Mathematical Biology

Lecture notes for MATH 365

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Preface

The following chapters are my lecture notes for Math 365: *Mathematical Biology*, taught every Spring Semester at the Hong Kong University of Science & Technology. This is a course in Applied Mathematics primarily for final year mathematics major and minor students. Biology students are also welcome to enroll, but unfortunately the standard biology curriculum would leave most students with inadaquate mathematical skills. Interested biology students can choose to audit the course.

My main emphasis is mathematical modeling, with biology the sole application area. I assume that students have no knowledge of biology, but hopefully 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 will also touch on topics in stochastic modeling, which requires some knowledge of probability. A full course on probability, however, is not a prerequisite, though may be helpful.

Biology, as is usually taught, requires memorizing a wide selection of facts and regurgitating them for the exams. For students exposed to biology in secondary school, my course will be a completely different experience. The ability to model problems using mathematics requires almost no rote memorization, but does require a deep understanding of basic principles and a considerable amount of mathematical skill. Biology offers a rich number of topics to practice modeling and to exercise mathematical skills, and my selection of specific topics are among the ones I find the most interesting.

If as a UST student you are undecided as to whether to take my course, please browse these lecture notes to see if you find the topics to be of interest. Other web surfers are welcome to download these notes and to use them freely as teaching and learning materials. Most of the subject matter is available elsewhere in textbooks, but I hope you will also find here some original material.

Chapter 1

Deterministic and Stochastic Modeling of Population Growth

Populations may grow in size if the birth rate exceeds the death rate. If we neglect interactions of individuals with their environment or with each other, then modeling population growth should be easy, and it is provided population sizes are large. But finite populations introduce 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.

1.1 Deterministic model of population growth

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

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

which can be rearranged to

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

and as $\Delta t \to 0$,

$$\frac{dN}{dt} = (b - d)N.$$

With an initial population size of N_0, the solution shows that the population size grows exponentially:

$$N(t) = N_0 e^{(b-d)t},$$

provided $b > d$. Our deterministic approach to population growth is clearly an approximation: the precise number of births and deaths in the population

during a time Δt should, in principle, be a random variable since b and d are only average rates. An exact equation within our simple model, however, could have been obtained by working with the expected number of individuals in a population at time t, $\bar{N}(t)$, rather than with the actual number of individuals, so that

$$\bar{N}(t) = N_0 e^{(b-d)t}.$$

Other important statistics such as the variance of $N(t)$ remain unknown.

In general, a deterministic approach to modeling is simplest and is usually the first approach to a problem when the biology of interest is unaffected by stochastic effects. Nevertheless, some fundamental problems such as extinction or genetic drift require a stochastic approach, and we show how to formulate a stochastic model for the simplest case of births in a population of specified initial size. Inclusion also of deaths will be left as an exercise.

1.2 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 Δt is given by $b\Delta t$. For example, if the average per capita birthrate is one offspring every two years, then the probability that a given individual gives birth in a given day is $1/730$. We neglect probabilities of an individual giving birth more than once in the time interval Δt 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

$$p_N(t + \Delta t) = p_{N-1}(t)b(N - 1)\Delta t + p_N(t)(1 - bN\Delta t).$$

Subtracting $p_N(t)$ from both sides, dividing by Δt, and taking the limit $\Delta t \to 0$ results in the *forward Kolmogorov differential equations*:

$$\frac{dp_N}{dt} = b\left[(N - 1)p_{N-1} - Np_N\right], \quad N = 1, 2, \ldots \tag{1.1}$$

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

$$\frac{dy}{dt} + ay = g(t), \quad y(0) = y_0, \tag{1.2}$$

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

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

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

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

and cancelling terms yields

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

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

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

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

$$y(t) = e^{-at}\left(y(0) + \int_0^t e^{as}g(s)ds\right). \tag{1.3}$$

The forward Kolmogorov differential equation (1.1) is of the form Eq. (3.12) with $a = bN$ and $g(t) = b(N-1)p_{N-1}$. Therefore, formal integration of this equation using Eq. (1.3) results in

$$p_N(t) = e^{-bNt}\left[p_N(0) + b(N-1)\int_0^t e^{bNs}p_{N-1}(s)ds\right],$$

and with the initial condition $p_N(0) = \delta_{N,N_0}$, where δ_{ij} is the Kronecker delta, defined as

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

the first few solutions can be obtained by successive integrations:

$$p_N(t) = \begin{cases} 0 & \text{if } N < N_0 \\ e^{-bN_0t} & \text{if } N = N_0 \\ N_0e^{-bN_0t}[1-e^{-bt}] & \text{if } N = N_0+1 \\ \frac{1}{2}N_0(N_0+1)e^{-bN_0t}[1-e^{-bt}]^2 & \text{if } N = N_0+2 \\ \dots & \text{if } \dots \end{cases}$$

Although we will not need this, for your information I will show you the form of the complete solution. Defining the binomial coefficient as the number of

ways one can select k objects from a set of n identical objects, where order of selection is immaterial:

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

(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 $\bar{N}$ and its variance σ^2 are

$$\bar{N} = \sum_{N=0}^{\infty} N p_N, \quad \sigma^2 = \sum_{N=0}^{\infty} (N-\bar{N})^2 p_N, \tag{1.4}$$

and we will make use of the equality

$$\sigma^2 = \overline{N^2} - \bar{N}^2. \tag{1.5}$$

Multiplying the differential equation (1.1) by the constant N, summing over N, and using $p_N = 0$ for $N < N_0$, we obtain

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

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

$$\begin{aligned}\sum_{N=N_0+1}^{\infty} N(N-1)p_{N-1} &= \sum_{N=N_0+1}^{\infty} (N-1)^2 p_{N-1} + \sum_{N=N_0+1}^{\infty} (N-1)p_{N-1} \\ &= \sum_{N=N_0}^{\infty} N^2 p_N + \sum_{N=N_0}^{\infty} N p_N,\end{aligned}$$

where the second equality was obtained by shifting the summation index downward by one. Therefore, we find the familiar equation

$$\frac{d\bar{N}}{dt} = b\bar{N}.$$

Together with the initial condition $\bar{N}(0) = N_0$, we have the solution $\bar{N}(t) = N_0 \exp(bt)$. We proceed similarly to find σ^2 by first determining the differential equation for $\overline{N^2}$. Multiplying the differential equation for p_N, Eq. (1.1) by N^2 and summing over N results in

$$\frac{d\overline{N^2}}{dt} = b\left[\sum_{N=N_0+1}^{\infty} N^2(N-1)p_{N-1} - \sum_{N=N_0}^{\infty} N^3 p_N\right].$$

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

$$\frac{d\overline{N^2}}{dt} - 2b\overline{N^2} = b\bar{N},$$

which is a first-order linear inhomogeneous equation for $\overline{N^2}$ since $\bar{N}$ is known, and can be solved using an integrating factor. The solution obtained using Eq. (1.3) is

$$\overline{N^2} = e^{2bt}\left(N_0^2 + \int_0^t e^{-2bs} b\bar{N}(s)ds\right),$$

with $\bar{N}(t) = N_0 e^{bt}$. Performing the integration, we obtain

$$\overline{N^2} = e^{2bt}\left[N_0^2 + N_0(1-e^{-bt})\right].$$

Finally, using $\sigma^2 = \overline{N^2} - \bar{N}^2$, we obtain the variance. Thus we collect our final results for the population mean and variance:

$$\bar{N} = N_0 e^{bt}, \quad \sigma^2 = N_0 e^{2bt}(1-e^{-bt}). \tag{1.6}$$

1.3 Limit of large initial populations

The main idea here is to find the limit of the probability mass function for large initial population sizes. Ideally, we would like to find an expansion in powers of $1/N_0$, since $1/N_0$ is small if N_0 is large. Our main result here will be that the deterministic model of population growth is recovered in the limit $N_0 \to \infty$. We will start directly with the differential equation for $p_N(t)$.

Now $p_N(t)$ is the probability mass function for N, where the population size N is a discrete random variable (taking only nonnegative integer values $0, 1, 2, \ldots$). 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 $0 \le x < \infty$. 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 $a \le x \le b$. 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

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

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

$$P(x,t) = N_0 p_N(t), \quad x = N/N_0, \tag{1.7}$$

which satisfies

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

the first equality being a Reimann sum approximation to the integral, exact as $N_0 \to \infty$.

We now transform the infinite set of ordinary differential equations (1.1) for $p_N(t)$ into a single partial differential equation for $P(x,t)$. We multiply (1.1) by N_0, and substitute $N = N_0 x$, $p_N(t) = P(x,t)/N_0$, and $p_{N-1}(t) = P(x - \frac{1}{N_0}, t)/N_0$ to obtain

$$\frac{\partial P(x,t)}{\partial t} = b\left[(N_0 x - 1)P(x - \frac{1}{N_0}, t) - N_0 x P(x,t)\right]. \tag{1.8}$$

We 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

$$\begin{aligned} P(x - \frac{1}{N_0}, t) &= P(x,t) - \tfrac{1}{N_0} P_x(x,t) + \tfrac{1}{2N_0^2} P_{xx}(x,t) - \dots \\ &= \textstyle\sum_{i=0}^{\infty} (-1)^i \frac{N_0^{-i}}{i!} \frac{\partial^i P}{\partial x^i}(x,t). \end{aligned}$$

There is a cancellation occuring between the two terms on the right-hand-side of (1.8), and if we group terms in powers of $1/N_0$ we obtain for the first three terms in the expansion

$$P_t = -b\left[(xP_x + P) - \frac{1}{N_0}\left(\frac{1}{2!}xP_{xx} + \frac{1}{1!}P_x\right) + \frac{1}{N_0^2}\left(\frac{1}{3!}xP_{xxx} + \frac{1}{2!}P_{xx}\right) + \dots\right], \tag{1.9}$$

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

First, we consider the limit $N_0 \to \infty$, for which the pde becomes independent of N_0 and reduces to the simple form

$$P_t + b(xP_x + P) = 0, \tag{1.10}$$

which is a first-order linear pde with a variable coefficient. One way to solve this equation is to try the substitution

$$P(x,t) = h(x,t)f(r), \quad r = r(x,t), \tag{1.11}$$

and find any solution for $h(x,t)$ and $r(x,t)$, after which $P(x,t)$ becomes the general solution of the pde. The free function f will then be determined by imposing an initial condition on $P(x,0)$. The partial derivatives of Eq. (1.11) are

$$P_t = h_t f + h r_t f', \quad P_x = h_x f + h r_x f',$$

which after substitution into Eq. (1.10) results in

$$\left[h_t + b(xh_x + h)\right] f + \left[r_t + bx r_x\right] h f' = 0.$$

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

$$h_t + b(xh_x + h) = 0, \quad r_t + bx r_x = 0. \tag{1.12}$$

The equation for $h(x,t)$ is easily satisfied if we take $h = h(t)$ independent of x and find a solution of the ode $\dot{h} + bh = 0$. One solution is $h = e^{-bt}$. To

determine a solution for r, we look for r of the form $r = r(x(t), t)$, and further require r to be independent of t. In other words, we require that r satisfies the equation

$$\frac{dr}{dt} = r_t + \dot{x} r_x = 0. \tag{1.13}$$

Comparison of Eq. (1.13) with Eq. (1.12) shows that $\dot{x} = bx$, or $x = Ce^{bt}$, where C is the integration constant. Therefore, since r was assumed to be independent of t, $r = r(x(t), t) = r(Ce^{bt}, t) = r(C, 0)$, where in the last step we have set $t = 0$. Hence, r is a function only of the integration constant C. We can then simply take $r = C$, or $r(x, t) = xe^{-bt}$. Thus our general solution to the original pde is given by

$$P(x, t) = e^{-bt} f(xe^{-bt}).$$

To determine f, we apply the boundary condition $p_N(0) = \delta_{N,N_0}$. From Eq. (1.7), the boundary condition becomes

$$P(x, 0) = \begin{cases} N_0 & \text{if } 1 - \frac{1}{2N_0} \leq x \leq 1 + \frac{1}{2N_0}, \\ 0 & \text{otherwise .} \end{cases}$$

In the limit $N_0 \to \infty$, $P(x, 0)$ becomes the Dirac delta-function, centered around 1, written as $\delta(x-1)$. 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 is what mathematicians call a distribution.

Now, since $P(x, 0) = f(x) = \delta(x - 1)$, our solution becomes $P(x, t) = e^{-bt}\delta(xe^{-bt} - 1)$. 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 identity, we can rewrite our solution in the more instructive form

$$P(x, t) = \delta(x - e^{bt}).$$

We say the probability density function of x remains sharp over time (i.e., with zero variance), and with peak moving to the right as $x = e^{bt}$, or equivalently, $N(t) = N_0 e^{bt}$. Hence, we see that the deterministic solution for $N(t)$ is obtained as $N_0 \to \infty$. In other words, a deterministic approximation to population growth improves as the initial population size increases. This general principle of large populations being modeled deterministically is fundamental to simplifying biological models and has wide applicability.

We now consider the full pde, Eq. (1.9). Again, of main interest is the mean and variance of the continuous random variable x, and the definitions analgous to Eqs. (1.4) and (1.5) are

$$\bar{x} = \int_0^\infty xP(x)dx, \quad \sigma_x^2 = \int_0^\infty (x-\bar{x})^2 P(x)dx,$$

and

$$\sigma_x^2 = \bar{x^2} - \bar{x}^2.$$

First, we compute the mean $\bar{x}$. Multiplying the pde by x and integrating, we apply integration by parts to remove the derivatives of P, assuming that P and all its derivatives vanish on the boundaries of integration (x equal to zero and infinity). The first term in the expansion after multiplication by x is integrated as

$$\int_0^\infty (x^2 P_x + xP)dx = \int_0^\infty (-2xP + xP)dx = -\bar{x}.$$

The second term is integrated as

$$\int_0^\infty \left(\frac{1}{2}x^2 P_{xx} + xP_x\right) dx = \int_0^\infty \left(-xP_x + xP_x\right) dx = 0;$$

and all other terms vanish. For instance,

$$\begin{aligned}\int_0^\infty \left(\frac{1}{3!}x^2 P_{xxx} + \frac{1}{2!}xP_{xx}\right) dx &= \int_0^\infty \left(-\frac{2}{3!}xP_{xx} - \frac{1}{2!}P_x\right) dx \\ &= -\frac{1}{6}\int_0^\infty P_x dx = 0,\end{aligned}$$

since we assume that P vanishes at $x = 0$ and as $x \to \infty$. Interestingly, the equation for $\bar{x}$ comes from only the first term in the expansion and is thus

$$\frac{d\bar{x}}{dt} = b\bar{x},$$

and with initial condition $\bar{x}(0) = 1$, yields $\bar{x} = e^{bt}$ as expected.

Similarly, we compute the second moment $\overline{x^2}$. Multiplying the pde by x^2 and integrating, the first term on the right-hand-side becomes

$$\int_0^\infty (x^3 P_x + x^2 P)dx = \int_0^\infty (-3x^2 P + x^2 P)dx = -2\overline{x^2}.$$

The second term becomes

$$\int_0^\infty (\frac{1}{2}x^3 P_{xx} + x^2 P_x)dx = \int_0^\infty xPdx = \bar{x}.$$

All other terms vanish, so that the variance is determined only from the first two terms in the expansion. The equation for the second-order moment is thus

$$\frac{d\overline{x^2}}{dt} - 2b\overline{x^2} = \frac{b}{N_0}\bar{x},$$

which should be familiar from our computation of the variance in the complete stochastic model. Its solution is

$$\overline{x^2} = e^{2bt}\left[1 + \frac{1}{N_0}(1 - e^{-bt})\right],$$

so that as expected

$$\sigma_x^2 = \frac{e^{2bt}}{N_0}(1 - e^{-bt}). \tag{1.14}$$

In general, calculation of the nth-order moment of x requires only the first n terms of the expansion in $1/N_0$.

It is instructive to consider why the variance of x, Eq. (1.14), has a factor of $1/N_0$. We make use of the following theorem:

> Suppose X_1, X_2, ..., X_n are independent and identically distributed (iid) random variables with mean μ and variance σ^2. Then the average of the X_i's, denoted as the random variable $Z = \frac{1}{n}\sum_{i=1}^{n} X_i$, has mean μ and variance σ^2/n.

The random variable $x(t)$ can be viewed as the average number of individuals descendent from each of the original ancestors. That is, if $n_i(t)$ are the number of individuals descendent from ancestor i (in our model, $n_i(t)$ also includes the original ancestor i since there are no deaths), then the number of individuals at time t is given by $N(t) = \sum_{i=1}^{N_0} n_i(t)$, and $x(t) = N(t)/N_0$ is the average. If the mean number of descendents of an ancestor is $\bar{n}$, and its variance is σ_n^2, then applying the Theorem $\bar{x} = \bar{n}$ and $\sigma_x^2 = \sigma_n^2/N_0$. Comparing with our results, we see that $\sigma_n^2 = e^{2bt}(1 - e^{-bt})$, independent of N_0 as it should be, since it is the variance in the number of descendents of a single individual.

1.4 Simulation of population growth

As we have seen, stochastic modeling is significantly more complicated than deterministic modeling. In fact, the simple example of population growth is the only example we will consider in our class. As the modeling becomes more detailed, it may become necessary to solve a stochastic model numerically. Here, for illustration, we consider how to simulate individual realizations of population growth.

A straightforward approach would make use of the birth rate b directly. In a time Δt, each individual of a population has probability $b\Delta t$ of giving birth, accurate to order Δt. 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 solve the problem provided Δt is sufficiently small.

There is, however, a more accurate and efficient way to solve the problem. The key idea is to compute the probability density function of the interevent time τ, defined as the time required for the population to increase from size N to size $N + 1$. A simulation from population size N_0 to size N_f would then only require computing $N_f - N_0$ different random values of τ.

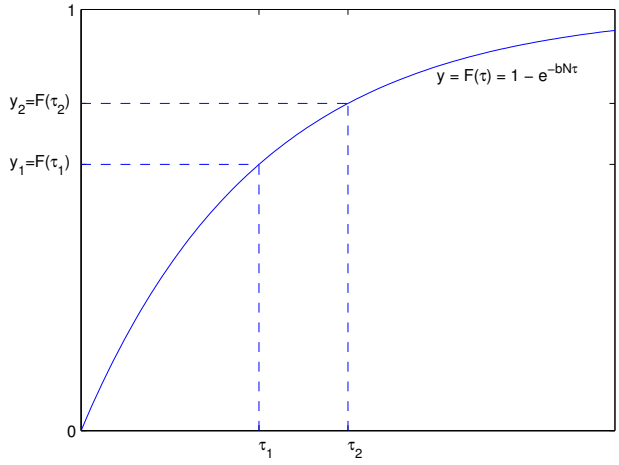

Figure 1.1: How to generate a random number with a given probability density function.

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 τ, and $G(\tau) = 1 - F(\tau)$ the probability that the interevent time is greater than τ. $P(\tau)$ is called the probability density function of τ, and $F(\tau)$ the cumulative distribution function of τ. 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 τ times the probability that no new births occur in the time interval $(\tau, \tau + \Delta\tau)$:

$$G(\tau + \Delta\tau) = G(\tau)(1 - bN\Delta\tau),$$

where $bN\Delta\tau$ is the probability there is a new birth in the time interval $(\tau, \tau + \Delta\tau)$, so that $(1 - bN\Delta\tau)$ is the probability there are no new births. Differencing and taking the limit $\Delta\tau \to 0$, yields the differential equation

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

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

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

Therefore,

$$F(\tau) = 1 - e^{-bN\tau}, \quad P(\tau) = bNe^{-bN\tau}. \tag{1.15}$$

This is the form of an exponential distribution.

We now need to compute random values for τ using its known distribution (1.15). This is done in reference to Figure 1.1, where we plot $y = F(\tau)$ versus τ. The idea is to sample y uniformly on the interval $(0, 1)$. Then for each y, we compute τ by inverting $y(\tau) = 1 - \exp(-bN\tau)$, that is

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

Now, the fraction of random numbers in the interval (y_1, y_2) is equal to the corresponding fraction of random numbers in the interval (τ_1, τ_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 (τ_1, τ_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 (τ_1, τ_2)) $= \int_{\tau_1}^{\tau_2} P(\tau)d\tau$, which is the definition of the random numbers τ having the probability density function $P(\tau)$.

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

```
function [t, N] = population_growth_simulation(b,N0,Nf)
% simulates population growth from N0 to Nf with growth 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:

```
% 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');
```

In Figure 1.2 are three graphs, showing 100 realizations of population growth starting with population sizes 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 Eq. (1.14).

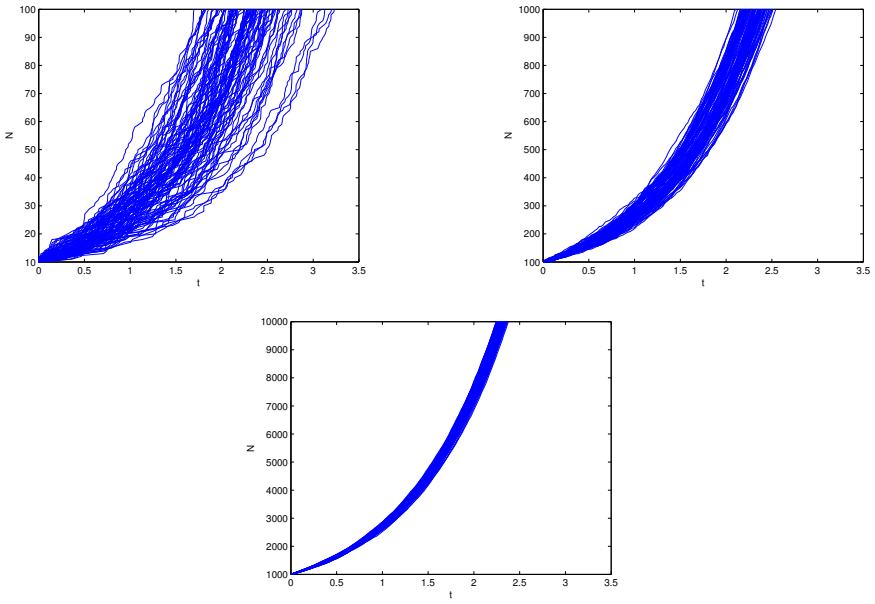

Figure 1.2: One-hundred realizations of population growth with initial population sizes 10, 100, and 1000, respectively.

Chapter 2

Age-structured populations

The determination of the age distribution of individuals within a given population may be useful for economic planning in human societies, or in obtaining a better theoretical understanding of specific life-history strategies. An age distribution occurs because individuals live for a nondeterministic length of time before dying. If average per capita birth and death rates are constant, then a stable age distribution arises. However, a rapid change in the birth or death rates can cause the age distribution to evolve between two different stable distributions. In these notes, we will show how to model the age-distibution in a given population. We will consider both discrete and continuous time models. We will also discuss 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 our discussion, however, with what is 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 biological development, before returning to our main topic.

2.1 Fibonacci's rabbits

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

> A certain man put a pair of newly born rabbits in a place surrounded on all sides by a wall. How many pairs of rabbits can be produced by that pair in a year if it is supposed that every month each pair begets a new pair, which from the second month on becomes productive?

To answer Fibonnaci's question, we first need to decide how to count rabbits. Let a_n be the number of rabbit pairs at the start of the nth month, censused before 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 minus the initial pair of rabbits will be the solution to Fibonacci's puzzle. Now $a_1 = 1$ since this is the initial newborn rabbit pair at the start of the first month; $a_2 = 1$ since this is still the initial rabbit pair before they have reproduced; and $a_3 = a_2 + a_1$ since a_2 are the number of rabbit pairs present in the previous month (here equal to one), and a_1 are the new rabbit pairs born to all rabbit pairs that are at least

one-month-old (here, also equal to one). In general

$$a_{n+1} = a_n + a_{n-1}. \tag{2.1}$$

For only 12 months we can count, so the Fibonacci numbers are

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

where $a_{13} = 233$, so that the solution to Fibonnaci's puzzle is 232 rabbit pairs.

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

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

or after division by λ^{n-1}:

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

with solution

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

These numbers are so important they have special names. Define

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

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

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

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

As in the solution of linear homogeneous differential equations, the two values of λ can be used to construct a general solution to the linear difference equation:

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

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

$$\begin{aligned} c_1 + c_2 &= 0, \\ c_1 \Phi - c_2 \phi &= 1. \end{aligned}$$

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

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

In this form, we see that as $n \to \infty$, $a_n \to \Phi^n/\sqrt{5}$, and $a_{n+1}/a_n \to \Phi$. From this last result, Φ is often called the golden ratio. Φ is also known as the most irrational number since in some well-defined way it is the hardest number to approximate by a rational number.

To understand why Φ is the most irrational number, we first need to understand an algorithm – continued fraction expansions – to approximate 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 which satisfy the following inequalities:

$$\begin{aligned} x > c_1 &= n_1, \\ x < c_2 &= n_1 + \tfrac{1}{n_2}, \\ x > c_3 &= n_1 + \cfrac{1}{n_2 + \tfrac{1}{n_3}}, \\ x < c_4 &= n_1 + \cfrac{1}{n_2 + \cfrac{1}{n_3 + \tfrac{1}{n_4}}}, \end{aligned}$$

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 reciprical $1/(x - c_1)$. The integer part of this inverse is n_2. One then takes the remainder $1/(x - c_1) - n_2$, and its reciprical. The integer part of this inverse is n_3. We follow this algorithm to find successively better rational approximations to $\pi = 3.141592654\ldots$:

c's			remainder	1/remainder
c_1	=	3	0.141592654	7.06251329
c_2	=	$3 + \frac{1}{7}$	0.06251329	15.99659848
c_3	=	$3 + \cfrac{1}{7 + \tfrac{1}{15}}$	0.99659848	1.00341313
c_4	=	$3 + \cfrac{1}{7 + \cfrac{1}{15 + \tfrac{1}{1}}}$		

Follow how this is working: The first rational approximation to π is $c_1 = 3$, which is less than π. The remainder is 0.141592654. The remainder's reciprical is 7.06251329. The integer part of this reciprical is 7, so our next rational approximation to π is $c_2 = 3 + 1/7$, which is larger than π since $1/7$ is greater than 0.141592654. The next remainder is $7.06251329 - 7 = 0.06251329$, and its reciprical 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 π. Rationalizing the continued fractions gives us the following successive rational number approximation to π: $\{3, 22/7, 333/106, 355/113, \ldots\}$, or in decimal: $\{3, 3.1428\ldots, 3.141509\ldots, 3.14159292\ldots\}$.

Now, consider a rational approximation for $\Phi = 1.61803399\ldots$:

c's			remainder	1/remainder
c_1	=	1	$0.61803399\ldots = \phi$	Φ
c_2	=	$1 + \frac{1}{1}$	ϕ	Φ

etc.

So all the n_i's are one, and the sequence results in the slowest possible convergence for the c_i's. Another derivation of the continued fraction expansion for Φ can be obtained from $\Phi^2 - \Phi - 1 = 0$, written as $\Phi = 1 + 1/\Phi$. Then inserting

this expression for Φ back into the right-hand-side gives $\Phi = 1 + 1/(1 + 1/\Phi)$, and interating infinitum shows that all the n_i's are one.

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 Φ in a sunflower. Now, let us return to our discussion of age-structured populations.

2.2 Fibonacci's rabbits as 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 age classes: juveniles and adults. The juveniles are less than one month old and do not reproduce, whereas adults are greater than one month old and reproduce at the start of every month. Again we census the population at the start of each month before rabbits give birth, beginning with the first month when the newborn pair is introduced. We define two age classes: let $u_{1,n}$ be the number of rabbit pairs that are less than one month old at the start of the nth month (juveniles) and $u_{2,n}$ the number of rabbit pairs that are greater than one month old at the start of the nth month (adults). Then 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, since each adult pair gives birth to a juvenile pair, and; the number of adult pairs at the start of the $(n + 1)$-th month is equal to the number of adult and juvenile pairs at the start of the n-th month, since there are no deaths and the juveniles have matured into adults. Therefore, we have

$$\begin{aligned} u_{1,n+1} &= u_{2,n} \\ u_{2,n+1} &= u_{1,n} + u_{2,n}, \end{aligned}$$

or written in matrix form

$$\begin{pmatrix} u_{1,n+1} \\ u_{2,n+1} \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ 1 & 1 \end{pmatrix} \begin{pmatrix} u_{1,n} \\ u_{2,n} \end{pmatrix}. \tag{2.3}$$

In vector form, we can write this as

$$\mathbf{u}_{n+1} = \mathrm{L}\mathbf{u}_n, \tag{2.4}$$

where the definition of the vector $\mathbf{u}_n$ and the matrix L are apparent. 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 (2.4), a system of coupled first-order linear difference equations, proceeds similarly to that of coupled first-order differential equations. Looking for a solution of the form $\mathbf{u}_n = \lambda^n \mathbf{v}$, we obtain upon substitution into Eq. (2.4) the eigenvalue problem

$$\mathrm{L}\mathbf{v} = \lambda \mathbf{v},$$

whose solution will yield two eigenvalues λ_1 and λ_2, with corresponding eigenvectors $\mathbf{v}_1$ and $\mathbf{v}_2$. The general solution to Eq. (2.4) is then

$$\mathbf{u}_n = c_1\lambda_1^n\mathbf{v}_1 + c_2\lambda_2^n\mathbf{v}_2, \tag{2.5}$$

with c_1 and c_2 determined from the initial conditions. Now, suppose $|\lambda_1| > |\lambda_2|$. If we rewrite Eq. (2.5) 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 since $|\lambda_2/\lambda_1| < 1$, as $n \to \infty$, $\mathbf{u}_n \to c_1\lambda_1^n\mathbf{v}_1$. Therefore, the long-time asymptotics of the population depend only on λ_1 and the corresponding eigenvector $\mathbf{v}_1$. For our Fibonacci's rabbits, the eigenvalues are obtained by solving $\det(\mathrm{L} - \lambda\mathrm{I}) = 0$, and we find

$$\det\begin{pmatrix} -\lambda & 1 \\ 1 & 1-\lambda \end{pmatrix} = -\lambda(1-\lambda) - 1 = 0,$$

or $\lambda^2 - \lambda - 1 = 0$, with solution Φ and $-\phi$. Since $\Phi > \phi$, the long-time asymptotics of the population are determined by the eigenvalue Φ and corresponding eigenvector. The eigenvector may be determined by solving

$$(\mathrm{L} - \Phi\mathrm{I})\mathbf{v}_1 = \mathbf{0},$$

or

$$\begin{pmatrix} -\Phi & 1 \\ 1 & 1-\Phi \end{pmatrix}\begin{pmatrix} v_1^{(1)} \\ v_1^{(2)} \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}.$$

The first equation is just $-\Phi$ times the second equation (use $\Phi^2 - \Phi - 1 = 0$), so that $v_1^{(2)} = \Phi v_1^{(1)}$. Taking $v_1^{(1)} = 1$, we have

$$\mathbf{v}_1 = \begin{pmatrix} 1 \\ \Phi \end{pmatrix}.$$

The asymptotic population structure, obtained from $\mathbf{v}_1$ shows that the asymptotic ratio of adults to juveniles is the golden mean, i.e., $v_1^{(2)}/v_1^{(1)} = \Phi$.

2.3 Age-structured populations: discrete model

In a discrete model, populations are censused at discrete times and individuals are assigned to an age class, which spans a range of ages. For instance, it is common for countries to census their populations every five or ten years, and to assign individuals to age classes spanning five years (e.g., 0-4 years old, 5-9 years old, etc.). Here, for simplicity we will assume that all age classes have the same age span, and that the time between censuses is the same as the age span. (This was *not* the case for Fibonacci's rabbits). We note that a discrete model is also directly applicable to species with discrete generations, for which all individuals in a given generation are born at approximately the same time. Examples are plants that flower at the same time each year, or animals with very short mating seasons.

$u_{i,n}$	number of individuals in age class i at census n
s_i	fraction of individuals surviving from age class $i-1$ to i
m_i	number of offspring from an individual in age class i
$l_i = s_1 \cdots s_i$	fraction of individuals surviving from birth to age class i
$f_i = m_i l_i$	number of offspring from a newborn after reaching age class i
$\mathcal{R}_0 = \sum_i f_i$	basic reproductive ratio
λ_1	only positive eigenvalue of the discrete Euler-Lotka equation
r	related to λ_1 by $\lambda_1 = e^r$

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

We will adopt the convention that for a sexual population we only count females and ignore males. Another possibility is to count females and males separately, and this is the standard approach when censusing human populations.

There are half-a-dozen or so 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 individuals in age class i at census n. We assume that $i = 1$ represents the first age class and that no individual survives past age class $i = \omega$. We define s_i to be the fraction of individuals from age class $i-1$ that survive to age class i (with s_1 the fraction of newborns that survive to their first census), and m_i the expected number of offspring from an individual in age class i before the next census.

We wish to write difference equations for $\{u_{i,n+1}\}$ in terms of $\{u_{j,n}\}$. First, consider the number of offspring born between census n and $n+1$: the number born is $u_{1,n+1}$ since these offspring are now in the first age class. These are offspring of individuals from different age classes, with m_i the expected number born from an individual in age class i. Also, only a faction s_1 of these offspring survive to their first census. Second, consider individuals that were previously counted in census n. Only a fraction s_i of individuals from age class i survive to be counted in census $n+1$ in age class $i+1$. Putting this together, we can determine the difference equations for $\{u_{i,n+1}\}$ to be

$$
\begin{aligned}
u_{1,n+1} &= s_1 m_1 u_{1,n} + s_1 m_2 u_{2,n} + \ldots + s_1 m_\omega u_{\omega,n}, \\
u_{2,n+1} &= s_2 u_{1,n}, \\
u_{3,n+1} &= s_3 u_{2,n}, \\
\ldots &= \ldots, \\
u_{\omega,n+1} &= s_\omega u_{\omega-1,n},
\end{aligned}
$$

which can be written as the matrix equation

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

or in vector form

$$
\mathbf{u}_{n+1} = \mathrm{L}\mathbf{u}_n,
$$

where L is called the Leslie Matrix. It is useful to define two more parameters (see Table 2.1). Let $l_i = s_1 s_2 \cdots s_i$ be the fraction of individuals that survive from birth to age class i, and; $f_i = m_i l_i$ the number of offspring expected of a newborn after reaching age class i (i.e., the product of the expected number of offspring produced in age class i, m_i, and the fraction of individuals that survive to age class i, l_i.). For homework, you will show that the characteristic equation derived from $\det(\mathrm{L} - \lambda \mathrm{I}) = 0$ is

$$
\lambda^\omega - f_1 \lambda^{\omega-1} - f_2 \lambda^{\omega-2} - \ldots - f_\omega = 0. \tag{2.6}
$$

Let the eigenvalues obtained from Eq. (2.6) be denoted as $\lambda_1, \lambda_2, \ldots, \lambda_\omega$, with corresponding eigenvectors $\mathbf{v}_1, \mathbf{v}_2, \ldots, \mathbf{v}_\omega$. For homework, you will also show that (2.6) admits only one positive eigenvalue and, furthermore, this eigenvalue is of largest magnitude. Let us denote this positive eigenvalue by λ_1. Since

$$
\begin{aligned}
\mathbf{u}_n &= c_1 \lambda_1^n \mathbf{v}_1 + c_2 \lambda_2^n \mathbf{v}_2 + \ldots + c_\omega \lambda_\omega^n \mathbf{v}_\omega \\
&= \lambda_1^n \left(c_1 \mathbf{v}_1 + c_2 \left(\frac{\lambda_2}{\lambda_1} \right)^n \mathbf{v}_2 + \ldots + c_\omega \left(\frac{\lambda_\omega}{\lambda_1} \right)^n \mathbf{v}_\omega \right),
\end{aligned}
$$

as $n \to \infty$, $\mathbf{u}_n \to c_1 \lambda_1^n \mathbf{v}_1$, and the asymptotics of the population are determined by λ_1 and $\mathbf{v}_1$. An equation for λ_1 can be determined. Since λ_1 is the only positive eigenvalue of (2.6), it is the only eigenvalue that can be written in the form

$$
\lambda_1 = e^r, \tag{2.7}
$$

where r is real (since $e^r > 0$ for all real r). Substitution of (2.7) into (2.6) yields

$$
e^{r\omega} - f_1 e^{r(\omega-1)} - \ldots - f_\omega = 0,
$$

or after division by $e^{r\omega}$

$$
1 = f_1 e^{-r} + f_2 e^{-2r} + \ldots + f_\omega e^{-\omega r}.
$$

This equation, known as the discrete Euler-Lotka equation, can be rewritten in the compact form

$$\sum_{j=1}^{\omega} f_j e^{-jr} = 1. \tag{2.8}$$

If numerical values of the f_j's are known, then the discrete Euler-Lotka equation (2.8) can be solved for r numerically, using Newton's method.

> Newton's method 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 interatively, starting with an initial guess x_0, until convergence.

Once λ_1 is determined, the corresponding eigenvector $\mathbf{v}_1$ can be computed using the Leslie matrix. We have

$$\begin{pmatrix} s_1m_1 - \lambda_1 & s_1m_2 & \ldots & s_1m_{\omega-1} & s_1m_\omega \\ s_2 & -\lambda_1 & \ldots & 0 & 0 \\ 0 & s_3 & \ldots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \ldots & -\lambda_1 & 0 \\ 0 & 0 & \ldots & s_\omega & -\lambda_1 \end{pmatrix} \begin{pmatrix} v_1^{(1)} \\ v_1^{(2)} \\ v_3^{(3)} \\ \vdots \\ v_1^{(\omega-1)} \\ v_1^{(\omega)} \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ \vdots \\ 0 \\ 0 \end{pmatrix}.$$

Arbitrarily taking $v_1^{(\omega)} = 1$, we have beginning with the last row and working backwards:

$$\begin{aligned} v_1^{(\omega-1)} &= \lambda_1/s_\omega \\ v_1^{(\omega-2)} &= \lambda_1^2/(s_\omega s_{\omega-1}) \\ &\vdots \\ v_1^{(1)} &= \lambda_1^{\omega-1}/(s_\omega s_{\omega-1} \cdots s_2). \end{aligned}$$

We may multiply this eigenvector by an arbitrary constant, and a reasonable normalization is to multiply by $(s_1 s_2 \cdots s_\omega)/\lambda_1^\omega$. Using the definition $l_i = s_1 \cdots s_i$, we then obtain the simpler result

$$v_1^i = l_i/\lambda_1^i, \quad \text{for } i = 1, 2, \ldots, \omega.$$

An interesting implication of this result can be observed by considering the ratio of two consecutive age classes. Asymptotically,

$$u_{i+1,n}/u_{i,n} = v_1^{(i+1)}/v_1^i = s_{i+1}/\lambda_1.$$

With the survival fractions $\{s_i\}$ fixed, a smaller λ_1 implies a larger ratio, so that a slower growing population has relatively more older people than a faster

growing population. In fact, we are now living through a time where developed countries, particularly Japan and Western Europe, have substantially lowered their population growth rates increasing the average age of their populations.

If one simply wants to determine if a population will grow ($r > 0$) or decay ($r < 0$), one need only calculate the *basic reproduction ratio* $\mathcal{R}_0$, defined as the expected number of offspring an individual produces over a lifetime. This is equal to the number of offspring expected from a newborn when she is in age class i, summed over all age classes, or

$$\mathcal{R}_0 = \sum_{i=1}^{\omega} f_i.$$

If $\mathcal{R}_0 > 1$ then the population grows, since each individual on average produces more than one offspring before dying (so replaces herself and then some), and if $\mathcal{R}_0 < 1$ then the population decays. (Remember we are counting only females, so zero population growth ($\mathcal{R}_0 = 1$) means a newborn female must produce one female over her lifetime. For humans, $\mathcal{R}_0 = 1$ means a newborn female must produce on average two children. Females that do not survive to adulthood obviously have no children, so one commonly sees the statistic that women in developed countries need to produce on average 2.2 children for zero population growth, where "women" presumably means women of child-bearing age. This implies that 0.2/2.2, or 9% of newborns do not survive to adulthood, which to me seems too high a figure for developed countries.)

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 governmental economic planning – for instance, determining 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:

http://www.census.gov/ipc/www/idbnew.html.

This website, created by the US census bureau, provides access to the International Data Base (IDB), which is a computerized source of demographic and socioeconomic 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, in particular those for Hong Kong and China.

2.4 Age-structured populations: continuous time model

The main purpose of this section is to derive the continuous time model by taking the limit of the discrete model as the age span of an age class goes to zero. That is, we let the age span of an age class in the discrete model be Δa, and take the limit $\Delta a \to 0$. Our main theoretical target is the continuous version of the Euler-Lotka equation (2.8), which will be used in a subsequent theoretical analysis.

A summary of new definitions can be found in Table 2.2. Let a represent the age of an individual, and t the time. Furthermore, suppose the starting age of age class i is a_i, so that age class i includes all ages a in the range

a	age of individual
t	time
$u(a,t)$	population age density
$m(a)$	maternity function
$l(a)$	survival function
$f(a) = l(a)m(a)$	net maternity function
R	population growth rate

Table 2.2: Definitions needed in an age-structured, continuous time population model

$a_i \leq a < a_i + \Delta a$. Furthermore, suppose the nth census occurs at time t_n. We define a population age density $u(a,t)$ so that the number of individuals in age class i during the nth census is given by $u_{i,n} = \int_{a_i}^{a_i+\Delta a} u(a,t_n)da$. As $\Delta a \to 0$, we have the appropriate definition

$$u(a_i, t_n) = u_{i,n}/\Delta a.$$

With this definition,

$$\begin{aligned} N(t_n) &= \sum_{i=1}^{\omega} u_{i,n} \\ &= \sum_{i=1}^{\omega} u(a_i,t_n)\Delta a \\ &= \int_0^{\infty} u(a,t_n)da \end{aligned}$$

where the last equality is a Riemann sum approximation to the integral as $\Delta a \to 0$, and we extend the upper limit of integration to ∞ since $u(a,t)$ is zero for a greater than the age of the oldest living individual. Therefore, the total number of individuals $N(t)$ in the population at time t is given by

$$N(t) = \int_0^{\infty} u(a,t)da.$$

Let the maternity function $m(a)$ be defined so that $m(a)\Delta a$ is the expected number of offspring per individual in the age interval $(a, a+\Delta a)$. In the discrete model, we have defined m_i as the expected number of offspring per individual in age class i. We have also assumed that the time between censuses is Δa, so as $\Delta a \to 0$, m_i is the expected number of offspring per individual over the ages a_i to $a_i + \Delta a$, which by definition is $m(a_i)\Delta a$. Therefore,

$$m_i = m(a_i)\Delta a.$$

Now l_i is the fraction of individuals living to age class i, so we can simply define the survival function $l(a)$ as the fraction of individuals living to age a, i.e.,

$$l_i = l(a_i)$$

Finally, we define the net maternity function $f(a) = l(a)m(a)$, in analogy to our definition of $f_i = l_i m_i$.

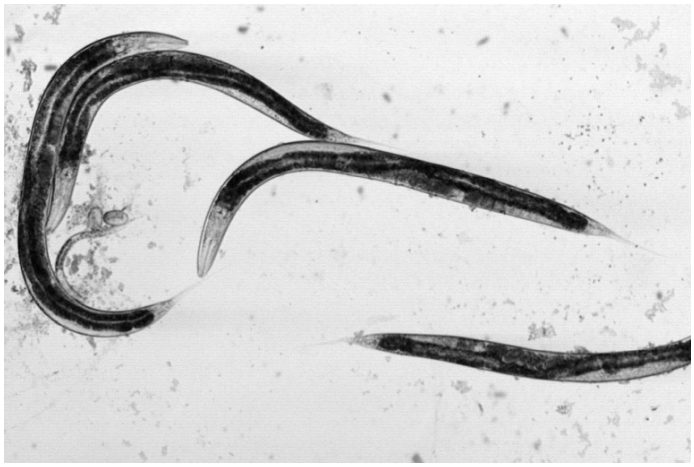

Figure 2.1: *Caenorhabiditis elegans*, a nematode worm used as a simple animal model of a multicellular organism by Biologists.

Now, for our main theoretical result. We take the limit $\Delta a \to 0$ of the discrete Euler-Lotka equation (2.8) as follows:

$$\begin{aligned}
1 &= \sum_{j=1}^{\omega} f_j e^{-jr} \quad (\text{Discrete Euler} - \text{Lotka equation}) \\
&= \sum_{j=1}^{\omega} l_j m_j e^{-j\Delta a(r/\Delta a)} \quad (\text{using } f_j = l_j m_j;\ r = \Delta a(r/\Delta a)) \\
&= \sum_{j=1}^{\omega} l(a_j) m(a_j) e^{-a_j R} \Delta a \quad (\text{using } m_j = m(a_j)\Delta a;\ a_j = j\Delta a; R = r/\Delta a) \\
&= \sum_{j=1}^{\omega} f(a_j) e^{-a_j R} \Delta a \quad (\text{using } l(a_j)m(a_j) = f(a_j) \\
&= \int_0^{\infty} f(a) e^{-aR} da. \quad (\text{by converting the Riemann sum to an integral})
\end{aligned}$$

Notice that in the discrete model, asymptotically $u_{i,n} \sim \lambda_1^n = e^{rn}$, so that since $t_n = n\Delta a$, in the continuous model $u(a, t_n) \sim e^{rt_n/\Delta a} = e^{Rt_n}$. Therefore, $N(t) \sim e^{Rt}$, and R is the asymptotic population growth rate. The continuous Euler-Lotka equation

$$\int_0^{\infty} f(a) e^{-aR} da = 1, \tag{2.9}$$

is thus an integral equation for the population growth rate R given the net maternity function $f(a)$. Again, this equation is usually solved numerically using Newton's method.

2.5 The brood size of a hermaphroditic worm

Caenorhabditis elegans, a soil-dwelling nematode worm about 1 mm in length,

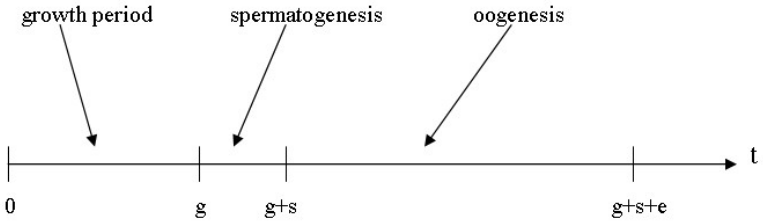

Figure 2.2: A hermaphrodite's life-history

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 a multicellular organism led 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 selfing hermaphrodite must be in some sense optimum. Here, we show how an age-structured model applied to *C. elegans* gives theoretical insight into the brood size of a selfing hermaphrodite.

To develop a mathematical model for *C. elegans*, we need to know details of its life-history. A simplified time chart of a hermaphrodite's life-history is shown in Fig. 2.2. The fertilized egg is laid at time $t = 0$. During a growth period, the immature worm develops through four larval stages (L1-L4). At the end of L4, spermatogenesis occurs and the hermaphrodite produces and stores all of the sperm it will later use. After the final L4 molt, the hermaphrodite produces eggs (oogenesis), self-fertilizes them using internally stored sperm, and lays them. In the absence of males, egg production ceases after the hermaphrodite is sperm depleted. We assume the growth period occurs for $0 < t < g$, spermatogenesis for $g < t < g + s$, and egg-production, self-fertilization, and laying for $g + s < t < g + s + e$.

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 other than metabolic to the hermaphrodite for producing additional sperm. To understand the basic biology, it is instructive to consider two limiting cases: (1) no sperm production; (2) infinite sperm production. In both cases, no offspring are produced: in the first case because there are no sperm, and in the second case because egg production never commences. The number of sperm a hermaphrodite produces before producing eggs is there-

g	growth period	64 hr
s	sperm production period	12 hr
e	egg production period	48 hr
p	sperm production rate	24 hr^{-1}
m	egg production rate	6 hr^{-1}
b	brood size	288

Table 2.3: Parameters in a life-history model of *C. elegans*, with experimental estimates

fore a compromise: although production of more sperm results in additional offspring, it also delays the start of egg production.

Our main theoretical assumption is that natural selection will select worms that have the largest growth rate R. Worms containing a genetic mutation that infers a larger value for R will eventually outnumber all other worms, and this genetic mutation will become fixed in the population. From the continuous Euler-Lotka equation (2.9), the growth rate R is determined from the net maternity function $f(a)$. Our mathematical attack on the problem is to model $f(a)$, determine $R = R(s)$, where s is the period of spermatogenesis, and then maximize R with respect to s. The value of s at which R is maximum will be considered the naturally selected value.

The parameters we need in our mathematical model are listed in Table 2.3. In addition to the growth period g, sperm production period s, and egg production period e (all in units of time), we also need the sperm production rate p and egg production rate m (both in units of inverse time). We also define the brood size b as the total number of fertilized eggs laid by a selfing hermaphrodite. It is reasonable to assume that the growth period g and the sperm and egg production rates p and m are independent of the length of the sperm production period s. The egg production period, e, however, depends on s since an increase in the number of sperm produced will correspondingly increase the number of eggs laid. In fact, the brood size is equal to the number of sperm produced, which is also equal to the number of eggs laid, so that $b = ps = me$. We can thus find $e = e(s)$ explicitly, as

$$e(s) = ps/m,$$

and e can be eliminated from our model in favor of the constants p and m, and the independent variable s.

One of the most challenging and difficult aspects of modeling is to connect the idealized parameters used in a model with real experimental data. Here, the most accessible experimental data that can be obtained by direct observation are: (i) the average time it takes for an egg that is laid to develop into an egg-laying adult hermaphrodite ($g + s$ hours); (ii) the average duration of the egg laying period (e hours); (iii) the average rate at which eggs are produced (m eggs per hour), and; (iv) the total brood size of a hermaphrodite (b fertilized eggs). Although direct observation can yield these values, different authors have reported different values, perhaps because of subtle differences in the culturing of the worms, and also because of the inherent variability of biological processes. The least accessible experimental data are those modeling the internal sperm production: (v) the sperm production period s, and (vi) the sperm production

rate p. Notice that $b = ps$, so experimental determination only of the brood size b and one of s or p is necessary. In Table 2.3, we list some reasonable experimental estimates for these parameters for worms cultured at 20°C, but note that we have slightly adjusted the experimental values to satisfy the constraint $ps = me = b$.

We will first use the experimental estimates of the growth period g, and the sperm and egg production rates p and m in Table 2.3 to predict the numerical values of the sperm production period s, the egg production period e, and the brood size b, which we will then compare to the values in Table 2.3. It is unrealistic to expect exact agreement: the values of Table 2.3 contain experimental error, and our model may be oversimplified.

The continuous Euler-Lotka equation (2.9) for the growth rate R requires a model for $f(a) = m(a)l(a)$, where $m(a)$ is the age-dependent maternity function and $l(a)$ is the age-dependent survival function. Now $l(a)$ is the probability of a worm surviving to age a. To model $l(a)$, we assume that the probability of a worm of age a dying in the next small interval of time da is $d \cdot da$, where d is the death rate of the worm, which we assume to be constant independent of a. Here, we assume that worms do not die of old age for which d would increase with age, but rather are eaten by predators, die of infectious disease, starve to death, etc. Under the assumption of constant d, the probability of a worm surviving to age $a+da$ is equal to the probability of surviving to age a times the probability of not dying in the next small interval of time da, that is $(1-d \cdot da)$. Hence,

$$l(a + da) = l(a)(1 - d \cdot da),$$

or

$$\frac{l(a + da) - l(a)}{da} = -d \cdot l(a),$$

and as $da \to 0$,

$$l' = -d \cdot l.$$

Since we assume the probability of an egg being layed is one, $l(0) = 1$ and the solution to the ode is

$$l(a) = \exp(-d \cdot a). \tag{2.10}$$

Now the age-dependent maternity function $m(a)$ is defined so that $m(a)da$ is the expected number of offpsring produced over the age interval da. We assume that a hermaphrodite lays eggs at a constant rate m over the ages $g+s < a < g+s+e$; therefore,

$$m(a) = \begin{cases} m & \text{for } g + s < a < g + s + e, \\ 0 & \text{otherwise.} \end{cases} \tag{2.11}$$

Using (2.10) and (2.11), the continuous Euler-Lotka equation (2.9) for the growth rate R becomes

$$\int_{g+s}^{g+s+e} m \exp[-(d + R)a]da = 1. \tag{2.12}$$

We will maximize R with respect to s. The value of s that maximizes R will also maximize $d + R$, since the death rate d is independent of s. Therefore, we can eliminate the unknown parameter d from the mathematical model by letting $B = d + R$, and maximize B with respect to s.

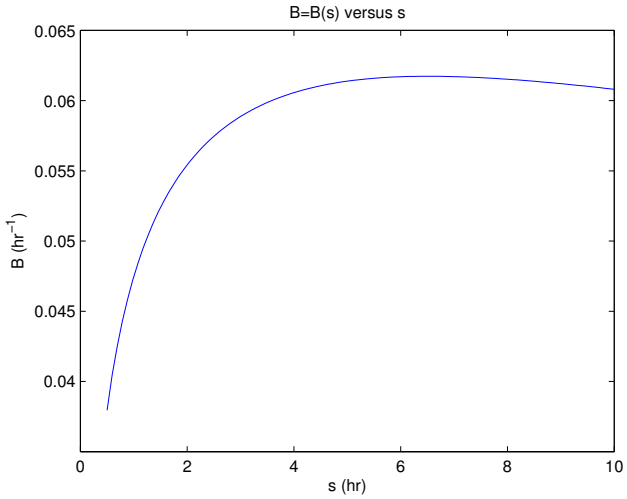

Figure 2.3: $B = B(s)$ versus s

First, we integrate the Euler-Lotka equation (2.12) as follows:

$$\begin{aligned} 1 &= \int_{g+s}^{g+s+e} m \exp(-Ba)da \\ &= \frac{m}{B}\left\{\exp\left[-(g+s)B\right] - \exp\left[-(g+s+e)B\right]\right\} \\ &= \frac{m}{B}\exp\left[-(g+s)B\right]\left\{1 - \exp\left[-(ps/m)B\right]\right\}, \end{aligned}$$

where in the last equality we have used $e = ps/m$. Thus, the Euler-Lotka equation reduces to a nonlinear transcendental equation for $B = B(s)$:

$$\frac{B}{m}\exp\left[(g+s)B\right] + \exp\left[-(ps/m)B\right] - 1 = 0. \tag{2.13}$$

This equation may be solved for $B = B(s)$ by Newton's method. We let

$$F(B) = \frac{B}{m}\exp\left[(g+s)B\right] + \exp\left[-(ps/m)B\right] - 1,$$

and differentiate with respect to B, to obtain

$$F'(B) = \frac{1}{m}\left(1 + (g+s)B\right)\exp\left[(g+s)B\right] - \frac{ps}{m}\exp\left[-(ps/m)B\right].$$

For a given s, we solve $F(B) = 0$ by iterating

$$B_{n+1} = B_n - \frac{F(B_n)}{F'(B_n)}.$$

Some numerical experimentation is necessary to find appropriate starting values for B. Fig. 2.3 is a graph of $B = B(s)$ versus s, and here is the MATLAB code I used to generate the figure:

```
function [s, B] = B_newton
global g p m
g=64; p=24; m=6; %experimental estimates
maxit=50; tol=5*eps; %for Newton's method
s=linspace(0.5,10,100);
for i=1:length(s)
    if i==1, B(i)=.35; else, B(i)=B(i-1); end
    for j=1:maxit
        delta = F(B(i),s(i))/Fp(B(i),s(i));
        B(i) = B(i) - delta;
        error=abs(F(B(i),s(i)));
        if error < tol, break, end
    end
    if j==maxit, disp(s(i)), end
end
plot(s,B); xlabel('s (hr)'); ylabel('B (hr^{-1})'); title('B=B(s) versus s');
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
function y=F(B,s)
global g p m
y=(B/m)*exp((g+s)*B) + exp(-(p*s/m)*B) - 1;
%
function y=Fp(B,s)
global g p m
y=(1/m)*(1+(g+s)*B)*exp((g+s)*B) - (p*s/m)*exp(-(p*s/m)*B);
```

To compute $B = B(s)$, we have used the values of g, p and m from Table 2.3. Clearly, $B = B(s)$ has a maximum value $B = 0.062\text{hr}^{-1}$ at $s = 6.5$ hr. With this value of s, we compute $e = 26$ hr and $b = 156$. The values for s, e and b are all approximately 45% less than the values of Table 2.3. Further research is required to understand the discrepancy, and I will comment further in class.

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Chapter 3

Population Dynamics

Previously, we considered population growth by neglecting interactions of individuals with their environment or with each other. If the birth rate exceeds the death rate then exponential growth ensues. Thomas Malthus, in *An Essay on the Principle of Population* (1798), used unchecked growth to famously predict a global famine among Mankind unless family size was governmentally regulated (an idea echoed by the Chinese mainland's one child policy). The reading of Malthus is said by Charles Darwin in his autobiography to have inspired his formulation of the principle of evolution by natural selection, which today forms the cornerstone of biological theory.

Unchecked exponential growth obviously does not occur in nature. Population growth may be regulated by the environment or by competition among individuals within a species or across species. Here, we will develop models for three types of regulation. First, we will discuss a simple mathematical model of environmentally regulated population growth. Second, we will extend this model to species competition. And third, we will present the famous Lotka-Volterra predator-prey model. Since all these mathematical models are nonlinear differential equations, mathematical methods to analyze such equations will be developed.

3.1 Logistic equation for population growth

The deterministic model of population growth is given by

$$\frac{dN}{dt} = rN,$$

where $r = b - d$ is the difference between the birth and death rates. If $r > 0$, then the population grows exponentially (so-called Malthusian growth). Clearly, populations when left alone do not grow exponentially forever. Eventually, their growth will be checked by the limited resources available. To model environmental limits, we assume that the environment can only continuously support a population of size K, which we call the environmental carrying capacity. Accordingly, we look for a nonlinear equation of the form

$$\frac{dN}{dt} = rNF(N),$$

where $F(N)$ is a function that provides a model for the carrying capacity K. In other words, $F(0) = 1$ (the population grows exponentially with growth rate r when N is small) and $F(K) = 0$ (the population stops growing at the carrying capacity). The simplest function $F(N)$ that can satisfy these two conditions is linear, and it is easy to see that $F(N) = 1 - N/K$. We thus have the logistic equation

$$\frac{dN}{dt} = rN(1 - N/K), \tag{3.1}$$

which is an important model for a variety of different processes besides bounded population growth.

Although Eq. (3.1) is a nonlinear equation, complete analytical solution is possible by separating variables. Before we embark on this algebra, it is worthwhile to illustrate some basic concepts used in analyzing nonlinear differential equations.

Fixed points, also called equilibria, of a differential equation such as (3.1) are defined as the values of N where $\dot{N} = 0$. Here, we see that the fixed points of (3.1) 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

$$\dot{x} = f(x), \tag{3.2}$$

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

$$x(t) = x_* + \epsilon(t), \tag{3.3}$$

where initially $\epsilon(0)$ is small but different from zero. Substituting (3.3) into (3.2), we obtain

$$\begin{aligned} \dot{\epsilon} &= f(x_* + \epsilon) \\ &= f(x_*) + \epsilon f'(x_*) + \dots \\ &= \epsilon f'(x_*) + \dots, \end{aligned}$$

where the second equality comes from a Taylor series expansion about $\epsilon = 0$, and the third equality uses the fact that x_* is a fixed point. If $f'(x_*) \neq 0$, we can take $\epsilon(0)$ small enough to neglect the higher-order terms in ϵ at least for small times, and integrating we have

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

Therefore, $\epsilon(t) \to 0$ as $t \to \infty$ provided $f'(x_*) < 0$. Our conditions on stability are

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

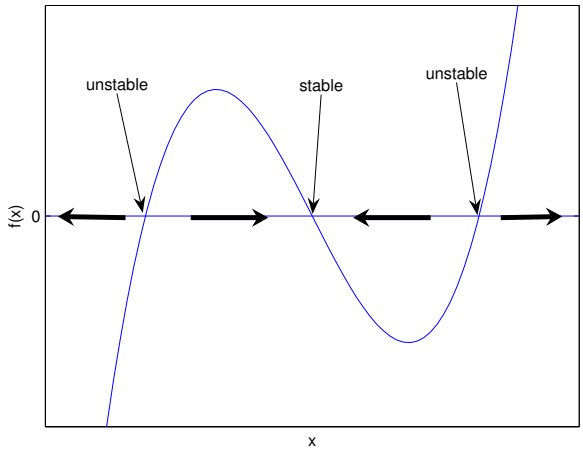


Figure 3.1: *Solving one-dimensional stability using a graphical approach.*

Another equivalent, but sometimes simpler approach to analyzing the stability of the fixed points of a one-dimensional nonlinear equation such as (3.2) is to plot $f(x)$ versus x. We show a generic example in Fig. 3.1. 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, since any initial condition for these values of x satisfy $\dot{x} < 0$, so that x will be decreasing. Likewise, if $f(x) > 0$, then the arrow points to the right. Fixed points with arrows on each side pointing in are stable, and fixed points with arrows on each side pointing out are unstable, as illustrated in Fig. 3.1. Clearly, this graphical approach is equivalent to the analytic method, since $f'(x_*) < 0$ implies f is decreasing at the x-intercept x_* so that f is positive to the left of x_* and negative to the right of x_*, and drawn arrows will point inward towards x_* indicating x_* is a stable fixed point. If $f'(x_*) > 0$, then f is increasing at x_*, and drawn arrows will point outwards away from x_* indicating instability.

Considering the logistic equation (3.1), the fixed points are observed to be $N_* = 0, K$. A sketch of $F(N) = rN(1 - N/K)$ versus N, with $r, K > 0$ in Fig. 3.2 immediately shows that $N_* = 0$ is an unstable fixed point and $N_* = K$ is a stable fixed point. The analytical approach computes $F'(N) = r(1-2N/K)$, so that $F'(0) = r > 0$ and $F'(K) = -r < 0$, and again we conclude that $N_* = 0$ is unstable and $N_* = K$ is stable.

We now demonstrate how to solve the logistic equation. Although this relatively simple equation can be solved directly, we first nondimensionalize to illustrate this very important technique that will later prove most useful. Perhaps we can guess that the appropriate unit of time will be $1/r$, and population size should be measured in fractions of K. Here, however, we nondimensionalize in a generic fashion and show how the choices just noted are in fact the most appropriate. Accordingly, we nondimensionalize time and population size as

$$\tau = t/t_*, \quad \eta = N/N_*,$$

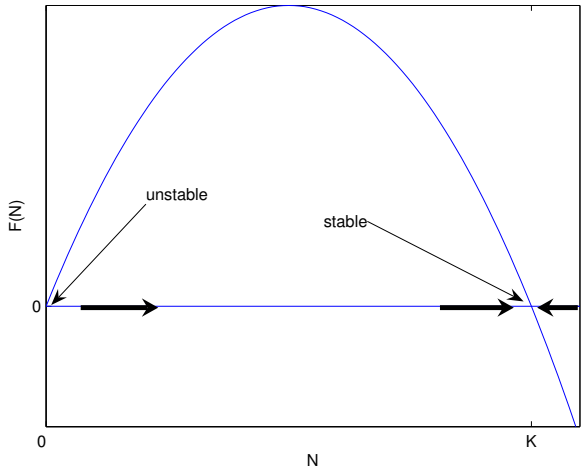


Figure 3.2: *Determining stability of the fixed points of the logistic equation.*

with t_* and N_* constants to be determined. 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, Eq. (3.1), 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 $N_* = K$. We thus choose to nondimensionalize our variables as

$$\tau = rt, \quad \eta = N/K,$$

and the logistic equation, in nondimensional form, becomes

$$\frac{d\eta}{d\tau} = \eta\left(1 - \eta\right), \tag{3.4}$$

with nondimensional initial condition $\eta(0) = \eta_0 = N_0/K$, where N_0 is the initial population size. Note that the nondimensional logistic equation, (3.4), has no free parameters, while the dimensional form of the equation, (3.1), 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 useful before proceeding to numerical solution, since the parameter space needed to explore may be substantially reduced.

Solution of the nondimensional logistic equation, (3.4), can proceed by separating variables. Separating, and integrating from $\tau = 0$ to τ, with correspond-

ing values of η: η_0 to η,

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

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

$$\begin{aligned} \frac{1}{\eta(1-\eta)} &= \frac{A}{\eta} + \frac{B}{1-\eta} \\ &= \frac{A + (B-A)\eta}{\eta(1-\eta)}; \end{aligned}$$

and equating the coefficients of the numerators proportional to η^0 and η^1, we have $A = 1$ and $B = 1$. Therefore,

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

Solving for η, we first exponentiate both sides and then isolate η:

$$\begin{aligned} \frac{\eta(1-\eta_0)}{\eta_0(1-\eta)} &= e^{\tau} \\ &\text{or} \\ \eta(1-\eta_0) &= \eta_0 e^{\tau} - \eta\eta_0 e^{\tau} \\ &\text{or} \\ \eta(1-\eta_0+\eta_0 e^{\tau}) &= \eta_0 e^{\tau} \\ &\text{or} \\ \eta &= \frac{\eta_0}{\eta_0 + (1-\eta_0)e^{-\tau}}. \end{aligned}$$

Returning to dimensional variables, we finally have

$$N(t) = \frac{N_0}{N_0/K + (1 - N_0/K)e^{-rt}}. \tag{3.5}$$

There are many ways to write Eq. (3.5), so please examine my carefully considered choice. Aesthetic considerations in writing the final result is an important element of mathematical technique that students all too often neglect (it's the right answer, how come I didn't get full marks!). In deciding how to write Eq. (3.5), 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) $\lim_{K\to\infty} N(t) = N_0 \exp(rt)$.

In Fig. 3.3, we plot the solution to the nondimensional logistic equation for initial conditions $\eta_0 = 0.02$, 0.2, 0.5, 0.8, 1.0, and 1.2. The lowest curve is the characteristic 'S-shape' usually associated with the solution of the logistic equation, and appears in many other types of modeling problems. The MATLAB script to produce this plot is shown below.

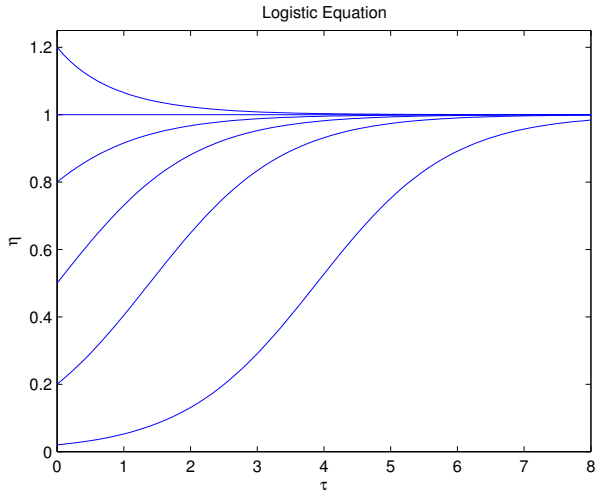


Figure 3.3: *Solution of the nondimensional logistic equation.*

```
eta0=[0.02 .2 .5 .8 1 1.2];
tau=linspace(0,8);
for i=1:length(eta0)
    eta=eta0(i)./(eta0(i)+(1-eta0(i)).*exp(-tau));
    plot(tau,eta);hold on
end
axis([0 8 0 1.25]);
xlabel('\tau'); ylabel('\eta'); title('Logistic Equation');
```

3.2 A model of species competition

Suppose we want to model the competition for resources between two species. We can start by modeling the population growth of each species by their own logistic equation. Different populations would be characterized by 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

$$\begin{aligned} \frac{dN_1}{dt} &= r_1 N_1(1 - N_1/K_1), \\ \frac{dN_2}{dt} &= r_2 N_2(1 - N_2/K_2). \end{aligned}$$

These are uncoupled equations so that clearly $N_1 \to K_1$ and $N_2 \to K_2$ as $t \to \infty$. How can we model the competition between species? If both N_1 and N_2 are small, then resources are plentiful for both species and their population sizes should grow exponentially with growth rates r_1 and r_2. If species one and two compete for some of the same resources, then when N_2 increases, the resources available to species one decreases, and when N_1 increases, the resources available to species two decreases. Since we do not know how much of an impact species one and species two have on each other, we introduce two parameters to model

the cross-species competition. A reasonable modification that couples the two logistic equations is

$$\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{N_1 + \alpha N_2}{K_1}\right), \tag{3.6}$$

$$\frac{dN_2}{dt} = r_2 N_2 \left(1 - \frac{\beta N_1 + N_2}{K_2}\right), \tag{3.7}$$

where α and β are dimensionless parameters that model the consumption of species one's resources by species two, and species two's resources by species one, respectively. As an example, suppose that both species eat exactly the same food, but species two consumes twice as much as species one. A model for this would have $\alpha = 2$ and $\beta = 1/2$, since one individual of species two is equivalent to two individuals of species one when considering the carrying capacity of the environment.

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 $\alpha = \beta = 1$, as appropriate for this example, the coupled logistic equations (3.6) and (3.7) become

$$\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{N_1 + N_2}{K_1}\right), \quad \frac{dN_2}{dt} = r_2 N_2 \left(1 - \frac{N_1 + N_2}{K_2}\right). \tag{3.8}$$

For sake of argument, we assume $K_1 > K_2$. 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 in this case a simpler argument can suffice. We first consider $(N_1, N_2) = (K_1, \epsilon)$, with ϵ small. Since $K_1 > K_2$, observe from (3.8) that $\dot{N}_2 < 0$ 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 ϵ small. Again, since $K_1 > K_2$, observe from (3.8) that $\dot{N}_1 > 0$ 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 extinct. This is the so-called principle of *competive exclusion*, also called K-selection since the species with the largest K wins. There is also r-selection, that is the species with the largest r wins, but this type of selection is not captured using our coupled-logistic equations.

For other values of α and β, coexistence of two species within our model is in fact possible. The calculation is more involved, and here I just present the result: the coexistence of two species is possible only if $\alpha K_2 < K_1$ and $\beta K_1 < K_2$.

3.3 Lotka-Volterra predator-prey model

Here, we model the interaction between predator and prey populations. The classic example is populations of hares (rabbits) and lynxes (foxes). We assume

that prey numbers will grow exponentially in the absence of predators (there is unlimited food available to the prey), and that predator numbers will decay exponentially in the absence of prey (predators must eat prey to survive). The coupling between the predator and the prey populations serve to increase the predator population and decrease the prey population.

Let $U(t)$ and $V(t)$ be the number of prey and predators, respectively, at time t. To develop a coupled differential equation model, we consider population sizes at a 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

$$\begin{aligned} U(t + \Delta t) &= U(t) + \alpha \Delta t U(t) - \gamma \Delta t U(t) V(t), \\ V(t + \Delta t) &= V(t) + e\gamma \Delta t U(t) V(t) - \beta \Delta t V(t). \end{aligned}$$

The parameters α and β are the average per capita birthrate of prey and average per capita deathrate of predators, respectively. The coupling terms can be understood as follows: γ is the fraction of prey caught per predator per unit time, so that the total number of prey caught by all the predators in a time Δt is $\gamma \Delta t UV$. The number of prey caught is then converted into newborn predators (view this as a conversion of biomass), with conversion factor e, so that the number of predators in the time Δt increases by $e\gamma \Delta t UV$.

We convert these equations into differential equations by letting $\Delta t \to 0$, and obtain the well-known Lotka-Volterra predator-prey equations:

$$\frac{dU}{dt} = \alpha U - \gamma UV, \quad \frac{dV}{dt} = e\gamma UV - \beta V. \tag{3.9}$$

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

$$\frac{dx}{dt} = f(x, y), \quad \frac{dy}{dt} = g(x, y), \tag{3.10}$$

though our results can be generalized to larger systems. The system given by (3.10) 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 one fixed point is (x_*, y_*). To determine the linear stability of this fixed point, we consider initial conditions for (x, y) near the fixed point with small independent perturbations in both directions, i.e., $x(0) = x_* + \epsilon(0)$, $y(0) = y_* + \delta(0)$. Our goal is to determine whether the initial perturbation grows or decays in time (unstable or stable fixed point) by solving the differential equations to obtain the time-dependence of the perturbation. Accordingly, we let

$$x(t) = x_* + \epsilon(t), \quad y(t) = y_* + \delta(t), \tag{3.11}$$

and substitute (3.11) into (3.10). Since x_* and y_* are constants, we have

$$\frac{d\epsilon}{dt} = f(x_* + \epsilon, y_* + \delta), \quad \frac{d\delta}{dt} = g(x_* + \epsilon, y_* + \delta).$$

Linear stability analysis assumes that the initial perturbations $\epsilon(0)$ and $\delta(0)$ are sufficiently small so that a two-dimensional Taylor series expansion of f and g about $\epsilon = \delta = 0$ may be truncated at first-order. Note that in general, the two-dimensional Taylor series of a function $F(x, y)$ about the origin is given by

$$\begin{aligned} F(x,y) &= F(0,0) + xF_x(0,0) + yF_y(0,0) \\ &+ \frac{1}{2}\left[x^2F_{xx}(0,0) + 2xyF_{xy}(0,0) + y^2F_{yy}(0,0)\right] + \ldots, \end{aligned}$$

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 of higher-order than ϵ and δ. 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

$$\frac{d}{dt}\begin{pmatrix}\epsilon\\ \delta\end{pmatrix} = \begin{pmatrix} f_x^* & f_y^* \\ g_x^* & g_y^*\end{pmatrix}\begin{pmatrix}\epsilon\\ \delta\end{pmatrix}, \tag{3.12}$$

where $f_x^* = f_x(x_*, y_*)$, etc. Equation (3.12) is a system of linear ode's, and solution proceeds by assuming the form

$$\begin{pmatrix}\epsilon\\ \delta\end{pmatrix} = e^{\lambda t}\mathbf{v}. \tag{3.13}$$

Upon substitution of (3.13) into (3.12), and cancelling $e^{\lambda t}$, we obtain the linear algebra eigenvalue problem

$$\mathrm{J}^*\mathbf{v} = \lambda\mathbf{v}, \text{ with } \mathrm{J}^* = \begin{pmatrix} f_x^* & f_y^* \\ g_x^* & g_y^*\end{pmatrix},$$

where λ is the eigenvalue and $\mathbf{v}$ the corresponding eigenvector, and J^* is the Jacobian matrix evaluated at the fixed point. The eigenvalue is determined from the characteristic equation

$$\det\left(\mathrm{J}^* - \lambda\mathrm{I}\right) = 0,$$

which for a two-by-two Jacobian matrix results in a quadratic equation for λ. From the form of the solution, (3.13), the fixed point is stable if for all eigenvalues λ, $\mathrm{Re}\lambda < 0$; and unstable if at least one λ satisfies $\mathrm{Re}\lambda > 0$, where $\mathrm{Re}\lambda$ means the real part of the (possibly) complex eigenvalue λ.

We now reconsider the Lotka-Volterra equations, (3.9). Fixed point solutions are found by solving $\dot{U} = \dot{V} = 0$, and the two solutions are

$$(U_*, V_*) = (0,0) \text{ or } (\frac{\beta}{e\gamma}, \frac{\alpha}{\gamma}). \tag{3.14}$$

Clearly, the trivial fixed point $(0, 0)$ is unstable since the prey population grows exponentially if 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

$$\begin{aligned} F_U = &\quad \alpha - \gamma V, \quad F_V = -\gamma U \\ G_U = &\quad e\gamma V, \quad G_V = e\gamma U - \beta. \end{aligned}$$

The Jacobian at the fixed point $(U_*, V_*) = (\beta/e\gamma, \alpha/\gamma)$ is

$$\mathrm{J}^* = \begin{pmatrix} 0 & -\beta/e \\ e\alpha & 0 \end{pmatrix};$$

and

$$\det(\mathrm{J}^* - \lambda \mathrm{I}) = \begin{vmatrix} -\lambda & -\beta/e \\ e\alpha & -\lambda \end{vmatrix} = \lambda^2 + \alpha\beta = 0$$

has solution $\lambda_\pm = \pm i\sqrt{\alpha\beta}$, which are pure imaginary. When the eigenvalues of a 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 frequence of oscillation is $\omega = \sqrt{\alpha\beta}$, and the period of the oscillation is $2\pi/\omega$.

It is informative to plot U and V versus t (time series plot), and V versus U (phase space diagram) to view the behavior of the solutions. For a nonlinear system of equations such as (3.9), a numerical solution is necessary. The Lotka-Volterra system has four free parameters α, β, γ and e. The relevant units here are time, number of prey, and number of predators, and the Buckingham Pi Theorem predicts that by appropriate nondimensionalization of the equations, the number of free parameters can be reduced by three, to a managable single nondimensional grouping of parameters. We choose to nondimensionalize time using the angular frequency of oscillation, and the number of prey and predators by their fixed point values. In other words, with carets denoting the nondimensional variables, let

$$\hat{t} = \sqrt{\alpha\beta}t, \quad \hat{U} = U/U_* = \frac{e\gamma}{\beta}U, \quad \hat{V} = V/V_* = \frac{\gamma}{\alpha}V. \tag{3.15}$$

Substitution into the Lotka-Volterra equations, (3.9), results in the nondimensional Lotka-Volterra equations

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

with single nondimensional group $r = \sqrt{\alpha/\beta}$. A numerical solution uses MATLAB's ode45.m built-in function to integrate the nondimensional differential equations. The code below produces Fig. 3.4. Notice how the predator population lags the prey population, as one would expect, since an increase in the prey population results in a delayed increase in predator numbers as the predators obtain more to eat. The phase space diagrams clearly show the periodic nature of the oscillation. Note that the curves move counterclockwise, since prey numbers increase when predator numbers are minimum, and prey numbers decrease when predator numbers are maximum.

```
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','Location','NorthOutside');
%phase space plot
xpos=[-4 -1 0]; ypos=[2 1 1];%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+delta],options,r(i));
         U=UV(:,1); V=UV(:,2);
         figure(2);subplot(3,1,i); plot(U,V); hold on;
     end
     ylabel('predator'); axis equal;
     text(xpos(i),ypos(i),['r=',num2str(r(i))]);
end
xlabel('prey')

function dUV=lv_eq(t,UV,r)
dUV=zeros(2,1);
dUV(1) = r*(UV(1)-UV(1)*UV(2));
dUV(2) = (1/r)*(UV(1)*UV(2)-UV(2));
```

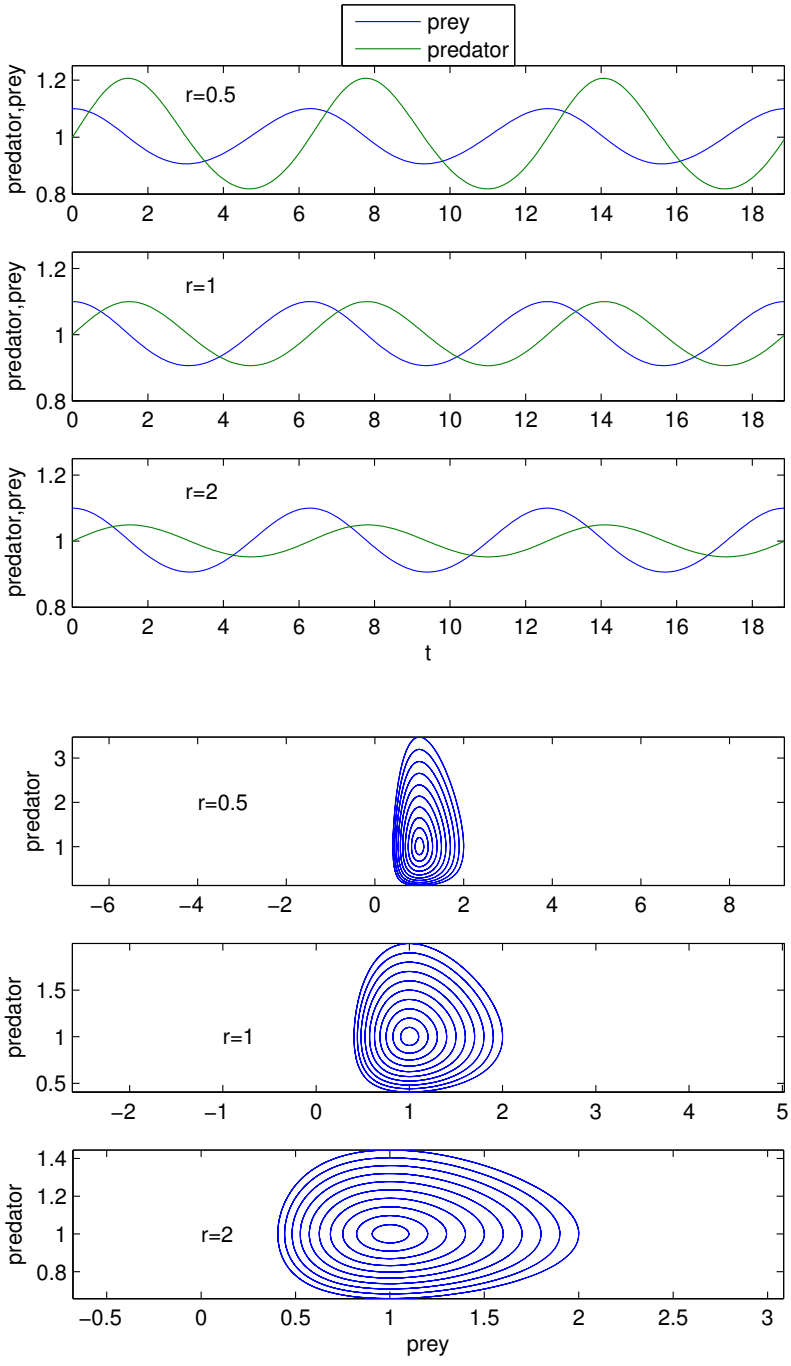


Figure 3.4: *Solution of the nondimensional Lotka-Volterra equations.*

Chapter 4

Infectious Disease Modeling

In the late 1320's, an outbreak of the the bubonic plague occured 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 occured in 1347. During the five year period 1347-1352, 25 million people in Europe died of the black death, representing approximately 1/3 of the population. Other more recent epidemics include the influenza pandemic known as the Spanish flu that killed 50-100 million people worldwide over the year 1918-1919, and the present AIDS epidemic, originating in Africa and first recognized in the USA in 1981, and currently responsible for killing more than 25 million people. For comparison, the SARS epidemic for which Hong Kong was the global epicenter resulted in 8098 probable SARS cases and more than 774 deaths. Yet, we know well that this relatively small epidemic had locally great social and economic impact.

Here, we introduce the most basic mathematical models of infectious disease. 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 of containment and eradication.

4.1 SI model

The simplest model of an infectious disease categorizes people as susceptibles or infectives, with S the number of susceptibles and I the number of infectives. Susceptibles are healthy, but become sick by contact with infectives. Here, and in all subsequent models, we assume that the population under study is well-mixed so that every individual has equal probability of coming into contact with every other individual. Note that this is a major approximation. As an example, while the population of Amoy gardens may 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 be considered well-mixed because of the larger geographical distances, and the limited travel of many individuals outside the districts in which they live.

We derive the governing differential equation for the SI model by considering the number of people that become sick in a time Δt. Let $\beta\Delta t$ be the probability that a random infective individual infects a random susceptible individual in a

time Δt. Then the expected number of newly infected individuals in the total population in a time Δt is $\beta \Delta t SI$. We thus have

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

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

$$\frac{dI}{dt} = \beta SI. \tag{4.1}$$

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 fixed population of size N, neglecting births and deaths, so that $S + I = N$, a constant. We can eliminate S and rewrite (4.1) in the form

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

which is immediately recognizable as a logistic equation, with growth rate βN and carrying capacity N. Thus, in the SI model, $I \to N$ as $t \to \infty$ and the entire population eventually becomes infective.

4.2 SIS model

The SI model may be simply extended to the SIS model, where infectives recover and become susceptible again. We assume that the probability that an infective recovers in a time dt is given by γdt. Then the total number of infectives that recover in a time dt is given by $I \times \gamma dt$, and we have

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

or as $dt \to 0$:

$$\frac{dI}{dt} = \beta SI - \gamma I, \tag{4.2}$$

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

$$\mathcal{R}_0 = \frac{\beta N}{\gamma}. \tag{4.3}$$

Equation(4.2) may then be rewritten as

$$\frac{dI}{dt} = \gamma(\mathcal{R}_0 - 1) I \left(1 - \frac{I}{N(1 - 1/\mathcal{R}_0)}\right),$$

which is again recognizable as a logistic equation but now with growth rate $\gamma(\mathcal{R}_0 - 1)$ and carrying capacity $N(1 - 1/\mathcal{R}_0)$. The disease will be removed from the population if the growth rate is negative, that is $\mathcal{R}_0 < 1$, and the disease will become endemic if the growth rate is positive, that is $\mathcal{R}_0 > 1$. For an endemic disease with $\mathcal{R}_0 > 1$, the number of infectives asymptotically approaches a

nonzero constant equal to the carrying capacity, that is $I \to N(1 - 1/\mathcal{R}_0)$ as $t \to \infty$.

We now give a biological interpretation to $\mathcal{R}_0$. 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 times the probability of not recovering during the time Δt, we have

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

or as $\Delta t \to 0$,

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

Therefore, with $l(0) = 1$,

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

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, times the expected number of secondary infections produced by a single infective over the 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 given by

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

where we have approximated $S(t) \approx N$ over 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. Note that we have seen another analgous definition of the *basic reproductive ratio* in our discussion of age-structured populations. There, the basic reproductive ratio was the number of female offspring expected of a new born female over her lifetime, and the population size would grow exponentially if this value was greater than unity. Here is a good example of how a mathematical idea can be recycled to model apparently unrelated problems.

4.3 SIR epidemic disease model

The SIR model, first published by Kermack & 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

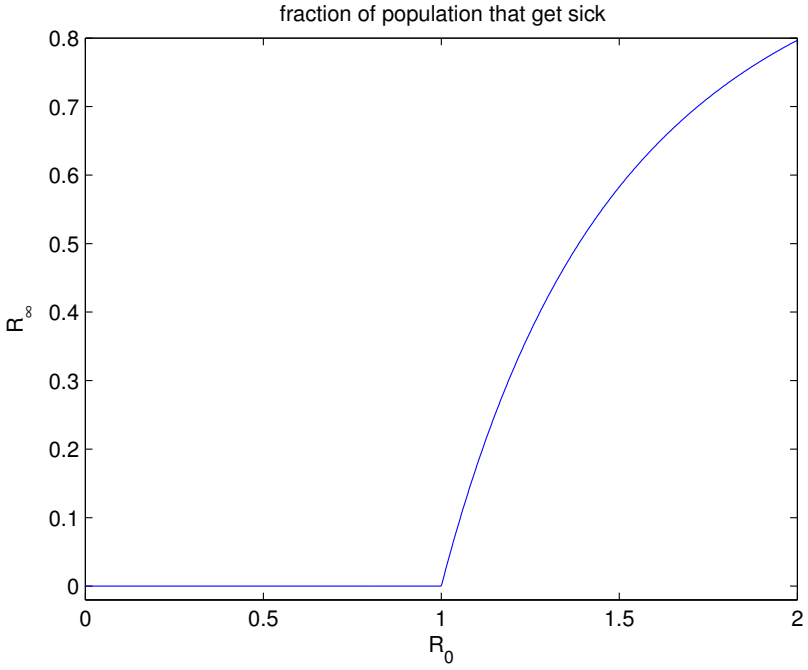


Figure 4.1: *Fraction of population that get sick in the SIR model as a function of the basic reproduction ratio* $\mathcal{R}_0$.

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 γ, but in the SIR model they move directly into the R class. The model may be diagrammed as

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

and the corresponding coupled differential equations are

$$\frac{dS}{dt} = -\beta SI, \quad \frac{dI}{dt} = \beta SI - \gamma I, \quad \frac{dR}{dt} = \gamma I, \tag{4.4}$$

with the constraint $S + I + R = N$, constant. For convenience, we nondimensionalize (4.4) using N for population size and γ^{-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 $\mathcal{R}_0 = \beta N/\gamma$. The nondimensional SIR equations are

$$\frac{d\hat{S}}{d\hat{t}} = -\mathcal{R}_0 \hat{S}\hat{I}, \quad \frac{d\hat{I}}{d\hat{t}} = \mathcal{R}_0 \hat{S}\hat{I} - \hat{I}, \quad \frac{d\hat{R}}{d\hat{t}} = \hat{I}, \tag{4.5}$$

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

We will use the SIR model to address two fundamental questions: (1) what is the condition for an epidemic to occur? and; (2) if an epidemic occurs, what fraction of the population gets sick?

Let $(\hat{S}_*, \hat{I}_*, \hat{R}_*)$ be the fixed points of Eq. (4.5). 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 (4.5) 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. Accordingly, we assume the initial population is at a fixed point with no infectives, perturb this fixed point by introducing a small number of infectives, and determine the fixed point's stability. The linear stability problem may be solved by considering only the equation for $d\hat{I}/dt$ in (4.5). With $\hat{I} << 1$ and $\hat{S} \approx \hat{S}_0$, we have

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

so that an epidemic occurs if $\mathcal{R}_0 \hat{S}_0 - 1 > 0$. Thus, the condition for an epidemic to occur in a given population is a condition on the basic reproductive ratio of the disease, that is an epidemic occurs if $\mathcal{R}_0 > 1/\hat{S}_0$. With the basic reproductive ratio given by $\mathcal{R}_0 = \beta N/\gamma$, and the nondimensional initial condition $\hat{S}_0 = S_0/N$, where S_0 is the number of initial susceptible individuals, the condition for an epidemic to occur is given by

$$\text{Condition for an epidemic to occur :} \quad \mathcal{R}_0 \hat{S}_0 = \frac{\beta S_0}{\gamma} > 1 \quad , \tag{4.6}$$

which could have been anticipated. That is, 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 (4.5) 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 (4.5). By the chain rule, $d\hat{S}/d\hat{t} = (d\hat{S}/d\hat{R})(d\hat{R}/d\hat{t})$, so that

$$\begin{aligned} \frac{d\hat{S}}{d\hat{R}} &= \frac{d\hat{S}/d\hat{t}}{d\hat{R}/d\hat{t}} \\ &= -\mathcal{R}_0 \hat{S}, \end{aligned}$$

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

$$\int_1^{\hat{1}-\hat{R}_\infty} \frac{d\hat{S}}{\hat{S}} = -\mathcal{R}_0 \int_0^{\hat{R}_\infty} d\hat{R},$$

which upon integration and simplification, results in the following transcendental equation for $\hat{R}_\infty$:

$$1 - \hat{R}_\infty - e^{-\mathcal{R}_0 \hat{R}_\infty} = 0, \tag{4.7}$$

which can be solved using Newton's method. We have

$$\begin{aligned} F(\hat{R}_\infty) &= 1 - \hat{R}_\infty - e^{-\mathcal{R}_0 \hat{R}_\infty}, \\ F'(\hat{R}_\infty) &= -1 + \mathcal{R}_0 e^{-\mathcal{R}_0 \hat{R}_\infty}, \end{aligned}$$

and Newton's method for solving $F(\hat{R}_\infty) = 0$ iterates

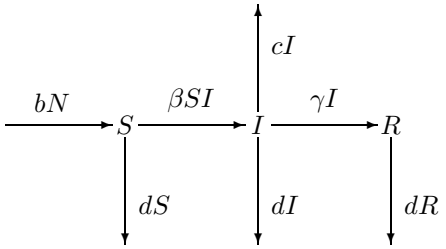
$$\hat{R}_\infty^{(n+1)} = \hat{R}_\infty^n - \frac{F(\hat{R}_\infty^{(n)})}{F'(\hat{R}_\infty^{(n)})}$$

for fixed $\mathcal{R}_0$ and suitable initial condition for $R_\infty^{(0)}$, which we take to be unity. My code for computing R_∞ as a function of $\mathcal{R}_0$ is given below. The result is shown in Fig. 4.1. Clearly, there is an explosion in the number of infections as $\mathcal{R}_0$ increases from unity. This is a classic example of what is known more generally as a *threshold phenomena*.

```
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 SIR endemic disease model

A disease is said to be endemic if it is always present in a population. If we wish to model an endemic disease over a long time-scale, we need to consider both the births of new individuals, and the natural death rate. We let the birth rate be b and the natural death rate d. We separately define c to be the death rate due to the disease, so that R is now the immune class. We may diagram a SIR model of an endemic disease as



and the differential equations can be written as

$$\frac{dS}{dt} = bN - \beta SI - dS, \quad \frac{dI}{dt} = \beta SI - (c + d + \gamma)I, \quad \frac{dR}{dt} = \gamma I - dR, \quad (4.8)$$

with $N = S + I + R$. Notice that in the endemic disease model, N satisfies the differential equation

$$dN/dt = (b - d)N - cI, \quad (4.9)$$

and is not necessarily constant.

To illustrate the existence of equilibrium solutions for which the disease is endemic, we model two simplifed situations. First, we assume no disease-related deaths ($c = 0$) and equal birth and death rates, $b = d$, so that the population size N is constant. Second, we assume that disease-related deaths, with death rate c, stabilize a growing population with $b > d$.

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 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

$$S_* = (\gamma + d)/\beta, \tag{4.10}$$

$$I_* = \frac{dN}{\gamma + d}\left(1 - \frac{\gamma + d}{\beta N}\right), \tag{4.11}$$

$$R_* = \frac{\gamma N}{\gamma + d}\left(1 - \frac{\gamma + d}{\beta N}\right). \tag{4.12}$$

Clearly, this solution only exists if $\beta N/(\gamma + d) \equiv \mathcal{R}_0 > 1$, defining the basic reproductive ratio $\mathcal{R}_0$ for this model. (Note that the probability that an infective leaves class I in a time Δt 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 $\mathcal{R}_0 > 1$.

In our second model, we consider the full system of equations (4.8)-(4.9) 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

$$R_* = \frac{\gamma(b - d)}{dc} N_*.$$

Therefore, since $N_* = S_* + I_* + R_*$, 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

$$\left(1 + \frac{\gamma}{d}\right)\left(\frac{b - d}{c}\right) < 1,$$

or

$$c > (b - d)\left(1 + \frac{\gamma}{d}\right). \tag{4.13}$$

When the disease-related death rate satisfies (4.13), then the population size will be stabilized.

Disease	Description	Symptoms	Complications
Diphtheria	A bacterial respiratory disease	Sore throat and low-grade fever	Airway obstruction, coma, and death
Haemophilus influenzae type b (Hib)	A bacterial infection occurring primarily in infants	Skin and throat infections, meningitis, pneumonia, sepsis, and arthritis	Death in one out of 20 children, and permanent brain damage in 10% - 30% of the survivors
Hepatitis A	A viral liver disease	Potentially none; yellow skin or eyes, tiredness, stomach ache, loss of appetite, or nausea	usually none
Hepatitis B	Same as Hepatitis A	Same as Hepatitis A	Life-long liver problems, such as scarring of the liver and liver cancer
Measles	A viral respiratory disease	Rash, high fever, cough, runny nose, and red, watery eyes	Diarrhea, ear infections, pneumonia, encephalitis, seizures, and death
Mumps	A viral lymph node disease	Fever, headache, muscle ache, and swelling of the lymph nodes close to the jaw	Meningitis, inflammation of the testicles or ovaries, inflammation of the pancreas and deafness
Pertussis (whooping cough)	A bacterial respiratory disease	Severe spasms of coughing	Pneumonia, encephalitis, and death, especially in infants
Pneumococcal disease	A bacterial disease	High fever, cough, and stabbing chest pains, bacteremia, and meningitis	death
Polio	A viral lymphatic and nervous system disease	Fever, sore throat, nausea, headaches, stomach aches, stiffness in the neck, back, and legs	Paralysis that can lead to permanent disability and death
Rubella (German measles)	A viral respiratory disease	Rash and fever for two to three days	Birth defects if acquired by a pregnant woman
Tetanus (lockjaw)	A bacterial nervous system disease	Lockjaw, stiffness in the neck and abdomen, and difficulty swallowing	Death in one third of the cases, especially people over age 50
Varicella (chickenpox)	A viral disease in the Herpes family	A skin rash of blister-like lesions	Bacterial infection of the skin, swelling of the brain, and pneumonia

Table 4.1: Previously common diseases for which vaccines have been developed.

4.5 Vaccination

Table 4.1 lists the diseases for which vaccines exist and are widely administrated to children. A basic problem considered by health care authorities is the determination of the fraction of a population requiring vaccination to prevent an epidemic.

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 can not occur and we say that the population has acquired *herd immunity*. Interestingly, herd immunity provides immunity even to nonvaccinated people since the population itself can not support an epidemic placing a nonvaccinated person at risk.

We assume that individuals are susceptible unless vaccinated, and vaccinated individuals are placed into the removed class. The initial population is then modeled as $(\hat{S}, \hat{I}, \hat{R}) = (1-p, 0, p)$. 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 (4.6), with $\hat{S}_0 = 1 - p$. Therefore, we have

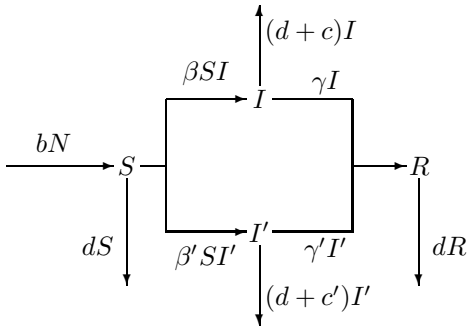
$$p_* = 1 - \frac{1}{\mathcal{R}_0}.$$

Diseases with smaller values of $\mathcal{R}_0$ are easier to eradicate than diseases with larger values $\mathcal{R}_0$, since a smaller fraction of the population needs to be vaccinated in order for the entire population to acquire herd immunity. For example, smallpox with $\mathcal{R}_0 \approx 4$ has been completely eradicated world-wide, whereas measles with $\mathcal{R}_0 \approx 17$ still has occasional outbreaks.

4.6 Evolution of virulence

Microorganisms continuously evolve due to selective pressures in their environment. A common source of selective pressure on pathogenic bacteria is antibiotics, and the development of antibiotic resistant strains presents one of the major health challenges to medical science. Viruses also compete directly with each other for reproductive success, and this can result in the evolution of virulence, which we study here using the SIR endemic disease model.

We assume that a population is initially in equilibrium with an endemic disease caused by a wildtype virus, say. Now, suppose a virus mutates (usually a random, undirected process that occurs naturally). Our goal is to determine the conditions under which the mutant virus will replace the wildtype virus in the population. We will frame this biological question as a mathematical stability problem: to determine the conditions under which the original endemic disease equilibrium solution becomes unstable upon introduction of a mutant viral strain. We assume that the original wildtype virus has infection rate β, removal rate γ, and disease-related death rate c, and that the mutant virus has corresponding rates β', γ' and c'. We further assume that an individual infected with either 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



with corresponding differential equations

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

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

$$S_* = \frac{\gamma + d + c}{\beta}. \tag{4.14}$$

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 (4.14), 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 algebra:

$$\frac{\beta'}{\gamma' + d + c'} > \frac{\beta}{\gamma + d + c}. \tag{4.15}$$

Our results suggest that endemic viruses (or other microorganisms) will tend to evolve (1) to be more easily transmitted between individuals ($\beta' > \beta$); (2) to make individuals sick longer ($\gamma' < \gamma$), and; (3) to be less deadly $c' < c$. In other words, viruses evolve to increase their basic reproductive ratio. For instance, viruses evolve to be less deadly because dead individuals do not spread disease (at least they do not in our model!). If dead individuals in fact did spread disease, which may be the case 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 or even cannabalism, then our result would not apply.

Chapter 5

Population Genetics

Deoxyribonucleic acid, or DNA – a large double-stranded, helical molecule, with rungs made from four base pairs adenine (A), cytosine (C), thymine (T) and guanine (G) – carries the 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. Most sexual species are *diploid*, carrying two copies of every gene, one from each parent. Bacterial species are *haploid* with only one copy. When we say there is a gene for eye color, we mean there is a particular DNA sequence that may vary in a population, and that there are at least two subtypes, called *alleles*, where individuals with two copies of the blue allele have blue eyes and those with two copies of the brown allele have brown eyes. An individual with two copies of the same allele is homozygous for that particular gene (or a *homozygote*), while an individual carrying two different alleles is heterozygous (or a *heterozygote*). For the eye-color gene, an individual carrying both a blue and brown allele has brown eyes, and we say that blue eyes is a recessive trait (or the blue-eye allele is *recessive*), and brown eyes is a dominant trait (or the brown-eye allele is *dominant*). The combination of alleles carried by an individual is called his *genotype*, while the actual trait (blue or brown eyes) is called his *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 genetics as the basis for biological inheritance forms the modern evolutionary synthesis (sometimes called the modern synthesis, the evolutionary synthesis, neo-Darwinian synthesis or neo-Darwinism). The primary founders of population genetics in the early twentieth century were Sewall Wright, J. B. S. Haldane and Ronald Fisher. Allele frequencies in a population can change due to the influence of four evolutionary forces: natural selection, genetic drift, mutation, and migration. The study of allele frequency changes due to natural selection can be viewed as the mathematization of Darwin's theory. Here, we will focus on natural selection and mutation. Genetic drift is the study of stochastic effects, and is of primary importance in small populations. Migration requires consideration of the spatial distribution of a population, and is usually modeled mathematically by partial differential equations.

genotype	A	a
number	n_A	n_a
viability fitness	g_A	g_a
fertility fitness	f_A	f_a

Table 5.1: Haploid genetics using population size and absolute viability and fertility fitnesses.

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

5.1 Introduction to 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. We will demonstrate how this model can be reformulated in terms of allele frequencies and relative fitness coefficients.

Table 5.1 formulates the basic model. We assume 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 we model deterministicly. Accordingly, with $n_A^{(i)}$ ($n_a^{(i)}$) representing the number of individuals carrying allele A (a) in the ith generation, and formulating a discrete generation model, we have

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

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 ith 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),

$$n_A^{(i+1)} + n_a^{(i+1)} = f_A g_A n_A^{(i)} + f_a g_a n_a^{(i)}, \tag{5.2}$$

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

$$\begin{aligned} p_{i+1} &= \frac{f_A g_A n_A^{(i)}}{f_A g_A n_A^{(i)} + f_a g_a n_a^{(i)}} \\ &= \frac{f_A g_A p_i}{f_A g_A p_i + f_a g_a q_i} \end{aligned}$$

genotype	A	a
freq. of gamete	p	q
relative fitness	$1+s$	1
freq after selection	$(1+s)p/w$	q/w
mean fitness	$w=(1+s)p+q$	

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

$$= \frac{p_i}{p_i + \left(\frac{f_a g_a}{f_A g_A}\right) q_i}, \tag{5.3}$$

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 $f_A g_A$. Similarly,

$$q_{i+1} = \frac{\left(\frac{f_a g_a}{f_A g_A}\right) q_i}{p_i + \left(\frac{f_a g_a}{f_A g_A}\right) q_i}, \tag{5.4}$$

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 $f_a g_a / f_A g_A$ of the alleles matters. Accordingly, in our models we will only consider relative fitnesses, and arbitrarily set one fitness to unity to simplify the algebra and make the final result more transparent.

5.2 Haploid genetics: 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!), the model equation is given by

$$p' = \frac{(1+s)p}{w} \tag{5.5}$$

$$= \frac{(1+s)p}{1+sp}, \tag{5.6}$$

where we have used $(1+s)p + q = 1 + sp$, since $p + q = 1$. Note that (5.6) is the same as (5.3) with $p' = p_{i+1}$, $p = p_i$, and $f_A g_A / f_a g_a = 1 + s$. Fixed points of (5.6) are determined from $p' = p$, and we find two fixed points: $p_* = 0$, corresponding to a population in which allele A is absent, and; $p_* = 1$, corresponding to a population in which allele A is *fixed*. Intuitively, $p_* = 0$ is unstable while $p_* = 1$ is stable.

To illustrate how a stability analysis is done analytically for a difference equation (instead of a differential equation), consider the general difference equation

$$p' = f(p). \tag{5.7}$$

With $p = p_*$ a fixed point so that $p_* = f(p_*)$, we write $p = p_* + \epsilon$, and (5.7) becomes

$$p_* + \epsilon' = f(p_* + \epsilon)$$

genotype	A	a
freq. of gamete	p	q
relative fitness	1	$1-s$
freq after selection	p/w	$(1-s)q/w$
freq after mutation	(1-u)p/w	$[(1-s)q+up]/w$
mean fitness	$w = p + (1-s)q$	

Table 5.3: Haploid genetic model of mutation-selection balance.

$$\begin{aligned} &= f(p_*) + \epsilon f'(p_*) + \dots \\ &= p_* + \epsilon f'(p_*) + \dots, \end{aligned}$$

where $f'(p_*)$ denotes the derivative of f evaluated at p_*. Therefore, to leading-order in ϵ

$$|\epsilon'/\epsilon| = |f'(p_*)|\,,$$

and the fixed point is stable provided $|f'(p_*)| < 1$. For our haploid model,

$$f(p) = \frac{(1+s)p}{1+sp}, \quad f'(p) = \frac{1+s}{(1+sp)^2},$$

so that $f'(p_* = 0) = 1 + s > 1$, and $f'(p_* = 1) = 1/(1+s) < 1$, confirming that $p_* = 0$ is unstable and $p_* = 1$ is stable.

If the selection coefficient s is small, the model equation (5.6) simplifies further. We have

$$\begin{aligned} p' &= \frac{(1+s)p}{1+sp} \\ &= (1+s)p(1 - sp + \mathrm{O}(s^2)) \\ &= p + (p - p^2)s + \mathrm{O}(s^2), \end{aligned}$$

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.

5.3 Haploid genetics: 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 sequence, we assume they share in common the same phenotype of reduced fitness. We model the opposing effects of two evolutonary 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,

$$A \underset{s}{\overset{u}{\rightleftarrows}} a$$

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 constructed to be

$$\begin{aligned} p' &= \frac{(1-u)p}{w} \\ &= \frac{(1-u)p}{1-s(1-p)}, \end{aligned} \tag{5.8}$$

and

$$\begin{aligned} q' &= \frac{(1-s)q+up}{w} \\ &= \frac{(1-s-u)q+u}{1-sq}, \end{aligned}$$

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 the equation for p', 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 $p_* = 1-u/s$, demonstrating that a polymorphism is possible. The stability of these two fixed points is determined by considering $p'=f(p)$, with $f(p)$ given by the right-hand-side of (5.8), and taking the derivative of f:

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

so that

$$f'(p_*=0) = \frac{1-u}{1-s}, \quad f'(p_*=1-u/s) = \frac{1-s}{1-u}.$$

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

5.4 Stochastic model of haploid mutation-selection balance

We formulate a stochastic model for haploid mutation-selection balance to demonstrate the relationship between the stochastic and deterministic models. The

genotype	A	a
population size	N	M
pmf	$p_N(t)$	$q_M(t)$
birth rate	b_A	b_a
relative fitness	1	$b_a/b_A = 1-s$

Table 5.4: Stochastic haploid genetic model of mutation-selection balance.

numbers of individuals N and M carrying the wildtype A and mutant a alleles in the population, respectively, are considered as discrete random variables. We define the time-dependent probability mass functions $p_N(t)$ and $q_M(t)$ to be the probabilities of N and M individuals carrying the A and a alleles at time t. Let b_A and b_a be the average per capita birth rates of individuals carrying the A and a alleles. We will assume that $b_a < b_A$, so that the reduced fitness of the mutant allele is reflected in a lowered birth rate, and selection should favor individuals of larger birth rate carrying the A allele. The fitness of the mutant genotype a relative to that of the wildtype genotype A is then b_a/b_A, which we defined as $1-s$ previously. The model is summarized in Table 5.4. Mutation is introduced to the model by assuming that an individual with the A allele gives birth to an individual with the a allele with probability u. We assume zero probability that an individual with the a allele will give birth to an individual with the A allele, that is, we neglect backmutation in the model. Furthermore, we suppose that initially N_0 individuals carry the A allele and M_0 individuals carry the a allele.

We can determine a system of differential equations for the probability mass function $p_N(t)$ as follows. For a population to have $N > 0$ individuals with the A allele at a time $t + \Delta t$, either it had $N-1$ individuals at time t and one non-mutant birth occured, or it had N individuals at time t and there were no non-mutant births, that is

$$p_N(t+\Delta t) = p_{N-1}(t)(1-u)b_A(N-1)\Delta t + p_N(t)(1-(1-u)b_A N\Delta t).$$

Subtracting $p_N(t)$ from both sides, dividing by Δt, and taking the limit $\Delta t \to 0$ results in the differential equations for $N = N_0, N_0+1, \ldots$:

$$\frac{dp_N}{dt} = (1-u)b_A\left[(N-1)p_{N-1} - Np_N\right]. \tag{5.9}$$

To obtain the system of differential equations for $q_M(t)$, we argue that for a population to have $M > 0$ individuals with the a allele at a time $t + \Delta t$, either it had $M-1$ individuals at time t and either an individual with the a allele gave birth, or an individual with the A allele gave birth and her child's gene mutated from A to a, or; it had M individuals at time t and there were no new births of a individuals, either directly or by mutation. Accordingly,

$$\begin{aligned} q_M(t+\Delta t) &= q_{M-1}(t)\left(b_a(M-1)\Delta t + \sum_{N=1}^{\infty} p_N(t)ub_A N\Delta t\right) \\ &\quad + q_M(t)\left(1-b_a M\Delta t\right)\left(1-\sum_{N=1}^{\infty} p_N(t)ub_A N\Delta t\right). \end{aligned}$$

Notice that

$$\begin{aligned}\sum_{N=1}^{\infty} p_N(t) u b_A N \Delta t &= u b_A \Delta t \sum_{N=1}^{\infty} N p_N(t) \\ &= u b_A \Delta t \bar{N}(t),\end{aligned}$$

where

$$\bar{N}(t) = \sum_{N=1}^{\infty} N p_N(t), \quad \bar{M}(t) = \sum_{M=1}^{\infty} M q_M(t)$$

are the expected number of individuals carrying the A and a alleles, respectively. Differencing the equation for q_M and taking the limit $\Delta t \to 0$ yields

$$\frac{dq_M}{dt} = b_a \left[(M-1)q_{M-1} - M q_M\right] + u b_A \bar{N} \left(q_{M-1} - q_M\right). \tag{5.10}$$

We can use (5.9) and (5.10) to solve for $\bar{N}(t)$ and $\bar{M}(t)$. Multiplying (5.9) by N and summing over N, we obtain

$$\frac{d\bar{N}}{dt} - (1-u) b_A \bar{N} = 0,$$

so that

$$\bar{N}(t) = N_0 e^{(1-u) b_A t}. \tag{5.11}$$

Multiplying (5.10) by M and summing over M, we obtain

$$\frac{d\bar{M}}{dt} - b_a \bar{M} = u b_A \bar{N}(t). \tag{5.12}$$

Equation (5.12) is a first-order linear inhomogeneous equation with a constant coefficient and can be solved using an integrating factor. The solution is

$$\bar{M}(t) = e^{b_a t} \left(M_0 + u b_A \int_0^t e^{-b_a s} \bar{N}(s) ds \right),$$

which may be integrated using (5.11) to obtain

$$\bar{M}(t) = e^{b_a t} \left(M_0 + u b_A N_0 \frac{e^{((1-u)b_A - b_a)t} - 1}{(1-u)b_A - b_a} \right). \tag{5.13}$$

Equations (5.11) and (5.13) are our solutions for the expected number of individuals carrying the A and a alleles, respectively. To make contact with our deterministic results, we determine the asymptotic expected allele frequencies as $t \to \infty$. With definitions for the A and a expected allele frequencies as

$$p_* = \lim_{t\to\infty} \frac{\bar{N}(t)}{\bar{N}(t) + \bar{M}(t)}, \quad q_* = \lim_{t\to\infty} \frac{\bar{M}(t)}{\bar{N}(t) + \bar{M}(t)},$$

we observe from (5.11) and (5.13) that the solution depends on the sign of $(1-u)b_A - b_a$. In particular, if $(1-u)b_A - b_a > 0$, then

$$p_* = \lim_{t\to\infty} \frac{N_0 e^{(1-u)b_A t}}{N_0 e^{(1-u)b_A t} + e^{b_a t} \left(M_0 + u b_A N_0 \frac{e^{((1-u)b_A - b_a)t} - 1}{(1-u)b_A - b_a} \right)}$$

genotype	AA	Aa	aa
referred to as	wildtype homozygote	heterozygote	mutant homozygote
frequency	P	Q	R

Table 5.5: Terminology of diploidy.

$$\begin{aligned} &= \frac{1}{1+\frac{ub_A}{(1-u)b_A-b_a}} \\ &= \frac{(1-u)b_A-b_a}{b_A-b_a} \\ &= 1-u\frac{b_A}{b_A-b_a}. \end{aligned}$$

On the other hand, if $(1-u)b_A - b_a < 0$, then

$$\begin{aligned} p_* &= \lim_{t\to\infty} \frac{N_0 e^{(1-u)b_A t}}{N_0 e^{(1-u)b_A t} + e^{b_a t}\left(M_0 + \frac{ub_A N_0}{b_a-(1-u)b_A}\right)} \\ &= \lim_{t\to\infty} \frac{N_0 e^{((1-u)b_A-b_a)t}}{N_0 e^{((1-u)b_A-b_a)t} + \left(M_0 + \frac{ub_A N_0}{b_a-(1-u)b_A}\right)} \\ &= 0. \end{aligned}$$

Now, from Table 5.4, the relative fitness of genotype a is given by $b_a/b_A = 1-s$, so that the condition $(1-u)b_A - b_a > 0$ becomes upon division by b_A: $(1-u)-(1-s) > 0$, or $s > u$. Therefore, for $s > u$, we have

$$\begin{aligned} p_* &= 1-u\frac{b_A}{b_A-b_a} \\ &= 1-u\frac{1}{1-\frac{b_a}{b_A}} \\ &= 1-\frac{u}{s}, \end{aligned}$$

and for $s < u$, $p_* = 0$, thus recovering the deterministic equilibrium result for the asymptotic expected frequencies.

5.5 Introduction to 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; most genes on the unmatched X and Y sex chromosomes in males are haploid (females are XX and are 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 5.5 presents the terminology of diploidy.

As for the case of 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 individuals with genotypes AA, Aa and aa number N_{AA}, N_{Aa} and N_{aa}, respectively. We have $N = N_{AA} + N_{Aa} + N_{aa}$. We define genotype frequencies P, Q and R by

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

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, respectively, with $n = n_A + n_a$ the total number of alleles. Since the population is of size N and diploidy, we have $n = 2N$. Now, 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, we have

$$\begin{aligned} p &= n_A/n \\ &= \frac{2N_{AA} + N_{Aa}}{2N} \\ &= P + \frac{1}{2}Q; \end{aligned}$$

and similarly,

$$\begin{aligned} q &= n_a/n \\ &= \frac{2N_{aa} + N_{Aa}}{2N} \\ &= R + \frac{1}{2}Q. \end{aligned}$$

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

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

5.6 Sexual reproduction: Random mating

Diploid reproduction may be sexual or asexual, and sexual reproduction may be of varying types (e.g., random mating, selfing, brother-sister mating, etc.). The simplest type of sexual reproduction to model mathematically is *random*

		progeny frequency		
mating	**frequency**	**AA**	**Aa**	**aa**
$AA \times AA$	P^2	P^2	0	0
$AA \times Aa$	$2PQ$	PQ	PQ	0
$AA \times aa$	$2PR$	0	$2PR$	0
$Aa \times Aa$	Q^2	$\frac{1}{4}Q^2$	$\frac{1}{2}Q^2$	$\frac{1}{4}Q^2$
$Aa \times aa$	$2QR$	0	QR	QR
$aa \times aa$	R^2	0	0	R^2
Totals	$(P+Q+R)^2$ $= 1$	$(P+\frac{1}{2}Q)^2$ $= p^2$	$2(P+\frac{1}{2}Q)(R+\frac{1}{2}Q)$ $= 2pq$	$(R+\frac{1}{2}Q)^2$ $= q^2$

Table 5.6: Random mating table.

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 frequences 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. Since 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

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

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

$$q = 1 - p, \quad P = p^2, \quad Q = 2p(1-p), \quad R = (1-p)^2.$$

Most modeling is done assuming random mating unless the biology under study depends on the choice of mating system.

The second approach uses a mating table (see Table 5.6). We explain this approach by consider 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 offpring will be AA and half Aa, and the frequencies PQ are denoted under *progeny frequency*. The sums of all the progeny frequencies is given in the *Totals* row, and use of the relationship between the genotype and allele frequencies recovers the random mating results.

5.7 Sexual reproduction: 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

		progeny frequency		
mating	**frequency**	**AA**	**Aa**	**aa**
$AA\otimes$	P	P	0	0
$Aa\otimes$	Q	$\frac{1}{4}Q$	$\frac{1}{2}Q$	$\frac{1}{4}Q$
$aa\otimes$	R	0	0	R
Totals	1	$P+\frac{1}{4}Q$	$\frac{1}{2}Q$	$R+\frac{1}{4}Q$

Table 5.7: Selfing mating table.

in its life-cycle), but provides both of the gametes. For example, we have already observed that the *C. elegans* hermaphrodite can reproduce by selfing. The mating table for selfing is given in Table 5.7. 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

$$P' = P + \frac{1}{4}Q, \quad Q' = \frac{1}{2}Q, \quad R' = R + \frac{1}{4}Q. \tag{5.14}$$

Notice that in the absence of evolutionary forces, allele frequencies remain constant. That is,

$$\begin{aligned} p' &= P' + \frac{1}{2}Q' \\ &= \left(P + \frac{1}{4}Q\right) + \frac{1}{2}\left(\frac{1}{2}Q\right) \\ &= P + \frac{1}{2}Q \\ &= p. \end{aligned}$$

Indeed, this is a general result. Mating by itself does not change allele frequencies in a population, but only reshuffles alleles into different genotypes. 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 with different color. If blending inheritence occured, 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. Unfortunately, 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), but later became widely celebrated after being rediscovered in 1900.

We can solve (5.14) with initial conditions $Q_0 = 1$ and $P_0 = R_0 = 0$, that is, an initially heterozygous population. In the worm lab, this type of initial condition 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 (5.14), 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

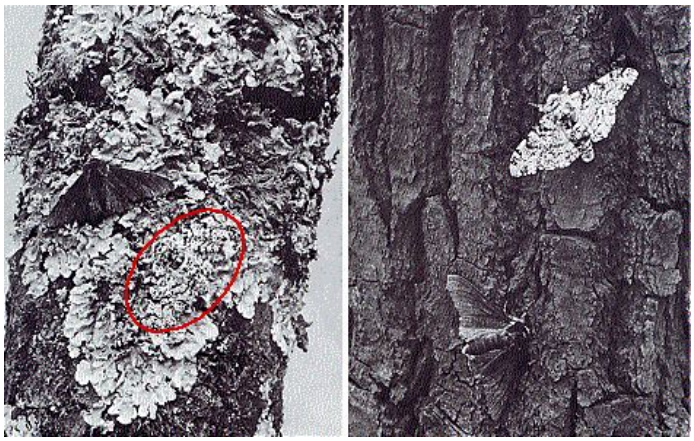


Figure 5.1: Evolution of peppered moths in industrializing England.

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 emphasised here is that the heterozygosity of the population decreases by a factor of two 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.

5.8 Diploid genetics: 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 5.8. 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, light color is the result of the absence of pigment, implying nonfunctioning pigment-producing genes, and is usually recessive (one functioning pigment-producing gene should result in a darker moth). If a is recessive (i.e., A dominant), than

genotype	AA	Aa	aa
freq. of zygote	p^2	$2pq$	q^2
relative fitness	$1+s$	$1+sh$	1
freq after selection	$(1+s)p^2/w$	$2(1+sh)pq/w$	q^2/w
mean fitness	$w=(1+s)p^2+2(1+sh)pq+q^2$		

Table 5.8: Diploid genetic model of the spread of a favored allele assuming random mating.

the phenotype of Aa is dark and $h \approx 1$. For the moment, we leave h as a free parameter in our model.

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 in the present generation after selection, we have

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

with $q = 1-p$, and

$$\begin{aligned} w &= (1+s)p^2 + 2(1+sh)pq + q^2 \\ &= 1 + s(p^2 + 2hpq). \end{aligned}$$

After some algebra, the final evolution equation written solely in terms of p is determined to be

$$p' = \frac{(1+sh)p + s(1-h)p^2}{1 + 2shp + s(1-2h)p^2}. \tag{5.15}$$

Clearly, 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 (5.15) is not particularly illuminating in its present form. In general, numerical solution requires specific values for s and h, and an initial condition for p. Here, I will investigate analytically the increase of a favored allele A assuming the selection coefficient $s << 1$. Of main interest is how the spread of A depends on the dominance coefficient h. We Taylor-series expand the right-hand-side of (5.15) in powers of s, keeping terms to order s:

$$\begin{aligned} p' &= \frac{(1+sh)p + s(1-h)p^2}{1 + 2shp + s(1-2h)p^2} \\ &= \frac{p + s\left(hp + (1-h)p^2\right)}{1 + s\left(2hp + (1-2h)p^2\right)} \\ &= \left[p + s\left(hp + (1-h)p^2\right)\right]\left[1 - s\left(2hp + (1-2h)p^2\right) + \mathrm{O}(s^2)\right] \\ &= p + sp\left(h + (1-3h)p - (1-2h)p^2\right) + \mathrm{O}(s^2). \end{aligned} \tag{5.16}$$

If $s << 1$, we expect a small change in allele frequency each generation, so we can approximate $p' - p \approx dp/dn$, where n denotes the generation number, and

disease	mutation	symptoms
Thalassemia	haemoglobin	anemia
Sickle cell anemia	haemoglobin	anemia
Haemophilia	blood clotting factor	uncontrolled bleeding
Cystic Fibrosis	chloride ion channel	thick lung mucous
Tay-Sachs disease	Hexosaminidase A enzyme	nerve cell damage
Fragile X syndrome	FMR1 gene	mental retardation
Huntington's disease	HD gene	middle-aged brain degeneration

Table 5.9: Seven common monogenic diseases.

we consider $p = p(n)$. Therefore, the approximate differential equation obtained from (5.16) is

$$\frac{dp}{dn} = sp\left(h + (1-3h)p - (1-2h)p^2\right). \tag{5.17}$$

If $h \neq 0$ so that A is partially dominant (*e.g.*, the heterozygous peppered-moth is darker than the homozgygous light-colored peppered moth), then (5.17) is similar to a logistic equation, where p initially grows exponentially as $p(n) = p_0 \exp(shn)$ and asymptotes to $p(n) \to 1$ as $n \to \infty$. If $h = 0$ so that A is recessive (*e.g.*, the heterozygous peppered-moth is as light-colored as the homozygous light-colored peppered moth), then (5.17) reduces to

$$\frac{dp}{dn} = sp^2(1-p), \quad \text{for } h = 0. \tag{5.18}$$

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

$$\begin{aligned} p(n) &= \frac{p_0}{1 - sp_0 n} \\ &\approx p_0(1 + sp_0 n). \end{aligned}$$

Therefore, the frequency of a recessive favored allele increases only linearly, which is a consequence of the heterozygote being hidden from natural selection. We can assume that the peppered-moth heterozygote must be significantly darker than the light-colored homozygote since the dark-colored allele substantially increased in frequency over a relatively short time period.

As a final comment, notice that our result of linear growth when $h = 0$ depends heavily on our assumption of random mating. If selfing occured, or other close family matings, then the favored allele may increase exponentially since heterozygote-heterozygote crossings will occur at much higher frequency, immediately producing a significant fraction of homozygous offspring on which selection can act.

5.9 Diploid genetics: Mutation-selection balance

There are thousands of known genetic diseases in humans, many of them caused by mutation of a single gene (denoted as a monogenic disease). For an easy-to-read overview of genetic disease in humans, see the website

`http://www.who.int/genomics/public/geneticdiseases.`

genotype	AA	Aa	aa
freq. of zygote	p^2	$2pq$	q^2
relative fitness	1	$1-sh$	$1-s$
freq after selection	p^2/w	$2(1-sh)pq/w$	$(1-s)q^2/w$
mean fitness	$w = p^2 + 2(1-sh)pq + (1-s)q^2$		

Table 5.10: Diploid genetic model of mutation-selection balance assuming random mating.

Table 5.9 lists seven common monogenic diseases. The first two diseases are maintained at significant frequencies in some human populations by heterosis. We will discuss the maintenance of a polymorphism by heterosis, for which the heterozygote has higher fitness than either homozygote, in the next Section. 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 found by a group led by Lap Chee Tsui, now the Vice-Chancellor of the University of Hong Kong.) The other disease genes listed are perhaps maintained by mutation-selection balance.

Our model for diploid mutation selection-balance is given in Table 5.10. We further assume that mutations of type $A \to a$ occur in gamete production with frequency u. Backmutation is neglected. The gametic frequency of A and a after selection but before mutation is given by $\hat{p} = P_s + Q_s/2$ and $\hat{q} = R_s + Q_s/2$, and the gametic frequency of a after mutation is given by $q' = u\hat{p} + \hat{q}$. Therefore,

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

with

$$\begin{aligned} w &= p^2 + 2(1-sh)pq + (1-s)q^2 \\ &= 1 - sq(2hp + q). \end{aligned}$$

Using $p = 1-q$, we write the evoluton 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

$$q' = \frac{u + [1 - u - sh(1+u)]q - s[1 - h(1+u)]q^2}{1 - 2shq - s(1-2h)q^2}. \tag{5.19}$$

Our main interest is in the equilibrium solutions of (5.19). Setting $q_* \equiv q' = q$ results in 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 fixed point 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, I determine equilibrium solutions under two approximations: (i) $0 < u << h, s$, and; (ii) $0 = h < u < s$. For (i) $0 < u << h, s$, we look for a solution of the form $q_* = au + \mathrm{O}(u^2)$, with a constant, and Taylor series expand in u (assuming $s, h = \mathrm{O}(u^0)$). If such a solution exists, then (5.19) will allow us to determine the unknown coefficient a. We have

$$au + \mathrm{O}(u^2) = \frac{u + (1-sh)au + \mathrm{O}(u^2)}{1 + \mathrm{O}(u^2)}$$

genotype	AA	Aa	aa
freq: $0 < u << s, h$	$1 + \mathrm{O}(u)$	$2u/sh + \mathrm{O}(u^2)$	$u^2/(sh)^2 + \mathrm{O}(u^3)$
freq: $0 = h < u < s$	$1 + \mathrm{O}(\sqrt{u})$	$2\sqrt{u/s} + \mathrm{O}(u)$	u/s

Table 5.11: Equlibrium frequencies of the genotypes at diploid mutation-selection balance.

$$= \quad (1 + a - sha)u + \mathrm{O}(u^2),$$

and equating powers of u: $a = 1 + a - sha$, or $a = 1/sh$. Therefore,

$$q_* = u/sh + \mathrm{O}(u^2), \quad \text{for } 0 < u << h, s.$$

For (ii) $0 = h < u < s$, we substitute $h = 0$ directly into (5.19):

$$q_* = \frac{u + (1-u)q_* - sq_*^2}{1 - sq_*^2},$$

which can be rewritten as a cubic equation for q_*:

$$q_*^3 - q_*^2 - \frac{u}{s}q_* + \frac{u}{s} = 0,$$

and then factored:

$$(q_* - 1)(q_*^2 - u/s) = 0.$$

Therefore, the polymorphic equilibrium solution is

$$q_* = \sqrt{u/s}, \quad \text{for } 0 = h < u < s.$$

Notice that $q_* < 1$ only if $s > u$, so that this solution does not exist if $s < u$.

Table 5.11 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, while 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 deteriation 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.

genotype	AA	Aa	aa
freq. of zygote	p^2	$2pq$	q^2
relative fitness	$1-s$	1	$1-t$
freq after selection	$(1-s)p^2/w$	$2pq/w$	$(1-t)q^2/w$
mean fitness	$w = (1-s)p^2 + 2pq + (1-t)q^2$		

Table 5.12: Diploid genetic model of heterosis assuming random mating.

5.10 Diploid genetics: Heterosis

Heterosis, also called *overdominance* or *heterozygote advantage*, describes the situation where the heterozygote has higher fitness than either homozygote. The classic examples are sickle-cell anemia and thalassemia, both diseases that affect hemoglobin, the oxygen carrier, in red blood cells. The sickle-cell mutations are more common in people of West African descent, while the thalassemia mutations are more common in people from the Mediteranean and Asia. In Hong Kong, the television stations occasionally play public service announcements about thalassemia. The heterozygote carrier of the sickle-cell or thalassemia gene is healthy and resistant to malaria. The wildtype homozgote is healthy, but susceptible to malaria while the mutant homozygote has a genetic disease, sometimes resulting in death. In class, we will watch and discuss the following short movie about the sickle cell gene, which you can also view at your convenience:

`http://www.pbs.org/wgbh/evolution/library/01/2/l_012_02.html.`

Table 5.12 presents our model for heterosis. Both homozygotes are of lower fitness than the heterozygote, whose relative fitness we set to unity. Writing the equation for p', we have

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

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

$$(s+t)p_*^3 - (s+2t)p_*^2 + tp_* = 0. \tag{5.20}$$

Clearly, $p_* = 0$ and $p_* = 1$ are fixed points and (5.20) can be factored as

$$p(1-p)\,(t - (s+t)p) = 0,$$

so that the polymorphic solution is

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

valid for $s, t > 0$. Since the value of q_* can be significant, mutations that cause disease but are highly prevalent in a population are usually suspected to be maintained by heterosis. The number of known genes clearly exhibiting heterosis, however, remains small.

player \ opponent	H	D
H	$E_{HH} = -2$	$E_{HD} = 2$
D	$E_{DH} = 0$	$E_{DD} = 1$

Table 5.13: General payoff matrix for the Hawk-Dove game, and the usually assumed values. The payoffs are payed to the player (first column) when playing against the opponent (first row).

genotype	H	D
freq of zygote	p	q
relative fitness	$K + pE_{HH} + qE_{HD}$	$K + pE_{DH} + qE_{DD}$
freq after selection	$(K + pE_{HH} + qE_{HD})p/w$	$(K + pE_{DH} + qE_{DD})q/w$
mean fitness	$w = (K + pE_{HH} + qE_{HD})p + (K + pE_{DH} + qE_{DD})q$	

Table 5.14: Haploid genetic model for frequency-selection in the Hawk-Dove game

5.11 Frequency-dependent selection

Finally, we consider a polymorphism caused by frequency-dependent selection. The most well-known model is the Hawk-Dove game, which we consider here. Commonly, frequency-dependent selection is studied in the context of game theory, and (following John Maynard Smith) one looks for an evolutionarily stable strategy (ESS). Here, we study frequency-dependent selection in the context of 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 define Hawk and Dove as follows: (i) when Hawk meets Dove, Hawk gets the resource and Dove retreats before injury; (ii) when Hawks meet, they engage in an escalating fight, seriously risking injury, and; (iii) when Doves meet, they share the resource. The Hawk-Dove game is modeled by a payoff matrix, as shown in Table 5.13. 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, Hawk in a population of Doves does well, whereas 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. 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 5.14. 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 Section 1.)

From Table 5.14, we write the equation for p':

$$p' = (K + pE_{HH} + qE_{HD})p/w, \tag{5.21}$$

with

$$w = (K + pE_{HH} + qE_{HD})p + (K + pE_{DH} + qE_{DD})q. \tag{5.22}$$

Both $p_* = 0$ and $p_* = 1$ are observed to be fixed points, and our aim is to determine the conditions under which these fixed points are unstable and a stable polymorphism exists.

First, consider the fixed point $p_* = 0$. With perturbation $p << 1$ and $q = 1 - p$, we have to leading-order in p

$$p' = \frac{(K + E_{HD})p}{K + E_{DD}},$$

so that $p_* = 0$ is an unstable fixed point when $|p'/p| > 1$, or since K is large and positive, $E_{HD} > E_{DD}$. Therefore, a population consisting only of Doves is unstable upon introduction of Hawks if Hawk playing Dove does better than Dove playing Dove. By symmetry, $p_* = 1$ is unstable if $E_{DH} > E_{HH}$, or a population consisting only of Hawks is unstable upon introduction of Doves if Dove playing Hawk does better than Hawk playing Hawk. Both $p_* = 0$ and $p_* = 1$ are unstable for the usual numerical values used in the Hawk-Dove game, Table 5.13.

The polymorphic solution is determined from (5.21) and (5.22). 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_*:

$$p_* = \frac{E_{HD} - E_{DD}}{(E_{HD} - E_{DD}) + (E_{DH} - E_{HH})}.$$

Since we have assumed $E_{HD} > E_{DD}$ and $E_{DH} > E_{HH}$, we have $0 < p_* < 1$, representing a valid polymorphism. With the numerical values of Table 5.13, we find

$$p_* = \frac{2 - 1}{(2 - 1) + (0 + 2)} = 1/3.$$

Therefore, a polymorphic population consisting of 1/3 Hawks and 2/3 Doves is a stable equilibrium, maintained by frequency-dependent selection.

5.12 Recombination and the approach to linkage equilibrium

When considering 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. Here we extend our discussion of polymorphism to two genetic loci, each with two distinct alleles. If the alleles at the first genetic loci are A and a, and those at the second B and b, then four distinct haploid gametes are possible, namely AB, Ab, aB and ab. Furthermore, ten distinct diploid genotypes are

possible: 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 genes obtained from the mother, say, and the denominator those obtained from the father. Obviously, modeling evolution at more than one locus may be complicated!

To proceed, we define the allelic and gametic frequencies for our two loci problem in Table 5.15. Now, 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 independent and the problem simplifies. Under the assumption of independence, the gametic frequencies are just the products of the allelic frequencies, so that $p_{AB} = p_A p_B$, $p_{Ab} = p_A p_b$, etc. The evolution of alleles at both loci can then be worked separately, and the gametic frequencies obtained by multiplying the corresponding allelic frequencies. Note that for the loci to remain independent, the relative fitness of a diploid genotype such as AB/aB would necessarily be given by the product of the relative fitnesses of Aa and BB in the corresponding single genetic locus problem.

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. Despite the apparent anomaly that modern women prefer tall men, usually the most fit phenotype is the average phenotype. This is called *normalizing* or *stabilizing* selection. Suppose A and B are tall alleles, and a and b are short alleles. Then natural selection could conceivably favor the genotypes yielding average heights: AB/ab, Ab/Ab, Ab/aB, aB/Ab, aB/aB, and ab/AB. Both the genotypes yielding above average heights: AB/aB, AB/Ab and AB/AB, and below average heights: Ab/ab, aB/ab and ab/ab, may be selected against. Here, the fitness of the A, a loci depends on which alleles are present at the B, b loci (e.g., A has higher fitness with b than with B) , so epistatic selection occurs.

The two loci may also not be independent because of a finite population size (i.e., stochastic effects). For instance, suppose a mutation $a \to A$ occurs only once in a finite population 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. The assumption of a finite population is necessary since in an infinite population the mutation $a \to A$ occurs an infinite number of times no matter how small the probability, and A would find itself linked with B or b with frequency p_B or p_b, respectively, so that the frequency of an AB gamete would be $p_A p_B$ (rather than simply p_A if the mutation occurred once linked to B) and the loci would be independent.

When the two loci are not independent, we say that the loci are in gametic phase disequilibrium, or more commonly *linkage disequilibrium*. When the loci are independent, we say they are in linkage equilibrium. Here, we will derive a model in which two loci initially in linkage disequilibrium approaches linkage

allele or gamete genotype	A	a	B	b	AB	Ab	aB	ab
frequency	p_A	p_a	p_B	p_b	p_{AB}	p_{Ab}	p_{aB}	p_{ab}

Table 5.15: Definition of allelic and gametic frequencies for two genetic loci each with two alleles.

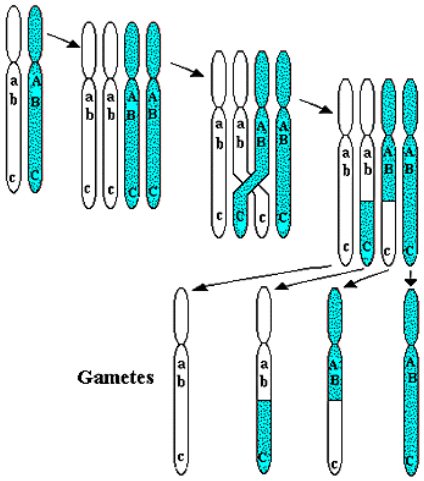


Figure 5.2: A schematic of crossing-over and recombination during meiosis (figure from Access Excellence @ the National Health Museum)

equilibrium.

First, we need a rudimentary understanding of *meiosis*. The process of meiosis produces the egg and sperm gametes. During meiosis, the 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 brings a haploid egg and sperm cell together to form a diploid zygote cell.

Fig. 5.2 presents a schematic of meiosis, and the important process of crossing-over resulting in recombination. Each diploid chromosome has a corresponding sister chromosome, one chromosome from the egg and the other 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 white chromosome, and alleles A, B, C on its sister's black chromosome. In the first step of meiosis, each 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 an egg by a female. If the chromosome from the females's father's sperm contains the alleles ABC and that from the females's mother's egg abc, recombination can result in the female's egg containing a chromosome with alleles ABc (the third haploid chromosome in Fig. 5.2). We say this chromosome is a recombinant, in that it contains alleles from both its maternal grandfather and maternal grandmother. Possibly, the precise combination of alleles on this chromosome may never have existed before.

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 recombination is less likely to separate them. Notice that genes on different chro-

mosomes are by definition unlinked, and inheritance from either the maternal grandfather or maternal grandmother is random independent of recombination.

We are now ready to define and model the evolution of linkage disequilibrium. Now, allele frequencies can be obtained from the gametic frequencies by

$$\begin{aligned} p_A &= p_{AB} + p_{Ab}, & p_a &= p_{aB} + p_{ab}, \\ p_B &= p_{AB} + p_{aB}, & p_b &= p_{Ab} + p_{ab}, \end{aligned} \tag{5.23}$$

and the sum of frequencies equals unity, that is

$$p_A + p_a = 1, \quad p_B + p_b = 1, \quad p_{AB} + p_{Ab} + p_{aB} + p_{ab} = 1. \tag{5.24}$$

There are eight unknowns and only seven equations, and in general it is not possible to obtain the gametic frequencies from the allelic frequencies unless we assume independent loci. We can, however, introduce a new variable called the coefficient of linkage disequilibrium D so that the gametic frequencies can obtained from the allelic frequencies and D. That is, we define D to be the difference between the actual gametic frequency and its value if the loci were independent:

$$D = p_{AB} - p_A p_B.$$

If A has stronger association with B than would be expected from assuming independence of loci, than we have positive linkage disequilibrium; if a weaker association then we have negative linkage disequilibrium. Now, using (5.23) and (5.24)

$$\begin{aligned} D &= p_{AB} - p_A p_B \\ &= (p_A - p_{Ab}) - p_A p_B \\ &= p_A (1 - p_B) - p_{Ab} \\ &= p_A p_b - p_{Ab}, \end{aligned}$$

and

$$\begin{aligned} D &= p_{AB} - p_A p_B \\ &= (p_B - p_{aB}) - p_A p_B \\ &= p_B (1 - p_A) - p_{aB} \\ &= p_a p_B - p_{aB}. \end{aligned}$$

Finally,

$$\begin{aligned} D &= p_a p_B - p_{aB} \\ &= p_a p_B - (p_a - p_{ab}) \\ &= p_a (p_B - 1) + p_{ab} \\ &= p_{ab} - p_a p_b. \end{aligned}$$

Therefore, the gametic frequencies can be written in terms of the allelic frequencies and the coefficient of linkage disequilibrium as

$$\begin{aligned} p_{AB} &= p_A p_B + D \\ p_{ab} &= p_a p_b + D \\ p_{Ab} &= p_A p_b - D \\ p_{aB} &= p_a p_B - D. \end{aligned} \tag{5.25}$$

		gamete freq / diploid freq			
diploid	**dip freq**	**AB**	**Ab**	**aB**	**ab**
AB/AB	p_{AB}^2	1	0	0	0
AB/Ab	$2p_{AB}p_{Ab}$	1/2	1/2	0	0
AB/aB	$2p_{AB}p_{aB}$	1/2	0	1/2	0
AB/ab	$2p_{AB}p_{ab}$	$(1-r)/2$	$r/2$	$r/2$	$(1-r)/2$
Ab/Ab	p_{Ab}^2	0	1	0	0
Ab/aB	$2p_{Ab}p_{aB}$	$r/2$	$(1-r)/2$	$(1-r)/2$	$r/2$
Ab/ab	$2p_{Ab}p_{ab}$	0	1/2	0	1/2
aB/aB	p_{aB}^2	0	0	1	0
aB/ab	$2p_{aB}p_{ab}$	0	0	1/2	1/2
ab/ab	p_{ab}^2	0	0	0	1

Table 5.16: Computation of gamete frequencies.

An equality obtainable from (5.25) that we will later find useful is

$$\begin{aligned} p_{AB}p_{ab} - p_{Ab}p_{aB} &= (p_Ap_B + D)(p_ap_b + D) - (p_Ap_b - D)(p_ap_B - D) \\ &= D(p_Ap_B + p_ap_b + p_Ap_b + p_ap_B) \\ &= D. \end{aligned} \tag{5.26}$$

We wish to determine the evolution of the coefficient of linkage disequilibrium D. In the absence of selection and mutation, D evolves only because of recombination. With primes representing the values in the next generation, and using $p'_A = p_A$ and $p'_B = p_B$ since sexual reproduction alone does not change allele frequencies, we have

$$\begin{aligned} D' &= p'_{AB} - p'_Ap'_B \\ &= p'_{AB} - p_Ap_B \\ &= p'_{AB} - (p_{AB} - D) \\ &= D + (p'_{AB} - p_{AB}), \end{aligned} \tag{5.27}$$

where we have used (5.25) to obtain the third equality. Therefore, the change in D: $D' - D$, is equal to the change in frequency of AB gametes: $p'_{AB} - p_{AB}$.

To understand how gametic frequencies change, we should first recognize when they do not change. If there was no genetic recombination during meiosis then chromosomes would maintain their exact identity across generations. Chromosomal frequencies would therefore be constant, and if the genetic loci with alleles A,a and B,b were on the same chromosome, then $p'_{AB} = p_{AB}$. In an infinite population without selection or mutation gametic frequencies can change only if the genetic loci are on different chromosomes, or there is genetic recombination.

Our goal is to compute the frequency p'_{AB} of AB gametes in the next generation, given the frequency p_{AB} of AB gametes in the present generation. The most straightforward computational method uses a 'mating' table (see Table 5.16). 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. If the A,a and B,b loci occur on different chromosomes, then $r = 1/2$, assuming the chromosomes assort independently. Notice that recombination 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,

$$\begin{aligned} p'_{AB} &= p_{AB}^2 + p_{AB}p_{Ab} + (1-r)p_{AB}p_{ab} + rp_{Ab}p_{aB} \\ &= p_{AB}(p_{AB} + p_{Ab} + p_{aB} + p_{ab}) + r(p_{Ab}p_{aB} - p_{AB}p_{ab}) \\ &= p_{AB} - rD, \end{aligned}$$

where the final equality makes use of (5.24) and (5.26). Using (5.27), we derive

$$D' = (1-r)D,$$

whose solution is

$$D_n = D_0(1-r)^n.$$

If the genes are on the same chromosome, recombination decreases linkage disequilibrium each generation by a factor $(1-r)$. Tightly linked genes in close proximity on a chromosome have small values of r. For genes on different chromosomes, $r = 1/2$ and linkage disequilibrium decreases by a factor of two 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.

Chapter 6

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 occuring in living organisms. The first application of biochemistry occured 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 proceeded 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. Physical sciences experienced early conflict – witness the famous prosecution of Galileo by the Catholic Church in 1633, in which he 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), proving for the first time that organic compounds can be created artificially.

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

6.1 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 rate of collision 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, which we write as

$$A + B \xrightarrow{k} C,$$

where k is called 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,

$$\frac{dC}{dt} = kAB. \tag{6.1}$$

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

$$\frac{dA}{dt} = -kAB, \quad \frac{dB}{dt} = -kAB. \tag{6.2}$$

Notice that when applying the law of mass action to write an equation for the time-derivative of a concentration, the chemical that the arrow points towards is increasing in concentration (positive sign), while 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,

$$\begin{aligned} \frac{d}{dt}(A + C) = 0 \qquad &\implies \quad A + C = A_0, \\ \frac{d}{dt}(B + C) = 0 \qquad &\implies \quad B + C = B_0, \end{aligned}$$

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

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

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

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

which is a complicated expression with the simple limits

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

Hence, the reaction stops after one of the reactants is depleted; and the final concentration of product is equal to the initial concentration of the depleted reactant.

If we also include the reverse reaction:

$$A + B \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C,$$

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 $A + C = A_0$ and $B + C = B_0$, we obtain

$$(A_0 - C)(B_0 - C) - \frac{k_-}{k_+} C = 0;$$

for which we define the equilibrium constant K_{eq} by

$$K_{eq} = k_-/k_+,$$

which has units of concentration. Therefore, at equilibrium the concentration of 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

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

If $K_{eq} << 1$, then A and B have a high affinity, and the reaction proceeds mainly to C.

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

(i)

$$A + X \underset{k_-}{\overset{k_+}{\rightleftharpoons}} 2X$$

(ii)

$$A + X \overset{k_1}{\to} 2X, \quad X + Y \overset{k_2}{\to} 2Y, \quad Y \overset{k_3}{\to} B$$

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 that we have considered previously, implying that the chemical concentrations X and Y oscillate in time.

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

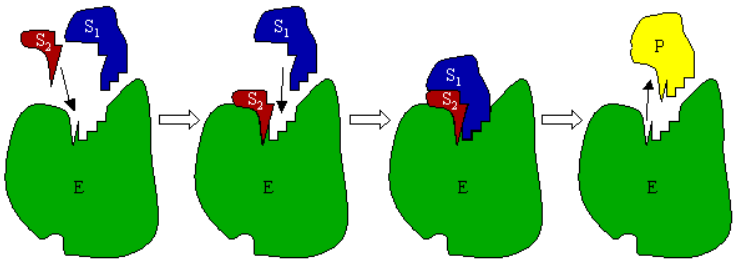


Figure 6.1: Michaelis-Menton reaction of two substrates converting to one product

enzyme has high specificity for at least one reaction, and can accelerate this reaction up to 10 million times or more. 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

$$S + E \stackrel{k}{\rightarrow} P + E,$$

is a bad model since it is known that increasing the substrate concentration above an upper limit no longer increases the reaction rate. Rather, Michaelis and Menton (1913) proposed the following reaction scheme with an additional step:

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

where C is a complex formed by the enzyme and the substrate. A graphical picture of the Michaelis-Menton reaction scheme with an enzyme catalyzing a reaction between two substrates to form a product is cartooned 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 are obtained from the law of mass action:

$$\begin{aligned} dS/dt &= k_{-1}C - k_1SE, \\ dE/dt &= (k_{-1} + k_2)C - k_1SE, \\ dC/dt &= k_1SE - (k_{-1} + k_2)C, \\ dP/dt &= k_2C. \end{aligned}$$

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 total enzyme concentration E_0. We can eliminate E in favor of E_0 from the conservation law which states that the

enzyme, free and bound, is conserved; that is

$$\frac{d(E+C)}{dt} = 0 \quad \Longrightarrow \quad E + C = E_0 \quad \Longrightarrow \quad E = E_0 - C.$$

We rewrite the equation for dC/dt eliminating E:

$$\begin{aligned} \frac{dC}{dt} &= k_1 S(E_0 - C) - (k_{-1} + k_2)C \\ &= k_1 E_0 S - (k_{-1} + k_2 + k_1 S)C. \end{aligned} \tag{6.4}$$

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 rate of formation equal to 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

$$\begin{aligned} \frac{dP}{dt} &= k_2 C \\ &= \frac{k_1 k_2 E_0 S}{k_{-1} + k_2 + k_1 S} \\ &= \frac{V_m S}{K_m + S}, \end{aligned} \tag{6.5}$$

where two fundamental constants are defined:

$$K_m = (k_{-1} + k_2)/k_1, \quad V_m = k_2 E_0; \tag{6.6}$$

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

$$\begin{aligned} &\text{as } S \to \infty, && C \to E_0 \quad \text{and} \quad dP/dt \to V_m, \\ &\text{if } S = K_m, && C = \frac{1}{2}E_0 \quad \text{and} \quad dP/dt = \frac{1}{2}V_m; \end{aligned}$$

so 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 active site. When an inhibitor is bound to the enzyme, no product is produced so competitive inhibition will reduce the velocity of the reaction. The cartoon of this process is shown in Fig. 6.2.

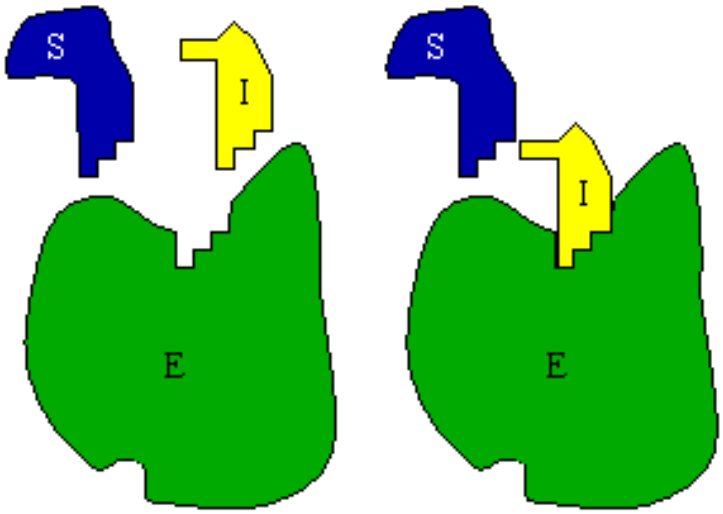


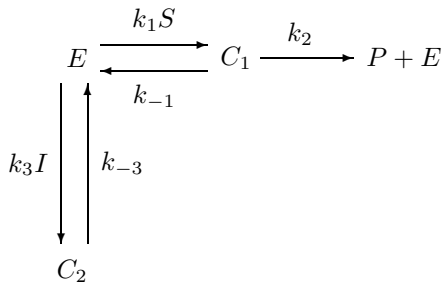
Figure 6.2: Competitive inhibition

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

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C_1 \xrightarrow{k_2} P + E,$$

$$I + E \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} C_2.$$

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 C_2 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 enzyme (free and bound). The law of mass action applied to the complex concentrations and the product results in

$$\begin{aligned}\frac{dC_1}{dt} &= k_1SE - (k_{-1}+k_2)C_1,\\ \frac{dC_2}{dt} &= k_3IE - k_{-3}C_2,\\ \frac{dP}{dt} &= k_2C_1.\end{aligned}$$

The enzyme, free and bound, is conserved so that

$$\frac{d}{dt}(E+C_1+C_2)=0 \quad\Longrightarrow\quad E+C_1+C_2=E_0 \quad\Longrightarrow\quad E=E_0-C_1-C_2.$$

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

$$\begin{aligned}k_1S(E_0-C_1-C_2)-(k_{-1}+k_2)C_1 &= 0,\\ k_3I(E_0-C_1-C_2)-k_{-3}C_2 &= 0,\end{aligned}$$

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

$$\begin{aligned}(k_{-1}+k_2+k_1S)C_1+k_1SC_2 &= k_1E_0S, &(6.7)\\ k_3IC_1+(k_{-3}+k_3I)C_2 &= k_3E_0I. &(6.8)\end{aligned}$$

We define the Michaelis-Menton 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

$$\begin{aligned}(K_m+S)C_1+SC_2 &= E_0S, &(6.9)\\ IC_1+(K_i+I)C_2 &= E_0I. &(6.10)\end{aligned}$$

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

$$\begin{array}{rrcl} & (K_m+S)(K_i+I)C_1+S(K_i+I)C_2 &=& E_0(K_i+I)S\\ - & SIC_1+S(K_i+I)C_2 &=& E_0SI.\\ \hline & [(K_m+S)(K_i+I)-SI]C_1 &=& K_iE_0S\end{array}$$

or after cancellation and rearrangement

$$\begin{aligned} C_1 &= \frac{K_i E_0 S}{K_m K_i + K_i S + K_m I} \\ &= \frac{E_0 S}{K_m(1 + I/K_i) + S}. \end{aligned}$$

Therefore, the reaction velocity is given by

$$\begin{aligned} \frac{dP}{dt} &= \frac{(k_2 E_0) S}{K_m(1 + I/K_i) + S} \\ &= \frac{V_m S}{K'_m + S}, \end{aligned} \tag{6.11}$$

where

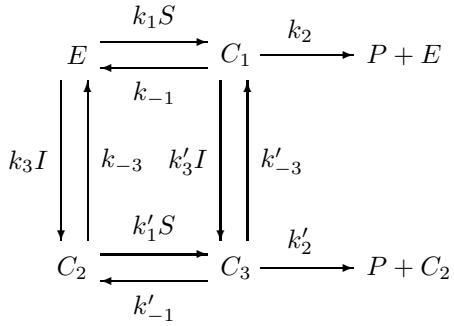
$$V_m = k_2 E_0, \quad K'_m = K_m(1 + I/K_i). \tag{6.12}$$

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-Menton constant of the reaction, but leaves the maximum reaction velocity unchanged. Hence, the presence of an inhibitor decreases the reaction velocity since the Michaelis-Menton constant is defined as the substrate concentration required to attain one-half of the maximum reaction velocity. Of course, if the reaction is saturated with substrate, then the uninhibited maximum reaction velocity will still be attained.

6.4 Allosteric inhibition

The term allostery comes from the Greek allos, "different," and stereos, "solid," and refers to an enzyme with a regulatory binding site separated from its active binding site. In our model for *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 by 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:



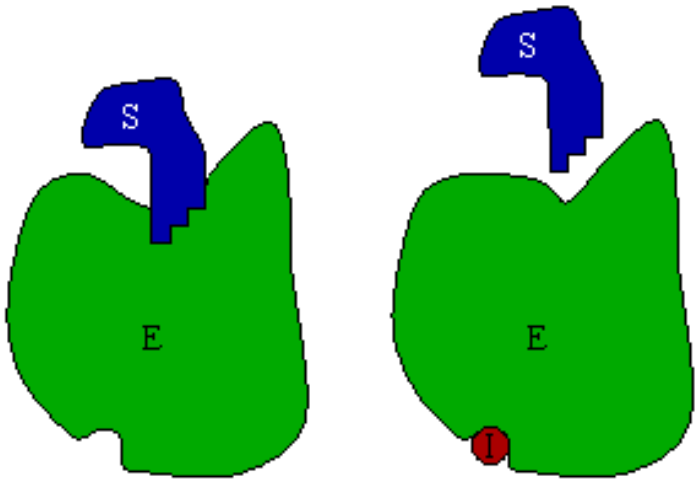
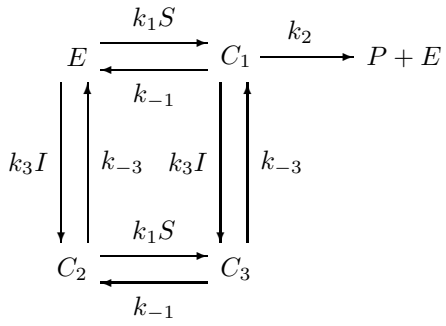


Figure 6.3: Allosteric inhibition

Clearly, the general model for allosteric inhibition with 10 independent rate constants is complicated and may be difficult to analyze. Here, we look for simplifications that will reduce the number of rate constants but will still demonstrate the unique features of allosteric inhibition. Now, the binding of both S and I to E at different sites defines allostery and must be retained in our model. One possible simplification assumes that if I binds to E, then S can not bind to E, but notice that this reduces allosteric inhibition to competitive inhibition (in which I takes the binding site of S preventing S from binding), and we do not consider it further. Instead, we will simplify by allowing both I and S to simultaneously bind to E, but assume that when I is bound to E no substrate is converted 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 are equal to the corresponding unprimed rate constants, e.g., $k_1' = k_1$, etc. With these simplifications, the schematic of the chemical reaction reduces to



where now there are only 5 independent rate constants. We write the equations for the complexes using the law of mass action:

$$\frac{dC_1}{dt} = k_1SE + k_{-3}C_3 - (k_{-1} + k_2 + k_3I)C_1, \tag{6.13}$$

$$\frac{dC_2}{dt} = k_3IE + k_{-1}C_3 - (k_{-3} + k_1S)C_2, \tag{6.14}$$

$$\frac{dC_3}{dt} = k_3IC_1 + k_1SC_2 - (k_{-1} + k_{-3})C_3, \tag{6.15}$$

while the reaction velocity is given by

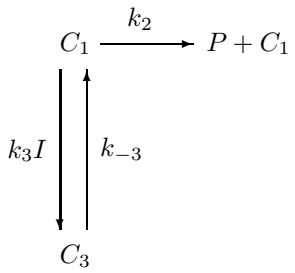
$$\frac{dP}{dt} = k_2C_1. \tag{6.16}$$

Again, enzyme free and bound 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 is still messy [1] and not particularly illuminating. We omit the complete analytical result here; rather we 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

$$V_m' = \lim_{S\to\infty} dP/dt = k_2 \lim_{S\to\infty} C_1.$$

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



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

$$\frac{dC_1}{dt} = k_{-3}C_3 - k_3 I C_1, \tag{6.17}$$

$$\frac{dC_3}{dt} = k_3 I C_1 - k_{-3}C_3, \tag{6.18}$$

and the quasi-equilibrium approximation yields the single independent equation

$$\begin{aligned} C_3 &= (k_3/k_{-3})IC_1 \\ &= (I/K_i)C_1, \end{aligned} \tag{6.19}$$

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 solution 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

$$\begin{aligned} V_m' &= \frac{k_2 E_0}{1 + I/K_i} \\ &= \frac{V_m}{1 + I/K_i}, \end{aligned}$$

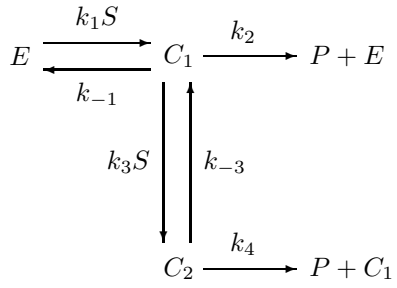
where V_m is the maximum reaction velocity of both the uninhibited and the competitive inhibited reaction. The allosteric inhibitor is thus seen to reduce the maximum velocity of the uninhibited reaction by the factor $(1 + I/K_i)$, which may be large if the concentration of allosteric inhibitor is significant.

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 been demonstrated to have an increased affinity for binding.

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. Because of the indistinguishability of the two binding sites, 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 rate constant for the binding of the second substrate molecule is larger than the rate constant for the binding of the first. We therefore consider the following reaction:



where cooperativity supposes that k_3 may be large compared to k_1. Application of the law of mass action results in

$$\begin{aligned}\frac{dC_1}{dt} &= k_1SE + (k_{-3} + k_4)C_2 - (k_{-1} + k_2 + k_3S)C_1,\\ \frac{dC_2}{dt} &= k_3SC_1 - (k_{-3} + k_4)C_2.\end{aligned}$$

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:

$$\begin{aligned}(k_{-1} + k_2 + (k_1 + k_3)S)C_1 - (k_{-3} + k_4 - k_1S)C_2 &= k_1E_0S, \quad (6.20)\\ k_3SC_1 - (k_{-3} + k_4)C_2 &= 0. \quad (6.21)\end{aligned}$$

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

$$\begin{aligned}(\epsilon K_1 + (1 + \epsilon)S)\,C_1 - (K_2 - \epsilon S)\,C_2 &= \epsilon E_0S, \quad (6.22)\\ SC_1 - K_2C_2 &= 0. \quad (6.23)\end{aligned}$$

We can substract (6.23) from (6.22) and cancel ϵ to obtain

$$(K_1 + S)\, C_1 + SC_2 = E_0 S. \tag{6.24}$$

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

$$C_1 = \frac{K_2 E_0 S}{S^2 + K_2 S + K_1 K_2}, \tag{6.25}$$

$$C_2 = \frac{E_0 S^2}{S^2 + K_2 S + K_1 K_2}, \tag{6.26}$$

so that the reaction velocity is given by

$$\begin{aligned} \frac{dP}{dt} &= k_2 C_1 + k_4 C_2 \\ &= \frac{(k_2 K_2 + k_4 S)\, E_0 S}{S^2 + K_2 S + K_1 K_2}. \end{aligned} \tag{6.27}$$

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 rate constant for binding of the second substrate is much larger than the rate constant for the binding of the first.

We consider first (i), with active sites acting independently. Now, E has two independent binding sites and C_1 has only a single binding site. Consulting the reaction schematic: k_1 is the rate constant for 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 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-Menton constant K_M 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

$$\begin{aligned} \frac{dP}{dt} &= \frac{(2k_2 K_M + 2k_2 S)\, E_0 S}{S^2 + 2K_M S + K_M^2} \\ &= \frac{2k_2 E_0 S}{S + K_m}, \end{aligned}$$

so that the reaction velocity for a dimer protein enzyme composed of independent identical monomers is simply double that of a monomer protein enzyme, as one would expect.

We now consider limiting case (ii) of extreme cooperativity. Here, we assume that immediately after the first substrate binds to the enzyme, the second substrate will bind. The number of enzymes bound to a single substrate molecule

should be small relative to the number bound to two substrate molecules, so that $C_1 << C_2$. Dividing (6.25) by (6.26), our inequality becomes

$$\frac{C_1}{C_2} = \frac{K_2}{S} << 1.$$

Dividing top and bottom of (6.27) by S^2, we have

$$\frac{dP}{dt} = \frac{\left(k_2 \frac{K_2}{S} + k_4\right) E_0}{1 + \frac{K_2}{S} + \frac{K_1}{S}\frac{K_2}{S}}.$$

We wish to take the limit of this expression as $K_2/S \to 0$, and we can do this by setting $K_2/S = 0$ everywhere except in the last term in the denominator, since we have not specified the behaviour of K_1/S in this limit. Therefore, taking the limit and multiplying top and bottom by S^2, we have

$$\frac{dP}{dt} = \frac{k_4 E_0 S^2}{S^2 + K_1 K_2}.$$

Here, the maximum reaction velocity is $V_m = k_4 E_0$, and the Michaelis-Menton 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

$$\frac{dP}{dt} = \frac{V_m S^n}{S^n + K_M^n},$$

which is known as the *Hill equation* and by varying n is used to fit experimental data as a model for cooperativity.

Bibliography

[1] Keener, J. & Sneyd, J. Mathematical Physiology . Springer-Verlag, New York (1998). Pg. 30, Exercise 2.

Chapter 7

Sequence Alignment

The software program BLAST (**B**asic **L**ocal **A**lignment **S**earch **T**ool) 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 yields important biological information about the query sequence. Almost all biologists use BLAST, making sequence alignment the most important algorithm 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 consist of a chain composed of four different nucleotides: A,C,T,G for DNA and A,C,U,G for RNA, whereas proteins consist of a chain composed of twenty different amino acids. The sequence of a DNA molecule or of a protein is the linear order of nucleotides or amino acids given in a specified direction, defined by the chemistry of the molecule. There is no need to know the exact details of the chemistry here; it is sufficient to understand 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 N-terminus to C-terminus. The specification of direction is more complicated for a DNA molecule than for a protein molecule because of the double helix structure of DNA, and we will give a detailed explanation of this in Section 7.1.

The basic sequence alignment algorithm aligns two or more sequences to highlight their similarity, allowing insertion of gaps into each sequence (usually denoted by dashes) so that wherever possible, identical or similar characters become aligned. For instance, Fig 7.1 presents an alignment using the software tool ClustalW of the hemoglobin beta-chain from Human, Chimpanzee, Rat, and Zebra fish. You can observe that the human and chimpanzee sequences are identical; this is due to 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 zebra fish sequence, though also clearly related, is significantly more diverged. Notice the insertion of a gap in each of the mammal sequences at the zebra fish amino acid position 122. This permits the subsequent zebra fish sequence to align better with the mammal sequences, and implies either an insertion of a new amino acid in fish relative to mammals, or a deletion of an amino acid in mammals. This evolutionary insertion or deletion of a character in a sequence is called an *indel*. Mismatches in sequence, such as that occuring between Zebra fish and Mammals at amino acid position 2 and

```
CLUSTAL W (1.83) multiple sequence alignment


Human      VHLTPEEKSAVTALWGKVNVDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGNPKV 60
Chimpanzee VHLTPEEKSAVTALWGKVNVDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGNPKV 60
Rat        VHLTDAEKAAVNGLWGKVNPDDVGGEALGRLLVVYPWTQRYFDSFGDLSSASAIMGNPKV 60
Zebra fish VEWTDAERTAILGLWGKLNIDEIGPQALSRCLIVYPWTQRYFATFGNLSSPAAIMGNPKV 60
           *. *  *::*: .****:* *::* :**.* *:********:* :**:**:. *:******

Human      KAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFGK 120
Chimpanzee KAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFGK 120
Rat        KAHGKKVINAFNDGLKHLDNLKGTFAHLSELHCDKLHVDPENFRLLGNMIVIVLGHHLGK 120
Zebra fish AAHGRTVMGGLERAIKNMDNVKNTYAALSVMHSEKLHVDPDNFRLLADCITVCAAMKFGQ 120
            ***:.*:..:. .: ::**:*.*:* ** :*.:******:*****.: :.   . ::*:

Human      E-FTPPVQAAYQKVVAGVANALAHKYH 146
Chimpanzee E-FTPPVQAAYQKVVAGVANALAHKYH 146
Rat        E-FTPCAQAAFQKVVAGVASALAHKYH 146
Zebra fish AGFNADVQEAWQKFLAVVVSALCRQYH 147
             *.. .* *:**.:* *..**.::**
```

Figure 7.1: *Multiple alignment of the hemoglobin beta-chain for Human, Chimpanzee, Rat and Zebra fish, obtained using ClustalW.*

3 is called a *mutation*. Clustal W places a '*' on the last line to denote exact amino acid matches across all sequences, and a '.' to denote chemically similar amino acids across all sequences (each amino acid has characteristic chemical properties, and can be grouped according to similar properties). In this chapter we will study the algorithms used to align sequences.

7.1 The minimum you need to know about DNA chemistry and the genetic code

When aligning two DNA sequences, a minimum understanding of DNA chemistry is essential. The DNA molecule consists of two strands wound around each other to form the 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). You need to remember this: A with T, G with C. For RNA, T is replaced by uracil (U). When reading the sequence of nucleotides from a single strand, it is necessary to specify the direction of the read, 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 strands of the DNA molecule are oriented in opposite directions. Below is the beginning of the DNA coding sequence for the

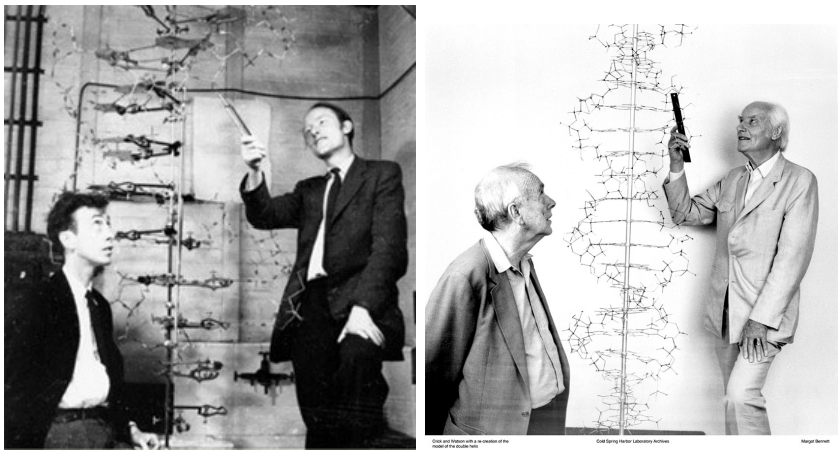


Figure 7.2: James Watson and Francis Crick posing in front of their DNA model. The original photograph was taken in 1953, the year of discovery, and was recreated in 2003, fifty years later. Francis Crick, the man on the right, died in 2004.

human hemoglobin beta chain protein discussed earlier:

```
5'-GTGCACCTGACTCCTGAGGAGAAGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTG-3'
   ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
3'-CACGTGGACTGAGGACTCCTCTTCAGACGGCAATGACGGGACACCCCGTTCCACTTGCAC-5'
```

It is important to realize that there are two unique DNA sequences here. Reading from 5'-to-3', the upper sequence begins 'GTGCACCTG...', while the lower sequence ends '...CAGGTGCAC'. Either sequence can be coding for a protein but here it is the upper sequence.

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*. 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. If you are interested, the entire genetic code can be obtained from any molecular biology textbook. The discovery of the structure of DNA and the elucidation of the genetic code is arguably the most monumental achievement of humankind in the 20th century.

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 (assuming some scoring system) and find the highest scoring alignment. The problem with this brute force approach is that the number of possible alignments is an exponential function of sequence length. For reasonably lengthed sequences, the computation is already impossible. As an example, the number of ways to align two sequences of 50 characters each, a rather small alignment problem, is about 1.5×10^{37}, already an astronomically large number. It is informative to show how to count the number of possible alignments between two sequences and we do so here.

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 capital letter alphabet and the lower case alphabet may align:

```
A   -A   A-
| , || , ||
a   a-   -a
```

and the five ways in which the first two characters of the capital letter alphabet can align with the first character of the lower case alphabet:

```
AB   AB   AB-   A-B   -AB
|| , || , ||| , ||| , ||| .
-a   a-   --a   -a-   a--
```

The total number of possible alignments of a sequence of i characters with a sequence of j characters may be counted by considering how the last character is aligned. There are three possibilities which we illustrate assuming the ith character is "F" and the jth character is "d":

(1) $i-1$ characters of the first sequence are already aligned with $j-1$ characters of the second sequence, and the ith character of the first sequence aligns exactly with the jth character of the second sequence:

```
...F
||||
...d
```

(2) $i-1$ characters of the first sequence are aligned with j characters of the second sequence and the ith character of the first sequence aligns with a gap in the second sequence:

```
...F
||||
...-
```

(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 jth character of the second sequence:

```
...-
||||
...d
```

If $C(i,j)$ is the number of ways to align an i character sequence with a j character sequence, then from our counting

$$C(i,j) = C(i-1,j-1) + C(i-1,j) + C(i,j-1). \tag{7.1}$$

This recursion relation requires boundary conditions to solve, and these are provided by $C(0,j) = C(i,0) = 1$ for all $i,j > 0$ since there is only one way to align an $i > 0$ character sequence against a zero character sequence, i.e., i characters against i gaps. We also add the boundary condition $C(0,0) = 1$ so that $C(1,1) = 3$.

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 $b_1b_2b_3b_4b_5$:

	-	a_1	a_2	a_3	a_4	a_5
-	1	1	1	1	1	1
b_1	1	3	5	7	9	11
b_2	1	5	13	25	41	61
b_3	1	7	25	63	129	231
b_4	1	9	41	129	321	681
b_5	1	11	61	231	681	1683

The matrix is constructed by writing $-a_1a_2a_3a_4a_5$ on top of the matrix and $-b_1b_2b_3b_4b_5$ down the left-hand-side, filling in ones across the zeroth row and down the zeroth column to satisfy the boundary conditions, and then applying the recursion relation by going across the first row from left-to-right, second row, etc. Notice that the dynamic matrix for two five character sequences has size 6×6, and for convenience we label the rows and columns starting from zero (i.e., row 0, row 1, ..., row 5). To fill in the matrix, we have across row 1: $1+1+1 = 3$, $1+1+3 = 5$, $1+1+5 = 7$, etc, and across row 2: $1+3+1 = 5$, $3+5+5 = 13$, $5+7+13 = 25$, etc. Finally, the last element computed yields the number of ways to align two five character sequences: 1683, which is already a remarkably large number.

It is possible to solve the recursion relation (7.1) together with the boundary conditions analytically for $C(i,j)$ by use of generating functions, and although the method of solution is interesting (and was shown to me by a student), the final analytical result is not very illuminating and we omit it here. In general, computation of $C(i,j)$ is best done by way of the dynamic matrix.

7.3 Sequence alignment by dynamic programming

Clearly, we can not align two reasonably sized sequences by brute force. Luckily, there is another method borrowed from computer science called *dynamic programming*, which makes use of a dynamic matrix.

To begin, we need a scoring system to judge the quality of an alignment. The goal, of course, is to find an alignment that has maximum score. Accordingly, we assume that the alignment of character a_i with character b_j has 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 assigned a score of +2, and a mismatch (A-C, A-T, A-G, etc.) a score of -1. Here, we assume the score of an indel (a nucleotide aligned with a gap) is g, and a typical value for DNA alignment is $g = -2$. In the next section, we will consider a better and more widely used model for indel scoring.

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 $T(i, j-1)$. In fact, our argument is the same as that given previously 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 ith character of the first sequence then aligns exactly with the jth 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 ith character of the first sequence aligns with a gap in the second sequence with updated maximium 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 jth character of the second sequence with updated maximum score $T(i, j-1) + g$. We then examine these three updated maximum scores, and select the maximum of the maxima. That is,

$$T(i,j) = \max \left\{ \begin{array}{l} T(i-1, j-1) + S(a_i, b_j) \\ T(i-1, j) + g \\ T(i, j-1) + g \end{array} \right\} \tag{7.2}$$

The recursion (7.2) can be used to fill in a dynamic matrix with the optimum scores. 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 know the alignment itself. The alignment is obtained by tracing back the path in the matrix along the one out of the three choices that was used to update $T(i, j)$ at each matrix element. There may possibly be more than one path for which case the best alignment is degenerate.

Obviously, sequence alignment is always done computationally and there are excellent software tools freely available on the web (see Section 7.6). Just to illustrate the dynamic programming algorithm, we compute the dynamic matrix for aligning two short sample DNA sequences $GAATT$ and $GGAT$, where a match is scored as +2, a mismatch -1 and an indel -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 a hand calculation, the two sequences to be aligned go on top of and to the left of the dynamic matrix, leading with a gap character "-". Row 0 and column 0 are then filled starting with 0 in position $(0, 0)$ and incrementing by the gap penalty -2 across row 0 and down column 0. This completes the prescription of the boundary conditions. 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. For each (i, j) entry, three numbers must be compared: (1) add to the $(i-1, j-1)$ entry either $+2$ for a match or -1 for a mismatch between the characters on top and on the left-hand-side of the matrix; (2) add to the $(i-1, j)$ entry -2 for an indel, and (3) add to the $(i, j-1)$ entry -2 for an indel. The maximum of these three numbers is placed into the (i, j) position. For example, consider the first computed element at position $(1, 1)$ in the matrix, here given by 2. This score was obtained by computing (1) $0 + 2 = 2$, since G-G is a match; (2) $-2 - 2 = -4$, and; (3) $-2 - 2 = -4$. The matrix element is filled in with $\max(2, -4, -4) = 2$. Test your understanding by continuing the computation of matrix elements.

After the matrix is completed, traceback to obtain the best scoring alignment starts at the bottom-right element of the matrix, here position $(4, 5)$ in the matrix with value 3. We determine which matrix element was used to compute 3, and here we see that it could have been either position $(4, 4)$ (horizontal move) or position $(3, 4)$ (diagonal move). The existence of two choices (at any step) means that the best alignment is degenerate. We arbitrarily choose one path now and later we show the other path. Choosing the diagonal move, we build the alignment from end to beginning with top sequence on top and left-hand sequence on bottom:

```
T
|
T
```

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						3

We work now from the 1 element in position $(3, 4)$. This element came from the 3 by a horizontal move. Therefore, the alignment is extended from the front to be

```
TT
||
-T
```

where a gap is inserted in the bottom sequence for a horizontal move, and a gap is inserted in the top sequence for a vertical move. The dynamic matrix now looks like

	-	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

Proceeding from the 3, it came from the 1 in a diagonal move, so the alignment is now extended to

```
ATT
|||
A-T
```

and the dynamic matrix now looks like

	-	G	A	A	T	T
-	0	-2	-4			
G	-2	2	0			
G	-4	0	1			
A				3	1	
T						3

Continuing in this fashion (try to do this), the final alignment is

```
GAATT
: : :  ,
GGA-T
```

where it is customary to represent a matching character with a colon ':'; and the traceback path in the dynamic matrix is

	-	G	A	A	T	T
-	0					
G		2				
G			1			
A				3	1	
T						3

If initially, the other degenerate path was taken, the final alignment would be

```
GAATT
: ::
GGAT-
```

and the traceback path is

	-	G	A	A	T	T
-	0					
G		2				
G			1			
A				3		
T					5	3

The score of both alignments is easily recalculated to be $2-1+2-2+2=3$ and $2-1+2+2-2=3$.

The algorithm for aligning two proteins is similar, but here the scoring system is a 20×20 matrix of values, called the *substitution matrix*, representing the score awarded for matching or mismatching the twenty different amino acids found in proteins. The most commonly used matrices are the PAM series, and BLOSUM series of matrices, with BLOSUM62 the commonly used default matrix. Construction of these matrices takes into consideration the evolutionary distance between the two aligning protein sequences.

7.4 Gap opening and gap extension penalties

Empirical evidence suggests that gaps cluster, in both nucleotide and protein sequences. This is usually modeled by introducing different penalties for gap opening (g_o) and gap extension (g_e), with $g_o < g_e < 0$. As an example, the default scoring scheme for the widely used BLASTN software is $+1$ for a nucleotide match, -3 for a mismatch, -5 for opening a gap, and -2 for extending a gap.

The introduction of two type of gaps (opening and extension) complicates our dynamic programming algorithm since when an indel is added to an existing alignment the scoring increment depends on whether the gap is a new gap opening or an extension to an existing gap. For example, the extended alignment

```
AB      AB-
||  ->  |||
ab      abc
```

is scored by adding a gap opening penalty g_o, whereas

```
A-      A--
||  ->  |||
ab      abc
```

is scored by adding a gap extension penalty g_e. The score increment depends not only on the current pair of aligned characters, but also on the previous pair.

The alignment of a sequence of length i with a sequence of length j can end with three possible alignments (top:bottom) (1) $a_i : b_j$, (2) $a_i : -$, or (3) $- : b_j$. The alignment ending as (1) is unambiguously scored by incrementing the previous score by $S(a_i, b_j)$. The score for alignments ending as (2) or (3) depend on the presence or absence of gaps in the previously aligned characters. For instance, for alignments ending as (2), $a_i : -$, the previous character alignment could have been one of: (i) $a_{i-1} : b_j$, (ii) $- : b_j$, (iii) $a_{i-1} : -$. If the previous character alignment was (i) or (ii), we would increment the score by the gap opening penalty g_o, but if it was (iii) we would increment the score by the gap extension penalty g_e.

We thus need to compute three dynamic matrices simultaneously, and we denote these three scores as $T(i,j)$, $T^{-}(i,j)$ and $T_{-}(i,j)$, depending on the presence or absence of a gap in the upper or lower sequence of the alignment at the last scored character. For the three possible ending alignments of a sequence of length i with a sequence of length j, we have:

(1) $a_i : b_j$

$$T(i,j) = \max \left\{ \begin{array}{l} T(i-1,j-1) + S(a_i, b_j) \\ T_-(i-1,j-1) + S(a_i, b_j) \\ T^-(i-1,j-1) + S(a_i, b_j) \end{array} \right\} \tag{7.3}$$

(2) $a_i : -$

$$T_-(i,j) = \max \left\{ \begin{array}{l} T(i-1,j) + g_o \\ T_-(i-1,j) + g_e \\ T^-(i-1,j) + g_o \end{array} \right\} \tag{7.4}$$

(3) $- : b_j$

$$T^-(i,j) = \max \left\{ \begin{array}{l} T(i,j-1) + g_o \\ T_-(i,j-1) + g_o \\ T^-(i,j-1) + g_e \end{array} \right\} \tag{7.5}$$

For aligning a sequence of length n with a sequence of length m, the optimum alignment score is the maximum of the scores obtained from the three dynamic matrices:

$$T_{\text{opt}}(n,m) = \max \left\{ \begin{array}{l} T(n,m) \\ T_-(n,m) \\ T^-(n,m) \end{array} \right\} \tag{7.6}$$

Traceback to obtain the optimum alignment of the two sequences proceeds by starting with the last aligned characters, obtained from one of the three dynamic matrices, and determining from which preceeding element among the three dynamic matrices this alignment came from. The optimum alignment is then built up from last-to-first as before, but now switching occurs between the three dynamic matrices.

7.5 Local alignments

Thus far we have discussed how to align two sequences over their entire length, a so-called *global alignment*, using the "Needleman-Wunsch" algorithm. Often, however, it is more useful to align two sequences over only part of their lengths, a so-called *local alignment*, and the corresponding algorithm is called "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 we consider a constant gap penalty g, then a local alignment can be obtained using the rule

$$T(i,j) = \max \left\{ \begin{array}{l} 0 \\ T(i-1,j-1) + S(a_i, b_j) \\ T(i-1,j) + g \\ T(i,j-1) + g \end{array} \right\}. \tag{7.7}$$

After the dynamic matrix is computed using (7.7), traceback proceeds by starting with the position in the matrix with highest score, and stops when hitting a score of zero.

If we apply the Smith-Waterman algorithm to locally align the two sequences $GAATT$ and $GGAT$ considered previously, with a match scored as $+2$, a mismatch -1 and an indel -2, the dynamic matrix is computed as

	-	G	A	A	T	T
-	0	0	0	0	0	0
G	0	2	0	0	0	0
G	0	2	1	0	0	0
A	0	0	4	3	1	0
T	0	0	2	3	5	3

Traceback starts at the highest scoring position, here the five in position $(4, 4)$, and ends at the zero in position $(0, 0)$. The resulting local alignment is

```
GAAT
: ::
GGAT
```

which has a score of five that is higher than the previous score of three for the global alignment.

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, one 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:

`http://www.ncbi.nlm.nih.gov/blast/bl2seq/wblast2.cgi`

Another useful software for global alignment of two or more long DNA sequences is PipMaker:

`http://pipmaker.bx.psu.edu/pipmaker/`

Mutiple global alignments of protein sequences are commonly done using 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 flavors depending on the type of sequence and database search one is performing:

`http://www.ncbi.nlm.nih.gov/BLAST/`