4 An Introduction to Continuous Models

The mathematics of uncontrolled growth are frightening. A single cell of the bacterium E. coli would, under ideal circumstances, divide every twenty minutes. That is not particularly disturbing until you think about it, but the fact is that bacteria multiply geometrically: one becomes two, two become four, four become eight, and so on. In this way, it can be shown that in a single day, one cell of E. coli could produce a super-colony equal in size and weight to the entire planet earth.

M. Crichton (1969), *The Andromeda Strain* (Dell, New York, p. 247).

This chapter introduces the topic of ordinary differential equation models, their formulation, analysis, and interpretation. A main emphasis at this stage is on how appropriate assumptions simplify the problem, how important variables are identified, and how differential equations are tailored to describing the essential features of a continuous process.

Because one of the most challenging parts of modeling is writing the equations, we dwell on this aspect purposely. The equations are written in stages, with appropriate assumptions introduced as they are needed. We begin with a rather simple ordinary differential equation as a model for bacterial growth. Gradually, more realistic aspects of the situation are considered, eventually leading to a system of two ordinary differential equations that describe the way that the microorganisms reproduce at the expense of nutrient consumption in a device called the *chemostat*.

Some of the simplest models are analytically solvable. However, as complexity increases, even formulating the equations correctly can be tricky. One technique that proves useful in detecting potential errors in the equations is *dimensional analysis*. This method forms an underlying secondary theme in the chapter.

After defining the problem and formulating a consistent set of equations, we turn to analysis of solutions. In the chemostat model we find that, due to complexity of the system, the only solutions that can be found analytically are the steady states. Their stability properties are of particular importance, and are explored in Section 4.10.

In a brief digression (Sections 4.7–4.9), we review some aspects of the mathematical background. Those of you familiar with differential equations may skip or skim over Section 4.8. Others who have had no previous exposure may find it helpful to supplement this terse review with readings from any standard text on ordinary differential equations (for example, Boyce and DiPrima, 1977 or Braun, 1979).

Culminating the analysis of the model in Section 4.10 is an interpretation of the various mathematical results in terms of the biological problem. We shall see that in this example predictions can be made about how the chemostat is to be operated for successful harvesting. Treatments of this problem with slightly different flavors are also to be found in Segel (1984), Rubinow (1975), and Biles (1982).

Methods applied to one situation often prove useful in a host of related or unrelated problems. Three such examples are described in a concluding section for further independent study.

4.1 WARMUP EXAMPLES: GROWTH OF MICROORGANISMS

One of the simplest experiments in microbiology consists of growing unicellular microorganisms such as bacteria and following changes in their population over several days. Typically a droplet of bacterial suspension is introduced into a flask or test tube containing *nutrient medium* (a broth that supplies all the essentials for bacterial viability). After this process of *inoculation,* the *culture* is maintained at conditions that are compatible with growth (e.g., at suitable temperatures) and often kept in an agitated state. The bacteria are then found to reproduce by undergoing successive cell divisions so that their numbers (and thus density) greatly increase.[1]

In such situations, one typically observes that the graph of log bacterial density versus time of observation falls along a straight line at least for certain phases of growth: after the initial adjustment of the organism and before its nutrient substrate has been depleted. Here we investigate more closely why this is true and what limitations to this general observation should be pointed out.

Let

$N(t)$ = bacterial density observed at time t.

Suppose we are able to observe that over a period of one unit time, a single bacterial cell divides, its daughters divide, and so forth, leading to a total of K new bacterial cells. We define the reproductive rate of the bacteria by the constant K, $(K > 0)$ that is,

K = rate of reproduction per unit time.

1. There are several ways of ascertaining bacterial densities in a culture. One is by successive cell counts in small volumes withdrawn from the flask. Even more convenient is a determination of the *optical density* of the culture medium, which correlates with cell density.

Now suppose densities are observed at two closely spaced times t and $t + \Delta t$. Neglecting death, we then expect to find the following relationship:

$$N(t + \Delta t) \simeq N(t) + KN(t)\,\Delta t,$$

total density at time $t + \Delta t$	$\simeq$	density at time t	$+$	increase in density due to reproduction during time interval Δt

This implies that

$$\frac{N(t + \Delta t) - N(t)}{\Delta t} = KN(t). \tag{1a}$$

We now approximate N (strictly speaking a large integer, e.g., $N = 10^6$ bacterial cells/ml) by a continuous dependent variable $N(t)$. Such an approximation is reasonable provided that (1) N is sufficiently large that the addition of one or several individuals to the population is of little consequence, and (2) the growth or reproduction of individuals is not correlated (i.e., there are no distinct population changes that occur at timed intervals).

Then in the limit $\Delta t \to 0$ equation (1) can be approximated by the following ordinary differential equation:

$$\frac{dN}{dt} = KN. \tag{1b}$$

This simple equation is sometimes known as the *Malthus law*. We can easily solve it as follows: multiplying both sides by dt/N we find that

$$\frac{dN}{N} = K\,dt.$$

Integrating both sides we obtain

$$\int_0^t \frac{dN}{N} = \int_0^t K\,ds,$$

$$\ln N\Big|_0^t = Kt,$$

$$\ln N(t) - \ln N(0) = Kt,$$

$$\ln N(t) = Kt + a, \tag{2a}$$

where $a = \ln N(0)$. This explains the assertion that a log plot of $N(t)$ is linear in time, at least for that phase of growth for which K may be assumed to be a constant.

We also conclude from equation (2a) that

$$N(t) = N_0 e^{Kt}, \tag{2b}$$

where $N_0 = N(0)$ = the initial population. For this reason, populations that obey equations such as (1b) are said to be undergoing *exponential growth*.

This constitutes the simplest minimal model of bacterial growth, or indeed, growth of any reproducing population. It was first applied by Malthus in 1798 to hu-

man populations in a treatise that caused sensation in the scientific community of his day. (He claimed that barring natural disasters, the world's population would grow exponentially and thereby eventually outgrow its resources; he concluded that mass starvation would befall humanity.) These deductions are discussed at greater length in problem 1.

Equation (1b), while disarmingly simple, turns up in a number of natural processes. By reversing the sign of K one obtains a model of a population in which a fraction K of the individuals is continually removed per unit time, such as by death or migration. The solution

$$N(t) = N_0 e^{-Kt}, \qquad (K > 0) \tag{2c}$$

thus describes a *decaying* population. This equation is commonly used to describe radioactive decay.

One defines a population *doubling time* τ_2 (for K), or *half-life* $\tau_{1/2}$ (for $-K$) in the following way. For growing populations, we seek a time τ_2 such that

$$\frac{N(\tau_2)}{N_0} = 2.$$

Substituting into equation (2b) we obtain

$$\begin{aligned} \frac{N(\tau)}{N_0} &= 2 = e^{K\tau}, \\ \ln 2 &= K\tau, \\ \tau &= \frac{\ln 2}{K}. \end{aligned} \tag{3}$$

The doubling time τ is thus inversely proportional to the reproductive constant K. In problem 3 a similar conclusion is obtained for the half-life of a decaying population.

Returning to the biological problem, several comments are necessary:

1. We must avoid the trap of assuming that the model consisting of equation (1b) is accurate for all time since, realistically, the growth of bacterial populations in the presence of a limited nutrient supply always *decelerates* and eventually stops. This would tend to imply that K is not a constant but changes with time.

2. Suppose we knew the bacterial growth rate $K(t)$ as a function of time. Then a simple extension of our previous calculations leads to

$$N(t) = N(0) \exp\left(\int_0^t K \, ds \right). \tag{4}$$

(See problem 4.) For example, if K itself decreases at an exponential rate, the population eventually ceases to grow. (This assumption, known as the *Gompertz law*, will be discussed further in Section 6.1.)

3. Generally we have no knowledge of the exact time dependence of the reproductive rate. However, we may know that it depends directly or indirectly on the density of the population, as in previous density-dependent models explored in connection with discrete difference equations. This is particularly true in populations that are known to regulate their reproduction in response to population pressure. This phenomenon will be discussed in more detail in Chapter 6.

4. Another possibility is that the growth rate depends directly on the resources available to the population (e.g., on the level of nutrient remaining in the flask). Suppose we assume that the reproductive rate K is simply proportional to the nutrient concentration, C:

$$K(C) = \kappa C. \tag{5}$$

Further assume that α units of nutrient are consumed in producing one unit of population increment ($Y = 1/\alpha$ is then called the *yield*). This then implies that bacterial growth and nutrient consumption can be described by the following pair of equations:

$$\frac{dN}{dt} = K(C)N = \kappa CN, \tag{6a}$$

$$\frac{dC}{dt} = -\alpha \frac{dN}{dt} = -\alpha\kappa CN. \tag{6b}$$

This *system* of ordinary differential equations is solvable as follows:

$$\frac{dC}{dt} = -\alpha \frac{dN}{dt},$$

so

$$\int dC = -\alpha \int dN,$$

$$C(t) = -\alpha N(t) + C_0, \tag{7}$$

where $C_0 = C(0) + \alpha N(0)$ is a constant. If the population is initially very small, C_0 is approximately equal to the initial amount of nutrient in the flask. By substituting (7) into equation (6a) we obtain

$$\frac{dN}{dt} = \kappa(C_0 - \alpha N)N. \tag{8}$$

[*Comment:* Observe that the assumptions set forth here are thus mathematically equivalent to assuming that reproduction is density-dependent with

$$K(N) = \kappa(C_0 - \alpha N). \tag{9}$$

This type of growth law, on which we shall comment further, is known as *logistic growth;* it appears commonly in population dynamics models in the form $dN/dt = r(1 - N/B)N$.] The solution to equation (8), obtained in a straightforward way, is

$$N(t) = \frac{N_0 B}{N_0 + (B - N_0)e^{-rt}}, \tag{10}$$

where $N_0 = N(0)$ = initial population,

$r = (\kappa C_0)$ = intrinsic growth parameter,

$B = (C_0/\alpha)$ = carrying capacity.

(See problem 5 for a discussion of this equation and problem 13 for another approach to the problem.) A noteworthy feature of equation (10) is that for large values

of t the population approaches a level $N(\infty) = B = C_0/\alpha$, whereas at very low levels the population grows roughly exponentially at a rate $r = \kappa C_0$. It is interesting to compare this prediction with the experimental data given by Gause (1969) for the cultivation of the yeast *Schizosaccharomyces kephir*. (See Figure 4.1.)

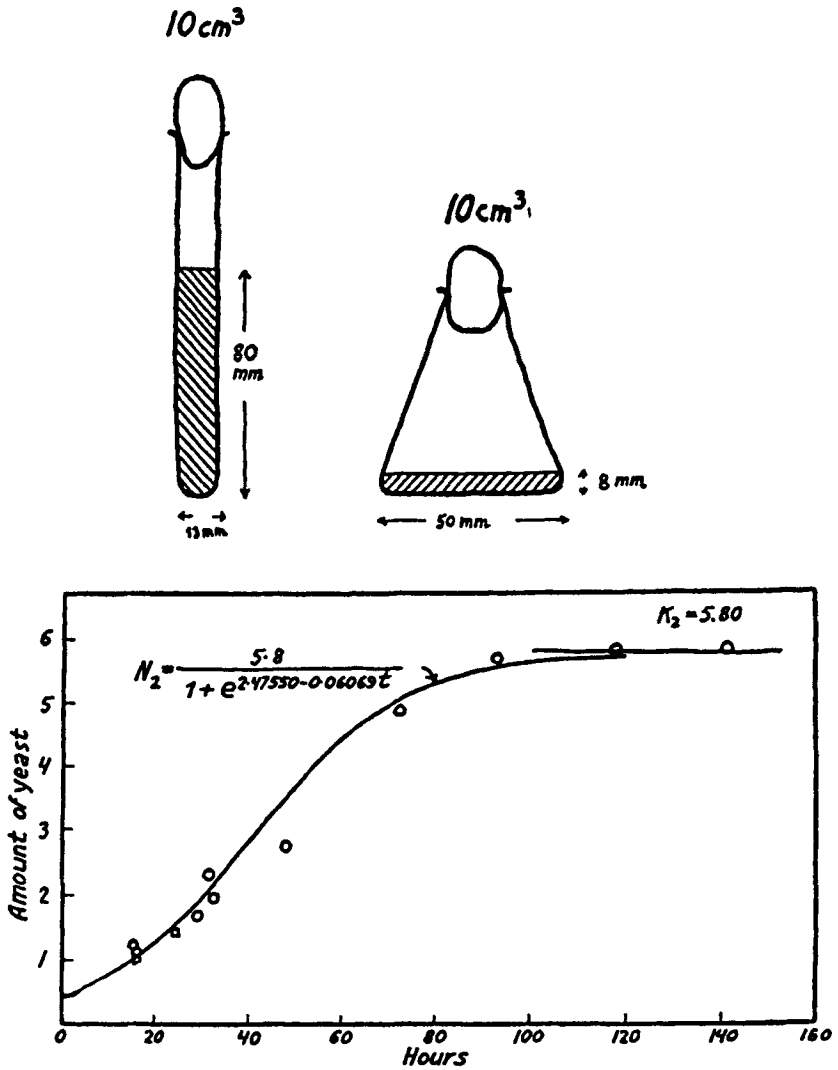


Figure 4.1 *Vessels for cultivating yeast or other microorganisms: (a) test tube, (b) Erlenmeyer flask. (c) Growth of the yeast* Schizosaccharomyces kephir *over a period of 160 h. The circles are experimental observations. The solid line is the curve*

$$N(t) = \frac{5.8}{1 + e^{2.47-0.0607t}}$$

[From Gause, G. F. (1969), Figs. 8 and 15. The Struggle for Existence, *Hafner, New York.* K_2 *in the figure is equivalent to* $B = C_0/\alpha$, *the carrying capacity in equations (8)–(10).*

In the following sections we consider a somewhat more advanced model for bacterial growth in a chemostat.

4.2 BACTERIAL GROWTH IN A CHEMOSTAT[2]

In experiments on the growth of microorganisms under various laboratory conditions, it is usually necessary to keep a stock supply of the strain being studied. Rather than use some dormant form, such as spores or cysts, which would require time to produce active cultures, a convenient alternative is to maintain a continuous culture from which actively growing cells can be harvested at any time.

To set up this sort of culture, it is necessary to devise a means of replenishing the supply of nutrients as they are being consumed and at the same time maintain some convenient population levels of the bacteria or other organism in the culture. This is usually done in a device called a *chemostat,* shown in Figure 4.2.

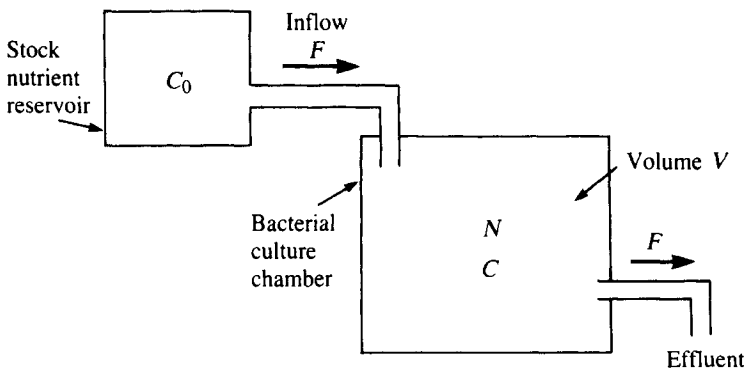


Figure 4.2 *The chemostat is a device for harvesting bacteria. Stock nutrient of concentration* C_0 *enters the bacterial culture chamber with inflow rate* F. *There is an equal rate of efflux, so that the volume* V *is constant.*

A stock solution of nutrient is pumped at some fixed rate into a growth chamber where the bacteria are being cultivated. An outflow valve allows the growth medium to leave at the same rate, so that the volume of the culture remains constant.

Our task is to design the system so that

1. The flow rate will not be so great that it causes the whole culture to be washed out and eliminated.

2. Portions of this material were adapted from the author's recollection of lectures given by L. A. Segel to students at the Weizmann Institute. It has also appeared recently in Segel (1984).

2. The nutrient replenishment is sufficiently rapid so that the culture continues to grow normally.

We are able to choose the appropriate stock nutrient concentration, the flow rate, and the size of the growth chamber.

In this example the purpose of the model will be twofold. First, the progression of steps culminating in precise mathematical statements will enhance our understanding of the chemostat. Second, the model itself will guide us in making appropriate choices for such parameters as flow rates, nutrient stock concentration, and so on.

4.3 FORMULATING A MODEL

A First Attempt

Since a number of factors must be considered in keeping track of the bacterial population and its food supply, we must take great care in assembling the equations. Our first step is to identify quantities that govern the chemostat operation. Such a list appears in Table 4.1, along with assigned symbols and dimensions.

Table 4.1 ***Chemostat Parameters***

Quantity	*Symbol*	*Dimensions*
Nutrient concentration in growth chamber	C	Mass/volume
Nutrient concentration in reservoir	C_0	Mass/volume
Bacterial population density	N	Number/volume
Yield constant	$Y = 1/\alpha$	(See problem 6)
Volume of growth chamber	V	Volume
Intake/output flow rate	F	Volume/time

We also keep track of assumptions made in the model; here are a few to begin with:

1. The culture chamber is kept well stirred, and there are no spatial variations in concentrations of nutrient or bacteria. (We can describe the events using ordinary differential equations with time as the only independent variable.)

At this point we write a preliminary equation for the bacterial population density N. From Fig. 4.2 it can be seen that the way N changes inside the culture chamber depends on the balance between the number of bacteria formed as the culture reproduces and the number that flow out of the tank. A first attempt at writing this in an equation might be,

$$\frac{dN}{dt} = KN - FN \qquad (11)$$

rate of change of bacteria = reproduction − outflow

where K is the reproduction rate of the bacteria, as before.

To go further, more assumptions must be made; typically we could simplify the problem by supposing that

2. Although the nutrient medium may contain a number of components, we can focus attention on a single growth-limiting nutrient whose concentration will determine the rate of growth of the culture.
3. The growth rate of the population depends on nutrient availability, so that $K = K(C)$. This assumption will be made more specific later, when we choose a more realistic version of this concentration dependence than that of simple proportionality.

Next we write an equation for changes in C, the nutrient level in the growth chamber. Here again there are several influences tending to increase or decrease concentration: inflow of stock supply and depletion by bacteria, as well as outflow of nutrients in the effluent. Let us assume that

4. Nutrient depletion occurs continuously as a result of reproduction, so that the rule we specified for culture growth and that for nutrient depletion are essentially going to be the same as before. Here α has the same meaning as in equation (6b).

Our attempt to write the equation for rate of change of nutrient might result in the following:

(*wrong*):
$$\frac{dC}{dt} = -\alpha K(C)N - FC + FC_0 \qquad (12)$$

minus for depletion during growth; minus for depletion due to outflow; plus due to replenishment from stock solution

Corrected Version

Equations (11) and (12) are not quite correct, so we now have to uncover mistakes made in writing them. A convenient way of achieving this is by comparing the *dimensions* of terms appearing in an equation. These have to match, clearly, since it would be meaningless to equate quantities not measured in similar units. (For example 10 msec^{-1} can never equal 10 lb.)

By writing the exact dimensions of each term in the equations, we get

(*wrong*): $$\frac{dN}{dt} = \underbrace{K(C)N} - FN$$

Dimensions: $$\frac{\text{number}}{\text{volume} \times \text{time}} = \frac{1}{\text{time}}\,\frac{\text{number}}{\text{volume}} - \frac{\text{volume}}{\text{time}}\,\frac{\text{number}}{\text{volume}}$$

From this we see that

1. $K(C)$, the growth rate, must have dimensions of 1/time.
2. The second term on the RHS is incorrect because it has an extra volume dimension that cannot be reconciled with the rest of the equation.

By considering dimensions, we have uncovered an inconsistency in the term FN of equation (11). A way of correcting this problem would be to divide FN by a quantity bearing dimensions of volume. Since the only such parameter available is V, we are led to consider FN/V as the appropriate correction. Notice that FN is the *number* of bacteria that leave per minute, and FN/V is thus the effective *density* of bacteria that leave per minute.

A similar analysis applied to equation (12) reveals that the terms FC and FC_0 should be divided by V (see problem 6). After correcting by the same procedure, we arrive at the following two corrected versions of equations (11) and (12):

$$\frac{dN}{dt} = K(C)N - \frac{FN}{V}, \tag{13a}$$

$$\frac{dC}{dt} = -\alpha K(C)N - \frac{FC}{V} + \frac{FC_0}{V}, \tag{13b}$$

As we have now seen, the analysis of dimensions is often helpful in detecting errors in this stage of modeling. However, the fact that an equation is dimensionally consistent does not always imply that it is correct from physical principles. In problems such as the chemostat, where substances are being transported from one compartment to another, a good starting point for writing an equation is the physical principle that *mass is conserved.* An equivalent conservation statement is that *the number of particles is conserved.* Thus, noting that

NV = number of bacteria in the chamber,

CV = mass nutrient in the chamber,

we obtain a mass balance of the two species by writing

$$\frac{d(NV)}{dt} = K(C)NV - FN, \tag{14a}$$

$$\frac{d(CV)}{dt} = -\alpha K(C)NV - FC + FC_0, \tag{14b}$$

(problem 9). Division by the constant V then leads to the correct set of equations (13a, b).

For further practice at formulating differential-equation models from word problems an excellent source is Henderson West (1983) and other references in the same volume.

4.4 A SATURATING NUTRIENT CONSUMPTION RATE

To add a degree of realism to the model we could at this point incorporate the fact that bacterial growth rates may depend on nutrient availability. For low nutrient abundance, growth rate typically increases with increasing nutrient concentrations. Eventually, when an excess of nutrient is available, its uptake rate and the resultant reproductive rate of the organisms does not continue to increase indefinitely. An appropriate assumption would thus be one that incorporates the effect of a *saturating* dependence. That is, we will assume that

5. The rate of growth increases with nutrient availability only up to some limiting value. (The individual bacterium can only consume nutrient and reproduce at some limited rate.)

One type of mechanism that incorporates this effect is Michaelis-Menten kinetics,

$$K(C) = \frac{K_{\max} C}{K_n + C}, \tag{15}$$

shown in Figure 4.3. Chapter 7 will give a detailed discussion of the molecular events underlying saturating kinetics. For now, it will suffice to note that $K_{\max}$ represents an upper bound for $K(C)$ and that for $C = K_n$, $K(C) = \frac{1}{2}K_{\max}$.

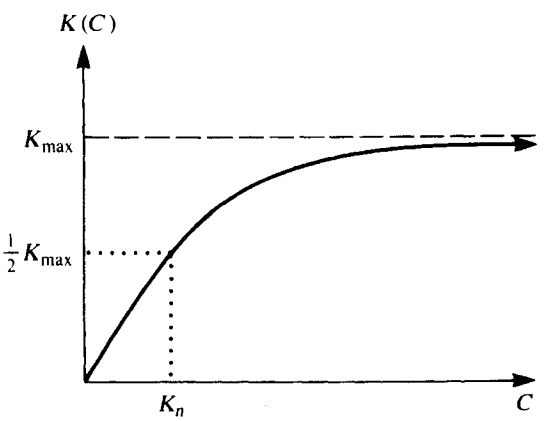


Figure 4.3 *Michaelis-Menten kinetics: Bacterial growth rate and nutrient consumption* K(C) *is assumed to be a saturating function of nutrient concentration. See equation (15).*

Our model equations can now be summarized as follows:

$$\frac{dN}{dt} = \left(\frac{K_{\max}C}{K_n + C}\right)N - \frac{FN}{V} \tag{16a}$$

$$\frac{dC}{dt} = -\alpha\left(\frac{K_{\max}C}{K_n + C}\right)N - \frac{FC}{V} + \frac{FC_0}{V}. \tag{16b}$$

In understanding these statements we draw a distinction between quantities that are variables, such as N and C and those that are parameters. There is little we can do to control the former *directly*, as they undergo changes in response to their inherent dynamics. However, we may be able to select values of certain parameters (such as F, C_0, and V) that will influence the process. (Other parameters such as $K_{\max}$ and K_n depend on the types of bacteria and nutrient medium selected in the experiment.)

It is of interest to determine what happens as certain combinations of parameters are varied over a range of values. Conceivably, an increase in some quantities could just compensate for a decrease in others so that, qualitatively, the system as a whole remains the same. Thus, while a total of six parameters appear in equations (16a,b) the chemostat may indeed have fewer than six *degrees of freedom*. This idea can be made more precise through further *dimensional analysis* of the equations in order to rewrite the model in terms of dimensionless quantities.

4.5 DIMENSIONAL ANALYSIS OF THE EQUATIONS

As shown in Table 4.1, quantities measured in an experiment such as that of the chemostat are specified in terms of certain conventional units. These are, to a great extent, arbitrary. For example a bacterial density of 10^5 cells per liter can be written in any one of the following equivalent ways:

$$\begin{aligned} N &= 10^5 \text{ cells/liter}, \\ &= 1 \text{ (unit of } 10^5 \text{ cells)/liter}, \\ &= 100 \text{ cells/milliliter}, \\ &= N^*\hat{N}. \end{aligned}$$

Here we have distinctly separated the measured quantity into two parts: a number N^*, which has no dimensions, and a quantity $\hat{N}$, which represents the units of measurement and carries the physical dimensions. The values 10^5, 1, 100, and N^* all refer to the same observation but in terms of different scales. As time evolves, N and N^* might change, but $\hat{N}$ is a constant, reflecting the fact that the scale of measurement does not change.

All of the original variables can be expressed similarly, as follows:

$$\begin{array}{lcll} \text{measured quantity} & = & \text{scalar multiple} & \times \quad \text{unit carrying dimensions,} \\ N & = & N^* & \times \quad \hat{N}, \\ C & = & C^* & \times \quad \hat{C}, \\ t & = & t^* & \times \quad \tau. \end{array}$$

We shall see presently that advantage is gained by expressing the equations in terms of such *dimensionless quantities* as N^*, C^*, and t^*. To do so, we first substitute the expressions $N^*\hat{N}$, $C^*\hat{C}$, $t^*\tau$ for N, C, and t respectively in equations (16a,b) and then exploit the fact that $\hat{N}$, $\hat{C}$, and τ are time-independent constants. We obtain

$$\frac{d(N^*\hat{N})}{d(t^*\tau)} = \left(\frac{K_{\max}C^*\hat{C}}{K_n + C^*\hat{C}}\right)N^*\hat{N} - \frac{F}{V}(N^*\hat{N}), \tag{17a}$$

$$\frac{d(C^*\hat{C})}{d(t^*\tau)} = -\alpha\left(\frac{K_{\max}C^*\hat{C}}{K_n + C^*\hat{C}}\right)N^*\hat{N} - \frac{FC^*\hat{C}}{V} + \frac{FC_0}{V}. \tag{17b}$$

Now multiply both sides by τ, divide by $\hat{N}$ or $\hat{C}$, and group constant terms together. The result is

$$\frac{dN^*}{dt^*} = \tau K_{\max}\left(\frac{C^*}{K_n/\hat{C} + C^*}\right)N^* - \frac{\tau F}{V}N^*, \tag{18a}$$

$$\frac{dC^*}{dt^*} = \left(\frac{-\alpha\tau K_{\max}\hat{N}}{\hat{C}}\right)\left(\frac{C^*}{K_n/\hat{C} + C^*}\right)N^* - \frac{\tau F}{V}C^* + \frac{\tau FC_0}{V\hat{C}}. \tag{18b}$$

By making judicious choices for the measuring scales $\hat{N}$, τ, and $\hat{C}$, which are as yet unspecified, we will be able to make the equations look much simpler and contain fewer parameters. Equations (18a,b) suggest a number of scales that are inherent to the chemostat problem. Notice what happens when we choose

$$\tau = \frac{V}{F}, \qquad \hat{C} = K_n, \qquad \hat{N} = \frac{K_n}{\alpha\tau K_{\max}}.$$

The equations now can be written in the following form, in which we have dropped the stars for notational convenience.

$$\frac{dN}{dt} = \alpha_1\left(\frac{C}{1 + C}\right)N - N, \tag{19a}$$

$$\frac{dC}{dt} = -\left(\frac{C}{1 + C}\right)N - C + \alpha_2. \tag{19b}$$

The equations contain two dimensionless parameters, α_1 and α_2, in place of the original six (K_n, $K_{\max}$, F, V, C_0, and α). These are related by the following equations:

$$\alpha_1 = (\tau K_{\max}) = \frac{VK_{\max}}{F},$$

$$\alpha_2 = \frac{\tau FC_0}{V\hat{C}} = \frac{C_0}{K_n}.$$

In problem 8 we discuss the physical meaning of the scales τ, $\hat{C}$, and $\hat{N}$ and of the new dimensionless quantities that appear here.

We have arrived at a dimensionless form of the chemostat model, given by equations (19a,b). Not only are these equations simpler; they are more revealing. By the above we see that only two parameters affect the chemostat. No other choice of τ, $\hat{C}$, and $\hat{N}$ yields less than two parameters (see problem 10). Thus the chemostat has two degrees of freedom.

Equations (19a,b) are nonlinear because of the term $NC/(1 + C)$. Generally this means that there is little hope of finding explicit analytic solutions for $N(t)$ and $C(t)$. However, we can still explore the nature of special classes of solutions, just as we did in the nonlinear difference-equation models. Since we are interested in maintaining a continuous culture in which bacteria and nutrients are present at some fixed densities, we will next determine whether equations (19a,b) admit a steady-state solution of this type.

4.6 STEADY-STATE SOLUTIONS

A steady state is a situation in which the system does not appear to undergo any change. To be more precise, the values of *state variables,* such as bacterial density and nutrient concentration within the chemostat, would be constant at steady state even though individual nutrient particles continue to enter, leave, or be consumed. Setting derivatives equal to zero,

$$\frac{dN}{dt} = 0, \tag{20a}$$

$$\frac{dC}{dt} = 0, \tag{20b}$$

we observe that the quantities on the RHS of equations (19a,b) must be zero at steady state:

$$F(\bar{N}, \bar{C}) = \alpha_1\left(\frac{\bar{C}}{1 + \bar{C}}\right)\bar{N} - \bar{N} = 0, \tag{21a}$$

$$G(\bar{N}, \bar{C}) = -\left(\frac{\bar{C}}{1 + \bar{C}}\right)\bar{N} - \bar{C} + \alpha_2 = 0. \tag{21b}$$

This condition gives two algebraic equations that are readily solved explicitly for $\bar{N}$ and $\bar{C}$.

From (21a) we see that

$$\text{either } \bar{N} = 0 \tag{22a}$$

$$\text{or } \frac{\bar{C}}{1 + \bar{C}} = \frac{1}{\alpha_1}. \tag{22b}$$

After some simplification, (22b) becomes $\bar{C} = 1/(\alpha_1 - 1)$. From equation (21b), if $\bar{N} = 0$ we get $\bar{C} = \alpha_2$; on the other hand, if $\bar{N} \neq 0$, we get

$$\left(\frac{\bar{C}}{1 + \bar{C}}\right)\bar{N} = (\alpha_2 - \bar{C}). \tag{23}$$

Using (22b), we get

$$\bar{N} = \frac{1 + \bar{C}}{\bar{C}}(\alpha_2 - \bar{C}) = \alpha_1(\alpha_2 - \bar{C}). \tag{24}$$

Combining the information in equations (23) and (24) leads to the conclusion that there are two steady states:

$$(\bar{N}_1, \bar{C}_1) = \left(\alpha_1\left(\alpha_2 - \frac{1}{\alpha_1 - 1}\right), \frac{1}{\alpha_1 - 1}\right). \tag{25a}$$

$$(\bar{N}_2, \bar{C}_2) = (0, \alpha_2). \tag{25b}$$

The second solution, $(\bar{N}_2, \bar{C}_2)$, represents a situation that is not of interest to the experimentalists: no bacteria are left, and the nutrient is at the same concentration as the stock solution (remember the meaning of α_2 and the concentration scale to which it refers). The first solution (25a) looks more inspiring, but note that it does not always exist biologically. This depends on the magnitudes of the terms α_1 and α_2. Clearly, if $\alpha_1 < 1$, we get negative values. Since population densities and concentrations must always be positive, negative values would be meaningless in the biological context. The conclusion is that α_1 and α_2 must be such that $\alpha_1 > 1$ and $\alpha_2 > 1/(\alpha_1 - 1)$. In problem 8 we reach certain conclusions about how to adjust the original parameters of the chemostat to satisfy these constraints.

4.7 STABILITY AND LINEARIZATION

Thus far we have arrived at two steady-state solutions that satisfy equations (19a, b). In realistic situations there are always small random disturbances. Thus it is of interest to determine whether such deviations from steady state will lead to drastic changes or will be damped out.

By posing these questions we return once more to stability, a concept that was intimately explored in the context of difference-equation models. In this section we retrace the steps that were carried out in Section 2.7 to reach essentially identical conclusions, namely that, *close to the steady state, the problem can be approximated by a linear one.*

Let us look at a more general setting and take our system of ordinary differential equations to be

$$\frac{dX}{dt} = F(X, Y), \tag{26a}$$

$$\frac{dY}{dt} = G(X, Y), \tag{26b}$$

where F and G are nonlinear functions. We assume that $\bar{X}$ and $\bar{Y}$ are steady-state solutions, i.e., they satisfy

$$F(\bar{X}, \bar{Y}) = G(\bar{X}, \bar{Y}) = 0. \tag{27}$$

Now consider the close-to-steady-state solutions

$$X(t) = \bar{X} + x(t), \tag{28a}$$

$$Y(t) = \bar{Y} + y(t). \tag{28b}$$

Frequently these are called *perturbations* of the steady state. Substituting, we arrive at

$$\frac{d}{dt}(\bar{X} + x) = F(\bar{X} + x, \bar{Y} + y), \tag{29a}$$

$$\frac{d}{dt}(\bar{Y} + y) = G(\bar{X} + x, \bar{Y} + y). \tag{29b}$$

On the left-hand side (LHS) we expand the derivatives and notice that by definition $d\bar{X}/dt = 0$ and $d\bar{Y}/dt = 0$. On the right-hand side (RHS) we now expand F and G in a Taylor series about the point $(\bar{X}, \bar{Y})$, remembering that these are functions of two variables (see Chapter 2 for a more detailed discussion). The result is

$$\frac{dx}{dt} = F(\bar{X}, \bar{Y}) + F_x(\bar{X}, \bar{Y})x + F_y(\bar{X}, \bar{Y})y + \text{terms of order } x^2, y^2, xy, \text{ and higher,} \tag{30a}$$

$$\frac{dy}{dt} = G(\bar{X}, \bar{Y}) + G_x(\bar{X}, \bar{Y})x + G_y(\bar{X}, \bar{Y})y + \text{terms of order } x^2, y^2, xy, \text{ and higher.} \tag{30b}$$

where $F_x(\bar{X}, \bar{Y})$ is $\partial F/\partial x$ evaluated at $(\bar{X}, \bar{Y})$, and similarly for F_y, G_x, G_y and other terms.

Again by definition, $F(\bar{X}, \bar{Y}) = 0 = G(\bar{X}, \bar{Y})$, so we are left with

$$\frac{dx}{dt} = a_{11}x + a_{12}y, \tag{31a}$$

$$\frac{dy}{dt} = a_{21}x + a_{22}y, \tag{31b}$$

where the matrix of coefficients

$$\mathbf{A} = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} = \begin{pmatrix} F_x & F_y \\ G_x & G_y \end{pmatrix}_{(\bar{X}, \bar{Y})}. \tag{32}$$

is the Jacobian of the system of equations (26a,b). See Section 2.7 for definition.

To ultimately determine the question of stability, we are thus led to the question of how solutions to equation (31a,b) behave. We shall spend some time on this topic in the next sections. The methods and conclusions bear a strong relation to those we use for systems of difference equations.

4.8 LINEAR ORDINARY DIFFERENTIAL EQUATIONS: A BRIEF REVIEW

In this section we rapidly survey the minimal mathematical background required for analysis of ordinary differential equations (ODEs) such as those encountered in this chapter. For a broader review this section could be supplemented with material from any standard text on ODEs. (See references for suggested sources.)

Terminology

Equivalent representations of the first derivative of a function $y = f(t)$ are dy/dt, y', and $\dot{y}$; also, $d^n y/dt^n = y^{(n)}$ is the nth derivative. An *ordinary differential equation* is any statement linking the values of a function to its derivatives and to a single independent variable; for example,

$$F(t, y, y', y'', \ldots, y^{(n)}) = 0.$$

The *order* of the equation is n, the degree of the highest derivative that appears in the equation. [See equation (33a) for an example of a *first-order* equation and (34) for an example of a *second-order* equation.]

The solution of an ODE is a function $y = f(t)$ that satisfies the equation for every value of the independent variable.

Linear equations have the special form

$$a_0 y^{(n)} + a_1 y^{(n-1)} + \cdots + a_{n-2} y'' + a_{n-1} y' + a_n y = g(t),$$

where no multiples or other nonlinearities in y or its derivatives occur. The coefficients $a_0, a_1, \ldots, a_n$ may be functions of the independent variable t. The case of *constant coefficients* (where $a_0, \ldots, a_n$ are all constants) is of particular importance to stability analysis and can in principle be solved completely.

The equation is called *homogeneous* when the term $g(t) = 0$.

Examples

1. A *second-order, nonhomogeneous, nonlinear* ODE:

$$\underset{\text{order} = 2}{\frac{d^2x}{dt^2}} + \underset{\substack{\text{nonlinear}\\ \text{term}}}{2x\frac{dx}{dt}} + \underset{\substack{\text{nonlinear}\\ \text{term}}}{x^2} = \underset{\substack{\text{term independent}\\ \text{of } x(t)\\ \text{(nonhomogeneous)}}}{\sin t.}$$

Independent variable = t; unknown function = $x(t)$.

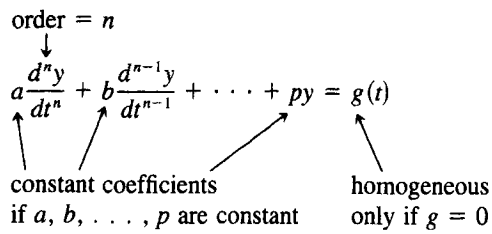
2. A *third-order, linear, homogeneous* ODE with *nonconstant coefficients:*

$$\underset{\text{order} = 3}{\frac{d^3x}{dt^3}} + \underset{\substack{\text{nonconstant}\\ \text{coefficient of}\\ dx/dt}}{2t\frac{dx}{dt}} + \underset{\substack{\text{nonconstant}\\ \text{coefficient}\\ \text{of } x}}{t^2x} = \underset{\substack{\text{homogeneous}\\ \text{equation}}}{0}$$

(terms linear in x and dx/dt)

Independent variable = t; unknown function = $x(t)$.

3. An *nth order, linear, constant-coefficient* ODE:



Independent variable = t; unknown function = $y(t)$.

Now we consider only the case of *linear, homogeneous, constant-coefficient* ordinary differential equations. (See box for an explanation of terminology.)

First-Order ODEs

The simplest first-order ODE and its solution are

$$\frac{dx}{dt} = Kx, \tag{33a}$$

$$x(t) = x_0 e^{Kt}. \tag{33b}$$

(See Section 4.1.) The constant x_0 is the initial value of x at time $t = 0$. Below we see that the exponential function is useful in solving higher-order equations.

Second-Order ODEs

Consider the ODE

$$a\frac{d^2x}{dt^2} + b\frac{dx}{dt} + c = 0. \tag{34}$$

(The second derivative implies that the order is 2; a, b, and c are assumed to be constants.) Following a strategy similar to that of Section 1.3, we proceed with the assumption that solutions to equation (33) might work for equation (34). Thus, consider assuming that

$$x(t) = e^{\lambda t} \tag{35}$$

(where λ is a constant) solves equation (34). Then

$$x'(t) = \lambda e^{\lambda t}, \qquad x''(t) = \lambda^2 e^{\lambda t}$$

so by substitution and cancellation of a common factor, we get

$$a\lambda^2 e^{\lambda t} + b\lambda e^{\lambda t} + ce^{\lambda t} = 0,$$

$$a\lambda^2 + b\lambda + c = 0. \tag{36}$$

The latter characteristic equation has two roots called the eigenvalues:

$$\lambda_{1,2} = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \tag{37}$$

so the two solutions to equation (34) are

$$x_1(t) = e^{\lambda_1 t}, \qquad x_2(t) = e^{\lambda_2 t}. \tag{38}$$

By the principle of linear superposition (see Chapter 1), if x_1 and x_2 are two solutions to a linear equation such as (34), then any linear combination is also a solution. The general solution is thus

$$x(t) = c_1 e^{\lambda_1 t} + c_2 e^{\lambda_2 t}, \tag{39}$$

where c_1 and c_2 are arbitrary constants determined from other information such as initial conditions. (See problems 17 and 18.)

Exceptional cases occur when

$$\lambda_1 = \lambda_2 = \lambda \qquad \text{(repeated eigenvalues)},$$
$$\lambda = a \pm bi \qquad \text{(complex conjugate eigenvalues)}.$$

The form of the solution is then amended as follows:

1. If $\lambda_1 = \lambda_2 = \lambda$, then

$$x(t) = c_1 e^{\lambda t} + c_2 t e^{\lambda t}.$$

(See problem 19.)

2. If $\lambda_{1,2} = a \pm bi$, then

$$x(t) = e^{at}\{c_1 \cos bt + c_2 \sin bt\}.$$

(See problem 20.)

(See problems or any standard text on differential equations.)

A System of Two First-Order Equations (Elimination Method)

Consider

$$\frac{dx}{dt} = a_{11}x + a_{12}y, \tag{40a}$$

$$\frac{dy}{dt} = a_{21}x + a_{22}y. \tag{40b}$$

This can be reduced by a procedure of elimination (see problem 21) to a single second-order equation in $x(t)$:

$$\frac{d^2x}{dt^2} - \beta\frac{dx}{dt} + \gamma x = 0, \tag{41}$$

where

$$\beta = a_{11} + a_{22},$$
$$\gamma = a_{11}a_{22} - a_{12}a_{21}.$$

By the procedure given in the subsection "Second-Order ODEs" we then find the general solution for $x(t)$ to be

$$x(t) = c_1 e^{\lambda_1 t} + c_2 e^{\lambda_2 t}, \tag{42a}$$

where

$$\lambda_{1,2} = \frac{\beta \pm \sqrt{\beta^2 - 4\gamma}}{2}. \tag{42b}$$

The quantity $\delta = \beta^2 - 4\gamma$ is called the *discriminant*. (When δ is negative, eigenvalues are complex.) $y(t)$ can be found by solving (40a); see problem 21b. (Again, in the cases of complex or multiple eigenvalues, the form of the general solution must be amended as before.)

A System of Two First-Order Equations (Eigenvalue-Eigenvector Method)

We write the system of equations in vector notation as

$$\frac{d\mathbf{x}}{dt} = \mathbf{A}\mathbf{x}, \tag{43a}$$

where

$$\mathbf{x} = \begin{pmatrix} x \\ y \end{pmatrix}, \tag{43b}$$

$$\mathbf{A} = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}, \tag{43c}$$

for a 2×2 system. (More generally, $\mathbf{A}$ is a $n \times n$ matrix, and $\mathbf{x}$ is an n-vector when we are dealing with a system of n differential equations in n variables.) The notes matrix multiplication, and $\dfrac{d\mathbf{x}}{dt}$ stands for a vector whose entries are dx/dt, dy/dt.

In the spirit of the example given in equations (33a, b) we shall assume solutions of the form

$$\mathbf{x}(t) = \mathbf{v}e^{\lambda t}. \tag{44}$$

Now $\mathbf{v}$ must be a vector whose entries are independent of time. Using this idea, we substitute (44) into (43a):

$$\frac{d\mathbf{x}}{dt} = \mathbf{v}\frac{d}{dt}e^{\lambda t} = \lambda \mathbf{v}e^{\lambda t} = \mathbf{A}\mathbf{v}e^{\lambda t}.$$

The last equality has to be satisfied if (44) is to be a solution of system (43). Cancelling the common factor $e^{\lambda t}$ results in

$$\mathbf{Av} = \lambda\mathbf{v}. \tag{45a}$$

Note: $\mathbf{v}$ cannot be "cancelled" since $\mathbf{Av}$ stands for matrix multiplication; however, we can rewrite (45a) as

$$\mathbf{Av} - \lambda\mathbf{Iv} = 0, \tag{45b}$$

where $\mathbf{I}$ is the identity matrix ($\mathbf{Iv} = \mathbf{vI} = \mathbf{v}$). Now $\lambda\mathbf{I}$ is also a matrix, namely

$$\begin{pmatrix} \lambda & & & & 0 \\ & \lambda & & & \\ & & \lambda & & \\ 0 & & & \ddots & \\ & & & & \lambda \end{pmatrix}$$

Thus equation (45b) can be written as

$$(\mathbf{A} - \lambda\mathbf{I})\mathbf{v} = 0. \tag{45c}$$

Readers familiar with linear algebra will recognize (45c) as an equation that is satisfied with eigenvalues λ and eigenvectors $\mathbf{v}$ of the matrix $\mathbf{A}$. For other than the trivial solution $\mathbf{v} = 0$, we must have

$$\det(\mathbf{A} - \lambda\mathbf{I}) = 0. \tag{46}$$

When λ satisfies this equation, vectors which satisfy (45c) can be found. These vectors will be nonunique; that is, they will depend on an arbitrary constant because the equations making up the algebraic system (45c) are redundant when (46) is true.

As in the subsection "First-Order ODEs" the eigenvalues of a 2×2 system will always be

$$\lambda_{1,2} = \frac{\beta \pm \sqrt{\delta}}{2},$$

where

$$\beta = \text{trace } \mathbf{A} = a_{11} + a_{22},$$
$$\gamma = \det \mathbf{A} = a_{11}a_{22} - a_{12}a_{21},$$
$$\delta = \text{disc } \mathbf{A} = \beta^2 - 4\gamma.$$

The eigenvectors will be

$$\begin{pmatrix} 1 \\ \mathbf{v}_i = \dfrac{\lambda_i - a_{11}}{a_{12}} \end{pmatrix}, \tag{47}$$

for $a_{12} \neq 0$. (See the examples 1 and 2 in the boxes at the end of this section.) Once the eigenvectors $\mathbf{v}_1$ and $\mathbf{v}_2$ are found, the general solution (provided $\lambda_1 \neq \lambda_2$ and both are real) is given by

$$\mathbf{x}(t) = c_1\mathbf{v}_1 e^{\lambda_1 t} + c_2\mathbf{v}_2 e^{\lambda_2 t}. \tag{48}$$

Recall that this is a shorthand version of the following:

$$x_1(t) = c_1 v_{11} e^{\lambda_1 t} + c_2 v_{21} e^{\lambda_2 t}, \tag{49a}$$
$$x_2(t) = c_1 v_{12} e^{\lambda_1 t} + c_2 v_{22} e^{\lambda_2 t}. \tag{49b}$$

Special cases

1. $\lambda_1 = \lambda_2 = \lambda$ (repeated eigenvalues; one eigenvector **v**):
The form of the general solution must be amended (to allow for two distinct linearly independent parts). See any text on ODEs for details of the method.

2. $\lambda_{1,2} = r \pm ci$ (complex eigenvalues): *(50a)*
This case occurs when disc $\mathbf{A} = \beta^2 - 4\gamma < 0$; then $r = \beta/2$ = real part of λ, $c = \sqrt{\delta}/2$ = imaginary part of λ, and $i = \sqrt{-1}$. Note that complex eigenvalues always come in conjugate pairs.

Complex eigenvalues always have corresponding complex conjugate eigenvectors

$$\mathbf{v}_{1,2} = \mathbf{a} \pm \mathbf{b}i, \tag{50b}$$

where **a** and **b** are two real constant vectors. The general solution can be expressed in the complex notation

$$\mathbf{x}(t) = c_1(\mathbf{a} + \mathbf{b}i)e^{(r+ci)t} + c_2(\mathbf{a} - \mathbf{b}i)e^{(r-ci)t}. \tag{50c}$$

A real-valued solution can also be constructed by using the identity

$$e^{(r+ci)t} = e^{rt}(\cos ct + i \sin ct). \tag{51}$$

Define

$$\begin{aligned} \mathbf{u}(t) &= e^{rt}(\mathbf{a} \cos ct - \mathbf{b} \sin ct), \\ \mathbf{w}(t) &= e^{rt}(\mathbf{a} \sin ct - \mathbf{b} \cos ct), \end{aligned} \tag{52}$$

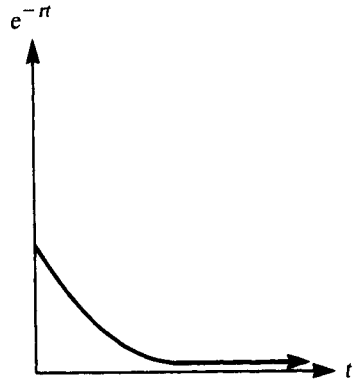
It can be shown that each of these parts is itself a real-valued solution, so that the general solution in the case of complex eigenvalues takes the form

$$\mathbf{x}(t) = c_1\mathbf{u}(t) + c_2\mathbf{w}(t). \tag{53}$$

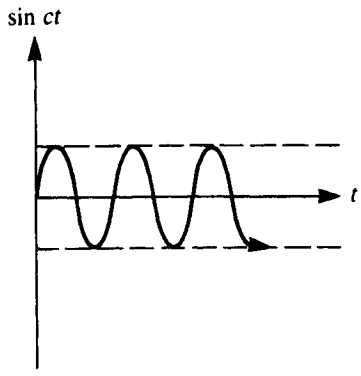
As seen in the previous analysis, complex eigenvalues lead to oscillatory solutions. The imaginary part c governs the frequency of oscillation. The real part r governs the amplitude.

Summary: Solutions of a second-order linear equation such as (34) or (41), or, of a system of first-order equations such as (43), are made up of sums of exponentials or else products of oscillatory functions (sines and cosines) with exponentials. Figure 4.4 illustrates how the three basic ingredients contribute to the character of the solution. In the case of real eigenvalues, if one or both eigenvalues are positive, the solution grows with time. Only if both are negative, as in case 1 does the solution decrease. Furthermore, if complex eigenvalues are found, i.e., if $\lambda = r \pm ci$, their real part r determines whether the amplitude of the oscillation increases ($r > 0$), decreases ($r < 0$), or remains constant ($r = 0$). The complex part c determines the frequency of oscillation.

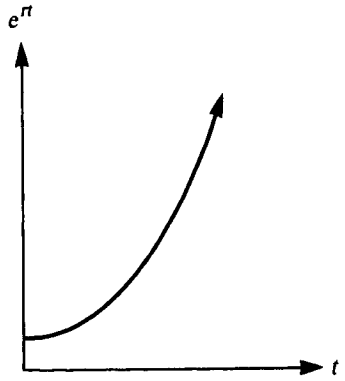
Figure 4.4 *The three basic ingredients of a solution to a linear system for* $r > 0$ *are (a) a decreasing exponential function* e^{-rt}*, (b) an oscillatory function such as* sin t *or* cos t*, and (c) an increasing exponential function* e^{rt}*. When eigenvalues are real, the linear combination* $x(t) = c_1e^{\lambda_1 t} + c_2e^{\lambda_2 t}$ *is a decreasing function only when both* λ_1 *and* λ_2 *are negative (case 1). When eigenvalues are complex, the solution is oscillatory with either increasing or decreasing amplitude. (opposite page)*



(a)

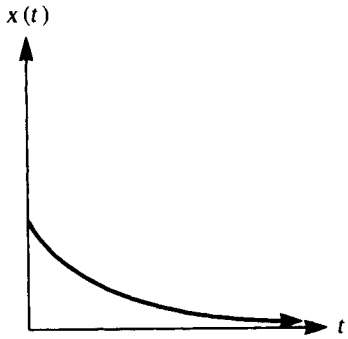


(b)

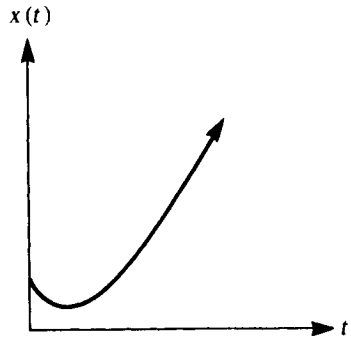


(c)

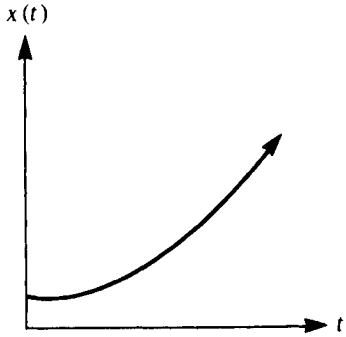
$$x(t) = c_1 e^{\lambda_1 t} + c_2 e^{\lambda_2 t}$$



Case 1: two negative real eigenvalues

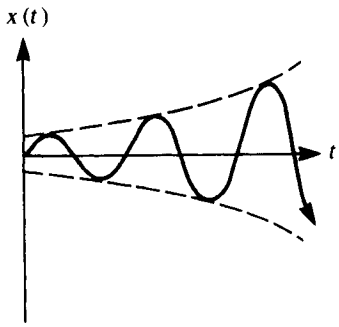


Case 2: one positive and one negative eigenvalue

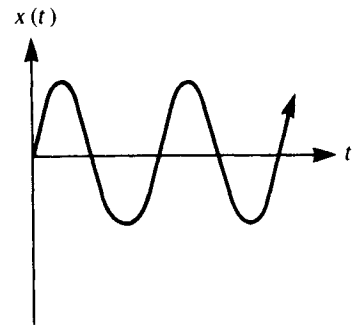


Case 3: two positive real eigenvalues

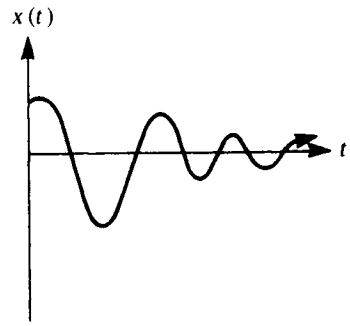
$$\lambda = r \pm ci$$
$$x(t) = e^{rt}(c_1 \cos ct + c_2 \sin ct)$$



Case 4: complex conjugate eigenvalues, positive real part



Case 5: zero real part



Case 6: negative real part

Remarks

1. From equations (33a, b) it is apparent that a solution to a first-order differential equation involves one arbitrary constant (e.g., z_0) whose value depends on other information, such as the initial conditions of the problem. Similarly, we see that a second-order equation, such as equation (34), will have a general solution containing two arbitrary constants [for example, c_1 and c_2 in equation (39)]. These would again be determined from initial conditions. (See problem 18.)
2. Given a linear equation of nth order,

$$a_0\frac{d^n x}{dt^n} + a_1\frac{d^{n-1}x}{dt^{n-1}} + \cdots + a_n x = 0,$$

the procedure outlined in equations (35) and (36) would lead to a characteristic equation

$$a_0\lambda^n + a_1\lambda^{n-1} + \cdots + a_n = 0,$$

that is, an nth-order polynomial. Generally it is not an easy matter to find the roots of this polynomial (and thus determine what the eigenvalues are) when $n > 2$. We can at best hope to find out something about these eigenvalues. (See Section 6.4 for details.)
3. Nonlinear equations or equations with nonconstant coefficients are not generally solved in a straightforward way, unless they are of special form. Indeed, we cannot always be assured that a solution exists. The mathematical theory that deals with the question of existence and uniqueness of solutions to ODEs can be found in most advanced texts on ordinary differential equations.

Example 1

Solve the following system of equations:

$$\frac{dx_1}{dt} = 3x_1 - x_2, \qquad \frac{dx_2}{dt} = 6x_1 - 4x_2. \tag{54}$$

Solution

Rewrite the equations as

$$\frac{d\mathbf{x}}{dt} = \mathbf{A}\mathbf{x},$$

$$\text{where} \quad \mathbf{x} = \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}, \quad \mathbf{A} = \begin{pmatrix} 3 & -1 \\ 6 & -4 \end{pmatrix}. \tag{55}$$

To find solutions $\mathbf{x}(t) = \mathbf{v}e^{\lambda t}$, we must find the eigenvalues λ and eigenvectors $\mathbf{v}$ of the matrix $\mathbf{A}$. The former are found by setting $\det(\mathbf{A} - \lambda\mathbf{I}) = 0$:

$$\begin{aligned} 0 &= \det(\mathbf{A} - \lambda\mathbf{I}) \\ &= \det\left[\begin{pmatrix} 3 & -1 \\ 6 & -4 \end{pmatrix} - \begin{pmatrix} \lambda & 0 \\ 0 & \lambda \end{pmatrix}\right] \\ &= \det\begin{pmatrix} 3-\lambda & -1 \\ 6 & -4-\lambda \end{pmatrix} \end{aligned}$$

$$= (3 - \lambda)(-4 - \lambda) - (-1)(6)$$
$$= \lambda^2 + \lambda - 12 + 6 = \lambda^2 + \lambda - 6$$
$$= (\lambda - 2)(\lambda + 3)$$

This quadratic equation has the two solutions

$$\lambda_1 = 2 \quad \text{and} \quad \lambda_2 = -3. \tag{56}$$

We now find eigenvectors associated with each eigenvalue by solving $(\mathbf{A} - \lambda\mathbf{I})\mathbf{v} = 0$. Corresponding to λ_1, $\mathbf{v}_1$ must satisfy

$$(\mathbf{A} - \lambda\mathbf{I})\mathbf{v}_1 = \begin{pmatrix} 3 - \lambda_1 & -1 \\ 6 & -4 - \lambda_1 \end{pmatrix}\begin{pmatrix} v_{11} \\ v_{12} \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}. \tag{57}$$

Since $\lambda_1 = 2$, the system of equations is

$$\begin{pmatrix} 1 & -1 \\ 6 & -6 \end{pmatrix}\begin{pmatrix} v_{11} \\ v_{12} \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix},$$

that is,

$$\begin{aligned} v_{11} - v_{12} &= 0, \\ 6v_{11} - 6v_{12} &= 0. \end{aligned} \tag{58}$$

Notice that the equations are redundant. We use one of these, with an arbitrary value for one of the variables (for example, $v_{11} = 1$) to conclude that

$$\mathbf{v}_1 = \begin{pmatrix} 1 \\ 1 \end{pmatrix}, \tag{59}$$

or any constant multiple of (59).

To find $\mathbf{v}_2$, repeat the procedure with the second eigenvalue, $\lambda_2 = -3$. The system of equations is then

$$\begin{pmatrix} 6 & -1 \\ 6 & -1 \end{pmatrix}\begin{pmatrix} v_{21} \\ v_{22} \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix},$$

that is,

$$\begin{aligned} 6v_{21} - v_{22} &= 0, \\ 6v_{21} - v_{22} &= 0. \end{aligned} \tag{60}$$

Arbitrarily selecting $v_{21} = 1$, we obtain

$$\mathbf{v}_2 = \begin{pmatrix} 1 \\ 6 \end{pmatrix}. \tag{61}$$

It is worth remarking that the computations in equations 57–60, here done to reinforce a concept, can be omitted in practice by using equation (47). We conclude that two solutions to the system of equations are

$$\begin{pmatrix} 1 \\ 6 \end{pmatrix}e^{-3t} \quad \text{and} \quad \begin{pmatrix} 1 \\ 1 \end{pmatrix}e^{2t}. \tag{62}$$

The general solution is thus

$$\mathbf{x}(t) = c_1\begin{pmatrix} 1 \\ 6 \end{pmatrix}e^{-3t} + c_2\begin{pmatrix} 1 \\ 1 \end{pmatrix}e^{2t}. \tag{63}$$

Example 2

Solve the following system of equations:

$$\frac{dx_1}{dt} = x_1 - x_2, \qquad \frac{dx_2}{dt} = x_1 + x_2. \tag{64}$$

Solution

This system is equivalent to

$$\frac{d\mathbf{x}}{dt} = \mathbf{A}\mathbf{x} \qquad \text{where} \quad \mathbf{A} = \begin{pmatrix} 1 & -1 \\ 1 & 1 \end{pmatrix}. \tag{65}$$

The eigenvalues of $\mathbf{A}$ satisfy the relation

$$\begin{aligned} 0 = \det(\mathbf{A} - \lambda\mathbf{I}) &= \det\begin{pmatrix} 1-\lambda & -1 \\ 1 & 1-\lambda \end{pmatrix} \\ &= (1-\lambda)^2 + 1 \\ &= \lambda^2 - 2\lambda + 2. \end{aligned}$$

Thus

$$\lambda_{1,2} = \frac{2 \pm \sqrt{4-8}}{2} = 1 \pm i. \tag{66}$$

The eigenvector of $\mathbf{A}$ corresponding to $\lambda_1 = 1 + i$ satisfies

$$\begin{aligned} \begin{pmatrix} 0 \\ 0 \end{pmatrix} &= (\mathbf{A} - \lambda_1\mathbf{I})\mathbf{v}_1 \\ &= \begin{pmatrix} 1-(1+i) & -1 \\ 1 & 1-(1+i) \end{pmatrix}\begin{pmatrix} v_{11} \\ v_{12} \end{pmatrix} \\ &= \begin{pmatrix} -i & -1 \\ 1 & -i \end{pmatrix}\begin{pmatrix} v_{11} \\ v_{12} \end{pmatrix}. \end{aligned} \tag{67}$$

Thus

$$-iv_{11} - v_{12} = 0.$$

Taking arbitrarily $v_{11} = 1$ one obtains $v_{12} = -iv_{11} = -i$. Thus

$$\mathbf{v}_1 = \begin{pmatrix} 1 \\ -i \end{pmatrix} = \begin{pmatrix} 1 \\ 0 \end{pmatrix} - i\begin{pmatrix} 0 \\ 1 \end{pmatrix} = \mathbf{a} - i\mathbf{b}. \tag{68}$$

It follows that $\mathbf{v}_2$ is the complex conjugate of $\mathbf{v}_1$; that is,

$$\mathbf{v}_2 = \begin{pmatrix} 1 \\ i \end{pmatrix} = \begin{pmatrix} 1 \\ 0 \end{pmatrix} + i\begin{pmatrix} 0 \\ 1 \end{pmatrix} = \mathbf{a} + i\mathbf{b}. \tag{69}$$

Note that this can again be obtained directly from equation (47). The complex form of the general solution is

$$\mathbf{x}(t) = c_1\begin{pmatrix} 1 \\ -i \end{pmatrix}e^{(1+i)t} + c_2\begin{pmatrix} 1 \\ i \end{pmatrix}e^{(1-i)t}. \tag{70}$$

Defining

$$\mathbf{u}(t) = e^t\left[\begin{pmatrix} 1 \\ 0 \end{pmatrix}\cos t - \begin{pmatrix} 0 \\ 1 \end{pmatrix}\sin t\right] \tag{71a}$$

$$\mathbf{w}(t) = e^t\left[\begin{pmatrix}1\\0\end{pmatrix}\sin t + \begin{pmatrix}0\\1\end{pmatrix}\cos t\right] \tag{71b}$$

one obtains the real-valued general solution

$$\begin{aligned}\mathbf{x}(t) &= c_1\mathbf{u}(t) + c_2\mathbf{w}(t)\\ &= e^t\left[c_1\begin{pmatrix}\cos t\\-\sin t\end{pmatrix} + c_2\begin{pmatrix}\sin t\\\cos t\end{pmatrix}\right].\end{aligned} \tag{72}$$

4.9 WHEN IS A STEADY STATE STABLE?

In Section 4.8 we explored solutions to systems of linear equations such as (31) and concluded that the key quantities were the eigenvalues λ_i given by

$$\lambda_{1,2} = \frac{\beta \pm \sqrt{\beta^2 - 4\gamma}}{2},$$

where $\beta = a_{11} + a_{22}$ and $\gamma = a_{11}a_{22} - a_{12}a_{21}$. We then saw that when λ_1 and λ_2 are real numbers and not equal, the basic "building blocks" for solutions to the system (31) have the time-dependent parts

$$e^{\lambda_1 t} \quad \text{and} \quad e^{\lambda_2 t}. \tag{73}$$

We are now ready to address the main question regarding stability of a steady-state solution that was posed back in Section 4.7, namely whether the small deviations away from steady state (28) will grow larger (instability) or decay (stability). Since these small deviations satisfy a system of linear ordinary differential equations, the answer to this question depends on whether a linear combination of (73) will grow or decline with time.

Consider the following two cases:

1. λ_1, λ_2 are real eigenvalues.
2. λ_1, λ_2 are complex conjugates:

$$\lambda_{1,2} = r \pm ci, \qquad r = \frac{\beta}{2}, \qquad c = \frac{1}{2}(4\gamma - \beta^2)^{1/2}.$$

In case 2 we require that e^{rt} be *decreasing* [see equations (52) and (53)]; that is, r, the real part of λ, must be negative. In case 1 both $e^{\lambda_1 t}$ and $e^{\lambda_2 t}$ must be decreasing. Thus λ_1 and λ_2 should both be negative.

To summarize: in a continuous model, a steady state will be stable provided that eigenvalues of the characteristic equation (associated with the linearized problem) are both negative (if real) or have negative real parts (if complex). That is,

$$\text{Re } \lambda_i < 0 \text{ for all } i.$$

In case 2 we see that this criterion is satisfied whenever $\beta < 0$. In case 1 we use the following argument to derive necessary and sufficient conditions. Let

$$\lambda_1 = \frac{\beta + \sqrt{\beta^2 - 4\gamma}}{2},$$
$$\lambda_2 = \frac{\beta - \sqrt{\beta^2 - 4\gamma}}{2}.$$

We want both λ_1 and $\lambda_2 < 0$. For $\lambda_1 < 0$ it is essential that

$$\beta < 0.$$

Notice that this will always make $\lambda_2 < 0$. However, it is also necessary that

$$|\beta| > \sqrt{\beta^2 - 4\gamma}.$$

Otherwise λ_1 would be positive, since the radical would dominate over β. Squaring both sides and rewriting, we see that

$$\beta^2 > \beta^2 - 4\gamma, \qquad \text{or} \qquad 0 > -\gamma,$$

so that

$$\gamma > 0.$$

We conclude that the steady state will be stable provided that the following condition is satisfied

Stability Condition

$$\beta = a_{11} + a_{22} < 0 \tag{74a}$$
$$\gamma = a_{11}a_{22} - a_{12}a_{21} > 0 \tag{74b}$$

Now we rephrase this in the context of Section 4.7:

A steady state $(\bar{X}, \bar{Y})$ of a system of equations

$$\frac{dX}{dt} = F(X, Y), \qquad \frac{dY}{dt} = G(X, Y),$$

will be stable provided

$$F_x(\bar{X}, \bar{Y}) + G_y(\bar{X}, \bar{Y}) < 0, \tag{75a}$$

and

$$F_x(\bar{X}, \bar{Y})G_y(\bar{X}, \bar{Y}) - F_y(\bar{X}, \bar{Y})G_x(\bar{X}, \bar{Y}) > 0. \tag{75b}$$

where the terms are partial derivatives of F and G with respect to X and Y that are evaluated at the steady state.

4.10 STABILITY OF STEADY STATES IN THE CHEMOSTAT

Returning to the chemostat problem, we shall now determine whether $(\bar{N}_1, \bar{C}_1)$ and $(\bar{N}_2, \bar{C}_2)$ are stable steady-states. Define

$$F(N, C) = \alpha_1\left(\frac{C}{1 + C}\right)N - N, \tag{76a}$$

$$G(N, C) = -\left(\frac{C}{1 + C}\right)N - C + \alpha_2. \tag{76b}$$

Then we compute the partial derivatives of F and G and evaluate them at the steady states. In doing the evaluation step it is helpful to note the following:

1. At $(\bar{N}_1, \bar{C}_1)$ we know that $\bar{C}_1/(1 + \bar{C}_1) = 1/\alpha_1$.
2. The derivative of $x/(1 + x)$ is $1/(1 + x)^2$. (You should verify this.)
3. We define

$$A = \frac{\bar{N}_1}{(1 + \bar{C}_1)^2}$$

to avoid carrying this cumbersome expression.

4. We also define

$$B = \frac{\alpha_2}{1 + \alpha_2}$$

to simplify notation for $(\bar{N}_2, \bar{C}_2)$.

We see from Table 4.2 that for the steady state $(\bar{N}_1, \bar{C}_1)$ given by equation (25a)

$$\beta < 0 \qquad \text{and} \qquad \gamma > 0,$$

thus the steady state is stable whenever it exists, that is, whenever $\bar{N}_1$ and $\bar{C}_1$ in (25a) are positive. We also remark that

$$\beta^2 - 4\gamma = (A + 1)^2 - 4A = (A - 1)^2 > 0,$$

Table 4.2 ***Jacobian Coefficients for the Chemostat***

Coefficient in J	*Relevant Expressions*	*Evaluated at* $(\bar{N}_1, \bar{C}_1)$	*Evaluated at* $(\bar{N}_2, \bar{C}_2)$
a_{11}	$F_N = \alpha_1 C/(1 + C) - 1$	0	$\alpha_1 B - 1$
a_{12}	$F_C = \alpha_1 N/(1 + C)^2$	$\alpha_1 A$	0
a_{21}	$G_N = -C/(1 + C)$	$-1/\alpha_1$	$-B$
a_{22}	$G_C = -N/(1 + C)^2 - 1$	$-A - 1$	-1
$\beta = \mathrm{Tr}(J)$	$a_{11} + a_{22}$	$-(A + 1)$	$\alpha_1 B - 2$
$\gamma = \det(J)$	$a_{11}a_{22} - a_{12}a_{21}$	A	$-(\alpha_1 B - 1)$

which means that the eigenvalues of the linearized equations for $(\bar{N}_1, \bar{C}_1)$ are always real. This means that no oscillatory solutions should be anticipated. Problem 10(d) demonstrates that the trivial steady state $(\bar{N}_2, \bar{C}_2)$ is only stable when $(\bar{N}_1, \bar{C}_1)$ is nonexistent.

As a conclusion to the chemostat model, we will interpret the various results so that useful information can be extracted from the mathematical analysis. To summarize our findings, we have determined that a sensibly operating chemostat will always have a stable steady-state solution (25a) with bacteria populating the growth chamber. Recall that this equilibrium can be biologically meaningful provided that α_1 and α_2 satisfy the inequalities

$$\alpha_1 > 1, \tag{77a}$$

$$\alpha_2 > \frac{1}{\alpha_1 - 1}, \tag{77b}$$

where these constraints must be satisfied to prevent negative values of the bacteria population $\bar{N}_1$ and nutrient concentration $\bar{C}_1$. In problem 8 it is shown that, in terms of original parameters appearing in the equations,

$$\alpha_1 = \frac{K_{\max} V}{F}, \tag{78a}$$

$$\alpha_2 = \frac{C_0}{K_n}. \tag{78b}$$

The first condition (77a) is thus equivalent to

$$K_{\max} > \frac{F}{V}. \tag{79}$$

We notice that both sides of this inequality have dimensions 1/time. It is more revealing to rewrite this as

$$\frac{1}{K_{\max}} < \frac{V}{F}. \tag{80}$$

To interpret this, observe that $K_{\max}$ is the maximal bacterial reproduction rate (in the presence of *unlimited* nutrient $dN/dt \simeq K_{\max} N$). Thus $1/K_{\max}$ is proportional to the doubling-time of the bacterial population. V/F is the time it takes to replace the whole volume of fluid in the growth chamber with fresh nutrient medium. Equation (80) reveals that if the bacterial doubling time τ_2 is smaller than the emptying time of the chamber ($\times$ 1/ln 2), the bacteria will be washed out in the efflux faster than they can be renewed by reproduction.

The second inequality (77b) can be rewritten in terms of the steady-state value $\bar{C}_1 = 1/(\alpha_1 - 1)$. When this is done the inequality becomes

$$\frac{C_0}{K_n} > C_1, \qquad \text{or} \qquad \frac{F}{V}\frac{K_n}{K_{\max} - F/V} < C_0. \tag{81}$$

Since $\hat{C} = K_n$ is the reference concentration used in rendering equations (16a,b) dimensionless, we see that

$$\overline{C} = \hat{C}\overline{C}_1 = K_n\overline{C}_1,$$

is the original dimension-carrying steady state (whose units are mass per unit volume). Thus (81) is equivalent to

$$C_0 > \overline{C}, \tag{82}$$

which summarizes an intuitively obvious result: that the nutrient concentration within the chamber cannot exceed the concentration of the stock solution of nutrients.

4.11 APPLICATIONS TO RELATED PROBLEMS

The ideas that we used in assembling the mathematical description of a chemostat can be applied to numerous related situations, some of which have important clinical implications. In this section we will outline a number of such examples and suggest similar techniques, mostly as problems for independent exploration.

Delivery of Drugs by Continuous Infusion

In many situations drugs that sustain the health of a patient cannot be administered orally but must be injected directly into the circulation. This can be done with serial injections, or in particular instances, using continuous infusion, which delivers some constant level of medication over a prolonged time interval. Recently there has even been an implantable infusion system (a thin disk-like device), which is surgically installed in patients who require long medication treatments. Apparently this reduces incidence of the infection that can arise from external infusion devices while permitting greater mobility for the individual. Two potential applications still in experimental stages are control of diabetes mellitus by insulin infusion and cancer chemotherapy. A team that developed this device, Blackshear et al. (1979), also suggests other applications, such as treatment of thromboembolic disease (a clotting disorder) by heparin, Parkinson's disease by dopamine, and other neurological disorders by hormones that could presumably be delivered directly to a particular site in the body.

Even though the internal infusion pump can be refilled nonsurgically, the fact that it must be implanted to begin with has its drawbacks. However, leaving aside these medical considerations we will now examine how the problem of adjusting and operating such an infusion pump can be clarified by mathematical models similar to one we have just examined.

In the application of cancer chemotherapy, one advantage over conventional methods is that local delivery of the drug permits high local concentrations at the tumor site with fewer systemic side effects. (For example, liver tumors have been treated by infusing via the hepatic artery.) Ideally one would like to be able to calcu-

late in advance the most efficient delivery of drug to be administered (including concentration, flow rate, and so forth). This question can never be answered conclusively unless one has detailed information about the tumor growth rate, the extent to which the drug is effective at killing malignant cells, as well as a host of other complicating effects such as geometry, effect on healthy cells, and so on.

However, to gain some practice with continuous modeling, a reasonable first step is to extract the simplest essential features of this complicated system and think of an idealized caricature, such as that shown in Figure 4.5. For example, as a first step we could assume that the pump, liver, and hepatic artery together behave like a system of interconnected chambers or compartments through which the drug can flow. The tumor cells are restricted to the liver. In this idealization we might assume that (1) the blood bathing a tumor is perfectly mixed and (2) all tumor cells are equally exposed to the drug. This, of course, is a major oversimplification. However, it permits us to define and make statements about two variables:

N = the number of tumor cells per unit blood volume,

C = the number of drug units in circulation per unit blood volume.

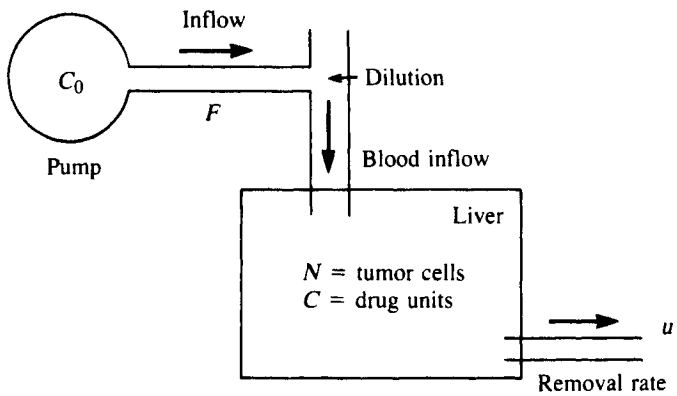


Figure 4.5 *In modeling continuous-injection chemotherapy, we might idealize the tumor as a collection of* N *identical cells that are all equally exposed to C units of drug.*

Several quantities might enter into the formulation of the equations. These include parameters that can be set or varied by the clinician, as well as those that are specific to the patient. We may also wish to define the following:

C_0 = the concentration of drug solution in the chamber (units/volume),

F = the pump flow rate (volume/unit time),

V = volume of the blood in direct contact with tumor area,

u = rate of blood flow away from tumor site,

a = reproductive rate of tumor cells.

Notice that these parameters are somewhat abstract quantities. In general, not all tumor cells will reproduce at the same rate, due to inherent variability and to differences in exposure rates to oxygen and nutrients in the blood. It may be difficult to estimate V and u. On the other hand, the parameters C_0 and F are theoretically known, since they are calibrated by the manufacturer of the pump; a typical value of F is in the range of 1.0–6.0 ml/day).

Keeping in mind the limitations of our assumptions, it is now possible to describe the course of chemotherapy as a system of equations involving the drug C and the tumor cells N. The equations might contain terms as follows:

$$\text{tumor} \quad \frac{dN}{dt} = \begin{matrix}\text{growth rate} \\ \text{of cells}\end{matrix} - \begin{matrix}\text{drug-induced} \\ \text{death rate}\end{matrix}, \tag{83a}$$

$$\text{drug} \quad \frac{dc}{dt} = \begin{matrix}\text{rate drug} \\ \text{infused}\end{matrix} - \begin{matrix}\text{rate of uptake} \\ \text{by cells}\end{matrix} - \begin{matrix}\text{rate of removal by} \\ \text{the circulation}\end{matrix}. \tag{83b}$$

Clearly this example is a somewhat transparent analog of the chemostat, because in abstracting the real situation, we made a caricature of the pump-tumor-circulatory system, as shown in Figure 4.5. A few remaining assumptions must still be incorporated in the model which in principle, can now be written fully. Some analysis of this example is suggested in problem 25.

It should be pointed out that this simple model for chemotherapy is somewhat unrealistic, as it treats all tumor cells identically. In most treatments, the drugs administered actually differentiate between cells in different stages of their cell cycle. Models that are of direct clinical applicability must take these features into account. Further reading on this subject in Swan (1984), Newton (1980), and Aroesty et al. (1973) is recommended. A more advanced approach based on the cell cycle will be outlined in a later chapter.

Modeling Glucose-Insulin Kinetics

A second area to which similar mathematical models can be applied is the physiological control of blood glucose by the pancreatic hormone *insulin*. Models that lead to a greater understanding of glucose-insulin dynamics are of potential clinical importance for treating the disorder known as *diabetes mellitus*.

There are two distinct forms of this disease, *juvenile-onset* (type I) and *adult-onset* (type II) diabetes. In the former, the pancreatic cells that produce insulin (islets of Langerhans) are destroyed and an insulin deficiency results. In the latter it appears that the fault lies with mechanisms governing the secretion or response to insulin when blood glucose levels are increased (for example, after a meal).

The chief role of insulin is to mediate the uptake of glucose into cells. When the hormone is deficient or defective, an imbalance of glucose results. Because glucose is a key metabolic substrate in many physiological processes, abnormally low or high levels result in severe problems. One way of treating juvenile-onset diabetes is by continually supplying the body with the insulin that it is incapable of making. There are clearly different ways of achieving this; currently the most widely used is a repeated schedule of daily injections. Other ways of delivering the drug are under-

going development. (Sources dating back several years are given in the references.)

Here we explore a simple model for the way insulin regulates blood glucose levels following a disturbance in the mean concentration. The model, due to Bolie (1960), contains four functions (whose exact forms are unspecified). These terms are meant to depict sources and removal rates of glucose, y, and of insulin, x, in the blood. The equations he gives are (see the definitions given in Table 4.3)

Table 4.3 ***Variables in Bolie's (1960) Model for Insulin-Glucose Regulation***

Symbol	*Definition*	*Dimensions*
V	Extracellular fluid volume	Volume
$\dot{I}$	Rate of insulin injection	Units/time
$\dot{G}$	Rate of glucose injection	Mass/time
$X(t)$	Extracellular insulin concentration	Units/volume
$Y(t)$	Extracellular glucose concentration	Units/volume
$F_1(X)$	Rate of degradation of insulin	(See problem 26)
$F_2(Y)$	Rate of production of insulin	"
$F_3(X, Y)$	Rate of liver accumulation of glucose	"
$F_4(X, Y)$	Rate of tissue utilization of glucose	"

$$\text{insulin:} \quad V\frac{dX}{dt} = \dot{I} - F_1(X) + F_2(Y), \tag{84a}$$

$$\text{glucose:} \quad V\frac{dY}{dt} = \dot{G} - F_3(X, Y) - F_4(X, Y). \tag{84b}$$

The model is a minimal one that omits many of the complicating features; see the original article for a discussion of the validity of the equations. Although the model's applicability is restricted, it serves well as an example on which to illustrate the ideas and techniques of this chapter. (See problem 26.)

An aspect of this model worth noting is that Bolie does not attempt to use experimental data to deduce the forms of the functions F_i, $i = 1, 2, 3, 4$, directly. Rather, he studies the behavior of the system close to the mean steady-state levels when no insulin or glucose is being administered [equations (84a, b) where $\dot{I} = \dot{G} = 0$ and $dX/dt = dY/dt = 0$]. He deduces values of the coefficients a_{11}, a_{12}, a_{21}, and a_{22} in a Jacobian of (84) by looking at empirical data for physiological responses to small disturbances. The approach is rather like that of the plant-herbivore model discussed in Section 3.5. His article is particularly suitable for independent reading and class presentation as it combines mathematical ideas with consideration of empirical results.

Equally accessible are contemporary articles by Ackerman et al. (1965, 1969), Gatewood et al. (1970), and Segre et al. (1973) in which linear models of the release of hormone and removal rate of both substances are presented and compared to data. An excellent recent summary of this literature and of the topic in general is given by Swan (1984, Chap. 3) whose approach to the problem is based on optimal control theory.

Aside from a multitude of large-scale simulation models that we will not dwell on here, more recent models have incorporated nonlinear kinetics (Bellomo et al, 1982) and much greater attention to the details of the physiology. Landahl and Grodsky (1982) give a model for insulin release in which they describe the spike-like pattern of insulin secretion in response to a stepped-up glucose concentration stimulus. Their model consists of four coupled ordinary differential equations. The same phenomenon has also been treated elsewhere using a partial differential equation model (for example, Grodsky, 1972; Hagander et al., 1978). These papers would be accessible to somewhat more advanced readers.

Compartmental Analysis

Physiologists are often interested in following the distribution of biological substances in the body. For clinical medicine the rate of uptake of drugs by different tissues or organs is of great importance in determining an optimal regime of medication. Other substances of natural origin, such as hormones, metabolic substrates, lipoproteins, and peptides, have complex patterns of distribution. These are also studied by related techniques that frequently involve radiolabeled tracers: the substance of interest is radioactively labeled and introduced into the blood (for example, by an injection at $t = 0$). Its concentration in the blood can then be ascertained by withdrawing successive samples at $t = t_1, t_2, \ldots, t_n$; these samples are analyzed for amount of radioactivity remaining. (Generally, it is *not* possible to measure concentrations in tissues other than blood.)

Questions of interest to a physiologist might be:

1. At what rate is the substance taken up and released by the tissues?
2. At what rate is the substance degraded or eliminated altogether from the circulation (for example, by the kidney) or from tissue (for example, by biochemical degradation)?

A common approach for modeling such processes is *compartmental analysis:* the body is described as a set of interconnected, well-mixed compartments (see Figure 4.6b) that exchange the substance and degrade it by simple linear kinetics. One of the most elementary models is that of a two-compartment system, where pool 1 is the circulatory system from which measurements are made and pool 2 consists of all other relevant tissues, not necessarily a single organ or physiological entity. The goal is then to use the data from pool 1 to make deductions about the magnitude of the exchange L_{ij} and degradation D_i from each pool.

To proceed, we define the following parameters:

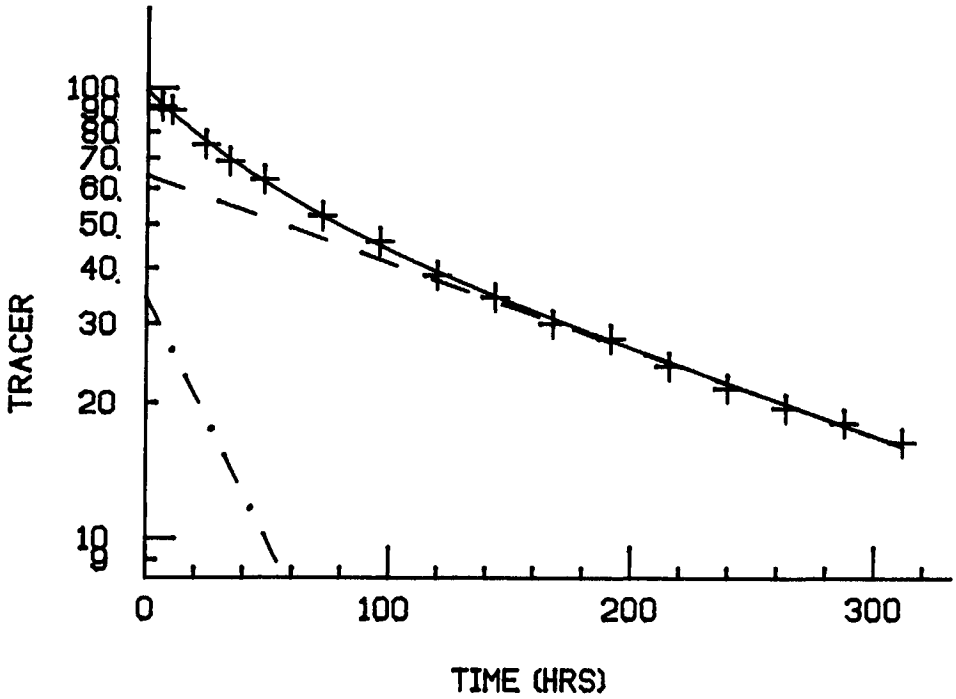
m_1 = mass in pool 1,

m_2 = mass in pool 2,

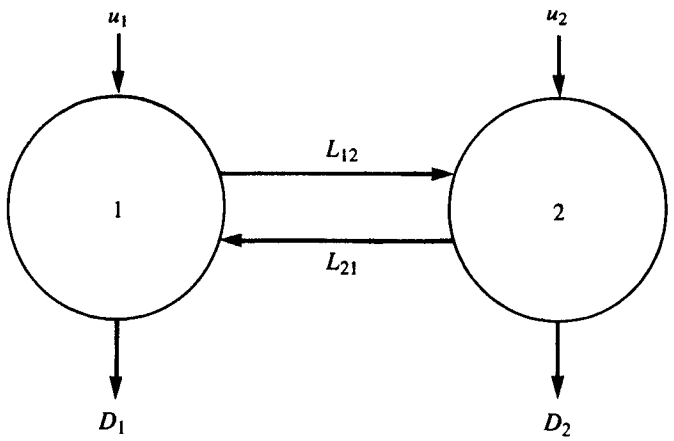
V_1 = volume of pool 1,

V_2 = volume of pool 2,

x_1 = mass per unit volume in pool 1,



(a)



(b)

Figure 4.6 *(a) Results of a physiological experiment in which the percentage of tracer remaining in the blood is followed over* 300 h *and is shown by points marked + on this semilog plot. Using such data one can estimate the quantities* λ_i, a_i, *and* b_i *in (88a,b) and thus make deductions about the distribution of the substance in the body. Dotted-dashed line:* $a_1e^{-\lambda_1 t}$; *dashed line:* $a_2e^{-\lambda_2 t}$; *and solid line,* $a_1e^{-\lambda_1 t} + a_2e^{-\lambda_2 t}$. *Here* $\lambda_2 < \lambda_1$. *(b) A two-compartment model with exchange rates* L_{ij}, *degradation rates* D_i *and rates of injection* u_1 *and* u_2. $u_1 = u_2 = 0$ *(see text).*

x_2 = mass per unit volume in pool 2,

L_{ij} = exchange from pool i to pool j,

D_j = degradation from pool j,

u_j = rate of injection of substance into pool j.

Note that L_{ij} and D_j have units of 1/time, while u_j has units of mass/time. A linear model would then lead to the following mass balance equations:

$$\frac{dm_1}{dt} = -L_{12}m_1 + L_{21}m_2 - D_1m_1 + u_1, \tag{85a}$$

$$\frac{dm_2}{dt} = L_{12}m_1 - L_{21}m_2 - D_2m_2 + u_2. \tag{85b}$$

In problem 30 we show that this can be rewritten in the form

$$\frac{dx_1}{dt} = -K_1x_1 + K_{21}x_2 + w_1, \tag{86a}$$

$$\frac{dx_2}{dt} = K_{12}x_1 - K_2x_2 + w_2, \tag{86b}$$

where

$$K_1 = L_{12} + D_1, \qquad K_2 = L_{21} + D_2,$$

$$K_{21} = \frac{L_{21}V_2}{V_1}, \qquad K_{12} = \frac{L_{12}V_1}{V_2},$$

$$w_1 = \frac{u_1}{V_1}, \qquad w_2 = \frac{u_2}{V_2}.$$

Note that now coefficients are corrected by terms that account for effects of dilution since compartment sizes are not necessarily the same. This illustrates why equations should proceed from mass balance rather than from concentration balance.

Now suppose that a mass M_0 of substance is introduced into the bloodstream by a *bolus injection* (i.e. all at one time, say at $t = 0$). Assuming that it is rapidly mixed in the circulation, we may take

$$m_1(0) = m_0, \qquad m_2(0) = 0, \qquad u_1 = u_2 = 0. \tag{87}$$

Then equations (86a,b) are readily solved since they are linear and we obtain

$$\mathbf{x} = c_1\mathbf{v}_1e^{-\lambda_1 t} + c_2\mathbf{v}_2e^{-\lambda_2 t} \tag{88a}$$

where

$$\mathbf{x} = \begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix} \qquad \text{and} \qquad c_i\mathbf{v}_i = \begin{pmatrix} a_i \\ b_i \end{pmatrix}. \tag{88b}$$

Note that the exponents are negative because substance is being removed. In problems 30 through 32 we discuss how, by fitting such solutions to data for $x_1(t)$ (concentration in the blood), we can gain appreciation for the rates of exchange and degradation in the body. A thorough treatment of this topic is to be found in Rubinow (1975).

PROBLEMS*

1. Discuss the deductions made by Malthus (1798) regarding the fate of humanity. Can the model in equation (1b) give long-range predictions of human population growth? Malthus assumed that food supplies increase at a linear rate at most, so that eventually their consumption would exceed their renewal. Comment on the validity of his model.

2. Determine whether Crichton's statement (The epigram at the beginning of this chapter. See p. 115) is true. Consider that the average mass of an *E. coli* bacterium is 10^{-12} gm and that the mass of the earth is 5.9763×10^{24} kg.

3. Show that for a decaying population
$$dN/dt = -KN \qquad (K > 0)$$
the time at which only half of the original population remains (the half-life) is
$$\tau_{1/2} = \frac{\ln 2}{K}.$$

4. Consider a bacterial population whose growth rate is $dN/dt = K(t)N$. Show that
$$N(t) = N_0 \exp\left(\int_0^t K\, ds\right).$$

5. Below we further analyze the nutrient-depletion model given in Section 4.1.
   (a) Show that the equation
   $$\frac{dN}{dt} = \kappa(C_0 - \alpha N)N$$
   can be written in the form
   $$\frac{dN}{dt} = r\left(1 - \frac{N}{B}\right)N,$$
   where $r = C_0\kappa$ and $B = C_0/\alpha$. This is called a logistic equation. Interpret r and B.
   (b) Show that the equation can be written
   $$\frac{dN}{(1 - N/B)N} = r\, dt,$$
   and integrate both sides.
   (c) Rearrange the equation in (b) to show that the solution thereby obtained is
   $$N(t) = \frac{N_0 B}{N_0 + (B - N_0)e^{-rt}}.$$
   (d) Show that for $t \to \infty$ the population approaches the density B. Also show that if N_0 is very small, the population initially appears to grow exponentially at the rate r.

*Problems preceded by an asterisk are especially challenging.

(e) Interpret the results in terms of the original parameters of the bacterial model.

(f) Find the values of B, N_0, and r in the curve that Gause (1934) fit to the growth of the yeast *Schizosaccharomyces kephir* (see caption of Figure 4.1*c*).

In problems 6 through 12 we explore certain details in the chemostat model.

6. **(a)** Analyze the dimensions of terms in equation 12 and show that an inconsistency is corrected by changing the terms FC and FC_0.

(b) What are the physical dimensions of the constant α?

7. Michaelis-Menten kinetics were selected for the nutrient-dependent bacterial growth rate in Section 4.4.

(a) Show that if $K(C)$ is given by equation (15) a half-maximal growth rate is attained when the nutrient concentration is $C = K_n$.

(b) Suppose instead we assume that $K(C) = K_m C$, where K_m is a constant. How would this change the steady state $(\bar{N}_1, \bar{C}_1)$?

(c) Determine whether the steady state found in part (b) would be stable.

8. **(a)** By using dimensional analysis, we showed that equations (16a,b) can be rescaled into the dimensionless set of equations (19a,b). What are the physical meanings of the scales chosen and of the dimensionless parameters α_1 and α_2?

(b) Interpret the conditions on α_1, α_2 (given at the end of Section 4.6) in terms of the original chemostat parameters.

9. **(a)** Show that each term in equation (14b) has units of (number of bacteria)(time)$^{-1}$.

(b) Similarly, show that each of the terms in equation (14a) has dimensions of (nutrient mass)(time)$^{-1}$.

10. It is usually possible to render dimensionless a set of equations in more than one way. For example, consider the following choice of time unit and concentration unit:

$$\tau = \frac{1}{K_{\max}}, \qquad \hat{C} = \frac{\tau F C_0}{V},$$

where $\hat{N}$ is as before.

(a) Determine what would then be the dimensionless set of equations obtained from (18a, b).

(b) Interpret the meanings of the above quantities τ and $\hat{C}$ and of the new dimensionless parameters in your equations. How many such dimensionless parameters do you get, and how are they related to α_1 and α_2 in equations (19a, b)?

(c) Write the stability conditions for the chemostat in terms of new parameters. Determine whether or not this leads to the same conditions on $K_{\max}$, V, F, C_0, K_n, and so forth.

(d) Show that $(\bar{N}_2, \bar{C}_2)$ is stable only when $(\bar{N}_1, \bar{C}_1)$ is not.

11. In industrial applications, one wants not only to ensure that the steady state $(\bar{N}_1, \bar{C}_1)$ given by equations (25a, b) exists, but also to increase the yield of bacteria, $\bar{N}_1$. Given that one can in principle adjust such parameters as V, F, and C_0, how could this be done?

12. In this question we deal with a number of variants of the chemostat.

(a) How would you expect the model to differ if there were two growth-limiting nutrients?

(b) Suppose that at high densities bacteria start secreting a chemical that inhibits their own growth. How would you model this situation?

(c) In certain cases two (or more) bacterial species are kept in the same chemostat and compete for a common nutrient. Suggest a model for such competition experiments.

13. Consider equation (8) for the growth of a microorganism in a nutrient-limiting environment.

(a) By making appropriate choices for units of measurement $\hat{N}$ and τ (for time), bring the equation to dimensionless form.

(b) What are the steady states of the equation?

(c) Determine the stability of these steady states by linearizing the equation about the steady states obtained in (b).

(d) Verify that your results agree with the exact solution given by equation (10).

14. In the hypothetical growth chamber shown here, the microorganisms (density $N(t)$) and their food supply are kept in a chamber separated by a semipermeable membrane from a reservoir containing the stock nutrient whose concentration $[C_0 > C(t)]$ is assumed to be fixed. Nutrient can pass across the membrane by a process of diffusion at a rate proportional to the concentration difference. The microorganisms have mortality μ.

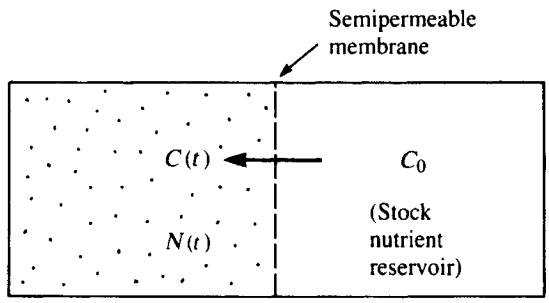


Figure for problem 14.

(a) Explain the following equations:

$$\frac{dN}{dt} = N\left(\frac{K_{\max}C}{K_n + C}\right) - \mu N,$$

$$\frac{dC}{dt} = D[C_0 - C(t)] - \alpha N\frac{K_{\max}C}{K_n + C}.$$

(b) Determine the dimensions of all the quantities in (a).

(c) Bring the equations to a dimensionless form.
(d) Find all steady states.
(e) Carry out a stability analysis and find the constraints that parameters must satisfy to ensure stability of the nontrivial steady state.

Problems 15 through 24 deal with ODEs and techniques discussed in Section 4.8.

15. Classify the following ordinary differential equations by determining whether they are linear, what their order is, whether they are homogeneous, and whether their coefficients are constant.

(a) $(\sin x)y'' + \cos x = 0.$

(b) $y'' + y^2 = 2y'.$

(c) $\dfrac{d^3y}{dt^3} + \dfrac{2dy}{dt} = \sin y.$

(d) $\dfrac{d}{dt}(y^2 + 2y) = y.$

(e) $\dfrac{d^2y}{dt^2} + 2\dfrac{dy}{dt} + 3y = e^t + e^{-t}.$

(f) $\dfrac{dy}{dt} = \dfrac{1}{1+y}.$

(g) $\dfrac{dy}{dx} = \dfrac{1}{1+x}.$

(h) $\dfrac{d^5y}{dx^5} = x^6 + 5x + 6.$

(i) $t\dfrac{dy}{dt} + ty = 1.$

16. Find the steady states of the following systems of equations, and determine the Jacobian of the system for these steady states:

(a) $\dfrac{dx}{dt} = x^2 - y^2,$ $\dfrac{dy}{dt} = x(1-y).$

(b) $\dfrac{dx}{dt} = y - xy,$ $\dfrac{dy}{dt} = xy.$

(c) $\dfrac{dx}{dt} = x - x^2 - xy,$ $\dfrac{dy}{dt} = y(1-y).$

(d) $\dfrac{dx}{dt} = x - xy,$ $\dfrac{dy}{dt} = xy - y.$

17. Consider the equation

$$\frac{d^2x}{dt^2} - 2\frac{dx}{dt} - 3x = 0.$$

(a) Show that $x_1(t) = e^{3t}$ and $x_2(t) = e^{-t}$ are two solutions.
(b) Show that $x(t) = c_1x_1(t) + c_2x_2(t)$ is also a solution.

18. The differential equation

$$\frac{d^2x}{dt^2} + 3\frac{dx}{dt} + 2x = 0$$

has the general solution

$$x(t) = c_1e^{-t} + c_2e^{-2t}.$$

If we are told that, when $t = 0$, $x(0) = 1$ and its derivative $x'(0) = 1$, we can determine c_1 and c_2 by solving the equations

$$x(0) = c_1e^{-0} + c_2e^{(-2)(0)} = c_1(1) + c_2(1) = 1,$$
$$x'(0) = c_1(-1)e^{-0} + c_2(-2)e^{-0} = -c_1 - 2c_2 = 1.$$

(a) Find the values of c_1 and c_2 by solving the above.

For questions (b) through (e) find the solution of the differential equation subject to the specified initial condition.

(b) $y' = 10y$; $y(0) = 0.001$.
(c) $y'' - 3y' - 4y = 0$; $y(0) = 0$, $y'(0) = 1$.
(d) $y'' - 9y = 0$; $y(0) = 5$, $y'(0) = 0$.
(e) $y'' - 5y' = 0$; $y(0) = 1$, $y'(0) = 2$.

19. When $\lambda_1 = \lambda_2 = \lambda$, one solution of equation (34) is

$$x_1(t) = e^{\lambda t}.$$

To find another solution (that is not just a constant multiple but is *linearly independent* of the above solution), consider the assumption

$$x_2(t) = v(t)e^{\lambda t}.$$

Find first and second derivatives, substitute into equation (34), and show that $v(t) = t$. Conclude that the general solution is

$$x(t) = c_1e^{\lambda t} + c_2te^{\lambda t}.$$

20. If $\lambda_{1,2} = a \pm bi$ are complex conjugate eigenvalues, the complex form of the solutions is

$$x_1(t) = e^{(a+bi)t}, \qquad x_2(t) = e^{(a-bi)t}.$$

Use the identity

$$e^{(a+bi)t} = e^{at}(\cos bt + i \sin bt)$$

and consider

$$u(t) = \frac{x_1(t) + x_2(t)}{2}, \qquad w(t) = \frac{x_1(t) - x_2(t)}{2i}.$$

Reason that these are also solutions by linear superposition and thus show that a real-valued solution (as in Section 4.8) can be defined.

21. **(a)** Show that system (40a, b) can be reduced to equation (41) by eliminating one variable. [*Hint:* differentiate both sides of (40a) first, and then make two other substitutions.]

(b) Once $x(t)$ is found [see equation (42a)], $y(t)$ can be found from (40a) by setting

$$y(t) = \frac{1}{a_{12}}\left(\frac{dx}{dt} - a_{11}x\right) \qquad (a_{12} \neq 0).$$

Determine $y(t)$ in terms of the expressions in (42a).

(c) Conclude that in vector form the solution can be written as

$$\begin{pmatrix} x(t) \\ y(t) \end{pmatrix} = c_1 \begin{pmatrix} 1 \\ \dfrac{\lambda_1 - a_{11}}{a_{12}} \end{pmatrix} e^{\lambda_1 t} + c_2 \begin{pmatrix} 1 \\ \dfrac{\lambda_2 - a_{11}}{a_{12}} \end{pmatrix} e^{\lambda_2 t}.$$

22. In the following exercises find the general solution to the system of equations $d\mathbf{x}/dt = \mathbf{Ax}$, where the matrix $\mathbf{A}$ is as follows:

(a) $\mathbf{A} = \begin{pmatrix} -1 & 0 \\ 0 & 1 \end{pmatrix}$.

(b) $\mathbf{A} = \begin{pmatrix} 3 & 1 \\ 1 & 3 \end{pmatrix}$.

(c) $\mathbf{A} = \begin{pmatrix} -2 & 7 \\ 2 & 3 \end{pmatrix}$.

(d) $\mathbf{A} = \begin{pmatrix} -1 & 4 \\ -2 & 5 \end{pmatrix}$.

(e) $\mathbf{A} = \begin{pmatrix} 2 & -3 \\ 1 & -2 \end{pmatrix}$.

(f) $\mathbf{A} = \begin{pmatrix} -4 & 1 \\ 3 & 0 \end{pmatrix}$.

23. For problem 22(a–f) write out the system of equations

$$\frac{dx_1}{dt} = a_{11}x_1 + a_{12}x_2, \qquad \frac{dx_2}{dt} = a_{21}x_1 + a_{22}x_2.$$

Then eliminate one variable to arrive at a single second-order equation, using the method given in problem 21. Find the characteristic equation and solve for the eigenvalues of the equation. Find solutions for $x_1(t)$ and $x_2(t)$.

24. Consider the nth-order linear ordinary differential equation

$$y^{(n)} + a_1 y^{(n-1)} + \cdots + a_{n-1}y' + a_n y = 0.$$

Show that by assuming solutions of the form

$$y(t) = Ce^{\lambda t}$$

one obtains a characteristic equation that is an nth-order polynomial.

25. In this problem we write equations to model the continuous chemotherapy described in Section 4.11.

(a) Assume that the effect of the drug on mortality of tumor cells is given by Michaelis-Menten kinetics [as in equation (15)] and that the drug is removed from the site at the rate u. Suggest equations for the tumor cell population N and the drug concentration C, assuming that tumor cells grow exponentially.

(b) Carry out dimensional analysis of your equations and indicate which dimensionless combinations of parameters are important.

(c) Determine whether the system admits steady-state solutions, and if so, what their stability properties are.

(d) Interpret your results in the biological context.

(e) A solid tumor usually grows at a declining rate because its interior has no access to oxygen and other necessary substances that the circulation supplies. This has been modeled empirically by the Gompertz growth law,

$$\frac{dN}{dt} = \gamma N \qquad \text{where} \quad \frac{d\gamma}{dt} = -\alpha\gamma.$$

γ is the effective tumor growth rate, which will decrease exponentially by this assumption. Show that equivalent ways of writing this are

$$\frac{dN}{dt} = \gamma_0 e^{-\alpha t}N = (-\alpha \ln N)N.$$

[*Hint:* use the fact that

$$\frac{1}{N}\frac{dN}{dt} = \frac{d}{dt}(\ln N)\Big].$$

(f) Use the Gompertz law to make the model equations more realistic. Assume that the drug causes an increase in α as well as greater tumor mortality.

26. *Insulin-glucose regulation.* Equations (84a,b) due to Bolie (1960) are a simple model for insulin-mediated glucose homeostasis. The following questions are a guide to investigating this model.

(a) When neither component is injected in normal, healthy individuals, the blood glucose and insulin levels are regulated to within fairly restricted concentration ranges. What does this imply about equations (84a, b)?

(b) Explain the appearance of the factor V on the LHS of equations (84a, b). What are the dimensions of the functions F_1, F_2, F_3, and F_4?

(c) Bolie defines X_0 and Y_0 as the mean equilibrium levels of insulin and glucose when none is being injected into the body. What equations do X_0 and Y_0 satisfy?

(d) Consider the following four parameters:

$$\alpha = \frac{1}{V}\left(\frac{\partial F_1}{\partial X}\right), \qquad \beta = \frac{1}{V}\left(\frac{\partial F_2}{\partial Y}\right),$$

$$\gamma = \frac{1}{V}\left(\frac{\partial F_3}{\partial X} + \frac{\partial F_4}{\partial X}\right), \qquad \delta = \frac{1}{V}\left(\frac{\partial F_3}{\partial Y} + \frac{\partial F_4}{\partial Y}\right)$$

[Partial derivatives are evaluated at (X_0, Y_0).]
Interpret what these represent and comment on the fact that these are assumed to be positive constants.

(e) Suppose that $\dot{I} = \dot{G} = 0$, but that at time $t = 0$ a rapid ingestion of glucose followed by a single insulin injection changes the internal concentrations to

$$X = X_0 + x', \qquad Y = Y_0 + y',$$

where x', y' are small compared to X_0, Y_0. Discuss what you expect to happen and how it depends on the parameters α, β, γ, and δ.

(f) By extrapolating empirical data for canines to the body mass of a human, Bolie suggests the values

$$\alpha = 0.8\ \text{hr}^{-1}, \qquad \gamma = 4.8\ \text{g hr}^{-1}\ \text{unit}^{-1},$$
$$\beta = 0.3\ \text{unit hr g}^{-1}, \qquad \delta = 3.2\ \text{hr}^{-1}.$$

Are these values consistent with a stable equilibrium?

27. The following equations were suggested by Bellomo et al. (1982) as a model for the glucose-insulin (g, i) hormonal system.

$$\frac{di}{dt} = -K_i i + K_g(g - g_d) + K_s i_r,$$

$$\frac{dg}{dt} = K_h g - K_0 g i - K_s K_f.$$

The coefficients K_i, K_g, K_s, K_h, K_0 are constants whose exact definitions may be ignored in this problem.

(a) Suggest an interpretation of the terms in these equations.

(b) Explore the steady state(s) and stability properties of this system of equations.

Note: For a more extended project, the problem can be extended to a full report or a class presentation based on this model.

28. A model due to Landahl and Grodsky (1982) for insulin secretion is based on the assumption that there are separate storage and labile compartments, a provisionary factor, and a signal for release. They define the following variables:

G = glucose concentration,

X = moiety formed from glucose in presence of calcium ions Ca^{++},

P = provisionary quantity required for insulin production,

Q = total amount of insulin available for release = CV, where C is its concentration and V is the volume,

S = secretion rate of insulin,

I = concentration of an inhibitory quantity.

(a) The following equation describes the amount of insulin available for release:

$$V\frac{dC}{dt} = k_+ C_s - k_- C + \gamma V P - S,$$

where k_+, k_- and γ are constant and C_s is the concentration in the storage compartment (of volume V_s), assumed constant. Explain the terms and assumptions made in deriving the equation.

(b) Show that another way of expressing part (a) is

$$\frac{dQ}{dt} = H(Q_0 - Q) + \gamma' P - S.$$

How do H, γ', and Q_0 relate to parameters which appear above?

(c) An equation for the provisional factor P is given as follows:

$$\frac{dP}{dt} = \alpha[P_\infty(G) - P],$$

where $P_\infty(G)$ is just some function of G (e.g., $P_\infty(G) = G$). Explain what has been assumed about P.

(d) The inhibitory entity I is assumed to be produced at the rate

$$\frac{dI}{dt} = B(NX - I),$$

where B is a rate constant and N is a proportionality constant. Explain this equation.

(e) Secretion of insulin S is assumed to be determined by two processes, and governed by the equation

$$S = [M_1 Y(G) + M_2(X - I)]Q,$$

where M_1 is constant, Y is a function of the glucose concentration, and M_2 is a step function; that is,

$$M_2(X - I) = \begin{cases} 0 & \text{if } X < I, \\ M_2 & \text{if } X \geq I. \end{cases}$$

Explain the equation for S.

29. A semitoxic chemical is ingested by an animal and enters its bloodstream at the constant rate D. It distributes within the body, passing from blood to tissue to bones with rate constants indicated in the figure. It is excreted in urine and sweat at rates u and s respectively. Let x_1, x_2, and x_3 represent concentrations of the chemical in the three pools. The equation for x_1 is

$$\frac{dx_1}{dt} = D - ux_1 - k_{12}x_1 + k_{21}x_2.$$

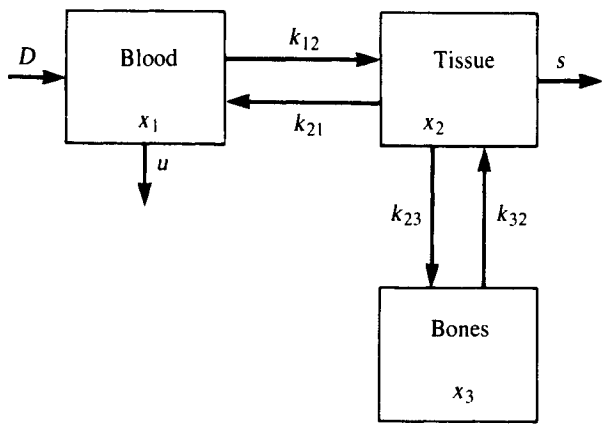


Figure for problem 29.

(a) Assuming *linear* exchange between the three compartments, write equations for x_2 and x_3.

(b) Find the steady-state values x_1, x_2, and x_3. Simplify notation by using your own symbols for ratios of rate constants that appear in the expressions.

(c) How would you investigate whether this steady state is stable?

[For an example of this type of model with realistic parameter values see Batschelet, E.; Brand, L.; and Steiner, A. (1979), On the kinetics of lead in the human body, *J. Math. Biol.*, *8*, 15 – 23.]

30. Verify and explain equations (85a, b) and (86a, b).

31. **(a)** Consider the set of measurements in Figure 4.6(a) indicated by (+). Assume that in equations 88 $\lambda_2 < \lambda_1$ and that both are positive. Then for large t it is approximately true that

$$x_1(t) \overset{\text{def}}{=} a_1 e^{-\lambda_1 t} + a_2 e^{-\lambda_2 t}.$$

Why? Use Figure 4.6(a) to indicate how λ_2 and a_2 can be approximated using this information.

(b) Now define

$$y(t) = x_1(t) - a_2 e^{-\lambda_2 t}.$$

This curve is shown in Figure 4.6(a) as the dotted-dashed line. Reason that

$$y(t) = a_1 e^{-\lambda_1 t},$$

and use Figure 4.6(a) to estimate a_1 and λ_1. This procedure is known as *exponential peeling*. It can be used to give a rough estimate of the eigenvalues of equations (86a, b). More sophisticated statistical and computational techniques are used when a more reliable estimate is desired.

32. **(a)** Show that the quantities in equations (86) and (88) are related as follows:

$$\begin{aligned}
\lambda_1 a_1 &= -K_1 a_1 + K_{21} b_1, \\
\lambda_1 b_1 &= K_{12} a_1 - K_2 b_1, \\
\lambda_2 a_2 &= -K_1 a_2 + K_{21} b_2, \\
\lambda_2 b_2 &= K_{12} a_2 - K_2 b_2.
\end{aligned}$$

(*Hint:* Use the fact that

$$\mathbf{x}_1 = \begin{pmatrix} a_1 \\ b_1 \end{pmatrix} e^{\lambda_1 t} \qquad \text{and} \qquad \mathbf{x}_2 = \begin{pmatrix} a_2 \\ b_2 \end{pmatrix} e^{\lambda_2 t}$$

are both solutions.)

(b) Another useful relation is

$$b_1 + b_2 = 0.$$

Why is this true if substance is injected only into pool 1?

(c) Assuming that the mass injected at $t = 0$ is m, what is the volume of pool 1?

***(d)** Show that

$$K_1 = \frac{a_1\lambda_1 + a_2\lambda_2}{a_1 + a_2}, \qquad K_2 = \frac{a_1\lambda_2 + a_2\lambda_1}{a_1 + a_2}.$$

(e) Find the product $K_{21}K_{12}$.

(f) Can any of the other parameters be determined (e.g., V_2, L_{12}, L_{21}, D_1, or D_2)?

(g) Discuss what sort of conclusions could be drawn from such determinations.

[A good source for further details on this topic is Rubinow (1975).]

REFERENCES

Ordinary Differential Equations

Boyce, W. E., and DiPrima, R. C. (1977). *Elementary Differential Equations*. 3rd ed. Wiley, New York.

Braun, M. (1979). *Differential Equations and Their Applications*. 3d ed. Springer-Verlag, New York.

Braun, M.; Coleman, C. S.; and Drew, D. A., eds. (1983). *Differential Equation Models*. Springer-Verlag, New York.

Henderson West, B. (1983). Setting up first order differential equations from word problems. Chap. 1 in Braun et al. (1983).

Spiegel, M. R. (1981). *Applied Differential Equations*. 3d ed. Prentice-Hall, Englewood Cliffs, N.J.

The Chemostat and Growth of Microorganisms

Biles, C. (1982). Industrial Microbiology, *UMAP Journal, 3*(1), 31–38.

Gause, G. F. (1969). *The Struggle for Existence*. Hafner Publishing, New York.

Malthus, T. R. (1970). *An essay on the principle of population*. Penguin, Harmondsworth, England.

Rubinow, S. I. (1975). *Introduction to Mathematical Biology*. Wiley, New York.

Segel, L. A. (1984). *Modeling Dynamic Phenomena in Molecular and Cellular Biology*. Cambridge University Press, Cambridge.

Chemotherapy and Continuous Infusion

Aroesty, J.; Lincoln, T.; Shapiro, N.; and Boccia, G. (1973). Tumor growth and chemotherapy: Mathematical methods, computer simulations, and experimental foundations. *Math Biosci., 17,* 243–300.

Blackshear, P. J.; Rohde, T. D.; Prosl, F.; and Buchwald, H. (1979). The implantable infusion pump: A new concept in drug delivery. *Med. Progr. Technol., 6,* 149–161.

Newton, C. M. (1980). Biomathematics in oncology: Modeling of cellular systems. *Ann. Rev. Biophys. Bioeng., 9,* 541–579.

Swan, G. W. (1984). *Applications of Optimal Control Theory in Biomedicine*. Marcel Dekker, New York, chap. 6.

Diabetes, Insulin, and Blood Glucose

Ackerman, E.; Gatewood, L. C.; Rosevear, J. W.; and Molnar, G. D. (1965). Model studies of blood-glucose regulation. *Bull. Math. Biophys., 27,* 21–37.

Ackerman, E. L.; Gatewood, L. C.; Rosevear, J. W.; and Molnar, G. (1969). Blood glucose regulation and diabetes. In F. Heinmets, ed., *Concepts and Models of Biomathematics*. Marcel Dekker, New York.

Albisser, A. M.; Leibel, B. S.; Ewart, T. G.; Davidovac, Z., Botz, C. K.; Zingg, W.; Schipper, H.; and Gander, R. (1974). Clinical control of diabetes by the artificial pancreas. *Diabetes, 23,* 397–404.

Bellomo, J.; Brunetti, P.; Calabrese, G.; Mazotti, D.; Sarti, E.; and Vincenzi, A. (1982). Optimal feedback glycaemia regulation in diabetics. *Med. Biol. Eng. Comp., 20,* 329–335.

Bolie, V. W. (1960). Coefficients of normal blood glucose regulation. *J. Appl. Physiol., 16,* 783–788.

Gatewood, L. C.; Ackerman, E.; Rosevear, J. W.; and Molnar, G. D. (1970). Modeling blood glucose dynamics. *Behav. Sci., 15,* 72–87.

Grodsky, G. M. (1972). A threshold distribution hypothesis for packet storage of insulin and its mathematical modeling. *J. Clin. Invest., 51,* 2047–2059.

Hagander, P.; Tranberg, K. G.; Thorell, J.; and Distefano, J. (1978). Models for the insulin response to intravenous glucose. *Math. Biosci., 42,* 15–29.

Landahl, H. D., Grodsky, G. M. (1982). "Comparison of Models of Insulin Release," *Bull. Math. Biol., 44,* 399–409.

Santiago, J. V.; Clemens, A. H.; Clarke, W. L.; and Kipnis, D. M. (1979). Closed-loop and open-loop devices for blood glucose control in normal and diabetic subjects. *Diabetes, 28,* 71–81.

Segre, G.; Turco, G. L.; and Vercellone, G. (1973). Modeling blood glucose and insulin kinetics in normal, diabetic, and obese subjects. *Diabetes, 22,* 94–103.

Swan, G. W. (1982). An optimal control model of diabetes mellitus. *Bull. Math. Biol., 44,* 793–808.

Swan, G. W. (1984). *Applications of Optimal Control Theory in Biomedicine.* Marcel Dekker, New York, chap. 3.

General References on Tracer Kinetics

Berman, M. (1979). Kinetic analysis of turnover data. (Intravascular metabolism of lipoproteins). *Prog. Biochem. Pharmacol., 15,* 67–108.

Matthews, C. (1957). The theory of tracer experiments with ^{131}I-Labelled Plasma Proteins. *Phys. Med. Biol., 2,* 36–53.

Rubinow, S. I. (1975). *Introduction to Mathematical Biology.* Wiley, New York.