ʏou have accomplished these goals, you should be ready to pro-
ɪrt Two of the book, which involves application of these methods
ɔer of models from a variety of biological fields.

CHAPTER 1

ANALYTICAL MODELS BASED ON DIFFERENTIAL EQUATIONS

Analytical models are often expressed as differential equations that define a rate of change of some dependent variable with respect to some independent variable. In biological models, the independent variable is usually time, distance or concentration. To show how models may be developed using differential equations, we will look at a model for biological growth, with time as the independent variable and growth as the dependent variable. Several other simple analytical models based on differential equations will also be presented as further illustrations. These simple models can be used in writing short computer programs for simulating biological processes. Even though they are brief, these programs will let you become familiar with techniques used for the remainder of the book.

1.1 A Model of Biological Growth

A major reason for using differential equations to develop models is that these equations are easily obtained from common sense "function equations". For the purpose of developing this growth model, we will be interested in a population of cells, perhaps cells in a tissue culture dish, or yeast cells or bacteria cells in a culture flask. We observe that cell growth rate (number of cells added per hour) depends on the number of cells already present. That is, if we have one culture with 10 cells and another with 100, the culture with 100 cells will produce more new cells in an hour than the culture with just 10 cells. Likewise, we note that a culture with 0 cells will not produce any new cells. From these general observations, we can write a simple function equation for growth of cell numbers:

$$G = f(N) \tag{1.1}$$

where G is the growth rate and N is number of cells.

If we assume that growth is a direct function of N (i.e. that growth depends directly on N, or that it is directly proportional to N), and if we also assume no other factors are involved, then the growth rate equation will take this form:

$$G = kN \tag{1.2}$$

where k is a constant of proportion. If you were to graph this equation, showing N (population number) on the x-axis and G (growth rate) on the y-axis, the result would be a straight line with a slope of k. That is, as N increases, G would increase in direct proportion.

The equation has limited value in this form, because just now we are interested in population numbers during the time of growth, rather than in the rate of growth. We need to convert our equation to a form giving this information. To do this, first we define growth rate G as dN/dt. This new expression symbolizes the instantaneous rate of change of number with respect to time. Our equation is now written as

$$\frac{dN}{dt} = kN \tag{1.3}$$

Equations 1.2 and 1.3 have identical meanings, but Equation 1.3 is in terms of the two variables we want, N and t. Now we can find the equation for growth of the population by integrating Equation 1.3. Mathematicians know how to perform integrations as a result of their experience with the reverse process of differentiation. From their experience they have developed a large number of integration rules, which are found in most textbooks of calculus.

If we use these rules, several useful forms of the equation will be obtained following integration:

$$\ln N_t - \ln N_0 = kt \tag{1.4}$$

and

$$\frac{N_t}{N_0} = e^{kt} \tag{1.5}$$

and

$$N_t = N_0 e^{kt} \tag{1.6}$$

The intermediate steps in this integration may be found in most textbooks of calculus and of population ecology (e.g. Hutchinson 1978). For biological purposes, Equation 1.6 is extremely useful and will occur in many different contexts. Here it describes the number of cells in the population at any time (N_t), based on the initial population size (N_0) and the growth constant (k). The base of natural logarithms is given as e. The form of the curve of numbers over time is shown in Figure 1.1. Over

a limited range of population sizes and time periods, this equation may be a useful model to describe growth of bacteria, rabbits, people, money, and other quantities.

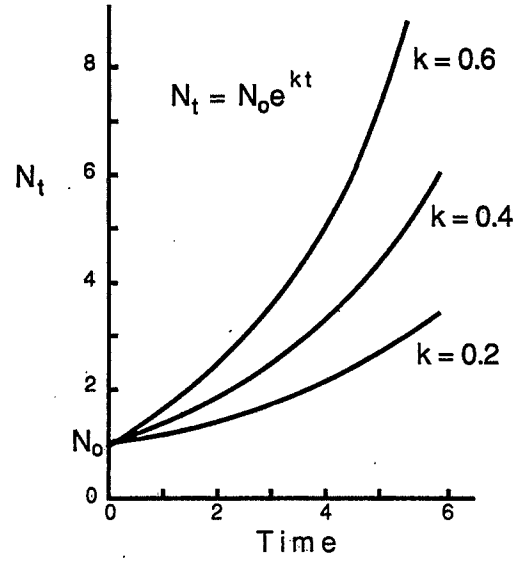

Figure 1.1. Exponential growth curves.

Exercise 1-1: When Equation 1.6 is used to describe growth of bacterial populations, it is often given in the form

$$N_t = N_0 e^{\mu t} \tag{1.6A}$$

where μ is the specific growth constant.

Write a BASIC computer program that uses this equation to simulate unlimited growth of a bacterial culture. Assume for a very rapidly multiplying bacterium that $\mu = 0.092$ min^{-1}, and that initial density $N_0 = 2$ bacteria ml^{-1}. To find powers of e, you may either use the EXP(X) function which is built into BASIC, or raise 2.71828 to the appropriate powers. Appendix 1 provides a review of some essentials of programming in BASIC.

Implement your program on a computer. Your program should have the computer print the results in two parallel columns, one indicating time (t) and the other showing the corresponding bacterial density (N_t) at each minute, $0, 1, 2, 3, \ldots, 50$.

Exercise 1-2: Rewrite your program from Exercise 1-1 so that it uses the graphical capabilities of your computer to produce a graph

```
100 REM SIMULATION OF EXPONENTIAL GROWTH
110 REM
120 LPRINT "TIME",,"POPULATION SIZE"
130 LPRINT"   0---------5---------10--------15--------20--------25"
140 U = .1
150 NO = 2
160 FOR T=0 TO 25
170    NT = NO * EXP (U*T)
180    Y = INT(NT*60/30)
190    LPRINT T; TAB(5); "+"; TAB(Y+5); "*"
200 NEXT T
210 LPRINT"   0---------5---------10--------15--------20--------25"
220 END
```

```
TIME                    POPULATION SIZE
    0---------5---------10--------15--------20--------25
0   +     *
1   +     *
2   +     *
3   +      *
4   +      *
5   +       *
6   +        *
7   +         *
8   +         *
9   +          *
10  +           *
11  +            *
12  +             *
13  +              *
14  +               *
15  +                *
16  +                 *
17  +                  *
18  +                   *
19  +                    *
20  +                     *
21  +                      *
22  +                       *
23  +                        *
24  +                         *
25  +                          *
    0---------5---------10--------15--------20--------25
```

Figure 1.2. Program and output for Exercise 1-2, set up for a simple line printer. (The program was written for the IBM-Microsoft BASIC interpreter. The LPRINT statements in Lines 120, 130, 190 and 210 send output to the "line printer". The LPRINT statement is not available in all versions of BASIC, although the equivalent exists in all BASICs.)

showing bacterial density as a function of time from 0 to 120 minutes. Set up the output so that bacterial density is plotted on the y-axis and time is plotted on the x-axis. Appendix 2 gives a listing of graphical programs for some microcomputers. Figure 1.2 shows the growth model used in a sample program that produces graphical output for computers equipped with simple printers.

1.2 Exponential Decay

As a sort of converse to the growth process described above, some biological systems will show a decline in concentration of a certain substance through time, with the loss rate proportional to the concentration of the substance present at any time. Following the same procedure as above, we can arrive at a differential equation describing this process of decline:

$$\frac{dC}{dt} = -kC \tag{1.7}$$

Here, C is the concentration of the substance being used up, and k is the rate constant. The negative sign is needed to indicate the reduction in C. This equation integrates to

$$C_t = C_0 e^{-kt} \tag{1.8}$$

This is the classical model for exponential decay used to describe processes such as weight loss during starvation, excretion of drugs or a radioisotope from an organism, light absorption in a liquid, radioactive decay, and other phenomena. Note that in each of these examples the dependent variable will approach zero as t approaches infinity.

Exercise 1-3: Write a program using Equation 1.8 to simulate the decay of the radioactive isotope ^{32}Phosphorus. Begin your simulation with a specific activity of 500 μcuries, and use a value of $k = 0.04847$ day^{-1}. Produce graphical output that shows remaining activity from 0 to 100 days. Use a pencil and straightedge to estimate the isotopic half-life (time for activity to be reduced by 50%).

1.3 Distribution of Organisms

The exponential decay model has been used in a variety of biological research areas to describe the distribution of plants and animals. The organisms are assumed to have a central location of maximum concentration. Their density away from that point is assumed to follow a classical

diffusion pattern, which will result in a negative exponential decline in density away from the central locus. Two such situations are given in the following pair of exercises.

Exercise 1-4: Aquatic crustaceans and immature insects that inhabit flowing water will at times release themselves from the streambed and drift downstream. McLay (1970) used the following model based on exponential decline to describe downstream densities:

$$N_x = N_0 e^{-Rx} \tag{1.9}$$

where N_0 is population density at the source of animals, N_x is the density at a distance x meters downstream from the source, and R is a constant that applies uniquely to the organism in a given stream. Write a program to simulate stream drift for larval chironomid insects in a stream, where $R = 0.13$ m^{-1}. Assume density of these animals is 1200 meter^{-2} at their source. Your graphical output should show density at each meter for a distance of 60 meters downstream from the source.

Exercise 1-5: Van Dover et al. (1987) used this same exponential model to describe distribution of a deepwater crab, *Bythograea*, that lives around hydrothermal vents in the Pacific Ocean. The animals were observed to be most abundant immediately around the vents, with a density of about 100 per unit of camera viewing area (about 845 m^2). In any direction from a vent, their density decreased, with $R = 8.56$ km^{-1}. Write and implement a program to find density of crabs as a function of distance from a hydrothermal vent. As output, produce a graph that shows their symmetrical distribution along a line running through a vent, from 600 meters on one side to 600 meters on the other.

1.4 Newton's Law of Cooling

The basic form of exponential decline given in Equation 1.8 has been modified slightly to provide the basis of numerous biological models. An example is Newton's Law of Cooling as a model for loss of heat from a cooling object. This law states that temperature of an object drops at a rate proportional to the difference between the temperature of the object and the temperature of the environment. The rate of temperature change with time is given by

$$\frac{dT}{dt} = -k(T - C) \tag{1.10}$$

where C is the environmental temperature and k is a cooling rate constant. Equation 1.10 integrates to an equation describing the temperature of a cooling object through time:

$$T_t = C + (T_0 - C)e^{-kt} \tag{1.11}$$

where T_t is the temperature of the object at time t and $(T_0 - C)$ is the difference between the initial temperature and the environmental temperature, with C held constant throughout the cooling process. The relationship of Equation 1.11 to Equation 1.8 for exponential decay is obvious when C is set to zero. (Note that Equation 1.11 also holds for "negative cooling" when C exceeds T_0.)

Exercise 1-6: Use Equation 1.11 to write a program for simulating the cooling of a human corpse with $k = 0.06$ hour^{-1}, which is the approximate value for an average clothed adult male in still air. Assume a normal body temperature of 37°C initially and a constant environmental temperature of 8°C. Set up your program to produce a graph showing body temperature during the 48-hour period following death.

1.5 Passive Diffusion Across a Membrane

An equation similar to Equation 1.10 may be used to model the process of passive diffusion. The rate of change of concentration of an internal solute of a cell, caused by passive diffusion into an environment with a constant solute concentration, is given with

$$\frac{dC}{dt} = -k(C - C_x) \tag{1.12}$$

where C is the internal concentration for a cell of unit volume and unit surface area, C_x is the environmental concentration, and k is the proportionality constant for diffusion rate. The integrated form of the equation is

$$C_t = (C_0 - C_x)e^{-kt} + C_x \tag{1.13}$$

where C_t is the concentration in the cell at time t, C_0 is the initial internal concentration, and C_x is concentration of the external environment, assumed to be constant for the duration of the diffusion process.

Exercise 1-7: Write a program using Equation 1.13 to simulate diffusion from a cell of unit volume and unit surface area having an initial internal solute concentration of 100 units per unit volume. At time

zero the cell is put into an environmental solute with a concentration of 50 units per unit volume. The diffusion rate constant is 0.20 minute^{-1}. The graphical output from your program should show the concentration of internal cell solute for a period of the first 120 minutes.

6 Von Bertalanffy's Model of Fish Growth

This classical model describes fish length as a function of age, based the assumption that fish growth is proportional to the difference beeen the length and a theoretical maximum length. That is, fish grow ore rapidly when they are smaller, with growth rate declining as their e approaches the maximum. The differential equation describing this ocess is

$$\frac{dL}{dt} = k(L_m - L) \tag{1.14}$$

ere L is fish length, L_m is the theoretical maximum length, and k is growth rate constant. This equation integrates to

$$L_t = (L_i - L_m)e^{-kt} + L_m \tag{1.15}$$

ere L_t is length at time t and L_i is length measured at $t = 0$.

xercise 1-8: DeMarais (1985) studied growth of a small flatfish, *Buglossidium luteum*, in a bay of the Mediterranean Sea. During the first year of their life these fish follow the Von Bertalanffy growth model, and may obtain a maximum length of 51.6 mm. Assuming an initial length of 8.2 mm and a growth rate constant of 0.23 month^{-1}, write a program that simulates growth of this species over a period of 12 months.

7 Model of Inhibited Growth

A model of population growth that is slightly more realistic than that nsidered in Section 1.1 can be developed by assuming that a population es not grow beyond some upper limit, L. One form of this model is en in the following differential equation:

$$\frac{dN}{dt} = kN(L - N) \tag{1.16}$$

ere N is population number or density as before. (In this model the e constant k will have different dimensions than the constant as defined

in Section 1.1.) Note that as N approaches the limit L, the term inside the parentheses approaches zero, as does the rate of growth, dN/dt. This equation can be integrated to give the following:

$$N_t = \frac{N_0 L}{N_0 + (L - N_0)e^{-Lkt}} \tag{1.17}$$

where N_t is the population number at time t, and N_0 is the initial population size at $t = 0$. This equation for limited growth produces an S-shaped curve of population size plotted against time. This model has been used for simulating the spread of disease, for growth obtained with a given amount of nutrient, and other processes that are limited by resources. Equation 1.16 will be discussed further in Chapter 7.

Exercise 1-9: Using Equation 1.17, write a program that simulates density of a population growing in a limited environment. Assume a limiting density of 800 individuals per unit area. Set $k = 0.0005$ individual^{-1} week^{-1}. Your graph of the simulation data should depict density over a 52-week period, beginning with an initial density of 5 organisms per unit area.

1.8 Kinetics of Bimolecular Reactions

Assume that two chemical reactants, A and B, interact to form a product P, as described in the following reaction:

$$A + B \xrightarrow{k} P$$

The rate at which reactant B is used up depends upon the concentrations of both A and B:

$$\frac{d[B]}{dt} = -k[A][B] \tag{1.18}$$

where $[A]$ and $[B]$ indicate the concentrations of reactants A and B respectively, and k is the constant for reaction rate. The reaction between A and B will proceed differently depending upon the relative concentrations of A and B.

If $[A] = [B]$, then Equation 1.18 becomes

$$\frac{d[B]}{dt} = -k[B][B] = -k[B]^2 \tag{1.19}$$

This equation may be integrated to obtain the equation

$$\frac{1}{[B]_t} = kt + \frac{1}{[B]_0} \tag{1.20}$$

$B]_t$ is the concentration of B at time t, and $[B]_0$ is the initial
:ation at $t = 0$. This equation may be rearranged to solve for

$$[B]_t = \frac{[B]_0}{1 + ([B]_0 kt)} \tag{1.21}$$

ions 1.20 and 1.21 are model equations for the kinetics of "second-
actions", in which the rate is proportional to the product of the
:ation of two reactants (or the square of either one, because $[A] =$
hen data are collected from such reactions and are plotted with
ı the y-axis and t on the x-axis, the result will be a straight line
pe equal to k and a y-intercept equal to $1/[B]_0$. This is easily
n Equation 1.20 which has the form $y = a + bx$.
ıtrast to the above, if the concentration of reactant A is much
than that of B, then the concentration of A will not change sig-
y as the reaction proceeds. $[A]$ may be considered constant in
e, and can be combined with k to produce a new constant, k'.
erential equation describing this is obtained from Equation 1.91
rs:

$$\frac{d[B]}{dt} = -k[A][B] = -k'[B] \tag{1.22}$$

ıation will integrate to:

$$\ln[B]_t = -k't + \ln[B]_0 \tag{1.23}$$

be solved for $[B]_t$:

$$[B]_t = [B]_0 e^{-k't} \tag{1.24}$$

ıuld recognize this last equation as that of exponential decay
ɔn 1.6). Equations 1.23 and 1.24 are the model equations for
tics of "first-order reactions", where the rate depends upon the
:ation of only one reactant. When data obtained from first-order
s are plotted with $\ln[B]$ on the y-axis and t on the x-axis, the
ill be a straight line with a slope of $-k'$ and a y-intercept of

erms zero-order, first-order and second-order were first employed
ibe the kinetics of chemical reactions. However, they are now
y used to describe any rate process which is constant (zero-order),
ɔendent on the concentration of a single variable (first-order), or
dent on the product of two variables or the square of one variable
order).
ions 1.22 and 1.24 are important because they show that reaction
affected when one reactant is held constant, whether from a high

relative initial concentration or from being maintained at constant level by other processes. First-order reactions will be encountered frequently in later chapters.

Exercise 1-10: Write a program that uses Equation 1.21 to simulate a second-order reaction. Start with B having a concentration of 5M, and set $k = 0.20$. Your program should find $[B]$ at one-second intervals from 0 to 20 seconds. Have your computer produce graphs showing both $[B]$ and $1/[B]$ over the 20-second period. (If your graphical capabilities permit, it is instructive to show both $[B]$ and $1/[B]$ on the same graph. In this case, the vertical axis will have to be labeled as arbitrary "units".)

Conclusion

This chapter has briefly introduced some fundamental analytical models that have been developed from differential equations. One objective has been to show that this important technique is useful in describing biological phenomena. Another objective has been to provide an opportunity for some elementary programming of biological simulations. In this chapter the techniques of calculus were used to convert differential equations into usable models. In subsequent chapters different methods of working with differential equations will be introduced.