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.

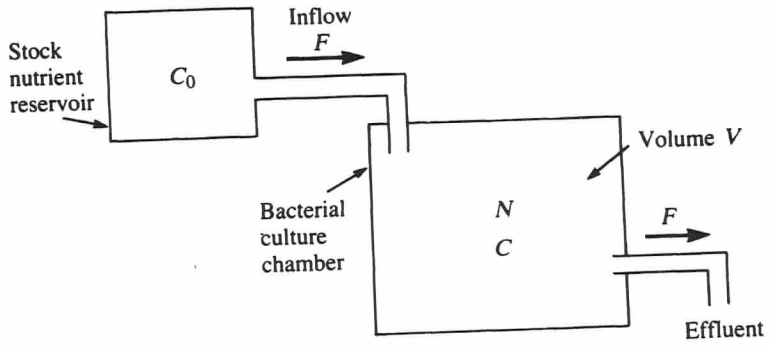

Figure 4.2 *The chemostat is a device for harvesting bacteria. Stock nutrient of concentration* C_0 *enters the bacterial culture chamber with inflow rate* F. *There is an equal rate of efflux, so that the volume* V *is constant.*

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.)

Corrected Ve

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 $C = K_n$, $K(C) = \frac{1}{2}K_{\max}$.

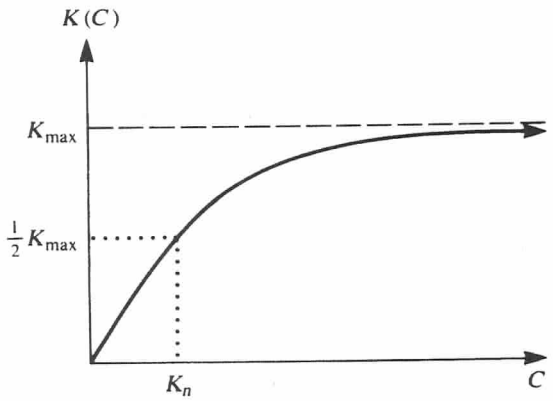

Figure 4.3 *Michaelis-Menten kinetics: Bacterial growth rate and nutrient consumption* K(C) *is assumed to be a saturating function of nutrient concentration. See equation (15).*