Mathematical and Computational Methods for the Life Sciences

Preliminary Lecture Notes

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Contents

Chapter 1

Preface

This notes are to be read as a work in progress. They will be updated throughout the semester. For the most part, they contain more material than can be covered during the lectures.

The main goal of this course is the exploration of mathematical topics that have relevance in the study of biological systems. The topics will range from difference and differential equations to linear algebra and probability. The mathematics is motivated by biological questions and developed in that context. Emphasis will be placed on the process of mathematical modeling; this consists of

1. translation of questions in Biology into mathematical formalism (variables, parameters, functions, equations, etc.);
2. formulation of mathematical problems (e.g., Can a given equation or system of equations be solved? What are the properties of the solutions?);
3. analysis of the mathematical problem; and
4. translation back into the Biological situation.

Another important aspect of the course will be computation and data analysis; this provides a link between the mathematical models and the actual biological systems under consideration.

Chapter 2

Introduction: An Example from Microbial Genetics

Bacteria have been known to develop resistance to adverse conditions in their environment; e.g., toxic agents like antibiotics, certain viruses that kill the bacteria, etc. A possible explanation for the development of resistance is that mutations in the genetic material lead to resistant bacterial variants. A fundamental question in microbial genetics is whether these mutations to resistant strains are the result of exposure to the toxic conditions, or whether they are random mutations that might have occured independently of the presence of the adverse conditions. The first alternative is known as the *hypothesis of acquired hereditary immunity,* while the second one is known as the *hypothesis of mutation to immunity* (see [LD43]). In 1943, Luria and Delbrück [LD43] devised a study that allowed them to choose between the two hypotheses. They determined theoretical consequences of each of the two hypotheses in the case of *E. Coli* bacteria exposed to a bacteriophage virus which infects the non–resistant bacteria and causes their destruction. Then, they were able to determine experimentally which predictions actually held true. One of the goals of this course is to develop the mathematical and computational machinery that will allow us to deduce consequences from each of the two hypotheses of Luria and Delbrück. The mathematics needed for this task ranges from the theory of difference and differential equations to probability and stochastic processes. Our approach to this particular example will be a gradual one. We start with the study of models of bacterial growth, which are deterministic in nature, and then proceed to the development of probabilistic or stochastic models.

Part I

Deterministic Models

Chapter 3

Modeling Bacterial Growth: Discrete Approach

Suppose we are tracking the number N_t of bacteria in a culture, where t denotes the number of units of time since we stated observing the population. Assume that when $t = 0$ we know the number of bacteria to be N_o. We would like to predict what N_t will be for any $t = 1, 2, 3, \ldots$ In order to do this, we need to develop a model based on assumptions about how the number of individuals will change over one unit of time; that is, we need to make assumptions about the change:

$$N_{t+1} - N_t.$$

A very important principle in modeling population growth is the following *conservation principle:*

$$N_{t+1} - N_t = \text{bacteria into the culture} - \text{bacteria out of the culture} \tag{3.1}$$

in one unit of time.

3.1 Geometric growth or the Malthusian model

The simplest assumption one could make about the terms on the right–hand side of equation (3.1) is that they are both proportional to the number of bacteria present at time t; that is,

$$\text{bacteria into the culture} = \alpha N_t \tag{3.2}$$

and

$$\text{bacteria out of the culture} = \beta N_t \tag{3.3}$$

where α and β are positive constants of proportionality. Here, α represents the *birth rate per–capita* and β the *death rate per–capita* of the bacterial population. Substituting these expressions into equation (3.1) and simplifying yields

$$N_{t+1} = \lambda N_t \tag{3.4}$$

where

$$\lambda = 1 + \alpha - \beta \tag{3.5}$$

is the *per-capita growth rate* of the population; this is the percent increase (or decrease) of the population in one unit of time.

Equation (3.4) is the Discrete Malthusian Model of population growth and is an example of a *difference equation.* Thus, in the Malthusian Model we are assuming the growth rate λ defined in (3.5) is constant; that is, it is independent of t and of N_t.

We can solve the difference equation (3.4) as follows:

First, observe that by substituting 0 for t into equation (3.4) we obtain

$$N_1 = N_{0+1} = \lambda N_o.$$

Similarly,

$$N_2 = N_{1+1} = \lambda N_1 = \lambda(\lambda N_o),$$

by the previous equation; so that

$$N_2 = N_{1+1} = \lambda^2 N_o = N_o \lambda^2.$$

In general, suppose that we have established that for $t = n$,

$$N_n = N_o \lambda^n.$$

Then, one unit of time later, by (3.4),

$$N_{n+1} = \lambda N_n = \lambda(N_o \lambda^n) = N_o \lambda^{n+1}.$$

We therefore conclude by Principle of Mathematical Induction that

$$N_t = N_o \lambda^t \quad \text{for} \quad t = 0, 1, 2, \ldots \tag{3.6}$$

is the solution to the difference equation (3.4).

Observe that the solution (3.4) to the Malthusian model predicts three possible types of behavior:

1. If $\lambda > 1$, the population will increases (geometrically) as t increases.
2. If $\lambda < 1$, the population will decrease as t increases.
3. If $\lambda = 1$, the population density will remain constant as t varies.

Example 3.1.1 *Suppose that a single cell of the bacterium E. coli divides every twenty minutes. Given that the average mass of an E. coli bacterium is* 10^{-12} *gr, if a cell of E. coli was allowed to reproduce without restrain to produce a super–colony, estimate the time that it would take for the total mass of the bacterial colony to be that of the earth (approximately* 6×10^{24} *Kg). (For this example, assume that the bacteria are not dying; that is, the death rate,* β*, is zero.)*

Solution: Let the unit of time be 20 minutes. This is the doubling time of the bacterial colony. Then, the Malthus difference equation (3.4) reads in this case

$$N_{t+1} = 2N_t.$$

Thus, its solution, by (3.6), is

$$N_t = N_o 2^t \quad \text{for} \quad t = 0, 1, 2, \ldots$$

where $N_o = 1$. We want to find t so that

$$2^t (10^{-12} \text{ gr}) \geq 6 \times 10^{27} \text{ gr},$$

or

$$2^t \geq 6 \times 10^{39}.$$

Solving this inequality for t we obtain

$$t \geq \frac{\ln 6 + 39 \ln 10}{\ln 2} \approx 132.14.$$

Thus, we may take $t = 133$, and so it will take $133 \times$ (20 min) or 44 hours and 20 minutes, or 3 hours and 40 minutes short of two days, for the bacteria to overtake the earth. □

3.2 Logistic growth or the Verhulst model

The previous example shows one of the limitations of the Malthusian model (3.4). If the growth parameter λ in (3.5) is bigger than 1, then the population will experience *unlimited* growth. This is unrealistic in an environment with limited or finite resources. In order to make the model more realistic, we need to modify the assumptions that we made in the derivation of the Malthusian model (3.4). One of those assumptions is that the rates of bacteria in an out of the culture in one unit of time (that is the terms on the right–hand side of the conservation equation (3.1)) were proportional to the population density at t (see equations (3.2) and (3.3)). We will now relax that assumption.

Substitute equations (3.2) and (3.3) into the conservation equation (3.1) and divide by N_t to get

$$\frac{N_{t+1} - N_t}{N_t} = \alpha - \beta, \tag{3.7}$$

where α and β are now not assumed to be constant, but may depend on the population density as well as other factors like the nutrient concentration in the medium. The left–hand side of equation (4.20) is the *per–capita growth rate* of the bacterial colony in one unit of time. Let's denote this rate by κ. In general, κ may depend on many factors; for instance,

$$\kappa = \kappa(t, N_t, C_t, \text{etc.}),$$

where C_t denotes the concentration of nutrient in the medium at t. We then obtain the more general equation

$$\frac{N_{t+1} - N_t}{N_t} = \kappa(t, N_t, C_t, \text{etc.}). \tag{3.8}$$

Let's assume for simplicity that κ is a function of the the nutrient concentration only and that it is proportional to it. We then obtain the difference equation

$$\frac{\Delta N}{N_t} = mC_t, \tag{3.9}$$

where m is a constant of proportionality and we have used the short–hand notation ΔN for $N_{t+1} - N_t$.

Next, we model the relationship between N_t and C_t.

Assume that γ units of nutrient are consumed in producing one unit of population increment. We then have that

$$\frac{\Delta C}{\Delta N} = -\gamma,$$

where the minus sign indicates that the nutrient concentration decreases as the bacterial density increases. We then get from (4.21) that

$$\Delta C = -\gamma \Delta N = -\gamma m C_t N_t.$$

Combining this equation with (4.21) leads to the following *system of difference equations*

$$\begin{cases} N_{t+1} &= (1 + mC_t)N_t \\ C_{t+1} &= (1 - \gamma m N_t)C_t \end{cases} \tag{3.10}$$

This is an example of a *nonlinear* system since the product of the unknown quantities N and C appears on the right–hand side of the equations. It models the interaction between the population density in a bacterial culture and the nutrient concentration in the culture medium. It is assumed that the bacteria depend solely on that particular nutrient for survival.

Observe that if we multiply the first equation in (3.10) by γ and add it to the second equation, the nonlinear term $N_t C_t$ can be eliminated and we obtain a single difference equation

$$\gamma N_{t+1} + C_{t+1} = \gamma N_t + C_t.$$

This is a difference equation for the quantity $\gamma N + C$ which can be shown to have the constant solution

$$\gamma N_t + C_t = \gamma N_o + C_o \quad \text{for } t = 1, 2, 3, \ldots, \tag{3.11}$$

where C_o and N_o denote the initial nutrient concentration and bacterial density, respectively. Put $A_o = \gamma N_o + C_o$ and solve for C_t in (3.11) in terms of N_t to get

$$C_t = A_o - \gamma N_t.$$

Substitute this into the first equation in (3.10) to obtain a single difference equation for N_t:

$$N_{t+1} = (1 + m(A_o - \gamma N_t))N_t.$$

This equation can be re–written as follows

$$N_{t+1} = N_t \left(1 + r\left(1 - \frac{N_t}{K}\right)\right), \tag{3.12}$$

where $r = mA_o$ is called the *intrinsic growth rate* and $K = \dfrac{1}{\gamma}A_o$ is called the *carrying capacity* of the environment.

The parameter $1/\gamma$ is called the *yield* of the nutrient medium; it gives a measure of how many new bacteria are produced due to consumption of one unit of nutrient. Since A_o represents the amount of nutrients present in the medium in the absence of bacteria ($N = 0$), K gives the maximum number of bacteria that the medium can sustain.

In order to understand the meaning of the intrinsic growth rate parameter r, go back to the general population model (4.22). The per–capita growth rate function κ on the right–hand side of the equation (4.22) was assumed to be constant in the derivation of the Malthusian model (3.4). In the case of the logistic model, κ was assumed to depend only on the nutrient concentration, C, in the medium. In (4.21), this dependence was assumed to be given my a simple proportionality relation

$$\kappa = mC.$$

Thus, m gives a measure of the net increment per–capita in the number of bacteria due to consumption of one unit of nutrients. Since A_o corresponds to the nutrient concentration in the medium in the absence of bacteria ($N = 0$), it then follows that $r = mA_o$ is the per–capita growth rate of the bacteria when the population density is very small, and overcrowding and competition for resources is not a significant factor on the growth of the population.

The right–hand side of the logistic difference equation (3.12) depends quadratically on the unknown function N_t; thus, the logistic difference equation is a *nonlinear* equation. In contrast to the *linear* Malthusian model (3.4), in which we were able to solve the equation explicitly (see (3.6)), we are not going to be able to find a formula for N_t in the logistic model. Instead, we will need to resort to computations.

3.2.1 Computing solutions to the logistic model

Example 3.2.1 *Consider a bacterial culture with an initial population density of* 1 *million cells in a medium that can sustain* 12 *million cells. Assume that the intrinsic growth rate is of* 50% *per unit of time (generation). Calculate the population densities predicted by the logistic growth model for the first* 15 *generations. Plot the values in a Population versus Time graph. What does the model predict?*

Solution: The main purpose of this example is to introduce the use of MATLAB®. This is a very powerful computational software produced by MathWorks. In this example we start out by thinking of MATLAB® as a very fancy graphing calculator and we then gradually introduce some of its programming capabilities, which is actually the main feature of the program.

We let N_t denote the bacterial population in millions at t units of time, where $t = 1, 2, 3, \ldots$ Then the logistic difference equation (3.12) in this case reads

$$N_{t+1} = N_t \left(1 + 0.5\left(1 - \frac{N_t}{12}\right)\right) = N_t + 0.5N_t\left(1 - \frac{N_t}{12}\right). \tag{3.13}$$

Start with an initial population $N_o = 1$ (millions of cells). In MATLAB® we can define a variable `N_0` to be equal to 1 using the following assignment statement:

```
>> N_0 = 1;
```

the semicolon at the end of the statement suppresses the program from printing back what you just typed; this is particularly useful when writing long programs.

Having the value of `N_0`, we can now use (3.13) to compute the value of a new variable `N_1` as follows

```
>> N_1 = N_0 + 0.5*N_0*(1-N_0/12)
```

We could continue in this fashion computing

```
>> N_{j+1} = N_j + 0.5*N_i*(1-N_j/12)
```

having computed the value of `N_j` previously, for $j = 1, 2, \ldots, 14$. However, that would be an utter under–use of MATLAB®. We could instead write the following short code

```
p=1;
N=p;
for i=1:15;
p = p + 0.5*p*(1 - p/12);
N=[N p];
end
```

This code can be written in a .m–file which we could name code1.m. This file can then be called in from the MATLAB®command input window by typing simply

```
>> code1
```

The net result of the code is a row of values

```
 1.0000
 1.4583
 2.0989
 2.9648
 4.0809
 5.4275
 6.9138
 8.3790
 9.6432
10.5902
11.2123
11.5803
11.7828
11.8894
11.9442
11.9720
```

of N_t for $t = 0, 1, \ldots, 15$. These values are all stored under the variable name `N`. This is an example of an *array.* An array is simply a list of data values of the same type. They are usually displayed as rows or columns or two–dimensional lists made up of both rows and columns. The mathematical term for a two–dimensional array is a *matrix.* Matrices that are listed as rows or columns are called *vectors.* MATLAB®, which stands for *Matrix Laboratory,* was originally designed as a program for computing with matrices. It has since then evolved into an integrated computational, graphical and programming software.

If we type `N` in the MATLAB® command window, the program will display the values of `N` as a *row vector.* If we type `N'` the program displays `N` as a *column vector.* The vector `N'` is called the *transpose* of `N`. The transposition operator ' turns rows into columns and vice–versa.

Before we talk about how to plot the values of `N` that we just computed, we will turn to the code that we wrote in code1.m in order to understand how it works. First notice that the code uses three variables: `N`, `p` and `i`. `N` is where we want the end result to be, `p` is an intermediary variable that is used in the calculations, and `i` is the index for the `for`–loop that is used to compute the values of N_j for $j = 1, 2, \ldots 15$. The first line in the code sets the initial condition $N_0 = 1$. The second line begins the process of building the array `N` by putting the initial value `p=1` as the first entry. Lines 3 and 6 set up the `for`–loop to run for 15 calculations since we are interested in the first 15 generations. Line 4 computes the next population value based on the previous one using equation (3.13). Observe that the command

```
p = p + 0.5*p*(1 - p/12)
```

is not to be understood as a standard mathematical equation like (3.13). In the MATLAB® programming language, this assignment statement evaluates the expression to the right of the equal sign based on the previous value of `p`, and then replaces the value of `p` to the left of the equal sign by the new computed value. Finally, the expression

```
N=[N p]
```

in line 5 appends or concatenates the new computed value of `p` to the array `N`.

In order to obtain the plot of the values of `N` versus time shown in Figure 3.2.1, type the following sequence of commands

```
plot([0:15], N, 'k*')
axis([0 15 0 13])
title('Logistic model with r=0.5, K=12')
xlabel('Time t')
ylabel('Population N')
```

The figure will appear in a separate graphics window. These commands could also be placed in a .m–file that you may call plot1.m. Typing `plot1` in the MATLAB® command window will then yield the graph in Figure 3.2.1.

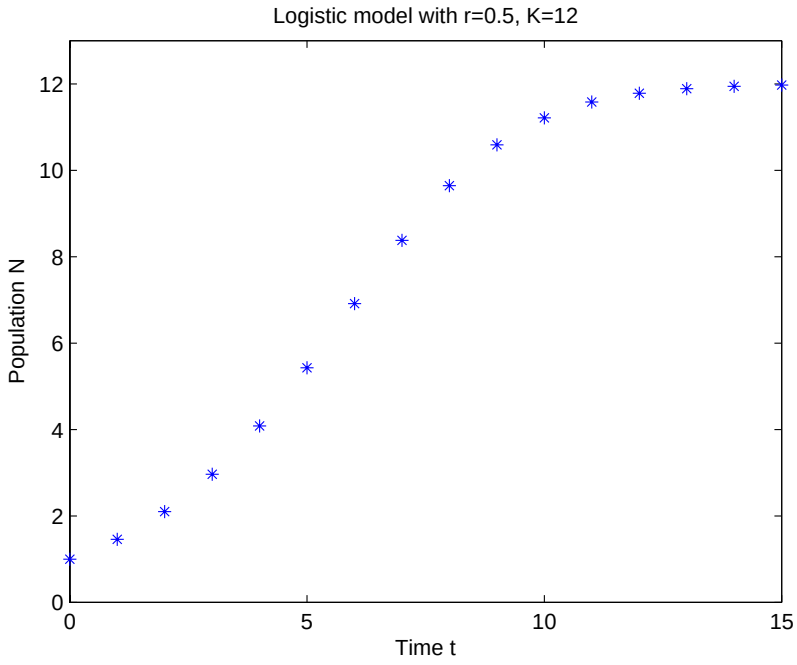

Figure 3.2.1: Solution to Example 3.2.1 generated with MATLAB®

Before getting into a discussion of the results of the calculations in this examples and the graph in Figure 3.2.1, let's go through each line in the `plot1.m` file. The last three lines are self–explanatory; they label the axes and provide a title for the graph. The MATLAB® expression `[0:15]` in the first line yields a row of integers from 0 to 15. The MATLAB® `plot` function in the first line then takes the array `N` (the second argument of the function) and plots it versus

the array `[0:15]` (the first argument of the function) and marks the points on the graph with a black $*$ (this is prescribed by the `'k*'` in the third argument of the `plot` function). The second line sets the range of values along the t–axis to go from 0 to 15 and the values along the N–axis to go from 0 to 13.

Looking at the plot of the results in Figure 3.2.1, we see that he logistic difference equation (3.13) predicts that the bacterial density will increase towards the carrying capacity of 12 millions of cells. At first the rate of increase gets bigger but at about $t = 6$ the rate of increase gets smaller and smaller. □

The power of MATLAB® lies in its programming functionality. We can modify the code in the code1.m file so as to incorporate interactive features that will allow as to input various initial conditions as well as different values for the parameters r and K. This kind of analysis can yield a lot of information about the behavior of solutions to the logistic difference equation (3.12). This analysis will be carried out in the next section.

3.2.2 Numerical analysis of the discrete logistic model

We can use K, the carrying capacity of the medium, as our unit of population density N_t. This amounts to introducing the new scaled variable

$$N_t' = \frac{1}{K} N_t. \tag{3.14}$$

Thus, N_t' measures the population by its proportion relative to the carrying capacity.

Divide the logistic difference equation (3.12) by K to obtain

$$\frac{N_{t+1}}{K} = \frac{N_t}{K}\left(1 + r\left(1 - \frac{N_t}{K}\right)\right),$$

which by virtue of (3.14) can be written as

$$N_{t+1}' = N_t'\left(1 + r\left(1 - N_t'\right)\right). \tag{3.15}$$

Observe that the difference equation in (3.15) has only one parameter; namely r, the intrinsic growth rate. In this section we investigate the effect that changing the parameter r in (3.15) has on the nature of the solution. Before we proceed, we shall suppress the ' on the N in (3.15) to obtain

$$N_{t+1} = N_t + rN_t(1 - N_t). \tag{3.16}$$

Note that this is equivalent to assuming that $K = 1$ in (3.12).

The file Logistic.m contains MATLAB® code (see Appendix A.1 on page 83) that solves equation 3.16 for various values of r and various initial conditions. The program also allows the user to input the range for the time variable t.

In the following exercises you are asked to use the MATLAB® program `Logistic.m` to explore how the nature of the solutions to (3.16) changes as one varies the parameter r and the initial condition N_o.

1. Start out with the initial condition $N_o = 0.1$ and consider the following values of r: 1, 1.5, 2, 2.1, 2.25, 2.5 and 2.7. Describe in words the long term behavior of the solution to (3.16) for each value of r. Is there any significant change in the structure of the solution? Is there anything striking?

2. Keep the value of r at 2.7 and try the following initial conditions:

$$N_o = 0.1 \quad \text{and} \quad N_o = 0.101.$$

   Before you try the second initial condition, type the MATLAB®command `hold on`. This will allow you to see the plots of the two solutions on the same graph. Is there anything that strikes you? What implications does this result might have on the question of predictability?

3. What happens when $r = 3$ and t is allowed to range from 0 to 100? How would you describe the solution?

4. What happens when $r = 3.01$? Does this result suggest that we need to impose a restriction on r? What should that restriction be?

In the following section we shall attempt to explain some of the results obtained in the previous numerical explorations.

3.2.3 Qualitative analysis of the discrete logistic model

We shall begin by re–writing equation (3.16) in the form

$$N_{t+1} = f(N_t), \tag{3.17}$$

where f is the quadratic polynomial function

$$f(x) = x + rx(1 - x). \tag{3.18}$$

We have seen numerically that for the case $r = 0.5$ solutions of the difference equation (3.17) tend towards the limiting value $N = 1$ as $t \to \infty$. This is an example of what is known as a *steady state* solution or an *equilibrium* point.

Definition 3.2.2 *For the case of a difference equation (3.17), an* **equilibrium point**, N^*, *is value of N such that, if $N_t = N^*$, then $N_{t+1} = N^*$. Equivalently, N^* is an equilibrium point of the difference equation (3.17), if whenever $N_t = N^*$, then $\Delta N = 0$.*

Thus, to find the equilibrium points of (3.17), we need to solve the equation

$$\Delta N = N_{t+1} - N_t = f(N_t) - N_t = 0,$$

or the equation

$$f(N) = N. \tag{3.19}$$

Solutions to equation (3.19) are called *fixed point* of the map f; thus, equilibrium points are usually referred to as fixed points as well.

Example 3.2.3 *(Fixed points of the logistic equation).* Equation (3.19) for the function f in (3.18) reads

$$f(x) = x$$

or

$$x + rx(1 - x) = x,$$

which leads to

$$x(1 - x) = 0.$$

This equation has solutions $x = 0$ and $x = 1$. Thus, the equilibrium points of (3.17) are $N = 0$ and $N = 1$.

Finding equilibrium points is an important first step in understanding the structure of the set of solutions of equation (3.17). We have seen in the numerical exploration of the previous section that some of those solutions tend towards the equilibrium point $N^* = 1$, and away from $N^* = 0$. Others tend to oscillate around the equilibrium point N^* for certain the values of the parameter r. This tendency of some equilibrium points of the equation (3.17) to *attract* other nearby solutions in the long run is known as *stability* or *asymptotic stability.* One way to measure the tendency of solutions, N_t, of (3.17) to get closer to an equilibrium point, N^*, is to consider the function $E_t = N_t - N^*$. Observe that $|E_t|$ measures the distance from N_t to N^*.

Example 3.2.4 Consider the equilibrium point $N^* = 1$ of equation (3.17) with f given by (3.18). In this case $E_t = N_t - 1$ so that, from (3.17),

$$\begin{aligned} E_{t+1} &= f(N_t) - 1 \\ &= N_t + rN_t(1 - N_t) - 1 \\ &= (N_t - 1) - rN_t(N_t - 1) \\ &= (N_t - 1) - rN_t(N_t - 1) + r(N_t - 1) - r(N_t - 1) \\ &= (1 - r)(N_t - 1) - r(N_t - 1)^2 \\ &= (1 - r)E_t - rE_t^2. \end{aligned}$$

It then follows that E_t satisfies the difference equation

$$E_{t+1} = \lambda E_t - rE_t^2 \tag{3.20}$$

where $\lambda = 1 - r$.

The idea behind stability is that if $|E_t|$ starts out being small, then we would expect $|E_{t+1}|$ to be even smaller. This is indeed the case provided that $|\lambda| < 1$ (that is, if $|r - 1| < 1$ or $0 < r < 2$) and $|E_o|$ is small enough.

Definition 3.2.5 *An equilibrium point, N^*, of (3.17), is said to be* **asymptotically stable** *if there exists some number $\delta_o > 0$ such that if N_t is a solution of (3.17) satisfying $|N_o - N^*| < \delta_o$, then*

$$\lim_{t \to \infty} |N_t - N^*| = 0.$$

Example 3.2.6 *(Continuation of Example 3.2.4).* In this example we show that if $0 < r < 2$, then $N^* = 1$ is an asymptotically stable equilibrium point of the logistic equation (3.16). According to Definition 3.2.5, we need to show that if N_t is a solution of (3.17) with $|N_o - 1|$ sufficiently small, $\lim_{t\to\infty} |N_t - 1| = 0$. This is equivalent to showing that

$$\lim_{t\to\infty} |E_t| = 0, \tag{3.21}$$

where E_t solves that difference equation (3.20) with $|\lambda| < 1$, provided that $|E_o|$ is sufficiently small.

Since $|\lambda| < 1$, we can find a number $\mu > 0$ such that $|\lambda| + \mu < 1$ (for instance, we can take $\mu = (1 - |\lambda|)/2$). Let E_t denote a solution of (3.20) satisfying

$$|E_o| < \frac{\mu}{r}. \tag{3.22}$$

Taking absolute values on both sides of (3.20) and using the triangle inequality ($|a + b| \leq |a| + |b|$, for any pair of real numbers a and b), we obtain that

$$|E_{t+1}| \leq |\lambda||E_t| + r|E_t|^2. \tag{3.23}$$

Applying this inequality to the case $t = 0$ we obtain

$$|E_1| \leq |\lambda||E_o| + r|E_o|^2,$$

which, by virtue of (3.22), implies that

$$|E_1| \leq (|\lambda| + \mu)|E_o|. \tag{3.24}$$

Applying (3.23) again, this time to the case $t = 1$, we get

$$|E_2| \leq |\lambda||E_1| + r|E_1|^2.$$

Using the estimate for $|E_1|$ in (3.24) on the last term of this inequality we obtain

$$|E_2| \leq |\lambda||E_1| + r|E_1|(|\lambda| + \mu)|E_o|,$$

which can be rearranged as

$$|E_2| \leq |\lambda||E_1| + (r|E_o|)(|\lambda| + \mu)|E_1|.$$

Using the fact that $|\lambda| + \mu < 1$ and the estimate (3.22) for $|E_o|$ in the last term of this inequality we gat, after factoring, that

$$|E_2| \leq (|\lambda| + \mu)|E_1|. \tag{3.25}$$

The same estimates leading from (3.24) to (3.24) can be used to yield

$$|E_3| \leq (|\lambda| + \mu)|E_2|,$$

which, by induction on n, yields the inequalities

$$|E_{n+1}| \leq (|\lambda| + \mu)|E_n|, \quad \text{for} \quad n = 0, 1, 2, 3, \ldots \tag{3.26}$$

It can be shown by induction on n that the *difference inequality* in (3.26) implies that

$$|E_n| \leq (|\lambda| + \mu)^n |E_o|, \quad \text{for} \quad n = 1, 2, 3, \ldots$$

Hence, since $|\lambda| + \mu < 1$,

$$\lim_{n\to\infty} |E_n| = 0,$$

which is (3.21). This shows that

$$\lim_{t\to\infty} |N_t - 1| = 0,$$

where N_t is a solution of (3.16) with $0 < r < 2$ and N_o sufficiently close to 1. Hence, $N^* = 1$ is an asymptotically stable equilibrium point of (3.16) for $0 < r < 2$. □

The procedure outlined in the previous two examples is a rather general one that applies not only to the logistic equation. Observe that the *multiplier* $\lambda = 1 - r$ in equation (3.20) is the derivative of the function $f(x) = x + rx(1 - x)$ at the fixed point $x = 1$. In fact, $f'(x) = 1 + r(1 - x) - rx$ and therefore $f'(1) = 1 - r$. Furthermore, equation (3.20) may be derived from the following expressions

$$f(x) = f(1) + f'(1)(x - 1) + R(x; 1) \tag{3.27}$$

involving the *linear approximation*

$$L(x; 1) = f(1) + f'(1)(x - 1)$$

to f around 1, and the error $R(x; 1)$ incurred in using $L(x; 1)$ to approximate $f(x)$. In fact, substituting N_t for x in (3.27)) and using the fact that $N^* = 1$ is a fixed point of f, we get that

$$f(N_t) - 1 = f'(1)(N_t - 1) + R(N_t; 1).$$

Recalling that $N_{t+1} = f(N_t)$, by (3.17), and that $E_t = N_t - 1$, we see that this equation leads to (3.20) with $R(N_t; 1) = -r(N_t - 1)^2$.

In general, given any differentiable function f with fixed point x^*, we can write

$$f(x) - x^* = f'(x^*)(x - x^*) + R(x; x^*),$$

where R has the property that

$$\lim_{x\to x^*} \frac{|R(x; x^*)|}{|x - x^*|} = 0.$$

Therefore, the argument outlined in Example 3.2.6 can be used prove the following result

Theorem 3.2.7 *[The Principle of Linearized Stability (Discrete Version)]. Let N^* be a fixed point of the differentiable map f, and suppose that*

$$|f'(N^*)| < 1.$$

Then, N^* is an asymptotically stable equilibrium point of the difference equation

$$N_{t+1} = f(N_t).$$

Remark 3.2.8 Theorem 3.2.7 is only a part of a theorem stated on page 23 in Allman and Rhodes [AR04]. One can prove more than stated in Theorem 3.2.7. In fact, if

$$|f'(N^*)| > 1,$$

then N^* is *unstable*. However, if $|f'(N^*)| = 1$, no statement about the stability or instability of N^* can be concluded.

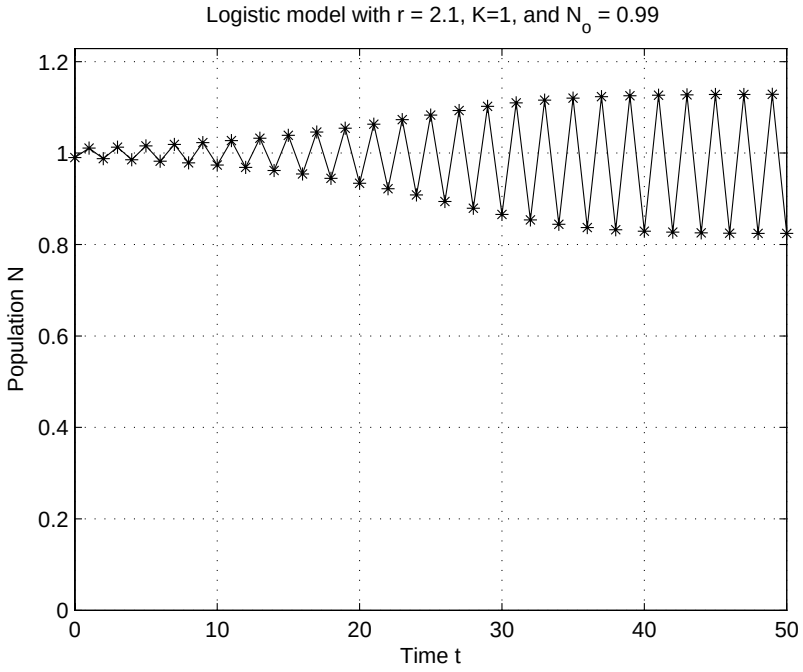

Figure 3.2.2: Solution to (3.16) with $r = 2.1$ and $N_o = .99$

Example 3.2.9 Use the Principle of Linearized Stability to determine whether the equilibrium point $N^* = 0$ of the logistic equation (3.16) is stable or not.

Solution: In this case, $f(x) = x + rx(1 - x)$ where $r > 0$. Then,

$$f'(x) = 1 + r(1 - x) - rx$$

and so $f'(0) = 1 + r$. Thus, $|f'(0)| = 1 + r > 1$, since $r > 0$, and therefore $N^* = 0$ is unstable for all $r > 0$. □

The Principle of Linearized Stability implies that, if $r > 2$ in the logistic equation (3.16). then solutions starting near the equilibrium point $N^* = 1$ will tend away from that point as t increases. In fact, numerical calculations show that, when $N_o = 0.99$, the solution will tend away from $N^* = 1$ and then settle into an oscillatory pattern about $N^* = 1$ for large values of t; see Figure 3.2.2. The Principle of Linearized Stability does not give information about the oscillatory behavior of the solution in the long run. In order to get that information (without having to solve the equation), we need to resort to a form of graphical analysis known as *cobweb analysis.*

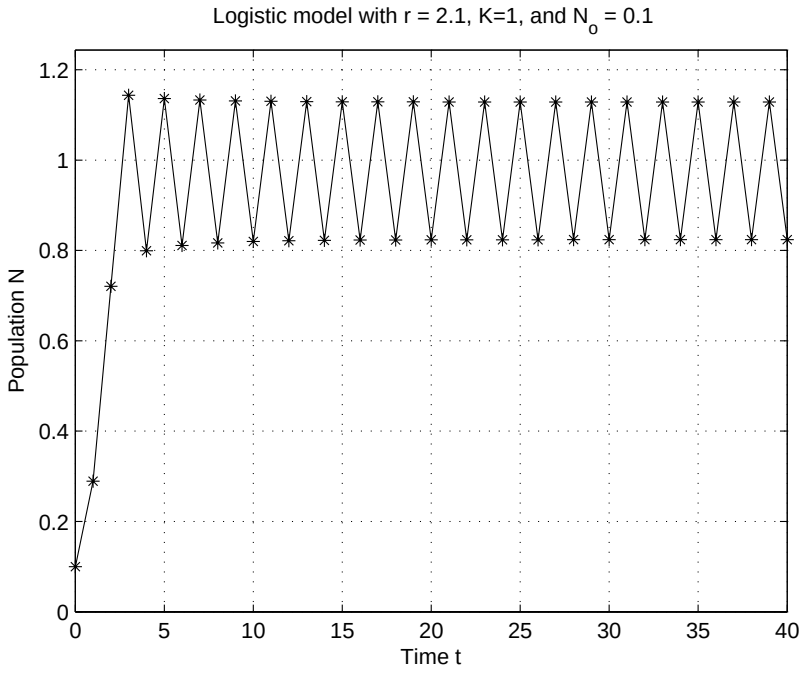

Figure 3.2.3: Numerical Solution of (3.16) with $r = 2.1$ and $N_o = 0.1$

The idea behind cobweb analysis is the observation that solutions of (3.17) can be obtained by *iterating* the map f. In fact, from (3.17)

$$N_{t+1} = f(N_t),$$

we get that

$$N_1 = f(N_o),$$

and therefore

$$N_2 = f(N_1) = f(f(N_o)) = f^2(N_o),$$

where the superscript 2 on f does not mean that we multiply f by itself, but rather that we apply f to the result obtained by applying f to N_o. We can then see, by induction on n, that

$$N_{n+1} = f^n(N_o) \quad \text{for all} \quad n = 0, 1, 2, \ldots$$

The *iterates* of N_o under the repeated applications of f can be represented pictorially in a graph of N_{t+1} versus N_t, as shown in Figure 3.2.4. In the figure we have sketched the graph of $N_{t+1} = f(N_t)$, where $f(x) = x + 2.1x(1 - x)$; that is we are looking at the case $r = 2.1$. In this particular case, the graph of $N_{t+1} = f(N_t)$ is a parabola opening downwards, going through the points $N = 0$ and $N = 31/21$, and having a maximum value at $N = 31/42$. We have also sketched the graph of the 45°–line $N_{t+1} = N_t$.

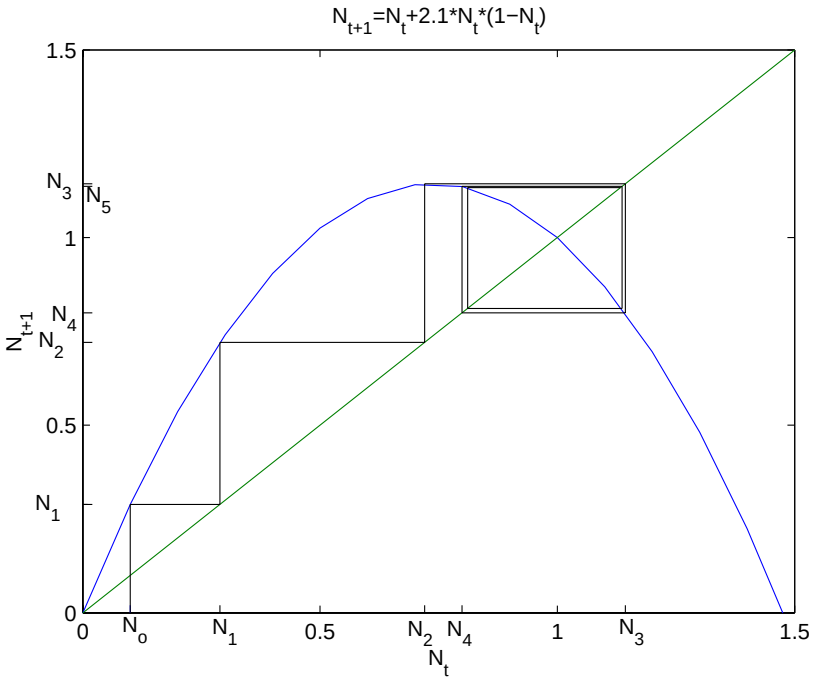

Figure 3.2.4: Cobweb Analysis for (3.16) with $r = 2.1$ and $N_o = 0.1$

We start out with the initial value $N_o = 0.1$ sketched on the N_t–axis. To find N_1, we move along a vertical line from N_o until we hit a point on the curve $N_{t+1} = f(N_t)$. The N_{t+1}–coordinate of that point is the value of N_1. Next, we move from that point along a horizontal line until we hit a point on the line $N_{t+1} = N_t$. Projecting down onto the N_t–axis gives N_1 on that axis. To obtain N_2, we proceed as before, this time starting from the point (N_1, N_1) on the line $N_{t+1} = N_t$. That is we draw a vertical line from that point until we hit a point of the curve $N_{t+1} = f(N_t)$, and then a horizontal line from that point to the

line $N_{t+1} = N_t$. The projection of that last point onto the N_t axis yields N_2. Repeating this procedure many times yields the cobweb–like pattern sketched in Figure 3.2.4. Observe that after a while the pattern tends to a rectangle with the line $N_{t+1} = N_t$ as a diagonal. The corners of that rectangle on that diagonal correspond to the two values at which the solution N_t will oscillate back and forth. This suggests the existence of a periodic solution to 3.16 for the case $r = 2.1$, which is corroborated by the numerical solution sketched in Figure 3.2.3.

Chapter 4

Modeling Bacterial Growth: Continuous Approach

In the previous chapter we modeled time, t, as a discrete variable that had increments at a fixed unit. The population density variable, N_t, in the models discussed in the previous section was also discrete by nature. After all, we are simply *counting* the *number* of bacteria in a given culture. It is convenient, in cases where it is appropriate, to assume that both the population density, which we shall now denote by $N(t)$, and the time t are both continuous variables. In fact, we will also assume that N is a *differentiable function* of t. What this means is that, for any t,

$$\lim_{h \to 0} \frac{N(t+h) - N(t)}{h}$$

exists, and is in fact equal to some value which we denote by $N'(t)$, the *derivative* of N at t. We will also assume that $N'(t)$ is a continuous function of t. The main reason to make these assumptions is that we can then bring to bear the power of the theory of *differential equations* to the study of biological problems. These assumptions are justified in situations for which

1. N is very large so that an increase (or decrease) of one or several individuals in the population may be considered to be insignificant; for instance, when modeling bacterial growth, N is measured in millions of cells per milliliters, so a change of a few individuals is in the order of 10^{-6} cells per milliliters;

2. there is an overlap between successive generations; this is the case, for instance, in human populations; or, if there is no overlap, the time interval between generations is very short.

We can go from the discrete models that we have discussed to continuous versions by considering smaller and smaller time increments. For a general discrete model

$$N_{t+1} = f(N_t) \tag{4.1}$$

each increment is in one unit of t. We would like to consider a growth process now in which we are interested in what happens in a fraction $h = 1/n$, where n is a positive integer, of a unit of time t; that is, we would like to know what N_{t+h} is. If we consider h now to be our new unit of time, this amounts to introducing a new time variable, τ, such that n units of τ correspond to one unit of t. We therefore get the relation $n\tau = t$ or $\tau = ht$. We would like to find out what the growth law expression (4.1) would look like in the new time unit τ; that is we would like to compute $N_{\tau+1}$.

Example 4.0.10 Suppose that the growth law (4.1) is Malthusian; that is, suppose that

$$N_{t+1} = \lambda N_t. \tag{4.2}$$

We would like to know what the growth law is in terms of τ; that is we would like to find a parameter μ such that

$$N_{\tau+1} = \mu N_\tau. \tag{4.3}$$

We know that the growth law (4.3) predicts that

$$N_\tau = \mu^\tau N_o. \tag{4.4}$$

We also know that when $\tau = n$, the value of the population density, N, should be the same as that for $t = 1$. According to (4.2), this should be λN_o. Thus, from (4.4), we get

$$\mu^n N_o = \lambda N_o$$

from which we get that

$$\mu = \lambda^{1/n} = \lambda^h.$$

It then follows from (4.3) that

$$N_{\tau+1} = \lambda^h N_\tau.$$

Translation this last equation in terms of t we get that

$$N_{t+h} = \lambda^h N_t.$$

Subtracting N_t from the previous equation and dividing by $h \neq 0$ we obtain

$$\frac{N_{t+h} - N_t}{h} = \frac{\lambda^h - 1}{h} N_t. \tag{4.5}$$

Thus, if $N_t = N(t)$ is a differentiable function of t, the limit as $h \to 0$ of the expression on the left–hand side of (4.5) exists and is given by $N'(t)$. We therefore have that

$$N'(t) = \lim_{h\to 0} \frac{\lambda^h - 1}{h} N(t). \tag{4.6}$$

The limit on the right–hand side of (4.6) can be evaluated by applying L'Hospital's Rule:

$$\lim_{h\to 0} \frac{\lambda^h - 1}{h} = \lim_{h\to 0} \frac{d}{dh}(\lambda^h) = \lim_{h\to 0} \lambda^h \ln(\lambda) = \ln(\lambda).$$

Hence, (4.6) yields the *differential equation*

$$\frac{dN}{dt} = (\ln(\lambda))N. \quad \square \tag{4.7}$$

4.1 Exponential Growth or Decay

The differential equation (4.7) is the continuous version of the Malthusian growth model

$$\frac{dN}{dt} = kN, \tag{4.8}$$

where $k = \dfrac{1}{N}\dfrac{dN}{dt}$ is the *per–capita growth rate,* which is this case is assumed to be constant; in fact, $k = \ln(\lambda)$, where λ is the growth rate in the discrete Malthusian model. We can solve (4.8) as follows:

First, rewrite the equation as

$$\frac{1}{N}\frac{dN}{dt} = k,$$

and then integrated with respect to t to get

$$\int \frac{1}{N}\frac{dN}{dt}dt = \int k dt. \tag{4.9}$$

By the Chain Rule the first integral in (4.9) can be written as $\displaystyle\int \frac{1}{N}dN$. Then (4.9) can be written as

$$\int \frac{1}{N}dN = \int k dt. \tag{4.10}$$

The process of going from (4.8) to (4.10) is usually referred to as the method of *separation of variables,* since the N and t variables have been "separated" by the equal sign in (4.10).

The left–hand side in equation (4.10) integrates to

$$\int \frac{1}{N}dN = \ln|N| + c_1$$

where c_1 is a constant of integration. If k is a constant, the second integral in (4.10) integrates to

$$\int k dt = kt + c_2$$

for some constant of integration c_2. Substituting the last two integrals into (4.10) we get

$$\ln|N| = kt + c_3, \tag{4.11}$$

where we have combined the constants c_1 and c_2 into the new constant c_3.

We would like to solve the equation in (4.11) for $N = N(t)$. In order to do this, first we exponentiate on both sides of (4.11) to get

$$|N| = e^{kt+c_3} = e^{c_3}e^{kt} = c_4e^{kt}, \tag{4.12}$$

where $c^4 = e^{c_3}$, and is therefore a non–negative constant. To get rid of the absolute value sign in (4.12), we rewrite the equation as

$$e^{-kt}|N| = c_4,$$

or

$$|e^{-kt}N(t)| = c_4$$

for all $t \in \mathbf{R}$. Next, since $N(t)$ and the exponential function are continuous functions, it follows from the last equation that $e^{-kt}N(t)$ must be constant (why?). We then have that

$$e^{-kt}N(t) = C \quad \text{for all } t \in \mathbf{R},$$

for some constant C, so that

$$N(t) = Ce^{kt} \quad \text{for all } t \in \mathbf{R}, \tag{4.13}$$

is a solution to the differential equation (4.8). We then see that the continuous Malthusian Model predicts *exponential, unlimited growth* if $k > 0$, and *exponential decay* if $k < 0$. If $k = 0$, the model predicts a *stationary* or *steady state* situation. Observe that these three possibilities correspond to the situations $\lambda > 1$, $0 < \lambda < 1$, and $\lambda = 1$, respectively, in the discrete Malthusian model.

Example 4.1.1 Suppose a bacterial colony grows according to the (continuous) Malthusian model. Find the time it takes for the population to double.

Solution: Suppose that at time $t = 0$, the population size is N_o. Then, the constant C in equation (4.13) is $C = N_o$, Thus, the population size as a function of t is given by

$$N(t) = N_oe^{kt} \quad \text{for all } t \in \mathbf{R}. \tag{4.14}$$

Let T denote the time at which $N = 2N_o$, It then follows from (4.14) that

$$N_oe^{kT} = 2N_o.$$

Canceling N_o in the previous equation and solving for T yields

$$T = \frac{\ln(2)}{k}. \tag{4.15}$$

This is called the *doubling time* of the population. In the case of bacteria, the doubling time would correspond to the *average division cycle.* Observe that the Malthusian model predicts that this time is independent of the population size; it depends only on the constant, *per–capita* growth rate k. □

From the expression (4.15) in the previous example, we also get an expression for the *per–capita* growth rate, k, in terms of the doubling time, T:

$$k = \frac{\ln(2)}{T}. \tag{4.16}$$

Substituting this expression for k into the solution to the (continuous) Malthusian model in (4.14), we obtain

$$N(t) = N_o e^{\left(\frac{\ln(2)}{T}\right)t} = N_o \left(e^{\ln(2)}\right)^{\frac{t}{T}} = N_o\ 2^{t/T}.$$

Thus, if t is measured in units of *doubling time,* or division cycle in the case of bacteria, then $N(t)$ is given by

$$N(t) = N_o\ 2^t,$$

where t counts the number of doubling times, or division cycles, from the time the population size was N_o.

4.2 General Continuous Growth Models

The procedure outlined in Example 4.0.10 for going from the discrete Malthus model to the continuous one can be applied to any discrete growth model of the form

$$N_{t+1} = f(N_t), \tag{4.17}$$

where f is a known continuous function. Suppose that able to obtain an expression for N_{t+h}, where h is a fraction of a unit of t from the growth–law expression in (4.17), and that

$$N_{t+h} = f(N_t; h), \tag{4.18}$$

where the right–hand side of (4.18) expresses a dependence on the new time parameter h (recall that, in the case of the Malthusian model, $f(N_t; h) = \lambda^h N_t$). Assume also that

$$\lim_{h\to 0} \frac{f(N; h) - N}{h}$$

exists and equals $g(N)$. Then, if $N_t = N(t)$ is a differentiable function of t, it follows that N satisfies the first order differential equation

$$\frac{dN}{dt} = g(N), \tag{4.19}$$

which prescribes the rate of change of the population.

More generally, a population model for a population of size $N = N(t)$ is a statement of the following *conservation principle:*

$$\frac{dN}{dt} = \text{Rate of individuals in} - \text{Rate of individuals out}; \tag{4.20}$$

that is, any change in the population size has to be accounted for by the number of new individuals, per unit time, that are added to the population minus those that are taken out of the population. A more specific form the *conservation equation* (4.20) would be

$$\frac{dN}{dt} = \text{births} - \text{deaths} + \text{migrations} - \text{harvesting} + \text{etc.}, \tag{4.21}$$

where all the quantities on the right–hand side of the equation are given per unit of time; in other words, they are given as *rates.* Rates in population studies are usually given *per capita;* that is, per unit of population. Thus, the conservation principle (4.21) can be further written as

$$\frac{1}{N}\frac{dN}{dt} = \text{birth rate} - \text{death rate} + \text{migration rate} + \text{etc.}, \tag{4.22}$$

where all the rates on the right–hand side are *per capita* rates.

4.3 Logistic Growth

The term $\dfrac{1}{N}\dfrac{dN}{dt}$ on the left–hand side of the conservation equation (4.22) is called the *per capita growth rate* of the population. If we assume that this is a constant, k, we obtain the Malthusian model (4.8). We saw in Section 4.1 that this leads to unlimited, exponential growth in the case $k > 0$. This is unrealistic in the case of large population sizes, since the population density, N, then becomes an important factor which may effect negatively the growth rate of the population due to competition for food and resources. In order to account for the negative effect large population densities have on the *per capita* growth rate, we may model it by a linear function of N that decreases with increasing N; more specifically, assume that

$$\frac{1}{N}\frac{dN}{dt} = r - \frac{r}{K}N,$$

where r, the *intrinsic growth rate,* approximates the *per capita* growth rate for very low population densities, and K is the *carrying capacity.* This leads to the (continuous) Logistic growth equation

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right). \tag{4.23}$$

We will show in Section 4.3.2 that equation (4.23) has a unique solution, $N = N(t)$, satisfying $N(0) = N_o$ for any initial population density N_o. Furthermore, if $N_o > 0$, the solution exists for all $t > 0$, and

$$\lim_{t\to\infty} N(t) = K. \tag{4.24}$$

We will do this by actually deriving a formula for computing $N(t)$, showing that any solution of (4.23) must in fact be given by that formula, seeing that,

if $N_o > 0$, the formula defining $N(t)$ makes sense for all $t > 0$, and computing the limit (4.24). We can, however, obtain a lot of qualitative information about solutions to (4.23), without actually computing the solution, directly from the equation. This will be done in the following section.

4.3.1 Qualitative Analysis of the Logistic Equation

The analysis to be carried out in this section for the logistic equation (4.23) applies to the larger class of continuous growth models in (4.19); namely,

$$\frac{dN}{dt} = g(N). \tag{4.25}$$

In the particular case of the logistic equation (4.23), the function g is given by

$$g(N) = rN\left(1 - \frac{N}{K}\right)$$

and it prescribes the *rate of change,* $N'(t)$, of the function $N = N(t)$ for any value of $N(t)$. Thus, for values of t for which $g(N(t)) > 0$, the solution $N(t)$ increases, while for values of t with $g(N(t)) < 0$, it decreases. Table 4.1 summarizes this information. The horizontal line in the table represents the N–axis.

$g(N)$	$+$	$-$
0		K
$N'(t)$	$+$	$-$
$N(t)$	increases	decreases

Table 4.1: Information about $N(t)$

The values of N for which $g(N) = 0$ yield the *equilibrium* solutions

$$\overline{N} = 0 \quad \text{and} \quad \overline{N} = K.$$

Definition 4.3.1 *A value of N, denoted $\overline{N}$, is said to be an* **equilibrium point***, or a* **fixed point***, of the equation (4.25), if it solves the equation*

$$g(N) = 0.$$

The constant function $N(t) = \overline{N}$, for all t, is called an **equilibrium solution** *or a* **steady state solution***.*

Thus, equilibrium points of the logistic equation (4.23) correspond to the N–intercepts of the graph of $g(N)$ versus N pictured in Figure 4.3.1.

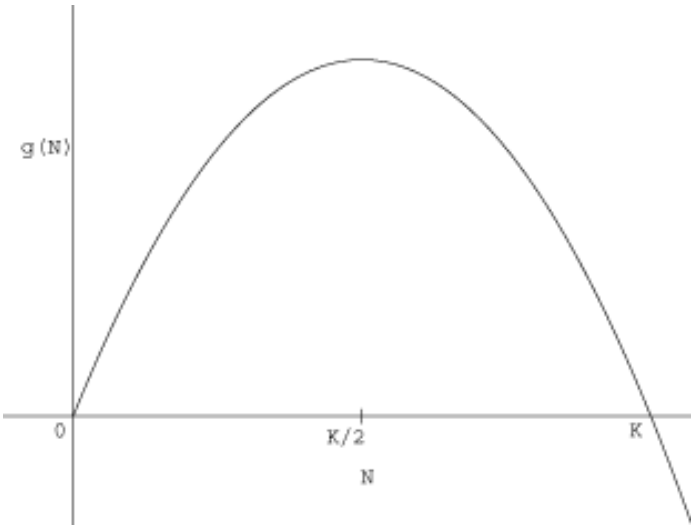

Figure 4.3.1: Graph of $g(N)$ versus N for the logistic equation (4.23)

To obtain more information about the graph of $N = N(t)$ as a function of t, we may look at the second derivative of N with respect to t:

$$N''(t) = \frac{d}{dt}(N'(t)) = \frac{d}{dt}(g(N)) = g'(N) \cdot \frac{dN}{dt},$$

where we have used the Chain Rule in the last step. Thus, by (4.25),

$$N''(t) = g(N) \cdot g'(N). \tag{4.26}$$

Thus, the concavity of the graph of $N = N(t)$ (i.e., whether the graph of $N = N(t)$ is concave–up or concave–down) is determined by the signs of both $g(N)$ and its derivative with respect to N, $g'(N)$. Table 4.2 summarizes all the concavity information on the graph of a solution to the logistic equation (4.23). As in Table 4.1, the horizontal line in Table 4.2 represents the N–axis.

$g(N)$		$+$	$+$	$-$
$g'(N)$		$+$	$-$	$-$
	0	$K/2$	K	
$N''(t)$		$+$	$-$	$+$
graph of $N(t)$		concave–up	concave–down	concave–up

Table 4.2: Concavity of the graph of $N = N(t)$

Combining the qualitative information contained in both tables, we can sketch graphs of possible solutions to (4.23). Figure 4.3.2 shows the two equilibrium solutions of (4.23), $N = 0$ and $N = K$, as well as sketches of possible solutions for various initial values N_o. Observe that if $0 < N_o < K/2$, then the graph of the solution has an inflection point at $N = K/2$ in accordance with the information in Table 4.2.

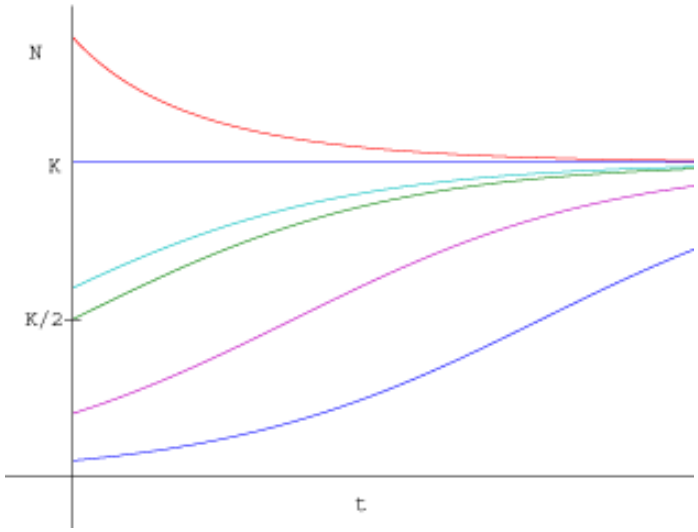

Figure 4.3.2: Graph of possible solutions of the logistic equation (4.23)

The curves in Figure 4.3.2 were sketched assuming that the solutions to the logistic equation (4.23), for given initial values $N_o > 0$, exist for all $t > 0$. This will be shown to be the case in the following section. The sketch also suggests that all these solutions tend towards the value K in the limit as $t \to \infty$; thus, the equilibrium solution $\overline{N} = K$ is asymptotically stable. This will also be proven to be the case in the next section. Finally, implied in the sketch is the fact that solution curves corresponding to different initial values N_o do not cross, or intersect. We will see why this is true in the next section as well.

The analysis of the logistic equation (4.23) carried out thus far also provides information about the stability properties of the equilibrium points $\overline{N} = 0$ and $\overline{N} = K$. In fact, from Table 4.1 we see that if a solution $N = N(t)$ of the equation is such that $N(0) = N_o$ is positive and $N_o < K$, then $N(t)$ will increase towards K as t increases; on the other hand, if $N_o > K$, then $N(t)$ will decrease towards K. Hence $\overline{N} = K$ is *stable* (as mentioned in the previous paragraph, in the next section we will see that $\overline{N} = K$ is actually asymptotically stable). Similarly, if N_o is positive and very close to zero then, since $N(t)$ increases for $0 < N < K$ (see Table 4.1), $N(t)$ will tend away from 0. Although not shown in Table 4.1, $N(t)$ will decrease for $N < 0$, and so if N_o is negative, $N(t)$ will also tend away from 0. Thus, $\overline{N} = 0$ is unstable.

4.3.2 Solving the Logistic Equation

In this section we derive a formula for computing a solution of the logistic equation (4.23) subject to the initial condition $N(0) = N_o$, where N_o is any given real value. In other words, we find a so–called *analytical solution* of the initial value problem (IVP)

$$\begin{cases} \frac{dN}{dt} &= rN\left(1 - \frac{N}{K}\right) \\ N(0) &= N_o. \end{cases} \tag{4.27}$$

First, note the if $N_o = 0$, the it is clear that the constant function $N(t) = 0$, for all t, solves the IVP (4.27). Thus, we have a formula for a solution of that problem in the case $N_o = 0$.

Next, assume that $N_o \neq 0$, and suppose that $N(t)$ is a solution of IVP (4.27). Then, the function $u(t) = \dfrac{1}{N(t)}$ satisfies

$$\frac{du}{dt} = -\frac{1}{N^2}\frac{dN}{dt},$$

by the Chain Rule. Substituting for $\dfrac{dN}{dt}$ its expression given by the logistic equation (4.23), we get

$$\frac{du}{dt} = -\frac{1}{N^2} rN\left(1 - \frac{N}{K}\right) = -r\left(\frac{1}{N} - \frac{1}{K}\right).$$

Thus, since $u = \dfrac{1}{N}$, it follows that u satisfies the first order *linear* differential equation

$$\frac{du}{dt} = -r\left(u - \frac{1}{K}\right). \tag{4.28}$$

Observe that u also satisfies the initial condition

$$u(0) = \frac{1}{N(0)} = \frac{1}{N_o}. \tag{4.29}$$

Equation (4.28) can be solved by separation of variables:

$$\int \frac{1}{u - 1/K}\, du = -\int r\, dt.$$

Integration yields

$$\ln\left|u - \frac{1}{K}\right| = -rt + c_1$$

for some constant c_1. Thus, exponentiating and solving for u yields

$$u(t) = \frac{1}{K} + Ce^{-rt}, \tag{4.30}$$

for all real values of t and some constant C. Substituting 0 for t in (4.30), and using the initial condition (4.29), we get that

$$C = \frac{1}{N_o} - \frac{1}{K}.$$

Thus, from (4.30) we get that

$$u(t) = \frac{1}{K} + \left(\frac{1}{N_o} - \frac{1}{K}\right) e^{-rt}.$$

Hence, since $N = \dfrac{1}{u}$, it follows that

$$N(t) = \frac{1}{\frac{1}{K} + \left(\frac{1}{N_o} - \frac{1}{K}\right) e^{-rt}},$$

or

$$N(t) = \frac{N_o K}{N_o + (K - N_o)e^{-rt}}. \tag{4.31}$$

Observe that this formula also yields a solution to IVP (4.27) for the case $N_o = 0$; namely, the constant function $N(t) = 0$ for all t.

The formula (4.31) defines a function as long as the denominator on the right–hand side of (4.31) is not zero. This is so for all $t > 0$ as long as $N_o > 0$. To see this, suppose that

$$N_o + (K - N_o)e^{-rt} = 0 \tag{4.32}$$

for some $t > 0$. It then follows that

$$N_o = -\frac{Ke^{-rt}}{1 - e^{-rt}}.$$

Thus, since $r > 0$, $N_o < 0$ for any $t > 0$. Therefore, (4.32) cannot happen for any $t > 0$ as long as $N_o > 0$. It then follows that, if $N_o > 0$, the formula for $N(t)$ in (4.31) yields a function which is defined for all $t > 0$. Hence, we conclude that, for $N_o > 0$, equation (4.31) defines a solution of IVP (4.27) for all $t > 0$. It also follows from that formula that

$$\lim_{t\to\infty} N(t) = K,$$

since $\lim\limits_{t\to\infty} e^{-rt} = 0$ for any $r > 0$.

Next, we show that **any** solution of the IVP 4.27) must be given by the formula (4.31). In other words, the IVP (4.27) has one and only one solution. We also say that IVP (4.27) has a *unique* solution. (Note that the solution will exist for all $t > 0$ in the case $N_o > 0$; in all cases, though, the solution exists at least in some interval around 0). So, let $N = N(t)$ denote any solution of IVP (4.27), which is not necessarily given by formula (4.31). Assume first that

$N_o \neq 0$. Then, there is some interval, I, around $t = 0$ such that $N(t) \neq 0$ for all $t \in I$. We can then define a function u given by $u(t) = \dfrac{1}{N(t)}$ fro all $t \in I$. Then, as in the derivation leading to (4.28), u satisfies $u'(t) = -r(u - 1/K)$. Put $w(t) = e^{rt}(u - 1/K)$ for all $t \in I$. Then, by the product rule,

$$\frac{dw}{dt} = re^{rt}(u - 1/K) + e^{rt}u' = re^{rt}(u - 1/K) - re^{rt}(u - 1/K) = 0$$

for all $t \in I$. It then follows that $w(t) = C$, a constant, for all $t \in I$. Since

$$w(0) = u(0) - 1/K = 1/N_o - 1/K,$$

it follows that $C = 1/N_o - 1/K = (K - N_o)/N_oK$. Thus,

$$e^{rt}(u(t) - 1/K) = (K - N_o)/N_oK,$$

for all $t \in I$, which can be solved for u to yield

$$u(t) = \frac{1}{K} + \frac{(K - N_o)e^{-rt}}{N_oK} = \frac{N_o + (K - N_o)e^{-rt}}{N_oK}$$

for all $t \in I$. Using the fact that $N = \dfrac{1}{u}$ we get that

$$N(t) = \frac{N_oK}{N_o + (K - N_o)e^{-rt}},$$

for all $t \in I$, which is the formula in (4.31). For the case in which $N_o > 0$ we see from the qualitative information in Table 4.1 that $N(t)$ will remain positive for all $t > 0$. Thus the interval I can be extended to include the positive half–line corresponding to $t > 0$, and so $N(t)$ agrees with the formula in (4.31) for all $t > 0$. This proves the uniqueness for the IVP (4.27) at least for the case $N_o > 0$. (The argument for case $N_o < 0$ will be omitted here since it is similar to the one we have just discussed, except that in that case, the interval I does not include all positive values of t).

We now deal with the case $N_o = 0$. In this case we know that we have the constant function 0 as a solution. The question is then, whether it is possible for the IVP (4.27) with $N_o = 0$ to have another solution differential from the 0 constant function. Suppose there is such a solution, and call it $N = N(t)$. Then, N solves the logistic equation (4.23), and satisfies the initial condition $N(0) = 0$, but, for some $t_1 > 0$, $N(t_1) \neq 0$. We first look at the case $N(t_1) > 0$. By the continuity of $N(t)$, we may assume that $0 < N(t_1) < K$ (Why?). Let $N_1 = N(t_1)$ and consider the IVP

$$\begin{cases} \frac{dy}{dt} &= ry\left(1 - \frac{y}{K}\right) \\ y(0) &= N_1; \end{cases} \tag{4.33}$$

that is, the IVP (4.27) with N_1 instead of N_o. By what we have already proved, since $N_1 > 0$, the IVP (4.33) has a unique solution for $t > 0$ given by

$$y(t) = \frac{N_1 K}{N_1 + (K - N_1)e^{-rt}}, \tag{4.34}$$

for all $t > 0$. Observe that since $N_1 < K$, the formula for $y(t)$ given in (4.34) is actually defined for **all** real values of t; that is, even for negative values of t. Define a new function $z(t) = y(t - t_1)$ for all $t \in \mathbf{R}$. Then, z satisfies the IVP

$$\begin{cases} \frac{dz}{dt} &= rz\left(1 - \frac{z}{K}\right) \\ z(t_1) &= N_1. \end{cases} \tag{4.35}$$

Observe that z is given by the formula

$$z(t) = \frac{N_1 K}{N_1 + (K - N_1)e^{-r(t-t_1)}}, \tag{4.36}$$

for all $t \in \mathbf{R}$. We now have two functions, $z(t)$ and $N(t)$, both of which solve the logistic equation (4.23), and both of which take on the same value, N_1, at $t = t_1$. Since $N_1 > 0$, they are both given by the same formula (4.36) for t in some interval I on which $N(t) > 0$. So that,

$$N(t) = \frac{N_1 K}{N_1 + (K - N_1)e^{-r(t-t_1)}} \tag{4.37}$$

for all $t \in I$. We can make the interval I so large so that $I = (a, b)$, where $0 \leq a < t_1$, and

$$\lim_{t \to a^+} N(t) = 0.$$

We then get by (4.37) and the continuity of $N(t)$ that

$$\frac{N_1 K}{N_1 + (K - N_1)e^{-r(a-t_1)}} = 0,$$

which implies that $N_1 = 0$. This contradicts the assumption that $N_1 > 0$, and so it must be the case that the constant function 0 is the only solution of the IVP (4.27) with $N_o = 0$.

The existence and uniqueness result that we have established in this section for the IVP (4.27) is a special case of a more general result that applies to continuous models of the form

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

where g is a differentiable function with continuous derivative. We state it here without proof and refer the reader to the text "Differential Equations: A Modeling Approach" by Borrelli and Coleman [BC87]. The theorem stated here is a special case the *Existence and Uniqueness Theorem* on page 38 of [BC87].

Theorem 4.3.2 *(Local Existence and Uniqueness) Let g be a differentiable function with continuous derivative defined in some open interval containing N_o. Then, for any $t_o \in \mathbf{R}$, the IVP*

$$\begin{cases} \frac{dN}{dt} &= g(N) \\ N(t_o) &= N_o \end{cases} \tag{4.38}$$

has a solution $N = N(t)$ defined in some open interval I which contains t_o. Furthermore, the IVP (4.38) cannot have more than one solution over any open interval containing t_o.

A proof of a result more general than this may be found in Appendix A of [BC87].

Part II

Probabilistic Models

Chapter 5

Modeling Bacterial Mutations

In this chapter we go back to the Luria and Delbrück study [LD43] mentioned in the Introduction. Luria and Delbrück were interested in determining the distribution of *E. Coli* bacteria that develop resistance to a certain virus over time. To be more specific, suppose there are N_o bacteria in a colony at time $t = 0$. We would like to know how many bacteria, $R(t)$, will have developed resistance to the virus t units of time later. According to the *mutation to immunity* hypothesis, $R(t)$ is related to the number of random mutations, $M(t)$, that the bacteria experience in the time interval $[0, 1]$.

The variable $M(t)$ is to be contrasted with the total number of bacteria, $N(t)$, of the previous part. In the models of population growth discussed previously, $N(t)$ was a discrete or continuous variable that could be determined precisely in terms of the initial number, N_o, of bacteria and some parameters used in modeling the growth of the population. In the case of the discrete Malthusian model, for instance, $N(t) = N_t$ was given by the formula

$$N_t = N_o \ \lambda^t,$$

where λ was the growth rate. In the case, of the continuous logistic model

$$N(t) = \frac{KN_o}{N_o + (K - N_o)e^{-rt}},$$

where r was the intrinsic growth rate and K the carrying capacity. The idea here is that if one knows the initial population size, N_o, at time $t = 0$ as well as the growth parameters, t units of time later the population size will be given by the formulas for $N(t)$. If we were to start over with the same initial number of bacteria, N_o, and under the same conditions, the number of bacteria in the colony t units of time later will be the same as the number obtained previously.

Hence, $N(t)$ in the previous models is completely determined by the initial conditions and the growth parameters. This is not the case for the variable $M(t)$.

A given bacterium might develop a mutation in its genetic material that leads to resistance, or it might not. We cannot predict with certainty whether a given bacterium might mutate or not. The best we can do is to obtain a measure or how *likely* the bacterium is to develop the mutation. This *measure of likelihood* is known as a *probability function.* Thus, if we start out with N_o bacteria with no mutations, t units of time later we might end up with a certain value for $M(t)$ of bacteria that developed the mutation. If we repeat the experiment, starting out with the same number of bacteria and under the same conditions, there is no guarantee that t units of time later we will get the same value for $M(t)$. Thus, $M(t)$ is not a *function* in the usual sense that we understand that term. After a time interval of length t, $M(t)$ can take one a range of values, and each value has a certain likelihood or probability of occurring. This notion of a "function" $M(t)$ whose values cannot be predicted, but for which we can obtain a measure of their likelihood is what is known as a *random variable.*

5.1 Random Variables and Random Processes

If $M(t)$ denotes the number of bacteria that developed a mutation from and initial number N_o in a time interval $[0, t]$, it is reasonable to model it as a random variable. Roughly speaking, random variables are quantities that are determined from outcomes of a *random experiment.* A random experiment is a process which can be repeated indefinitely under the same set of conditions, but whose outcome cannot be predicted with certainty before the experiment is performed. For instance, suppose you start with one bacterium in medium conducive to growth; t units of time later we count how many have developed a mutation that leads to resistance. The number of bacteria that have developed resistance is a random variable.

Thus, for each t, $M(t)$ is a random variable whose values are any of the numbers

$$0, 1, 2, 3, \ldots$$

That is, $M(t)$ is a discrete random variable for each time t. Notice that the time variable, t, can be modeled as a continuous variable. $M(t)$, where t is continuous, is an example of a *random process.*

5.1.1 The Poisson Process

We are interested in computing the probability that $M(t)$ attains each of the values $0, 1, 2, \ldots$ for each time t. In symbols, we would like to compute

$$P[M(t) = m] \qquad \text{for } m = 0, 1, 3, \ldots \quad \text{and } t > 0.$$

Here, P is denotes a probability function which measures the likelihood of an *event.* An event is a possible outcome, or set of outcomes, of a random experiment. In this particular case, the event denoted by $[M(t) = m]$ represents an outcome, or set of outcomes, in the Luria and Delbrück experiment in which m

bacteria have developed a mutation leading to resistance. A probability function assigns a value between 0 and 1 to an event. A probability of 0 means an impossible event, and a probability of 1 means that the event will surely happen. The assignments of probability for events in between depend on assumptions made about the experiment at hand.[1]

We shall denote $P[M(t) = m]$ by $P_m(t)$, and so we would like to compute $P_m(t)$, for each $m = 1, 2, 3, \ldots$ and $t > 0$, under the following assumptions:

(i) $P_0(0) = P[N(0) = 0] = 1$; that is, initially no bacterium has mutated into a strain resistant to the virus. It then follows that $P_m(0) = 0$ for all $m \geq 1$.

(ii) The probability that any bacterium develops a mutation in a short time interval $[t, t + \Delta t]$ depends only on Δt and not on the number of mutant bacteria at previous times.

(iii) The probability of a new mutation in the short interval $[t, t + \Delta t]$ is proportional to Δt; in symbols

$$P(\text{new mutation in } [t, t + \Delta t]) = \lambda \Delta t,$$

where $\lambda > 0$ is a constant of proportionality.

(iv) Δt is so small that the probability of two or more mutations occurring in the short time interval $[t, t + \Delta t]$ is zero.

In order to determine $P_m(t)$ for each $m = 1, 2, 3, \ldots$ and $t > 0$, first we need to estimate $P_m(t + \Delta t)$ for Δt small enough. The picture below can be used to better understand the process of going from time t to the time $t + \Delta t$. Each possible value of the variable $M(t)$ is represented by a circle and is called a *state*. Thus, a state represents the number of mutations at any given stage.

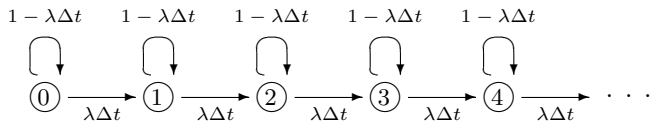

Figure 5.1.1: State diagram for $M(t)$

The arrows indicate the probabilities of going from one state to the next, or those of remaining in the same state, in a short time interval $[t, t + \Delta t]$. For instance, if at time t there are no mutants in the colony (i.e., the system is in state 0 at that time), then at time $t + \Delta t$ there might a bacterium that has developed a mutation. The system would then go from state 0 to state 1 in the time interval $[t, t + \Delta t]$; the probability of this occurrence is $\lambda \Delta t$ by assumption

[1] For example, in the experiment of tossing a "fair die," it is assumed that all faces of the die are equally likely; thus, the probability of any given face is 1/6.

(iii), and this is indicated by the arrow in the diagram that goes from state 0 to state 1. On the other hand, there might not be a new mutation in the time interval $[t, t+\Delta t]$; the probability of this occurring is $1-\lambda\Delta t$ (why?), and this is shown by the arrow that starts at state 0 and which winds back again to 0. The picture in Figure 5.1.1 is an example of a *state diagram.* Observe that assumption (iv) is implicit in the state diagram since the states can only increase by 1 and not by 2 or more; thus, arrows from a given state either return to that state or go to the next one.

The state diagram in Figure 5.1.1 can be used to compute $P_m(t+\Delta t)$ given that we know $P_m(t)$. We start out with the case $m = 0$ as follows

$$P_0(t+\Delta t) = P_0(t) \cdot P(\text{no new mutations in } [t, t+\Delta t] \big| M(t) = 0),$$

where the notation $P(A\big|B)$ denotes the *conditional probability* of event A given the event B. Then, by the independence[2] assumption (ii),

$$P_0(t+\Delta t) = P_0(t) \cdot P(\text{no new mutations in } [t, t+\Delta t]).$$

It then follows by assumption (iii) that

$$P_0(t+\Delta t) = P_0(t) \cdot (1-\lambda\Delta t),$$

or

$$P_0(t+\Delta t) = P_0(t) - \lambda\Delta t P_0(t).$$

From the last equation we get

$$\frac{P_0(t+\Delta t) - P_0(t)}{\Delta t} = -\lambda P_0(t);$$

Thus, letting $\Delta t \to 0$ we conclude that $P_0(t)$ is differentiable and

$$\frac{dP_0}{dt} = -\lambda P_0;$$

that is, $P_0(t)$ a first order differential equation. This differential equation can be solved by separation of variables to yield

$$P_0(t) = Ce^{-\lambda t},$$

for some constant C. Since $P_0(0) = 1$ by assumption (i), it follows that $C = 1$, and so the probability of no mutations in the colony at time t is given by

$$P_0(t) = e^{-\lambda t} \tag{5.1}$$

for all $t \geq 0$.

We next proceed to compute $P_1(t)$. Using the state diagram in Figure 5.1.1 we obtain that

$$P_1(t+\Delta t) = P_0(t) \cdot \lambda\Delta t + P_1(t) \cdot (1-\lambda\Delta t), \tag{5.2}$$

[2]Events A and B are said to be *independent,* if $P(A\big|B) = P(A)$.

since, according to the state diagram, the system can get to state 1 at $t + \Delta t$ via two routes: (i) from state 0 through a new mutation which occurs with probability $\lambda \Delta t$, or (ii) from state 1 if no new mutation occurs in the time interval $[t, t + \Delta t]$, and the probability of this occurrence is $1 - \lambda \Delta t$.

Rearranging equation (5.2) we obtain

$$\frac{P_1(t + \Delta t) - P_1(t)}{\Delta t} = -\lambda P_1(t) + \lambda P_0(t);$$

thus, letting $\Delta t \to 0$, we conclude that P_1 is differentiable and satisfies the differential equation

$$\frac{dP_1}{dt} = -\lambda P_1 + \lambda P_0(t) \tag{5.3}$$

or, using (5.1),

$$\frac{dP_1}{dt} = -\lambda P_1 + \lambda e^{-\lambda t}. \tag{5.4}$$

The differential equation (5.4) can be solved as follows: Rewrite the equation as

$$\frac{dP_1}{dt} + \lambda P_1 = \lambda e^{-\lambda t}$$

and multiply by $e^{\lambda t}$ to get

$$e^{\lambda t} \frac{dP_1}{dt} + \lambda e^{\lambda t} P_1 = \lambda \tag{5.5}$$

Observe that, by the Product Rule,

$$\frac{d}{dt}(e^{\lambda t} P_1) = e^{\lambda t} \frac{dP_1}{dt} + \lambda e^{\lambda t} P_1,$$

and so the differential equation in (5.5) reduces to

$$\frac{d}{dt}(e^{\lambda t} P_1) = \lambda. \tag{5.6}$$

This last equation can be integrated to yield

$$e^{\lambda t} P_1 = \lambda t + C,$$

for some arbitrary constant C, and therefore

$$P_1(t) = \lambda t \; e^{-\lambda t} + C e^{-\lambda t}$$

for all $t \geq 0$.

Using the initial condition $P_1(0) = 0$, which follows from assumption (i) for the random process $M(t)$, we get that $C = 0$, and therefore

$$P_1(t) = \lambda t \; e^{-\lambda t} \tag{5.7}$$

for all $t \geq 0$.

To compute $P_2(t)$ we proceed in a way similar to that used to compute $P_1(t)$. From the state diagram in Figure (5.1.1) we get that

$$P_2(t+\Delta t) = P_1(t)\cdot\lambda\Delta t + P_2(t)\cdot(1-\lambda\Delta t),$$

from which we are led to the differential equation

$$\frac{dP_2}{dt} = -\lambda P_2 + \lambda P_1(t) \tag{5.8}$$

or, using (5.7),

$$\frac{dP_2}{dt} = -\lambda P_2 + \lambda^2 t e^{-\lambda t}. \tag{5.9}$$

We can solve this differential equation as we solved (5.4), by first rearranging and multiplying by $e^{\lambda t}$ to get

$$e^{\lambda t}\frac{dP_2}{dt} + \lambda e^{\lambda t}P_2 = \lambda^2 t,$$

and then re–writing the left–hand side of this equation. Thus,

$$\frac{d}{dt}(e^{\lambda t}P_2) = \lambda^2 t$$

and, after integrating and using the initial condition $P_2(0) = 0$,

$$P_2(t) = \frac{(\lambda t)^2}{2}e^{-\lambda t} \tag{5.10}$$

for all $t \geq 0$.

One can go through the same procedure leading to (5.10) to obtain the formula

$$P_3(t) = \frac{(\lambda t)^3}{3!}e^{-\lambda t}$$

for $P_3(t)$, and this suggests the general formula for $P_m(t)$, $m = 0, 1, 2, \ldots$, to be

$$P_m(t) = \frac{(\lambda t)^m}{m!}e^{-\lambda t} \quad \text{for } t \geq 0. \tag{5.11}$$

We will establish this formula by induction on m. Observe that we have already established the basic case $m = 0$ in the formula (5.1) (note that $0! = 1$). Next, for the inductive step, assume that the formula (5.11) holds for m, and we seek to show that it also holds for $m+1$. Using the state diagram 5.1.1 we see that

$$P_{m+1}(t+\Delta t) = P_m(t)\cdot\lambda\Delta t + P_{m+1}(t)\cdot(1-\lambda\Delta t),$$

from which we are led to the differential equation

$$\frac{d}{dt}(P_{m+1}) = -\lambda P_{m+1} + \lambda P_m(t) \tag{5.12}$$

or, using the inductive hypothesis (5.11),

$$\frac{d}{dt}(P_{m+1}) = -\lambda P_{m+1} + \frac{\lambda^{m+1}t^m}{m!}e^{-\lambda t}.$$

We can solve this differential equation as we solved (5.9), by first rearranging and multiplying by $e^{\lambda t}$ to get

$$e^{\lambda t}\frac{d}{dt}(P_{m+1}) + \lambda e^{\lambda t}P_{m+1} = \frac{\lambda^{m+1}t^m}{m!},$$

and then re–writing the left–hand side of this equation. Thus,

$$\frac{d}{dt}(e^{\lambda t}P_{m+1}) = \frac{\lambda^{m+1}t^m}{m!}$$

and, after integrating and using the initial condition $P_{m+1}(0) = 0$,

$$P_{m+1}(t) = \frac{(\lambda t)^{m+1}}{(m+1)!}e^{-\lambda t}$$

for all $t \geq 0$, since $(m+1)! = (m+1)m!$. This establishes the formula (5.11) for the case $m+1$, and formula (5.11) is now proved for all $m = 0, 1, 2, \ldots$

The formula (5.11) gives the probabilities of the events $[M(t) = m]$ for all values, m, of the random variable $M(t)$. It is called the *distribution* of $M(t)$, or the *probability mass function,* or pmf, of the random variable $M(t)$. This probability distribution function is called the *Poisson distribution* with parameter λt. We will see in the next section that λt is the *expected value* of $M(t)$; that is λt measures the *average* number of mutations that occur in the time interval $[0, t]$. Thus, λ is the average number of mutations per unit time.

Since $M(t)$ has a Poisson distribution with parameter λt for each t, $M(t)$ is called a *Poisson random process.* This particular random process is characterized by the assumptions (i)–(iv) that we made on $M(t)$.

5.1.2 Expected Value and Variance of the Poisson Distribution

Let X denote a discrete random variable which takes on a sequence of values

$$x_0,\ x_1,\ x_2,\ x_3,\ \ldots$$

Suppose that we know the probability mass function for X; that is, suppose that we know

$$P[X = x_i] \quad \text{for each } i = 0, 1, 2, \ldots$$

We define the *expected value,* $E(X)$, of X to be given the infinite series

$$E(X) = \sum_{i=0}^{\infty} x_i P[X = x_i]. \tag{5.13}$$

Example 5.1.1 Let $X = M(t)$ for a fixed $t > 0$, where $M(t)$ denotes the number of mutations in a bacterial culture that occur in the time interval $[0, t]$. Then the values of X in this case are

$$m = 0,\ 1,\ 2,\ 3,\ \ldots$$

each with probability

$$P[X = m] = \frac{(\lambda t)^m}{m!} e^{-\lambda t} \quad \text{for } m = 0,\ 1,\ 2,\ 3,\ \ldots$$

by (5.11). Thus, applying the formula (5.13) for the expected value of X,

$$\begin{aligned} E(X) &= \sum_{m=0}^{\infty} m \cdot \frac{(\lambda t)^m}{m!} e^{-\lambda t} \\ &= \sum_{m=1}^{\infty} m \cdot \frac{(\lambda t)^m}{m!} e^{-\lambda t} \\ &= e^{-\lambda t} \sum_{m=1}^{\infty} \frac{(\lambda t)^m}{(m-1)!}. \end{aligned}$$

Making the change of variables $k = m - 1$, we obtain

$$\begin{aligned} E(X) &= e^{-\lambda t} \sum_{k=0}^{\infty} \frac{(\lambda t)^{k+1}}{k!} \\ &= e^{-\lambda t} \sum_{k=0}^{\infty} \frac{(\lambda t)^k (\lambda t)}{k!} \\ &= \lambda t\ e^{-\lambda t} \sum_{k=0}^{\infty} \frac{(\lambda t)^k}{k!}. \end{aligned}$$

Recognizing the last series as the Mclaurin series expansion for $e^{\lambda t}$, we then have that

$$E(X) = \lambda t.$$

The previous example shows that the expected value of the random variable $M(t)$ is λt for each $t \geq 0$. This means that, on average, we should expect λt mutations on the time interval $[0, t]$. We then have an interpretation for the parameter λ as the average number of mutations per unit time. What this means in terms of the Luria and Delbrück experiment is that, if we are able to count the number of mutations in a unit of time that occur after exposure to the virus, and repeat the experiment many times, then the average number of mutations should be close to λ. Of course, there will be some variability in the mutation counts for each experiment. This variability can be measured since we know the distribution for the random variable $M(t)$ when $t = 1$.

Variability in the values of a random variable, X, can be measured by a quantity called the *variance* of X, which is denoted by $\text{var}(X)$. We van compute

var(X), for a discrete random variable X, as follows: Suppose the values of X form a sequence

$$x_0,\ x_1,\ x_2,\ x_3,\ \ldots$$

and let $\mu = E(X)$ denote the expected value of X; the parameter μ is usually called the *mean* of the distribution of X. Then,

$$\text{var}(X) = \sum_{i=0}^{\infty}(x_i - \mu)^2 P[X = x_i]. \tag{5.14}$$

That is, the variance of X is the expected square–deviation of the values of X from the mean.

The formula for var(X) in (5.14) can be re–written as follows

$$\begin{aligned}
\text{var}(X) &= \sum_{i=0}^{\infty}(x_i - \mu)^2 P[X = x_i] \\
&= \sum_{i=0}^{\infty}(x_i^2 - 2\mu x_i + \mu^2) P[X = x_i] \\
&= \sum_{i=0}^{\infty} x_i^2 P[X = x_i] - \sum_{i=0}^{\infty} 2\mu x_i P[X = x_i] + \sum_{i=0}^{\infty} \mu^2 P[X = x_i] \\
&= \sum_{i=0}^{\infty} x_i^2 P[X = x_i] - 2\mu \sum_{i=0}^{\infty} x_i P[X = x_i] + \mu^2 \sum_{i=0}^{\infty} P[X = x_i] \\
&= \sum_{i=0}^{\infty} x_i^2 P[X = x_i] - 2\mu E(X) + \mu^2,
\end{aligned}$$

where we have used the definition of $E(X)$ in (5.13) and the fact that the probability that X attains any of its values should be 1. Thus, since $E(X) = \mu$, we obtain

$$\text{var}(X) = \sum_{i=0}^{\infty} x_i^2 P[X = x_i] - \mu^2. \tag{5.15}$$

Example 5.1.2 Let $X = M(1)$; that is X denotes the number of mutations in a bacterial culture that occur in one unit of time. Then the values of X are

$$m = 0,\ 1,\ 2,\ 3,\ \ldots$$

each with probability

$$P[X = m] = \frac{\lambda^m}{m!} e^{-\lambda} \quad \text{for } m = 0,\ 1,\ 2,\ 3,\ \ldots$$

by (5.11).

By the calculation in the previous example, $\mu = E(X) = \lambda$ in this case.

Next, we compute

$$\begin{aligned}\sum_{i=0}^{\infty} x_i^2 P[X = x_i] &= \sum_{m=0}^{\infty} m^2 \cdot \frac{\lambda^m}{m!} e^{-\lambda} \\ &= \sum_{m=1}^{\infty} m^2 \cdot \frac{\lambda^m}{m!} e^{-\lambda} \\ &= e^{-\lambda} \sum_{m=1}^{\infty} m \cdot \frac{\lambda^m}{(m-1)!}.\end{aligned}$$

Making the change of variables $k = m - 1$, we obtain

$$\begin{aligned}\sum_{i=0}^{\infty} x_i^2 P[X = x_i] &= e^{-\lambda} \sum_{k=0}^{\infty} (k+1) \frac{\lambda^{k+1}}{k!} \\ &= \lambda e^{-\lambda} \left(\sum_{k=0}^{\infty} k \cdot \frac{\lambda^k}{k!} + \sum_{k=0}^{\infty} \frac{\lambda^k}{k!} \right) \\ &= \lambda e^{-\lambda} \left(\sum_{k=1}^{\infty} \frac{\lambda^k}{(k-1)!} + e^{\lambda} \right)\end{aligned}$$

Making the change of variables $n = k - 1$ in the last series we get

$$\begin{aligned}\sum_{i=0}^{\infty} x_i^2 P[X = x_i] &= \lambda e^{-\lambda} \left(\sum_{n=0}^{\infty} \frac{\lambda^{n+1}}{n!} + e^{\lambda} \right) \\ &= \lambda e^{-\lambda} \left(\lambda \sum_{n=0}^{\infty} \frac{\lambda^n}{n!} + e^{\lambda} \right) \\ &= \lambda e^{-\lambda} \left(\lambda e^{\lambda} + e^{\lambda} \right) \\ &= \lambda^2 + \lambda.\end{aligned}$$

Thus, by formula (5.15), $\text{var}(X) = \lambda^2 + \lambda - \lambda^2 = \lambda$. Hence, the variance of $X = M(1)$ is the same as its mean.

Observe that the calculations in the previous example can also be used to show that $\text{var}(M(t)) = \lambda t$, which is the same as the expected value of $M(t)$. Equality of the mean and variance is characteristic of the Poisson process. This fact can sometimes be used to test wheter a process in nature truly follows the Poisson model.

Chapter 6

Modeling Bacterial Resistance

The model for $M(t)$, the number of mutations that occur in a culture in the time interval $[0, 1]$, that we developed in the previous chapter does not take into account the fact that the bacterial population is growing with time. In actually, the expected number of mutations that occur in that period of time should depend on the population size (the more bacteria in the culture, the higher the chances of more mutations). Thus, we need to incorporate the population size, $N(t)$, and the fact that it is growing into a new model for $M(t)$.

In the previous chapter we modeled $M(t)$ by a Poisson process with mean $E(M(t)) = \lambda t$, where λ, the average number of mutations per unit time, was assumed to be constant. We will modify the model by making λ depend on the population size. In order to do this, we will denote the expected value of $M(t)$ by $\mu(t)$, the average number of mutations in the time interval $[0, t]$. The function $\mu(t)$ will be differentiable, and will depend on the the bacterial density $N(t)$; the form of the relationship between μ and N will be made explicit shortly. We will again model $M(t)$ by a Poisson process; this time, the parameter will be $\mu(t)$ instead of λt. This is equivalent to replacing the assumption (iii) in the previous chapter by

$$P(\text{new mutation in } [t, t + \Delta t]) = \mu'(t)\Delta t.$$

We then get the following distribution formulas for $M(t)$:

$$P_0(t) = P[M(t) = 0] = e^{-\mu(t)}, \tag{6.1}$$
$$P_m(t) = P[M(t) = m] = \frac{(\mu(t))^m}{m!} e^{-\mu(t)},$$

for $t \geq 0$ and $m = 1, 2, 3, \ldots$

The formula in (6.1) suggests an experimental way for estimating $\mu(t)$. Suppose a series of cultures is run during some time interval $[0, t]$, and the fraction of those that do not show mutations is determined. This fraction yields an estimate for $P_0(t)$, and from that estimate $\mu(t)$ can be estimated.

6.1 Modeling the Average Number of Mutations

In order to model $\mu(t)$, we may postulate that the number of new mutations in a short time interval $[t, t+\Delta t]$ is proportional to the population size at time t. More specifically, assume that

$$M(t+\Delta t) - M(t) \cong a\Delta t\ N(t),$$

where a measures the probability that one bacterium will develop a mutation in a unit of time. This is usually referred to as the *mutation rate.* Taking expected values on both sides of the previous equation and dividing by Δt yields

$$\frac{\mu(t+\Delta t) - \mu(t)}{\Delta t} \cong aN(t).$$

Thus, letting $\Delta t \to 0$, we conclude that $\mu(t)$ is differentiable and

$$\frac{d\mu}{dt} = aN(t). \tag{6.2}$$

If we assume that the bacterial colony is growing according the Malthusian model

$$\begin{cases} \dfrac{dN}{dt} = kN \\ N(0) = N_o, \end{cases}$$

where $k = \dfrac{\ln 2}{T}$, T being the doubling time or the duration of a division cycle, then $N(t) = N_o e^{kt}$. Substituting this into (6.2) we get

$$\frac{d\mu}{dt} = aN_o e^{kt},$$

which can be integrated to yield

$$\begin{aligned} \mu(t) - \mu(0) &= \int_0^t aN_o e^{k\tau}\ \mathrm{d}\tau \\ &= \frac{a}{k} N_o (e^{kt} - 1). \end{aligned}$$

If there no mutations at time $t = 0$, $\mu(0) = 0$, and so

$$\mu(t) = \frac{a}{k}(N_o e^{kt} - N_o),$$

or

$$\mu(t) = \frac{a}{k}(N(t) - N_o). \tag{6.3}$$

Hence, the average number of mutations which occur in the interval $[0, t]$ is proportional to the population increment during that time period. The constant of proportionality is the mutation rate divided by the growth rate.

Observe that equations (6.3) and (6.1) can be combined to yield an experimental estimate of the mutation rate a.

Example 6.1.1 In one of the experiments involving *E. coli* and a bacterial virus that Luria and Delbrück performed in 1943 (see page 504 in [LD43]), 20 cultures, each containing about 5.6×10^8 bacteria, were plated with the virus. Out of the 20 cultures, 11 showed no resistance to the virus (i.e., they all died after being exposed to the virus). Out of the other nine cultures, two showed only 1 resistant bacterium, one showed 3, two showed 5, one showed 6, and the other three showed 35, 64 and 107, respectively.

We assume that each culture was the result of one normal bacterium (sensitive to the virus) undergoing cell division for n division cycles. It then follows that

$$2^n \approx 5.6 \times 10^8,$$

from which we obtain that n is about $\dfrac{\ln(5.6) + 8\ln 10}{\ln 2}$ or 29. If no bacterium in the culture survives the attack of the virus, then no mutation to resistance occurred during the n cycles. The probability of this occurring is given by $P_0(t)$ where $t = n$, and t is measured in division cycles. Now, by (6.1),

$$P_0(n) = e^{-\mu(n)}. \tag{6.4}$$

This probability is estimated by the fraction, p_o, of cultures which show no resistant cells. In this example $p_o = \dfrac{11}{20}$. From (6.4) we therefore an estimate for the average number of mutation in the n cycles

$$\mu(n) \approx -\ln p_o \doteq 0.60.$$

Hence, an estimate for the mutation rate is given by 6.3 as

$$a \approx \frac{k\mu(n)}{N(n)} \doteq \frac{(\ln 2)\mu(n)}{2^n},$$

where $n \approx 29$. It then follows that

$$a \approx \frac{(\ln 2)(0.60)}{5.6 \times 10^8} \doteq 7.43 \times 10^{-10}$$

6.2 Modeling the Number of Resistant Bacteria

In this section we shall model the number of resistant bacteria, $R(t)$, in the time interval $[0, t]$. We shall do this under the two different hypotheses studied by Luria and Delbrück in their 1943 paper [LD43]; namely, (i) the hypothesis of acquired immunity, and (ii) the hypothesis of mutation to immunity. We begin with the first one.

6.2.1 Hypothesis of Acquired Resistance

We assume that bacteria become resistant as a result of interaction with the virus. Thus, if a culture is obtained by cell division from a single bacterium

which is sensitive to the virus over a time interval $[0, t]$, and no exposure to the virus has occurred during that time period, then no generation of resistant cells should have occurred. Suppose the culture is exposed to the virus at time t. Then, after interacting with the virus, some bacteria might develop resistance, while others will just die. Suppose there is a very small positive probability, a, that a given bacterium will turn into a resistant one in one division cycle. Let R denote the number of bacteria that have become resistant after interacting with the virus. If N is the total number of bacteria in the colony at the time, then R follows a binomial distribution with parameters a and N. Namely, the distribution of R is given by

$$P[R = r] = \binom{N}{r} a^r (1-a)^{N-r} \quad \text{for} \quad r = 0, 1, 3, \ldots, N,$$

where N is the binomial coefficient defined by

$$\binom{N}{r} = \frac{N!}{r!(N-r)!}.$$

It can be shown that the expected value of this distribution is aN, so that the expected number of resistant bacteria is given by $E(R) = aN$. Also, the variance of R can be computed to be $\text{var}(R) = Na(1-a)$.

It can also be shown that if N is allowed to grow to $+\infty$ as a decreases to 0 (i.e., a is very small and positive) in such a way that the expected value of R, aN, is kept at a constant value of λ, then

$$\lim_{N\to\infty} P[R = r] = \frac{\lambda^r}{r!} e^{-\lambda} \quad \text{for all} \quad r = 0, 1, 2, 3, \ldots \tag{6.5}$$

The expression in (6.5) can be interpreted as saying that if the number of bacteria, N, is very large and the probability of a given bacterium becoming immune to the virus is very small (but positive), then the distribution for R can be approximated by that of a Poisson distribution with parameter $\lambda = aN$. It then follows that the expected number of resistant bacteria is $\lambda = aN$, and its variance is also given by λ. Hence, for large culture of size N, the hypothesis of acquired immunity predicts that the number of resistant bacteria follows a Poisson distribution with parameter $\lambda = aN$, where a is the mutation rate. This assertion can be tested against experimental data.

Example 6.2.1 *(Continuation of Example 6.1.1).* Consider again the Luria and Delbrück experiment in which 20 cultures of about 5.6×10^8 *E. coli* bacterial each were exposed to a lethal virus.

According to the expression in (6.5), the probability that a given culture shows no resistant bacteria is approximated by $e^{-\lambda}$. In turn, this probability can be estimated by the proportion $p_o = \dfrac{11}{20}$ of cultures that show no resistant bacteria. We can therefore get the following estimate for λ:

$$\lambda \approx -\ln p_o \doteq 0.60.$$

We can then use this value of λ to estimate the probabilities that R takes on other values according to the expression in (6.5). For instance we get that

$$P[R = 1] \approx \lambda e^{-\lambda} \doteq 0.33$$

Thus, if R has a Poisson distribution, then we would expect to see about 33% of the cultures showing exactly one resistant bacterium. This amounts to about 7 of the cultures. According to the data in the Luria and Delbrück study collected for this particular experiment, only 2 out of the twenty cultures show exactly one resistant bacterium. Similarly, since $P[R = 2] \approx \frac{\lambda^2}{2} e^{-\lambda} \doteq 0.1$ by (6.5), we would expect to see 2 of the cultures showing 2 resistant bacteria; the data show none. These divergences from what a Poisson distribution predicts suggest that, perhaps, the distribution of R does not following a Poisson model, as the hypothesis of acquired immunity predicts. However, the data provided in Example 6.1.1 come from a small sample of cultures, and therefore do not provide a strong support for that assertion. A more careful analysis is therefore required.

6.2.2 Goodness of Fit

We would like to test the hypothesis that the number of resistant bacteria that the hypothesis of acquired immunity predicts actually follows the Poisson distribution as described in equation (6.5). In other words, do the data collected by Luria and Delbrück support the hypothesis of a Poisson distribution for R? The data considered in the previous examples come from a small sample of cultures, therefore the conclusion in Example 6.2.1 that R might not follow a Poisson distribution is only a suggestion that needs further study. Fortunately, Luria and Delbrück ran several experiments involving many cultures. The data in Table 6.1 show the distribution of resistant bacteria in an experiment involving 87 cultures, each of about 2.4×10^8 bacteria ([LD43], p.505).

Assuming that the distribution of R follows a Poisson model with parameter λ, we can estimate λ from the fraction of cultures that show no resistant bacteria, p_o, as we did in Example 6.2.1. We obtain

$$\lambda \approx -\ln p_o = -\ln\left(\frac{29}{87}\right) \doteq 1.1.$$

We can then use this value for λ to estimate the probabilities of seeing r resistant bacteria according to (6.5). These, in turn yield the expected proportions of cultures with r resistant bacteria which are predicted by the Poisson distribution. For instance, the estimated proportion of cultures that are expected to have exactly one resistant bacterium is approximated by

$$P[R = 1] \approx \lambda e^{-\lambda} \approx (1.1)e^{-1.1} \doteq 0.37 = 37\%.$$

Thus, we expect 37% of the 87 cultures, or about 32 cultures, to have exactly one resistant bacterium. Note that this diverges vastly from the observed value

Table 6.1: Distribution of Resistant Bacteria in Similar Cultures

Resistant Bacteria	Number of Cultures
0	29
1	17
2	4
3	3
4	3
5	2
6–10	5
11–20	6
21–50	7
51–100	5
101–200	2
201–500	4
501–1000	0

of 17 in Table 6.1. We can continue in this fashion computing expected values of number of resistant bacteria for various values of r, or ranges of value of r. Table 6.2 shows the results of the calculations. Observe that we have re-categorized the entries of the "Resistant Bacteria" column to guarantee that the entries in the "Expected Number" column are all at least 5 (the reason for this will be discussed shortly).

Table 6.2: Expected and Observed Numbers of Resistant Bacteria

Resistant Bacteria	Number of Cultures	Expected Number	$\frac{(O-E)^2}{E}$
0	29	29	0
1	17	32	7.03
2	4	18	11.89
3 or more	37	8	105.13

The fourth column in Table 6.2 shows the relative square–deviation of the observed values from the predicted values. The sum of the entries in this column is a *statistic*[1] known as the χ^2–square statistic. It measures how close the

[1]Statistics are quantities computed from sample data. Examples of statistics are the mean or average of the sample, the sample variance (whose square root yields the standard deviation), proportions of observed frequencies, etc.

observed distribution is to the predicted distribution. A large value suggests that the observed frequencies do not support the hypothesis of the number of resistant bacteria follow the predicted distribution. A small value means that the observed frequencies are very close to the predicted ones, and therefore there is a strong suggestion that the observed distribution follows the predicted one. For the data summarized in Table 6.2, the χ^2–statistic is

$$\chi^2 \approx 124,$$

which is quite big. Thus, it seems plausible that the number of resistant bacteria does not follow a Poisson distribution as predicted by the hypothesis of acquired immunity. It is possible to make this assertion more precise by estimating the probability that a similar experiment involving the same kind of bacteria, the same number of cultures, and the same number of bacteria per culture, will yield the same value, or higher, for the χ^2–statistic. This probability is estimated under the assumption that the distribution for the number of resistant bacteria is given by the Poisson distribution.

Let X^2 denote a random variable whose values are the sum of the relative square–deviations of observed values from expected ones in a series of n categories, or bins. In the case illustrated in Table 6.2, n is 4. If an experiment yields a sample with a value, χ^2, for X^2, we are interested in computing the probability

$$P[X^2 \geq \chi^2]. \tag{6.6}$$

This probability is usually referred to as the *p–value* for the hypothesis test.[2] In the example we are dealing with, the p–value would be

$$p\text{–value} = P[X^2 \geq 124].$$

The random variable X^2 is obtained from discrete data; however, if the expected numbers in the bins are big enough (for instance, bigger than 5), then X^2 can be approximated by a continuous random variable. If we knew the probability density function, $f(x)$, of the continuous approximation, we would be able to compute the probability in (6.6) by integrating $f(x)$ from χ^2 to infinity:

$$P[X^2 \geq \chi^2] = \int_{\chi^2}^{\infty} f(x)\ \mathrm{d}x.$$

It turns out that this probability density function is known, and is called the χ^2*–distribution with* $n-1$ *degrees of freedom,* and is denoted by χ^2_{n-1}. In our example, we are dealing with χ^2_3 since $n = 4$. In this case, the probability density function is given by

$$f(x) = \begin{cases} \sqrt{\dfrac{x}{2\pi}}\ e^{-x/2} & \text{if } \ x \geq 0; \\ \\ 0 & \text{otherwise.} \end{cases}$$

[2]This is the probability that a given *test–statistic* attains the observed value, or more extreme ones, under the assumption that certain hypothesis, H_o, known as the *null hypothesis,* holds true.

The graph of this function is sketched in Figure 6.2.1 The p–value would then

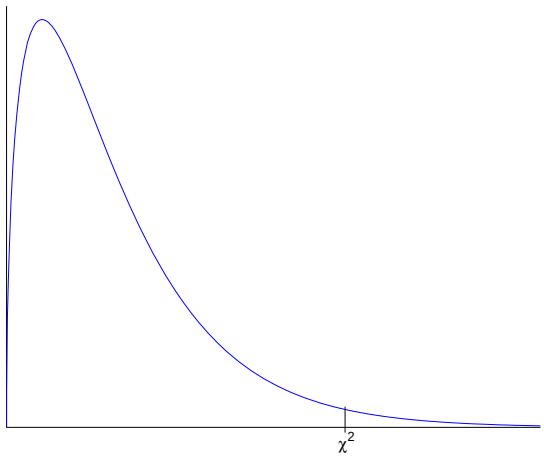

Figure 6.2.1: Probability density function for a χ^2_3 distribution

be the area under the graph of the function to the right of the test–statistic χ^2.

The formulas and graphs of the probability density functions for χ^2_d distributions depend of the degrees of freedom parameter d; that is, different values of d will yield different formulas and, hence, different graphs. In all cases, though, the p–value is computed in the same way. For the example at hand we can use a statistical or mathematical software package to approximate it. We can also use a spreadsheet program, like MS Excel, to obtain an estimate of the p–value. MS Excel has the built–in function CHIDIST(x, d) which returns the so–called one–tailed probability at x; in other words, CHIDIST(x, d) yields the p–value for the test statistic $x = \chi^2$.

For the data in Table 6.2, with $\chi^2 \approx 124$, we obtain, using MS Excel, that

$$p\text{–value} = \text{CHIDIST}(124, 3) \approx 1.06 \times 10^{-26}.$$

A very tiny probability indeed! Thus, the likelihood that Luria and Delbrück would have gotten the results in Table 6.1, under the assumption that the hypothesis of acquired immunity is true, is practically 0. Hence, the data offer very strong support for rejecting the hypothesis of acquired immunity.[3] We therefore need to set out to look for *alternative* hypotheses that can explain the distribution of resistant bacteria observed by Luria and Delbrück.

The test for determining whether a set of observation follows a hypothesized distribution illustrated in this section is called a χ^2 *Goodness of Fit Test.*

[3] In the statistical jargon of *Hypothesis Testing,* we would say that the data provide *statistically significant* evidence for *rejecting* the *null hypothesis* H_o.

6.2.3 Hypothesis of Mutation to Immunity

The largest discrepancy between the predicted and observed frequencies in Table 6.2 is found for large values of r. In other words, the distribution of the observed numbers of resistant bacteria has a "thicker tail" than that for the Poisson distribution for large value of r. This translates, for instance, into a larger average value of resistant bacteria than that predicted by the Poisson distribution (which is λ). This suggests that bacteria must have been mutating into resistant ones long before being exposed to the virus. In addition to this, mutants have also been replicating into more resistant bacteria just by the natural growth of the bacteria. This is precisely what the hypothesis of mutation to immunity in Luria and Delbrück [LD43] says. In the following section we show how to incorporate the contributions of these two growth processes into a model for the average number of resistant bacteria under the hypothesis of mutation to immunity.

Modeling the Expected Number of Resistant Bacteria

Let $R(t)$ denote the number of resistance bacteria in a culture in a time interval $[0, t]$. If we assume the *hypothesis of mutation to immunity* in the Luria and Delbrück 1943 study [LD43], some bacteria have been mutating randomly into resistant ones during that time interval. This contributes to the growth of $R(t)$. In addition, mutant bacteria have also been replicating and producing new mutants during that time also. In order to model $R(t)$ in this situation, we consider the change

$$\Delta R = R(t + \Delta t) - R(t)$$

in the number of resistant bacteria during a short time interval $[t, t+\Delta t]$, where Δt is small. If we assume that bacteria are not dying and that there are no back mutations, then the change ΔR has to be accounted for by

(i) new resistant bacteria resulting from the replication of existing ones; for simplicity we will assume that the resistant population grows at the same rate as that of the entire population; that is, with the same *per capita* growth rate k; and

(ii) new bacterial mutations to resistance occur during the time integral $[t, t + \Delta t]$.

We therefore have that

$$R(t + \Delta t) - R(t) \cong k\Delta t\ R(t) + M(t + \Delta t) - M(t) \tag{6.7}$$

for small Δt.

In this section we will derive an expression for the expected number of resistant bacteria in the time interval $[0, t]$. We will denote that value by $\rho(t)$, so that $\rho(t) = E(R(t))$. Thus, taking expected values on both sides of (6.7),

$$\rho(t + \Delta t) - \rho(t) \cong k\Delta t\ \rho(t) + \mu(t + \Delta t) - \mu(t),$$

and so, after dividing by Δt and letting $\Delta t \to 0$, we obtain the differential equation

$$\frac{d\rho}{dt} = k\rho(t) + \mu'(t), \tag{6.8}$$

where $\mu'(t) = aN(t)$ by (6.2). Since $N(t) = N_o e^{kt}$, it follows from (6.8) that

$$\frac{d\rho}{dt} = k\rho(t) + aN_o e^{kt}. \tag{6.9}$$

We can solve the differential equation in (6.9) by first re-writing it as

$$e^{-kt}\frac{d\rho}{dt} - ke^{-kt}\rho(t) = aN_o,$$

and observing that the left–hand side of the equation is the derivative of $e^{-kt}\rho(t)$. In then follows by integration that

$$e^{-kt}\rho(t) = aN_o t + C,$$

for some arbitrary constant C, so that

$$\rho(t) = aN_o te^{kt} + Ce^{kt}.$$

for all $t \geq 0$. If we assume that $\rho(0) = 0$, it follows that $C = 0$, and therefore

$$\rho(t) = aN_o te^{kt}$$

or

$$\rho(t) = at\ N_o e^{kt}.$$

Hence,

$$\rho(t) = atN(t) \quad \text{for} \quad t \geq 0. \tag{6.10}$$

Thus, the fraction of the average number of resistant bacteria, $\dfrac{\rho(t)}{N(t)}$, increases linearly with time.

Example 6.2.2 We consider again the data from the Luria and Delbrück experiment discussed in Example 6.1.1. Table 6.3 shows the observed frequencies of resistant bacteria for that experiment.

Each of the 20 cultures contained about 5.6×10^8 bacteria. Thus, if we assume that each culture was the result of one normal bacterium (sensitive to the virus) undergoing cell division for n division cycles, it follows that

$$2^n \approx 5.6 \times 10^8,$$

from which we obtain that n is about 29.

Thus, if t is measured in division cycles, it follows from (6.10) that the average number of resistant bacteria at time $t = n$ is given by

$$\rho(n) = anN(n),$$

Table 6.3: Distribution of Resistant Bacteria in Similar Cultures

Resistant Bacteria	Number of Cultures
0	11
1	2
3	1
5	2
6	1
35	1
64	1
107	1

where the mutation rate, a, was estimated in Example 6.1.1 to be about 1.07×10^{-9}. Thus, the average number of resistant bacteria per culture is about 18. This is to be contrasted to the value predicted by the hypothesis of acquired immunity. In this case, the average number of resistant bacteria is simply $aN(n) \approx 0.60$. The mean number of resistant bacteria obtained from the data in Table 6.3 is about 11. This estimate of the expected number of resistant bacteria is closer to the one predicted by the hypothesis of mutation to immunity than that predicted by the acquired immunity hypothesis. □

Modeling the Number of Resistant Bacteria

Let $R(t)$ denote the number of resistant bacteria in a time interval $[0, t]$. According to the hypothesis of acquired immunity, $R(t)$ is determined by the number of mutations, $M(t)$, that occur in that time interval, as well as number of new resistant bacteria that come about as the result of replication of mutant cells. Here we are assuming that bacteria are not dying in the time interval $[0, t]$, and that there are no back–mutations from resistance to sensitivity to the virus. Assume also that the resistant population of bacteria is growing at the same rate as the total population, and that the growth is Malthusian with *per capita* growth rate k.

We have seen that mutations occur randomly according to a Poisson process of parameter $\mu(t)$, where $\mu'(t) = aN(t)$, a being the mutation rate, and $N(t)$ being the total number of bacteria at time t. These mutations occur at various times τ_i, where $i = 1, 2, 3, \ldots, M(t)$, during the time interval $[0, t]$; thus, τ_i is the time at with the i^{th} mutation occurred. After that time τ_i, a single mutant cell will grow exponentially into $e^{k(t-\tau_i)}$ resistant bacteria at time t (Why?). It then follows that

$$R(t) = \sum_{i=1}^{M(t)} e^{k(t-\tau_i)}. \tag{6.11}$$

It is not an easy task to determine the probability distribution, $P[R(t) = r]$

for $r = 0, 1, 2, 3, \ldots$, for this random process. Luria and Delbrück were able to compute the expected value and variance for $R(t)$ in their 1943 paper [LD43]. It was not until six years later that Lea and Coulson [LC49] derived a formula that can be used to generate the probabilities

$$p_r(t) = P[R(t) = r] \qquad \text{for} \quad r = 0, 1, 2, 3, \ldots \tag{6.12}$$

In this section, and the next one, we outline how that might be done.

First note that the probabilities, p_r, in (6.12) are functions of $N = N(t)$, the total bacterial population, which in turn is a function of t. The reason for this is that the average number of mutations, $\mu(t)$, is a is a function of N according to (6.3). Thus, (6.12) should read

$$p_r(N) = P[R(t) = r, N(t) = N] \qquad \text{for} \quad r = 0, 1, 2, 3, \ldots \tag{6.13}$$

For each $r = 0, 1, 2, \ldots$, the probability $p_r(N)$ can be estimated by the proportion of cultures of size N which show r resistant bacteria.

Assume that each culture in the Luria and Delbrück experiment was grown from a single bacterium. Then, from (6.3) we get

$$\mu(t) = \frac{a}{k}(N(t) - 1),$$

where a is the mutation rate. If t is such that $N(t)$ is of the order of 10^8, as was the case in the Luria and Delbrück experiments, then we have the approximation

$$\mu(t) = \frac{a}{k}N(t). \tag{6.14}$$

We consider the change in the resistant population over a small time interval $[t, t + \Delta t]$. Over that time period, the total population changes from N to $N + \Delta N$, where $\Delta N \approx kN\Delta t$. We would like to estimate the probability that a culture containing $N + \Delta N$ bacteria will have r resistant bacteria (namely $p_r(N + \Delta N)$) for a very small population increment ΔN. In order to do this, we consider the state diagram pictured in Figure 6.2.2.

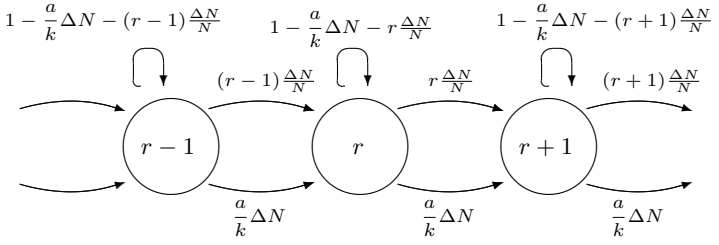

Figure 6.2.2: State diagram for $R(t)$

The arrows indicate transition probabilities from a given value of $R(t)$ to next value, or the same, at the end of the small time interval $[t, t + \Delta t]$ (we

are assuming here that the time interval $[0, \Delta t]$ is so small that at most one addition to the resistant population can be made). To understand the state diagram in Figure 6.2.2, consider the state of there being r resistant bacteria at the end of the time interval $[t, t + \Delta t]$, when the total bacterial population is about $N + \Delta N$. This might have come about as the result of three possible transitions into that state (pictured in Figure 6.2.2 as the three arrows pointing to the circle around r):

(i) one sensitive bacterium might have mutated into a resistant one; the probability of this occurrence is approximately

$$\mu'(t)\Delta t = aN\Delta t = \frac{a}{k}(kN\Delta t) \approx \frac{a}{k}\Delta N.$$

These probabilities are printed below the bottom arrows in the diagram;

(ii) one of the $r - 1$ resistant bacteria present at time t (when the population was N) might have divided producing one additional resistant bacterium; the probability of this occurrence is approximated by

$$R'(t)\Delta t = kR(t)\Delta t = k(r - 1)\Delta t,$$

by the assumption that the resistant population is growing at the same *per capita* growth rate, k, as the total population. From $\Delta N \approx kN\Delta t$, we get that the probability of this transition for small values of Δt is approximated by

$$(r - 1)\frac{\Delta N}{N},$$

which is printed in the diagram above the arrow connecting the state $r-1$ to the state r.

(iii) there might have been r resistant bactria at the start of the interval $[t, t + \Delta t]$ and no mutation to resistance, or division of a resistant bacterium, occured in that time interval. This is represented in the diagram by the arrow from state r that loops back to that state. The probability of this occurrence is approximated by

$$1 - \frac{a}{k}\Delta N - r\frac{\Delta N}{N}.$$

It then follows that

$$p_r(N+\Delta N) \approx p_{r-1}(N)\left(\frac{a}{k}\Delta N + (r-1)\frac{\Delta N}{N}\right) + p_r(N)\left(1 - \frac{a}{k}\Delta N - r\frac{\Delta N}{N}\right).$$

Rearranging and dividing by ΔN, we get

$$\frac{p_r(N + \Delta N) - p_r(N)}{\Delta N} \approx p_{r-1}(N)\left(\frac{a}{k} + \frac{r-1}{N}\right) - p_r(N)\left(\frac{a}{k} + \frac{r}{N}\right).$$

Thus, letting $\Delta N \to 0$, we conclude that p_r is differentiable with respect to N and

$$\frac{dp_r}{dN} = p_{r-1}(N)\left(\frac{a}{k} + \frac{r-1}{N}\right) - p_r(N)\left(\frac{a}{k} + \frac{r}{N}\right),$$

which we can rewrite as

$$\frac{dp_r}{dN} + \left(\frac{a}{k} + \frac{r}{N}\right)p_r = \left(\frac{a}{k} + \frac{r-1}{N}\right)p_{r-1}. \tag{6.15}$$

This is the differential equation that Lea and Coulson derived in their 1949 paper [LC49]. It is a linear first order equation for $p_r = p_r(N)$ in terms of p_{r-1}. Thus, the equations in (6.15) for $r = 1, 2, 3, \ldots$ also represent a system of difference equations. These can be solved recursively if we know $p_o(N)$. To find out what p_o is, we consider the beginning of the state diagram in Figure 6.2.2; namely, the portion of the diagram starting at state $r = 0$ (i.e., there are not resistant bacteria at a time when the population size equals N) and which is pictured in Figure 6.2.3.

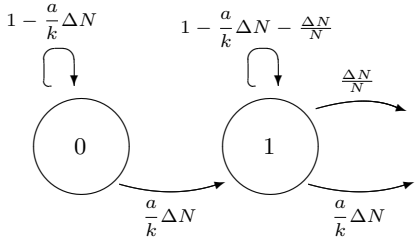

Figure 6.2.3: State diagram for $R(t)$ around $r = 0$

From the state diagram in Figure 6.2.3 we get that

$$p_o(N + \Delta N) \approx p_o(N)\left(1 - \frac{a}{k}\Delta N\right).$$

Rearranging and dividing by ΔN we have that

$$\frac{p_o(N + \Delta N) - p_o(N)}{\Delta N} \approx -\frac{a}{k}p_o(N),$$

which, after letting $\Delta N \to 0$, leads to the differential equation

$$\frac{dp_o}{dN} = -\frac{a}{k}p_o. \tag{6.16}$$

This equation can be solved by separating variables to yield

$$p_o(N) = Ce^{-\frac{a}{k}N},$$

for some constant C. Thus, by virtue of (6.14), we have that

$$p_o(t) = Ce^{-\mu(t)},$$

where $\mu(t)$ is the average number of mutations in the interval $[0, t]$. Since there are no mutations at $t = 0$, $p_o(0) = 1$ and so $C = 1$, from which we get that

$$p_o = e^{-\mu}. \tag{6.17}$$

This is the expression we have seen before for the fraction of cultures in the Luria and Delbrück experiments that show no resistant bacteria. This provides a way for estimating the average number of mutations μ. Equation (6.17) also suggests that p_o, as well as p_r for all $r \geq 1$, can be thought as a function of μ instead of N. In fact, from 6.14 we get the change of variables

$$\mu = \frac{a}{k}N, \tag{6.18}$$

which can be used, along with the chain rule, to show that

$$\frac{dp_r}{d\mu} = \frac{dN}{d\mu}\frac{dp_r}{dN} = \frac{k}{a}\frac{dp_r}{dN}, \tag{6.19}$$

for $r = 0, 1, 2, \ldots$ Thus, multiplying equation (6.16) by $\dfrac{k}{a}$ yields

$$\frac{dp_o}{d\mu} = -p_o, \tag{6.20}$$

which yields (6.17) as a solution satisfying $p_o(0) = 1$.

Similarly, multiplying the differential equation in (6.15) by $\dfrac{k}{a}$ and using the change of variables formulas (6.18) and (6.19), we get from (6.15) that

$$\frac{dp_r}{d\mu} + \left(1 + \frac{r}{\mu}\right) p_r = \left(1 + \frac{r-1}{\mu}\right) p_{r-1} \tag{6.21}$$

for $r = 1, 2, 3 \ldots$

In the next section we will solve the system of difference–differential equations (6.20)–(6.21), for $r = 1, 2, 3, \ldots$ subject to the initial conditions

$$p_o(0) = 1 \tag{6.22}$$

$$p_r(0) = 0 \qquad \text{for } r = 1, 2, 3, \ldots \tag{6.23}$$

The solution to this initial value problem have come to be known in the literature of microbial genetics as the *Luria–Delbrück Distribution.*

6.2.4 The Luria–Delbrück Distribution

In this section we solve the system of difference–differential equations (6.20)–(6.21) subject to the initial conditions (6.22)–(6.23). First, rewrite the equations in (6.21) as

$$\frac{dp_r}{d\mu} + p_r + \frac{r}{\mu}p_r = \left(1 + \frac{r-1}{\mu}\right) p_{r-1},$$

and multiply by e^{μ} to get

$$e^{\mu}\frac{dp_r}{d\mu} + e^{\mu}p_r + \frac{r}{\mu}e^{\mu}p_r = \left(1 + \frac{r-1}{\mu}\right)e^{\mu}p_{r-1},$$

or

$$\frac{d}{d\mu}\left(e^{\mu}p_r\right) + \frac{r}{\mu}\left(e^{\mu}p_r\right) = \left(1 + \frac{r-1}{\mu}\right)\left(e^{\mu}p_{r-1}\right).$$

Thus, introducing the new variable

$$q_r = e^{\mu}p_r, \tag{6.24}$$

we get that

$$\frac{dq_r}{d\mu} + \frac{r}{\mu}q_r = \left(1 + \frac{r-1}{\mu}\right)q_{r-1} \qquad \text{for } r = 1, 2, 3, \ldots, \tag{6.25}$$

where

$$q_0 = 1 \tag{6.26}$$

by (6.17). We then need to solve the system of difference–differential equations (6.25) subject to the initial conditions

$$q_r(0) = 0 \qquad \text{for } r = 1, 2, 3, \ldots, \tag{6.27}$$

by virtue of (6.24) and (6.23), given that $q_0 = 1$ by (6.26).

We begin with the case $r = 1$. In this case (6.25) and (6.26) lead to the differential equation

$$\frac{dq_1}{d\mu} + \frac{1}{\mu}q_1 = 1.$$

To solve this equation, multiply on both sides by μ to get

$$\mu\frac{dq_1}{d\mu} + q_1 = \mu,$$

and observe that this equation can be written as

$$\frac{d}{d\mu}\left(\mu q_1\right) = \mu.$$

This last equation can be integrated with respect to μ to get

$$\mu q_1 = \frac{\mu^2}{2} + C,$$

for some constant C. Solving for q_1 we get

$$q_1 = \frac{\mu}{2} + \frac{C}{\mu}.$$

For this function to be defined at $\mu = 0$, we must have that $C = 0$. We therefore get that

$$q_1 = \frac{\mu}{2}. \tag{6.28}$$

Thus, by (6.24), we also get that

$$p_1 = \frac{\mu}{2} e^{-\mu}. \tag{6.29}$$

Next, we proceed with the case $r = 2$. In this case (6.25) and (6.28) yield the differential equation

$$\frac{dq_2}{d\mu} + \frac{2}{\mu} q_2 = \left(1 + \frac{1}{\mu}\right) \frac{\mu}{2},$$

or

$$\frac{dq_2}{d\mu} + \frac{2}{\mu} q_2 = \frac{\mu}{2} + \frac{1}{2}.$$

Multiply on both sides of this equation by μ^2 to get

$$\mu^2 \frac{dq_2}{d\mu} + 2\mu q_2 = \frac{\mu^3}{2} + \frac{\mu^2}{2},$$

and observe that this can be rewritten as

$$\frac{d}{d\mu}\left(\mu^2 q_2\right) = \frac{\mu^3}{2} + \frac{\mu^2}{2}.$$

Integrating this last equation with respect to μ we get

$$\mu^2 q_2 = \frac{\mu^4}{8} + \frac{\mu^3}{6} + C,$$

where, as before, C must be taken to be 0 for q_2 to be defined when $\mu = 0$. Thus,

$$q_2 = \frac{\mu^2}{8} + \frac{\mu}{6}, \tag{6.30}$$

and therefore, by (6.24),

$$p_2 = \left(\frac{\mu^2}{8} + \frac{\mu}{6}\right) e^{-\mu}. \tag{6.31}$$

We can continue in this fashion, recursively computing q_r given that q_{r-1} is known. For instance, in the case $r = 3$ we are lead to the differential equation

$$\frac{dq_3}{d\mu} + \frac{3}{\mu} q_3 = \frac{1}{8}\mu^2 + \frac{5}{12}\mu + \frac{1}{3} \tag{6.32}$$

Multiplying[4] this equation by μ^3 and rewriting, leads to

$$\frac{d}{d\mu}\left(\mu^3 q_3\right) = \frac{1}{8}\mu^5 + \frac{5}{12}\mu^4 + \frac{1}{3}\mu^3 \tag{6.33}$$

[4]The process of going from (6.32) to (6.33) my multiplying by μ^3 is an instance of the *integrating factor* technique to solve a linear first order differential equation of the form $\frac{dq}{d\mu} + f(\mu)q = g(\mu)$. In this case, μ^3 is the integrating factor for the differential equation (6.32). In an Appendix we show how to find an integrating factor in general

Integrating (6.33), and making sure that q_3 is defined at $\mu = 0$, as before, we obtain

$$q_3 = \frac{1}{48}\mu^3 + \frac{1}{12}\mu^2 + \frac{1}{12}\mu \tag{6.34}$$

and therefore, by (6.24),

$$p_3 = \left(\frac{1}{48}\mu^3 + \frac{1}{12}\mu^2 + \frac{1}{12}\mu\right) e^{-\mu}. \tag{6.35}$$

Proceeding in a similar way for the case $r = 4$, given that we know q_3 by (6.34), we obtain

$$p_4 = \left(\frac{1}{384}\mu^4 + \frac{1}{48}\mu^3 + \frac{1}{18}\mu^2 + \frac{1}{20}\mu\right) e^{-\mu}. \tag{6.36}$$

Lea and Coulson provide a scheme for computing p_r for $r = 1, 2, 3, \ldots$ in there 1949 paper [LC49]. However, more recently in 1992, Ma, Sandri and Sarkar [MSS92] established the recursive formula

$$p_r = \frac{\mu}{r} \sum_{i=0}^{r-1} \frac{p_i}{r+1-i} \qquad \text{for } r = 1, 2, 3, \ldots \tag{6.37}$$

given that $p_o = e^{-\mu}$, as established in (6.17). It can be verified that the formula (6.37) leads to the formulas (6.29), (6.31), (6.35) and (6.36).

Table 6.4: Distribution of Resistant Bacteria in Similar Cultures

Resistant Bacteria	Number of Cultures
0	29
1	17
2	4
3	3
4	3
5	2
6–10	5
11–20	6
21–50	7
51–100	5
101–200	2
201–500	4
501–1000	0

Goodness of Fit for the Luria–Delbrück Distribution

We would like to test how close the data in Table 6.4 are to the expected values predicted by the Luria–Delbrück distribution given by the recursive formulas in

(6.37). The data in Table 6.4 come from Experiment No. 23 in [LD43] (p. 505) involving 87 cultures, each of about 2.4×10^8 bacteria. Table 6.5 summarizes the data along with the probabilities predicted by the hypothesis of mutation to immunity. These are listed in the third column. As was done when we were testing the hypothesis of acquired immunity, the entries in the "Resistant Bacteria" column in Table 6.4 have been re-categorized so that the entries in the "Expected Number" column are all at least 5; in addition, we kept the same categories as in Table 6.2 so we are able to compare the analysis here to that done for the hypothesis of acquired immunity (the one that predicts that the distribution should be Poisson).

Table 6.5: Expected and Observed Numbers of Resistant Bacteria

Resistant Bacteria	Number of Cultures	p_r	Expected Number	$\frac{(O-E)^2}{E}$
0	29	0.3333	29	0
1	17	0.1831	16	0.0625
2	4	0.1113	10	3.6
3 or more	37	0.3723	31	1.1613

The fifth column in Table 6.5 contains the relative square–deviations of observed values from the expected ones. Adding the entries in this column yields the χ^2–statistic for this test; namely, $\chi^2 = 4.8238$. Since there are four categories or bins, the number of degrees of freedoms is 3. We therefore use the χ^2_3 distribution to estimate the p–value for this test. Using the MS Excel CHIDIST function we obtain the p–value

$$p\text{–value} = \text{CHIDIST}(4.8238, 3) \approx 0.1852 \quad \text{or} \quad 18.52\%.$$

This probability is much larger than the one obtained for the hypothesis of acquired immunity, and therefore the distribution of resistant bacteria described by the data is closer to that predicted by the Luria–Delbrück distribution than to that predicted by the Poisson distribution.

Alternatively, since the p–value is larger than 10%, then χ^2–statistic is smaller than the critical value for χ^2_3–distribution at the significance level $\alpha = 0.1$ or 10%. In fact, in this case $\chi^2_{\text{critical}} = 6.2514$, and so $\chi^2 < \chi^2_{\text{critical}}$. Therefore, at the 10% significance level, the data in Table 6.4 are in accord with the Luria–Delbrück distribution, and hence with the hypothesis of mutation to immunity.

Chapter 7

Exercises

1. Show that the solution to the difference equation

$$X_{t+1} = X_t$$

must be constant.

2. Consider the population model given by the difference equation

$$N_{t+1} - N_t = m,$$

where m is a constant, for $t = 0, 1, 2, \ldots$.

   (a) Give an interpretation for this model.

   (b) If the initial population density is N_o, what does this model predict in the long run? Consider the two possibilities $m < 0$ and $m > 0$.

   (c) How does this model compare with the Malthusian model?

3. Assume that the *per–capita* growth rate λ of a population is less than 1; that is, left on its own, the population will go extinct. To avoid extinction, suppose that after each unit of time, a constant number m of individuals of the same species is added to the population.

   (a) Write down a difference equation that models this situation.

   (b) Solve the difference equation and discuss what this model predicts in the long run.

   For this problem, it will be helpful to know that

$$1 + \lambda + \lambda^2 + \cdots + \lambda^{n-1} = \frac{\lambda^n - 1}{\lambda - 1} \quad \text{for } \lambda \neq 1,$$

   and that

$$\lim_{n\to\infty} \lambda^n = 0 \quad \text{if} |\lambda| < 1.$$

(c) How does this model compare with the Malthusian model?

4. Problem 1.1.2 on page 6 in [AR04].

5. Problem 1.1.6 on page 7 in [AR04].

6. Problem 1.1.10 on page 7 in [AR04].

7. *Modeling Red Blood Cell Production*[1]. In the circulatory system, red blood cells (RBCs) are constantly being filtered out and destroyed by specialized "clean–up" cells in the spleen and liver, and replenished by the bone marrow. Since the cells carry oxygen throughout the body, their numbers must be maintained at some constant level. In this set of problems, we model the removing of RBCs by the spleen and liver, and their replenishing by the bone marrow in order to understand how the RBC levels may be maintained.

   Assume that the spleen and liver remove a fraction f of the RBCs each day, and that the bone marrow produces new cells at a daily rate proportional to the number of RBCs lost on the previous day with proportionality constant γ.

   Derive a system of two difference equations for R_t, the RBC count in circulation on day t, and M_t, the number of RBCs produced by the bone marrow on day t, where $t = 1, 2, 3, \ldots$

   Suggestion: Consider the number of RBCs in circulation on day $t + 1$, R_{t+1}. By the conservation principle, the change $R_{t+1} - R_t$ in the number of RBCs from day t to day $t + 1$ must be equal the number of new RBCs produced on day t minus the number of RBCs that were removed on that same day. On the other hand, the number of new RBCs produced by the bone marrow on day $t + 1$, M_{t+1}, must be given by the expression

   $$M_{t+1} = \gamma \times (\text{Number of RBCs removed on day } t).$$

8. *Red Blood Cell Production (continued).* By considering the number of RBCs in circulation on day $t+2$, we are able to combine the two difference equations derived in the previous problem into a single difference equation of the form

   $$R_{t+2} = bR_{t+1} + cR_t, \tag{7.1}$$

   where b and c are constants. Determine expressions for b and c in terms of f and γ.

   Equation (7.1) is an example of a *linear second order difference equation.*

9. *Red Blood Cell Production (continued).* We may seek to find a solution to the linear second order difference equation (7.1) as follows:

[1] Edelstein–Keshet [EK88], pg. 27

(a) Assume that the sought after solution is of the form $R_t = A\lambda^t$, where A is some constant that will depend on the initial conditions, and λ is a parameter that is to be determined by substituting into the difference equation. Substitute this assumed form for R_t into equation (7.1) to obtain an expression for λ. Assuming that neither A nor λ are zero, simplify the expression to get the second order equation

$$\lambda^2 = b\lambda + c. \tag{7.2}$$

(b) Solve equation (7.2) for λ to obtain two possible solutions λ_1 and λ_2 in terms of f and γ, where $\lambda_1 < \lambda_2$.

(c) Verify that $A_1\lambda_1^t$ and $A_2\lambda_2^t$, where A_1 and A_2 are arbitrary constants, both solve the difference equation (7.1).

(d) Verify that

$$R_t = A_1\lambda_1^t + A_2\lambda_2^t, \tag{7.3}$$

where A_1 and A_2 are arbitrary constants, also solves the difference equation (7.1).

The function R_t in equation (7.3) is called the *general solution* of the difference equation (7.1).

10. *Red Blood Cell Production (continued).* Assume that 1% of the RBCs are filtered out of circulation by the spleen and liver in a day; that is $f = 0.01$.

(a) If $\gamma = 1.50$, what does the general solution (7.3) predict about the RBC count as $t \to \infty$?

(b) Suppose now that $\gamma = 0.50$. What does the general solution (7.3) predict about the RBC count as $t \to \infty$?

(c) Suppose now that $\gamma = 1$. What does the general solution (7.3) predict about the RBC count as $t \to \infty$?

(d) Which of the three values of γ discussed in the previous three parts seems to yield a reasonable prediction? What implication does that have about RBC levels in the long run?

11. Problem 1.1.11 on page 8 in Allman and Rhodes.

12. Problem 1.2.7 on page 18 in Allman and Rhodes.

13. Problem 1.2.8 on page 18 in Allman and Rhodes.

14. *(US Census Data.)* The MS Excel file CensusDataUS in the Math 36 webpage (see the courses website at `http://pages.pomona.edu/~ajr04747`) contains the total US population (in millions of people) for each year that a census has been taken in the United States.

(a) Use MATLAB®to get a plot of the US population as a function of t, where t is in units of 10 years since the year 1790.

(b) If the US population follows a Malthusian model, what would the growth rate λ be? Using this value of λ, compute the population values that the model predicts for $t = 1, 2, 3, \ldots$ Plot the predicted and actual values on the same graph. How well do these predictions compare with the actual data?

15. *(US Census Data, continued).* Starting with the solution to the Malthusian model: $N_t = N_0\lambda^t$, take logarithms on both sides to get

$$\ln N_t = \ln N_0 + t \ln(\lambda).$$

Thus, the relationship between $\ln N_t$ and t should be linear with slope $\ln(\lambda)$ and y–intercept $\ln N_0$.

(a) If `X` represents a row of values, and `Y` another row of values of the same size, the MATLAB® function `polyfit(X,Y,1)` returns the slope m and y–intercept y_o of the line that best fits the data (in the sense of least squares regression) in `X` and `Y`:

$$y = mx + y_o.$$

Use this function to obtain estimates for the values of $\ln N_0$ and $\ln(\lambda)$

(b) Obtain estimates for N_0 and λ, and use them to generate a new set of predicted values for the US population. Plot these, along with the actual data, and assess how good the fit is.

16. *(Numerical Analysis of the Logistic Equation).* In this problem and the next two, you are asked to use the MATLAB® program `Logistic.m` to explore how the nature of the solutions to the logistic difference equation

$$N_{t+1} = N_t + rN_t(1 - N_t) \tag{7.4}$$

changes as one varies the parameter r and the initial condition N_o. The code for `Logistic.m` may be found in the Math 36 webpage of the courses website at `http://pages.pomona.edu/~ajr04747`.

Start out with the initial condition $N_o = 0.1$ and consider the following values of r: 1, 1.5, 2, 2.1, 2.25, 2.5 and 2.7. Describe in words the long term behavior of the solution to (7.4) for each value of r. Is there any significant change in the structure of the solution? Is there anything striking?

17. *(Numerical Analysis of the Logistic Equation, continued).* Keep the value of r at 2.7 and try the following initial conditions:

$$N_o = 0.1 \quad \text{and} \quad N_o = 0.101.$$

Before you try the second initial condition, type the MATLAB® command `hold on`. This will allow you to see the plots of the two solutions on the same graph. Is there anything that strikes you? What implications does this result might have on the question of predictability?

18. *(Numerical Analysis of the Logistic Equation, continued).*

    (a) What happens when $r = 3$ and t is allowed to range from 0 to 100? How would you describe the solution?

    (b) What happens when $r = 3.01$? Does this result suggest that we need to impose a restriction on r? What should that restriction be?

19. Problems 1.1.16 (a)(b) on pages 9 and 10 in Allman and Rhodes.

20. Problems 1.1.16 (c)(d) on page 10 in Allman and Rhodes.

21. Suppose that X_t satisfies the *difference inequality*

$$|X_{t+1}| \leq \eta |X_t| \quad \text{for} \quad t = 0, 1, 2, 3, \ldots$$

    where $0 < \eta < 1$. Prove that

$$\lim_{t \to \infty} X_t = 0.$$

22. The *Principle of Linearized Stability* for the difference equation

$$N_{t+1} = f(N_t)$$

    states that, if f is differentiable at a fixed point N^* and

$$|f'(N^*)| < 1,$$

    then N^* is an asymptotically stable equilibrium solution.

    In this problem we use the Principle of Linearized stability to analyze the following population model:

$$N_{t+1} = \frac{kN_t}{b + N_t}$$

    where k and b are positive parameters.

    (a) Write the model in the form $N_{t+1} = f(N_t)$ and give the fixed points of f. What conditions of k and b must be imposed in order to ensure that the model will have a non–negative steady state?

    (b) Determine the stability of the equilibrium points found in part (a).

23. Problems 1.3.6 (d)(e) on page 29 in Allman and Rhodes.

24. Problems 1.3.7 (d)(e) on page 29 in Allman and Rhodes.

25. Problems 1.3.111 (a)(b)(c)(d) on page 30 in Allman and Rhodes.

    Note: The code for the MATLAB® program `onepop` *may be downloaded from the courses website at* `http://pages.pomona.edu/~ajr04747`.

26. Problems 1.2.9 and 1.2.10 on page 18 in Allman and Rhodes.

27. Problems 1.3.1 and 1.3.2 on page 28 in Allman and Rhodes.

28. *(US Census Data, Revisited.)* In this problem and the next, we fit a logistic curve to the US Census data contained in the MS Excel file CensusDataUS.xls in the Math 36 website (`http://pages.pomona.edu/~ajr04747`)

    The idea for this fit is to observe that, if we write the logistic difference equation

    $$N_{t+1} = N_t + rN_t\left(1 - \frac{N_t}{K}\right)$$

    in the form $\dfrac{\Delta N}{N_t} = r - \dfrac{r}{K}N_t$, where $\Delta N = N_{t+1} - N_t$, then the logistic model predicts that the relationship between the *relative increments* $\dfrac{\Delta N}{N_t}$ and N_t should be linear with slope $-r/K$ and y–intercept r. Thus, the parameters r and K can be estimated from the data by a linear, least–squares regression fit of the relative increments versus the population density.

    (a) Use MATLAB® to define an array, `Y`, made up of the relative increments of the US population since census started being taken. The size of this new array should be one less than the size of the US population array.

    (b) Define an array, `N`, made up of the US population values up to the next to the last one (i.e., the census values from 1790 to 1990).

    (c) Plot `Y` versus `N`. Use the MATLAB® command `plot(N,Y,'k*')` and then type `hold on` in the command window in order to keep the plot.

    (d) Use the MATLAB® command `polyfit(N,Y,1)` to obtain the slope, m, and y–intercept, b, of the least–squares regression line of `Y` versus `N`, and sketch the this line on the same graph obtained in the previous part.

    (e) Use the slope and y–intercept obtained in the previous part to estimate the intrinsic growth rate, r, and carrying capacity, K, for the US population.

29. *(US Census Data, Revisited (continued).)*

    (a) Use the estimates for r and K obtained in the previous problem, and the US population in 1790 as N_o, to compute population values predicted by the logistic model for each of the decades since 1790 until 2000. You may use the MATLAB® .m–file `LogisticK.m` to do these calculations

    (b) Plot the predicted and actual values on the same graph. How well do these predictions compare with the actual data? How does this fit compare with the Malthusian model fit of the data done in Problem (5) of Assignment #3?

30. Use the procedure outlined in the previous two problems to fit a logistic curve through the *Insect Population Values* data found in Table 1.6, p. 18, in Allman and Rhodes. What are the estimated values of r and K for the insect population?

Appendix A

MATLAB Files

A.1 Solving the Discrete Logistic Equation

A.1.1 Code for Logistic.m

```
% Logistic.m
% Author: Adolfo J. Rumbos
% This program  allows the user to input initial condition for a logistic
% difference equation.  It also allows for the input of the intrinsic growth
% rate.  The carrying capacity is assumed to be K=1.  The program can also
% iterate the equation for as many generations as desired.
%
%
disp(' ')
disp('This program finds and plots solutions to the logistic difference equation')
disp(' ')
disp('                        N_{t+1} = N_t + r*N_t*(1-N_t)')
disp(' ')
disp(' ')
disp('Enter the intrinsic growth rate "r"')
r=input ('r = ');
%
disp(' ')
disp('Enter the initial population value "N_0"')
N_0=input ('N_0 = ');
%
disp(' ')
disp('Enter the number of generations:');
gen=input('(Default is 20)   ');
if isempty(gen) gen=20; end;
%
p=N_0;
```

```
N=p;
for i=1:gen; p = p + r*p*(1 - p);
N=[N p]; end
%
% Plotting routine
plot([0:gen], N, 'k-*')
y_max = max([N_0 N]) + 0.1;
axis([0 gen 0 y_max]); grid on;
title(['Logistic model with r = ', num2str(r), ', K=1, ', 'and ',
'N\_0 = ', num2str(N_0)])
xlabel('Time t');
ylabel('Population N');
```

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