc}
- & G & A & A & T & T \\
0 & 2 \\
G & 1 \\
A & 3 \\
T & & & & & 5 & 3 \\
\end{array}
\]
The score of both alignments is easily recalculated to be the same, with $2 - 1 + 2 - 2 + 2 = 3$ and $2 - 1 + 2 + 2 - 2 = 3$.

The algorithm for aligning two proteins is similar, except match and mismatch scores depend on the pair of aligning amino acids. With twenty different amino acids found in proteins, the score is represented by a $20 \times 20$ substitution matrix. The most commonly used matrices are the PAM series and BLOSUM series of matrices, with BLOSUM62 the commonly used default matrix.

### 7.4 Gap opening and gap extension penalties

Empirical evidence suggests that gaps cluster, in both nucleotide and protein sequences. Clustering is usually modeled by different penalties for gap opening ($g_o$) and gap extension ($g_e$), with $g_o < g_e < 0$. For example, the default scoring scheme for the widely used BLASTN software is $+1$ for a nucleotide match, $-3$ for a nucleotide mismatch, $-5$ for a gap opening, and $-2$ for a gap extension.

Having two types of gaps (opening and extension) complicates the dynamic programming algorithm. When an indel is added to an existing alignment, the scoring increment depends on whether the indel is a gap opening or a gap extension. For example, the extended alignment

\[
\begin{align*}
\text{AB} & \quad | \quad \text{AB} - \\
\text{||} & \quad | \quad |||
\end{align*}
\]

adds a gap opening penalty $g_o$ to the score, whereas

\[
\begin{align*}
\text{A} - & \quad | \quad \text{A} -- \\
\text{||} & \quad | \quad |||
\end{align*}
\]

adds a gap extension penalty $g_e$ to the score. The score increment depends not only on the current aligning pair, but also on the previously aligned pair.

The final aligning pair of a sequence of length $i$ with a sequence of length $j$ can be one of three possibilities (top-bottom): (1) $a_i : b_j$; (2) $a_i : -$; (3) $- : b_j$. Only for (1) is the score increment $S(a_i, b_j)$ unambiguous. For (2) or (3), the score increment depends on the presence or absence of indels in the previously aligned characters. For instance, for alignments ending with $a_i : -$, the previously aligned character pair could be one of (i) $a_{i-1} : b_j$, (ii) $- : b_j$, (iii) $a_{i-1} : -$. If the previous aligned character pair was (i) or (ii), the score increment would be the gap opening penalty $g_o$; if it was (iii), the score increment would be the gap extension penalty $g_e$.

To remove the ambiguity that occurs with a single dynamic matrix, we need to compute three dynamic matrices simultaneously, with matrix elements denoted by $T(i,j)$, $T_-(i,j)$ and $T^-(-i,j)$, corresponding to the three types of aligning pairs. The recursion relations are

(1) $a_i : b_j$

\[
T(i,j) = \max \begin{cases} 
T(i-1,j-1) + S(a_i, b_j), \\
T_-(i-1,j-1) + S(a_i, b_j), \\
T^-(i-1,j-1) + S(a_i, b_j); 
\end{cases}
\]

(2) $a_i : -$
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\[ T_-(i, j) = \begin{cases} 
T(i-1, j) + g_o, \\
T_-(i-1, j) + g_c, \\
T^-(i-1, j) + g_o; 
\end{cases} \quad (7.4) \]

(3) − : bj

\[ T^-(i, j) = \begin{cases} 
T(i, j-1) + g_o, \\
T_-(i, j-1) + g_o, \\
T^-(i, j-1) + g_c; 
\end{cases} \quad (7.5) \]

To align a sequence of length \( n \) with a sequence of length \( m \), the best alignment score is the maximum of the scores obtained from the three dynamic matrices:

\[ T_{\text{opt}}(n, m) = \max \{T(n, m), T_-(n, m), T^-(n, m)\}. \quad (7.6) \]

The traceback algorithm to find the best alignment proceeds as before by starting with the matrix element corresponding to the best alignment score, \( T_{\text{opt}}(n, m) \), and tracing back to the matrix element that determined this score. The optimum alignment is then built up from last-to-first as before, but now switching may occur between the three dynamic matrices.

### 7.5 Local alignments

We have so far discussed how to align two sequences over their entire length, called a *global alignment*. Often, however, it is more useful to align two sequences over only part of their lengths, called a *local alignment*. In bioinformatics, the algorithm for global alignment is called “Needleman-Wunsch,” and that for local alignment “Smith-Waterman.” Local alignments are useful, for instance, when searching a long genome sequence for alignments to a short DNA segment. They are also useful when aligning two protein sequences since proteins can consist of multiple domains, and only a single domain may align.

If for simplicity we consider a constant gap penalty \( g \), then a local alignment can be obtained using the rule

\[ T(i, j) = \max \begin{cases} 
0, \\
T(i-1, j-1) + S(a_i, b_j), \\
T(i-1, j) + g, \\
T(i, j-1) + g. 
\end{cases} \quad (7.7) \]

After the dynamic matrix is computed using (7.7), the traceback algorithm starts at the matrix element with the highest score, and stops at the first encountered zero score.

If we apply the Smith-Waterman algorithm to locally align the two sequences GGAT and GAATT considered previously, with a match scored as +2, a mismatch as −1 and an indel as −2, the dynamic matrix is
7.6 Software

If you have in hand two or more sequences that you would like to align, there is a choice of software tools available. For relatively short sequences, you can use the LALIGN program for global or local alignments:

http://www.ch.embnet.org/software/LALIGN_form.html

For longer sequences, the BLAST software has a flavor that permits local alignment of two sequences:


Another useful software for global alignment of two or more long DNA sequences is PipMaker:

http://pipmaker.bx.psu.edu/pipmaker/

Multiple global alignments of protein sequences use ClustalW or Tcoffee:

http://www.ebi.ac.uk/clustalw/index.html
http://igs-server.cnrs-mrs.fr/Tcoffee/tcoffee_cgi/index.cgi

Most users of sequence alignment software want to compare a given sequence against a database of sequences. The BLAST software is most widely used, and comes in several versions depending on the type of sequence and database search one is performing: