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

### 4.2 BACTERIAL GROWTH IN A CHEMOSTAT

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.

![Diagram of chemostat](image)

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

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,
culture continues to
ion, the flow rate,
ld. First, the pro-
will enhance our
e us in making ap-
concentration, and
the bacterial pop-
the equations. Our
on. Such a list ap-

Dimensions

<table>
<thead>
<tr>
<th>Mass</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass</td>
<td>Volume</td>
</tr>
<tr>
<td>Number</td>
<td>Volume</td>
</tr>
<tr>
<td>(See problem 6)</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>time</td>
</tr>
</tbody>
</table>

are a few to begin
atual variations in the events using lent variable.)
ulation density N. lture chamber de-
te the culture repro-
writing this in an

dN
K \frac{dt}{dN} = KN - FN \tag{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 \( \alpha \) 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:

\[
\frac{dC}{dt} = -\alpha K(C)N - FC + FC_0 \tag{12}
\]

(wrong):

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

\[ \frac{dN}{dt} = K(C)N - \frac{FN}{V} \]

Dimensions: \( \frac{\text{number}}{\text{volume} \times \text{time}} = \frac{\text{number}}{\text{time volume}} \cdot \frac{\text{volume number}}{\text{time volume}} \)

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):

\[ \frac{dN}{dt} = K(C)N - \frac{FN}{V}, \quad (13a) \]
\[ \frac{dC}{dt} = -\alpha K(C)N - \frac{FC}{V} + \frac{FC_0}{V}, \quad (13b) \]

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

\[ NV = \text{number of bacteria in the chamber}, \]
\[ CV = \text{mass nutrient in the chamber}, \]

we obtain a mass balance of the two species by writing

\[ \frac{d(NV)}{dt} = K(C)NV - FN, \quad (14a) \]
\[ \frac{d(CV)}{dt} = -\alpha K(C)NV - FC + FC_0, \quad (14b) \]
(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,

$$K(C) = \frac{K_{\text{max}} C}{K_s + C}$$

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 $K_{\text{max}}$ represents an upper bound for $K(C)$ and that for $C = K_s$, $K(C) = \frac{1}{2}K_{\text{max}}$.

---

*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:

\[
\frac{dN}{dt} = \left( \frac{K_{\text{max}}C}{K_n + C} \right)N - \frac{FN}{V} \quad (16a)
\]

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

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 \( K_{\text{max}} \) 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 \( 10^9 \) cells per liter can be written in any one of the following equivalent ways:

\[
N = 10^9 \ \text{cells/liter},
\]

\[
= 1 \ \text{(unit of} \ 10^9 \ \text{cells)/liter},
\]

\[
= 100 \ \text{cells/milliliter},
\]

\[
= N^* \hat{N}.
\]

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:

\[
\begin{align*}
\text{measured} & \quad = \text{scalar} \times \text{unit carrying dimensions}, \\
N & \quad = N^* \times \hat{N}, \\
C & \quad = C^* \times \hat{C}, \\
t & \quad = t^* \times \tau.
\end{align*}
\]
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 \( N^*\dot{N} \), \( C^*\dot{C} \), \( t^*\tau \) for \( N \), \( C \), and \( t \) respectively in equations (16a,b) and then exploit the fact that \( N \), \( \dot{N} \), \( \dot{C} \), and \( \tau \) are time-independent constants. We obtain

\[
\frac{d(N^*\dot{N})}{d(t^*\tau)} = \left( \frac{K_{\text{max}}C^*\dot{C}}{K_n + C^*C} \right) N^*\dot{N} - \frac{F}{V} (N^*\dot{N}),
\]

\[
\frac{d(C^*\dot{C})}{d(t^*\tau)} = -\alpha \left( \frac{K_{\text{max}}C^*\dot{C}}{K_n + C^*C} \right) N^*\dot{N} - \frac{FC^*\dot{C}}{V} + \frac{FC_0}{V}.
\]

Now multiply both sides by \( \tau \), divide by \( \dot{N} \) or \( \dot{C} \), and group constant terms together. The result is

\[
\frac{dN^*}{dt^*} = \tau K_{\text{max}} \left( \frac{C^*}{K_n/\dot{C} + C^*} \right) N^* - \frac{\tau F}{V} N^*,
\]

\[
\frac{dC^*}{dt^*} = -\left( \alpha \tau K_{\text{max}} \dot{N} \right) \left( \frac{C^*}{K_n/\dot{C} + C^*} \right) N^* - \frac{\tau F}{V} C^* + \frac{\tau FC_0}{V\dot{C}}.
\]

By making judicious choices for the measuring scales \( \dot{N} \), \( \tau \), and \( \dot{C} \), 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

\[
\tau = \frac{V}{F}, \quad \dot{C} = K_n, \quad \dot{N} = -\frac{K_n}{\alpha \tau K_{\text{max}}}
\]

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

\[
\frac{dN}{dt} = \alpha_1 \left( \frac{C}{1 + C} \right) N - N,
\]

\[
\frac{dC}{dt} = -\left( \frac{C}{1 + C} \right) N - C + \alpha_2.
\]

The equations contain two dimensionless parameters, \( \alpha_1 \) and \( \alpha_2 \), in place of the original six (\( K_n, K_{\text{max}}, F, V, C_0 \), and \( \alpha \)). These are related by the following equations:

\[
\alpha_1 = (\tau K_{\text{max}}) = \frac{VK_{\text{max}}}{F},
\]

\[
\alpha_2 = \frac{\tau FC_0}{V\dot{C}} = \frac{C_0}{K_n}.
\]

In problem 8 we discuss the physical meaning of the scales \( \tau \), \( \dot{C} \), and \( \dot{N} \) 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 \( \tau \), \( \dot{C} \), and \( \dot{N} \) 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,

\[
\frac{dN}{dt} = 0, \quad (20a)
\]
\[
\frac{dC}{dt} = 0, \quad (20b)
\]

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

\[
F(\bar{N}, \bar{C}) = \alpha_1 \left( \frac{\bar{C}}{1 + \bar{C}} \right) \bar{N} - \bar{N} = 0, \quad (21a)
\]
\[
G(\bar{N}, \bar{C}) = -\left( \frac{\bar{C}}{1 + \bar{C}} \right) \bar{N} - \bar{C} + \alpha_2 = 0. \quad (21b)
\]

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

From (21a) we see that

\[
either \bar{N} = 0 \quad (22a)
\]
\[
or \quad \bar{C} = \frac{1}{\alpha_1}. \quad (22b)
\]

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

\[
\left( \frac{\bar{C}}{1 + \bar{C}} \right) \bar{N} = (\alpha_2 - \bar{C}). \quad (23)
\]

Using (22b), we get

\[
\bar{N} = \frac{1 + \bar{C}}{\bar{C}} (\alpha_2 - \bar{C}) = \alpha_0 (\alpha_2 - \bar{C}). \quad (24)
\]
Combining the information in equations (23) and (24) leads to the conclusion that there are two steady states:

\[
\begin{align*}
(N_1, C_1) &= \left( \alpha_1 \left( \frac{1}{\alpha_2} - \frac{1}{\alpha_1 - 1} \right), \frac{1}{\alpha_1 - 1} \right), \\
(N_2, C_2) &= (0, \alpha_2).
\end{align*}
\] (25a) (25b)

The second solution, \((N_2, C_2)\), 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 \(\alpha_2\) 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 \(\alpha_1\) and \(\alpha_2\). 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 \(\alpha_1\) and \(\alpha_2\) 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

\[
\begin{align*}
\frac{dX}{dt} &= F(X, Y), \\
\frac{dY}{dt} &= G(X, Y),
\end{align*}
\] (26a) (26b)

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

\[
F(\bar{X}, \bar{Y}) = G(\bar{X}, \bar{Y}) = 0.
\] (27)

Now consider the close-to-steady-state solutions

\[
\begin{align*}
X(t) &= \bar{X} + x(t), \\
Y(t) &= \bar{Y} + y(t).
\end{align*}
\] (28a) (28b)
Continuous Processes and Ordinary Differential Equations

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

\[
\frac{d}{dt}(\vec{x} + x) = F(\vec{x} + x, \vec{y} + y),
\]  
(29a)

\[
\frac{d}{dt}(\vec{y} + y) = G(\vec{x} + x, \vec{y} + y).
\]  
(29b)

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

\[
\frac{dx}{dt} = F(\vec{x}, \vec{y}) + F_x(\vec{x}, \vec{y})x + F_y(\vec{x}, \vec{y})y + \text{terms of order } x^2, y^2, xy, \text{ and higher},
\]  
(30a)

\[
\frac{dy}{dt} = G(\vec{x}, \vec{y}) + G_x(\vec{x}, \vec{y})x + G_y(\vec{x}, \vec{y})y + \text{terms of order } x^2, y^2, xy, \text{ and higher}.
\]  
(30b)

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

Again by definition, \( F(\vec{x}, \vec{y}) = 0 = G(\vec{x}, \vec{y}) \), so we are left with

\[
\frac{dx}{dt} = a_{11}x + a_{12}y,
\]  
(31a)

\[
\frac{dy}{dt} = a_{21}x + a_{22}y,
\]  
(31b)

where the matrix of coefficients

\[
A = \begin{pmatrix}
    a_{11} & a_{12} \\
    a_{21} & a_{22}
\end{pmatrix} = \begin{pmatrix}
    F_x & F_y \\
    G_x & G_y
\end{pmatrix}_{\vec{x}, \vec{y}}.
\]  
(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.)
\[ w(t) = e^t \begin{pmatrix} 1 \\ 0 \\ 1 \end{pmatrix} \sin t + \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} \cos t \]  
(71b)

one obtains the real-valued general solution

\[ x(t) = c_1 u(t) + c_2 w(t) \]
\[ = e^t \begin{pmatrix} \cos t \\ -\sin t \\ \cos t \end{pmatrix} c_1 + c_2 \begin{pmatrix} \sin t \\ \sin t \\ \cos t \end{pmatrix}. \]  
(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 \( \lambda_i \) 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 \( \lambda_1 \) and \( \lambda_2 \) are real numbers and not equal, the basic "building blocks" for solutions to the system (31) have the time-dependent parts

\[ e^{\lambda_1 t} \quad \text{and} \quad e^{\lambda_2 t}. \]  
(73)

We are now ready to address the main question regarding stability: Is 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. \( \lambda_1, \lambda_2 \) are real eigenvalues.
2. \( \lambda_1, \lambda_2 \) are complex conjugates:

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

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

\[ \text{Re } \lambda_i < 0 \quad \text{for all } i. \]
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 \( \lambda_1 \) 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 \( \lambda_1 \) would be positive, since the radical would dominate over \( \beta \). Squaring both sides and rewriting, we see that

\[
\beta^2 > \beta^2 - 4\gamma,
\]

or

\[
0 > -\gamma,
\]

so that

\[
\gamma > 0.
\]

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

\[
\text{Stability Condition}
\]

\[
\begin{align*}
\beta &= a_{11} + a_{22} < 0 \\
\gamma &= a_{11}a_{22} - a_{12}a_{21} > 0
\end{align*}
\]

Now we rephrase this in the context of Section 4.7:

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

\[
\frac{dX}{dt} = F(X, Y), \quad \frac{dY}{dt} = G(X, Y),
\]

will be stable provided

\[
F_x(\bar{X}, \bar{Y}) + G_y(\bar{X}, \bar{Y}) < 0,
\]

and

\[
F_x(\bar{X}, \bar{Y})G_y(\bar{X}, \bar{Y}) - F_y(\bar{X}, \bar{Y})G_x(\bar{X}, \bar{Y}) > 0.
\]

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

\[
F(N, C) = \alpha_1 \left( \frac{C}{1 + C} \right) N - N, \quad (76a)
\]

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

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

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

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)

\[
\beta < 0 \quad \text{and} \quad \gamma > 0,
\]

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

<table>
<thead>
<tr>
<th>Coefficient in (J)</th>
<th>Relevant Expressions</th>
<th>Evaluated at ((\bar{N}_1, \bar{C}_1))</th>
<th>Evaluated at ((\bar{N}_2, \bar{C}_2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a_{11})</td>
<td>(F_N = \alpha_1 \bar{C}/(1 + \bar{C}) - 1)</td>
<td>0</td>
<td>(\alpha_1 B - 1)</td>
</tr>
<tr>
<td>(a_{12})</td>
<td>(F_C = \alpha_1 \bar{N}/(1 + \bar{C})^2)</td>
<td>(\alpha_1 A)</td>
<td>0</td>
</tr>
<tr>
<td>(a_{21})</td>
<td>(G_N = -\bar{C}/(1 + \bar{C}))</td>
<td>(-1/\alpha_1)</td>
<td>(-B)</td>
</tr>
<tr>
<td>(a_{22})</td>
<td>(G_C = -\bar{N}/(1 + \bar{C})^2 - 1)</td>
<td>(-A - 1)</td>
<td>(-1)</td>
</tr>
<tr>
<td>(\beta = \text{Tr}(J))</td>
<td>(a_{11} + a_{22})</td>
<td>(-(A + 1))</td>
<td>(\alpha_1 B - 2)</td>
</tr>
<tr>
<td>(\gamma = \text{det}(J))</td>
<td>(a_{11}a_{22} - a_{12}a_{21})</td>
<td>(A)</td>
<td>(-\alpha_1 B - 1)</td>
</tr>
</tbody>
</table>
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 \(\alpha_1\) and \(\alpha_2\) 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,

\[
\alpha_1 = \frac{K_{\text{max}}}{F}, \tag{78a}
\]

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

The first condition (77a) is thus equivalent to

\[
K_{\text{max}} > \frac{F}{V}. \tag{79}
\]

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

\[
\frac{1}{K_{\text{max}}} < \frac{V}{F}. \tag{80}
\]

To interpret this, observe that \(K_{\text{max}}\) is the maximal bacterial reproduction rate (in the presence of unlimited nutrient \(dN/dt = K_{\text{max}}N\)). Thus \(1/K_{\text{max}}\) 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 \(\tau_2\) 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

\[
\frac{C_0}{K_n} > C_1, \quad \text{or} \quad \frac{F}{V} \frac{K_n}{K_{\text{max}} - F/V} < C_0. \tag{81}
\]
Since \( \hat{C} = K_c \) is the reference concentration used in rendering equations (16a,b) dimensionless, we see that
\[
\bar{C} = \hat{C}\bar{C}_1 = K_c\bar{C}_1,
\]
is the original dimension-carrying steady state (whose units are mass per unit volume). Thus (81) is equivalent to
\[
C_0 > \bar{C}, \tag{82}
\]
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-
g the fate of human
cations of human pop-
ase at a linear rate at
their renewal. Com-

the beginning of this
us of an E. coli bac-
3 \times 10^{24} \text{ kg}

ains (the half-life) is

\frac{dN}{dt} = K(t)N. \text{ Show

en in Section 4.1.

otic equation. Inter-

ution thereby ob-

sity B. Also show
i to grow exponen-

(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 \( \text{Schizosaccharomyces kefiri} \) (see caption of Figure 4.1c).

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 in-
consistency is corrected by changing the terms \( FC \) and \( FC_0 \).

(b) What are the physical dimensions of the constant \( \alpha \)?

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 \( C = K_m \).

(b) Suppose instead we assume that \( K(C) = K_mC \), 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 \( \alpha_1 \) and \( \alpha_2 \)?

(b) Interpret the conditions on \( \alpha_1, \alpha_2 \) (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 concen-
tration unit:

\[ \tau = \frac{1}{K_{\text{max}}}, \quad \hat{C} = \frac{\tau F C_0}{V}, \]

where \( \hat{N} \) is as before.

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

(b) Interpret the meanings of the above quantities \( \tau \) and \( \hat{C} \) and of the new
dimensionless parameters in your equations. How many such dimension-
less parameters do you get, and how are they related to \( \alpha_1 \) and \( \alpha_2 \) in
equations (19a, b)?

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

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