

Substituting into (4.15)

$$C(t) = C^* e^{-kt} + \bar{C}, \quad dC/dt = dC^*/dt, \quad (3a, b)$$

we obtain as the equation for  $C^*$  [using (1)],

$$dC^*/dt = -kC^*, \quad \text{where } k = k_1 S_0 + k_{-1} + k_2. \quad (4a, b)$$

Equation (4a) has the solution [compare equation (A4.2)]

$$C^* = C^* \exp(-kt).$$

Here,  $C^*$  is a constant that must be determined by the initial conditions. To this end we first use (3a) to find that the original concentration  $C$  is given by

$$C(t) = C^* \exp(-kt) + \bar{C}.$$

The initial condition  $C(0) = C_0$  thus requires

$$C_0 = C^* + \bar{C}, \quad \text{i.e., } C^* = C_0 - \bar{C},$$

which at once yields the final result (4.17).

## 5

### The chemostat

Construction and analysis of a model for the chemostat is the goal of this chapter. The chemostat is a device that enables us continuously to grow and harvest bacteria. The consequent "continuous culture" of bacteria is in contrast with "batch culture," in which a fixed quantity of nutrient is supplied and bacteria are harvested after a certain growth period.

A schematic view of the chemostat is provided in Figure 5.1. We shall assume that all materials necessary for growth are supplied in abundance, except for one critical nutrient that is typically in somewhat short supply. A solution containing the critical nutrient is supplied to the growth chamber, and an equal volume (per unit time) of solution containing bacteria and partly consumed nutrient is removed. The chemostat is stirred to keep conditions uniform.

Virtually all the information necessary for the construction of a mathematical model of chemostat operation has been supplied. The reader is invited to think about the construction of such a model before reading further. A few additional assumptions must be made; the simplest reasonable possibilities should be used, as is the case in all first attempts at model building. We shall shortly sketch the classic theory of the chemostat, due to Novick and Szilard (1950) and Monod (1950). Part of our presentation is similar to that of Rubinow (1975). The reader probably will have little difficulty in following the discussion, but congratulations are in order if he or she has been able to make significant progress toward the model construction. On a number of occasions the author has presented the facts in the previous paragraph to a class and then asked for suggestions on how to proceed. In every case the model was constructed only after about two hours of class debate, and a certain number of hints. This reflects the fact that construction of mathematical models is an art that requires considerable experience. But it is not nearly so difficult to learn to "read" the equations proposed by someone as a mathematical representation of a biological situation, to see what they imply, and hence to judge the suitability of the model. The acquisition of a good

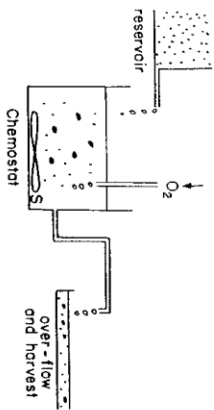


Figure 5.1. Schematic diagram of a chemostat with nutrient supplied from a reservoir, oxygen being bubbled in, and the chemostat chamber being agitated by a stirrer  $S$  to keep concentration uniform. Heavy dots represent bacteria. The overflow contains partially used nutrient and the bacterial harvest.

measure of such "reading ability" is one goal of the instruction that we are attempting to impart here.

### Choice of variables

We wish to follow the behavior of the chemostat as time passes. In some instances it is appropriate to assume that time progresses in discrete units. For example, yearly time intervals are natural when considering populations of insects that emerge each spring, lay eggs in the fall, and then die in the winter. Here it seems more natural to think of time as an independent variable that continuously increases (but see Exercise 12). The constituents of some systems vary from place to place, necessitating the introduction of further independent variables - the spatial coordinates  $x$ ,  $y$ , and  $z$ . Here the stirring creates conditions that can be regarded as spatially homogeneous, so that the time  $t$  is the only independent variable required.

Having decided on independent variables, the next step is to select dependent variables, the "unknowns." One of these is  $N(t)$ , the total number of bacteria in the chemostat at any time  $t$ . The other is  $C(t)$ , the concentration of critical nutrient at time  $t$ . Given this selection (which is not obvious to beginners in the art of modeling), we must now try to write some mathematical description that will allow us to compute  $N(t)$  and  $C(t)$ . Here and in many other instances this description takes the form of differential equations that describe the factors that cause the dependent variables to change.

For differential equations to be appropriate, the functions in question must, of course, have derivatives. Here  $N$  is an integer, so that its graph

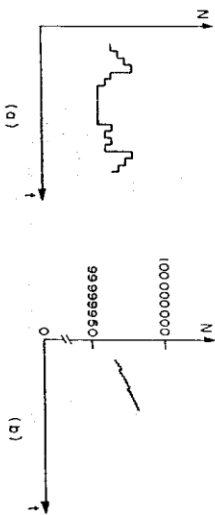


Figure 5.2. Two views of the number of bacteria  $N$  as a function of time. (a) A "close up," clearly showing the birth and death of individual bacteria. (b) A more rapidly varying scale  $N$ ; the steps in the graph are hardly noticeable.

must have the steplike character of Figure 5.2(a), and the derivative is either zero or nonexistent. Nevertheless, because our equations necessarily provide approximate descriptions of the true biological situation, there may be no harm in considering an approximate dependent variable. Indeed, the number of bacteria in the chemostat is very large, and the death or birth of a single bacterium is of no interest to us. Consider the graph of Figure 5.2(b), where a somewhat realistic scale has been provided for  $N$ . The jumps in the curve are virtually undetectable. It is thus reasonable to replace the "true" steplike function  $N(t)$  by a smooth approximation (to which we shall apply the same letter  $N$ ).

We now assume that  $N(t)$  and  $C(t)$  are smooth functions with as many derivatives as we care to calculate. Strictly speaking, as we have pointed out, this is "wrong." But here and in other modeling situations it is important to realize that a model cannot be dismissed (as untrained people are wont to do) merely because it is wrong. Essentially all models of physical situations contain errors, called "simplifications." The question is, Are these simplifications so drastic or foolish that the resulting model is indeed without validity, or can the model provide useful results in a given situation? Here, for example, with inevitable errors in measurement of bacterial and chemical concentrations, the individual bacteria and molecules that inhabit the chemostat are essentially undetectable; so it seems permissible (indeed, wise) to blur their contributions to the state of the system.

### Differential equations and initial conditions

There are two major contributions to the change in the total bacteria number  $N$ : the net birth of the bacteria (births minus deaths) and the

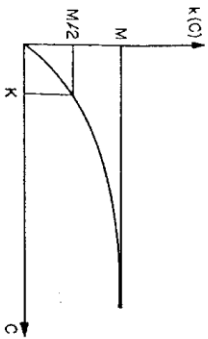


Figure 5.3. The bacterial growth rate  $k$  as a function of the critical nutrient concentration  $C$ . When  $C = K$ ,  $k$  is half of its asymptotic value  $M$ .

washing of bacteria out of the chemostat. The rate of the latter step is easy to characterize. Suppose that  $Q$  units (e.g., cubic centimeters) of fluid drip out of the chemostat per unit time. The number of bacteria per unit volume is  $N/V$ , where  $V$  is the volume of the chemostat. Thus, bacteria leave the system at a rate  $QN/V$ . Because the rate of change of  $N$  is given by the derivative  $dN/dt$ , we can write

$$dN/dt = (\text{net births}) - (QN/V). \quad (1)$$

Let  $k$  be the average bacterial birthrate. In the absence of other effects, the simplest equation to assume is  $dN/dt = kN$ , where  $k$  is a constant. This yields  $N = N_0 \exp(kt)$ , so that  $k$  can be determined by the doubling time  $T$ :

$$2N_0 = N_0 \exp(kT), \quad \text{i.e., } k = (\ln 2)/T.$$

When the bacterial population gets large, the net birthrate (or growth rate)  $k$  will not remain constant. It may be reduced by the accumulation of poisons, for example. Such effects are often modeled by making  $k$  a decreasing function of the population size  $N$ . Here the population of bacteria is limited because bacteria are washed out of the chemostat, so that the dependence of  $k$  on  $N$  need not be taken into account in a first modeling attempt. What is important, however, is the dependence of  $k$  on the critical nutrient concentration  $C$ . When no critical nutrient is present,  $k = 0$ . Presumably, as critical nutrient concentration rises, the growth rate increases. One foresees a limit to such an increase, for there is a limit to how fast the bacteria can absorb any nutrient. Thus, we expect the dependence of  $k$  on  $C$  to be given by a curve such as that in Figure 5.3. (Actually, the curve probably decreases at very high values of  $C$ , but such an effect is secondary, and we shall ignore it.)

At this point, we have completed our formulation of the equation for  $N$ :

$$dN/dt = k(C)N - qN. \quad (2)$$

Here we have introduced the convenient abbreviation

$$q = Q/V. \quad (3)$$

The critical nutrient concentration  $C$  increases because of inflow into the chemostat, and  $C$  decreases because of outflow and consumption by the bacteria. Denote by  $C_i$  the concentration of critical nutrient in the incoming fluid. Because the fluid enters at the constant rate  $Q$ , the amount of nutrient increases from inflow at the constant rate  $QC_i$ . The fluid that leaves at time  $t$  is at concentration  $C(t)$ . At this time, therefore, the efflux of material from the chemostat decreases the net amount of critical nutrient at the rate  $QC$ . Finally, let us assume that some function  $r(C)$  describes the rate at which an individual bacterium consumes  $C$ . Taking account of the fact that there are  $N$  bacteria in the chemostat at time  $t$ , we are led to the following equation for the change in the total amount of critical nutrient:

$$d(CV)/dt = QC_i - QC - Nr(C). \quad (4)$$

What form should we assume for the consumption function  $r(C)$ ? Obviously,  $r = 0$  when  $C = 0$ . Moreover,  $r$  should saturate (approach an asymptote, in mathematical language) when  $C$  becomes large, for there must be a limit as to how fast the nutrient can be absorbed. The function  $r(C)$  thus has the same general shape as the growth-rate function  $k(C)$  depicted in Figure 5.3. In fact, it is reasonable and convenient to assume that the growth rate  $k$  is proportional to the nutrient uptake rate  $r$ . This is almost certainly appropriate at sufficiently low values of  $C$ , when both  $k(C)$  and  $r(C)$  generally are proportional to  $C$  (Exercise 5). Later we can determine what changes in our results will occur if this assumption is not made (Exercise 6). We therefore assume that

$$r(C) = yr(C), \quad (5)$$

where  $y$  is a constant. We now use (5) to replace  $r$  in (4). Remembering that  $V$  is a constant, we write  $d(CV)/dt = V(dC/dt)$ , divide through by  $V$ , and recall that  $q = Q/V$ . This gives as our final version of the equation for the critical nutrient concentration

$$dC/dt = q(C_i - C) - N(yr)^{-1}k(C). \quad (6)$$

Equations (2) and (6) describe how the number of bacteria  $N$  and the

nutrient concentration  $C$  change with time. We should thus be able to calculate the **state** of the chemostat system at any time (i.e., the values of the dependent variables  $N$  and  $C$ ) provided that we know how the system was constituted at some initial time. Let us call this time  $t = 0$ . We assume that the critical nutrient initially was present at concentration  $C_0$  and that a certain number of bacteria  $N_0$  were inoculated into the chemostat as it was started. This gives the initial conditions

$$N(0) = N_0, \quad C(0) = C_0. \quad (7)$$

The differential equations (2) and (6) and the initial conditions (7) constitute a mathematical model for the chemostat. The model contains the parameters  $q, C_1, y, V, N_0, C_0$  and the function  $k(C)$ ; these must be prescribed before any numerical results can be obtained. It will be convenient later to choose a specific expression for the function  $k$ . The simplest function that starts at the origin and saturates is given by the "Michaelis-Menten" expression

$$k(C) = MC/(K+C), \quad C \geq 0. \quad (8)$$

Here,  $M$  and  $K$  are constants. Note that [as was pointed out in connection with the analogous equation (4.29)]  $M$  is the value of  $k$  that is approached as  $C \rightarrow \infty$ , whereas  $K$  is the half-saturation constant, in that  $k = M/2$  when  $C = K$  (see Figure 5.3).

It is worth collecting all the equations (2), (6), (7), and (8) of our explicit mathematical model:

$$\frac{dN(t)}{dt} = \frac{MN(t)C(t)}{K+C(t)} - qN(t), \quad (9a)$$

$$\frac{dC(t)}{dt} = q[C_1 - C(t)] - \frac{N(t)MC(t)}{y[K+C(t)]V}, \quad (9b)$$

$$N(0) = N_0, \quad C(0) = C_0. \quad (9c, d)$$

To retain biological meaningfulness, we must add the conditions  $N \geq 0$ ,  $C \geq 0$ . Note that the model contains eight parameters  $q, C_1, y, V, N_0, C_0, M$ , and  $K$ .

At the beginning of this chapter the reader was asked to attempt the unaided construction of a mathematical model of a chemostat. If such an effort was made, the model (9) will not be dismissed as obvious.

We now turn to a mathematical analysis of the model. Here, too, it is recommended that the reader attempt to anticipate the results. We wish to know, for example, if the chemostat will operate as designed. That is,

after an initial transient period, will the chemostat settle down to a steady mode of operation in which constant numbers of bacteria per unit time are produced? Is it certain that steady-state production of bacteria will always take place? If so, about how long will it take to achieve a steady state? What parameter values give the maximum production? Is it possible that the bacteria population might oscillate in time? If it does, approximately what is the period of the oscillation? What is the amplitude? Under what conditions will an oscillation occur? If the reader can confidently answer all questions such as these, then there is no need to consider a mathematical model. Otherwise, the use of a mathematical model will doubtless be a useful adjunct to an experimental program.

#### Steady solutions

Will the chemostat settle down to a steady state of operation? That is, does  $N \rightarrow$  constant and  $C \rightarrow$  constant, whatever the initial conditions, as  $t \rightarrow \infty$ ? This is a difficult question to answer. But considerable insight can be gained into this problem, and similar problems, if we ask a somewhat different (and much simpler) question: Can the system remain forever in exactly the same **steady state**? That is, do the original equations (2) and (6) admit the following very simple solutions?

$$N(t) = \bar{N}, \quad C(t) = \bar{C}, \quad \bar{N} \text{ and } \bar{C} \text{ constants.} \quad (10)$$

Because the derivative of a constant is zero, (10) will hold if and only if

$$k(\bar{C})\bar{N} - q\bar{N} = 0, \quad q(C_1 - \bar{C}) - \bar{N}(yV)^{-1}k(\bar{C}) = 0. \quad (11a, b)$$

The algebraic equation (11a) has two solutions: one if  $\bar{N} = 0$ , and another if  $k(\bar{C}) = q$ . Let us consider these possibilities one at a time.

If  $\bar{N} = 0$ , then (11a) is satisfied, whereas (11b) is satisfied if and only if  $\bar{C} = C_1$ . This solution is so "trivial" that it is easily overlooked, but it makes perfect biological sense. The chemostat can run forever with no bacteria inside, and hence with no change in the concentration of critical nutrient.

We must now ask about the solutions to the equation  $k(\bar{C}) = q$ . Does this equation always have a solution? Could it have more than one solution? The answer (as is so often the case) is easily seen by drawing some graphs. We see from Figure 5.4 that  $k(\bar{C}) = q$  has no solutions if  $q \geq M$  and exactly one solution if  $q < M$ . Again, this makes sense biologically. As far as the bacteria in the chemostat are concerned, "washout" at rate  $qN$  is the same as death, for the washed-out bacteria disappear. If the

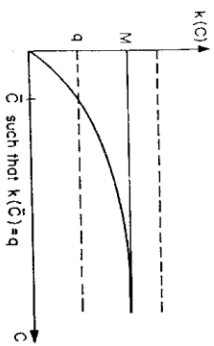


Figure 5.4. Demonstration of the fact that the equation  $k(C) = q$  has a unique solution when  $q < M$  and no solution when  $q \geq M$ .

washout rate  $q$  is greater than the maximum birthrate  $M$ , then there can be no nonzero steady population level of bacteria in the chemostat.

Once  $\bar{C}$  is obtained, by solving  $k(\bar{C}) = q$ , then a unique value of  $\bar{N}$  can be obtained by solving (11b). For this value to be positive,  $q$  must be such that  $C < C_1$ .

To summarize, there are two possible steady-state solutions of the equations (2) and (6). One solution is

$$\bar{N} = 0, \quad \bar{C} = C_1. \quad (12a)$$

Corresponding to every positive flow parameter  $q$  that is less than the maximum value of  $k(C)$  and is also small enough so that  $C_1 > \bar{C}$ , there is a second solution  $\bar{C}, \bar{N}$ , where

$$k(\bar{C}) = q, \quad \bar{N} = Y(C_1 - \bar{C}). \quad (12b)$$

If we use (8), we can find explicit formulas for the solution (12b):

$$\text{If } q < M, \quad \bar{C} = \frac{qK}{M-q}, \quad \bar{N} = Y\left(C_1 - \frac{qK}{M-q}\right). \quad (13a, b)$$

Here we see algebraically that  $\bar{C} > 0$  requires

$$q < M,$$

whereas  $\bar{N} > 0$  if

$$C_1 > \frac{qK}{M-q}.$$

To transform the latter inequality into a condition on the flow-rate parameter  $q$ , we multiply both sides by  $M - q$ . Because this quantity must be positive, as we have just seen, we obtain

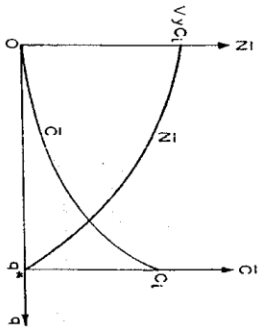


Figure 5.5. Graphs of the steady-state bacteria number ( $\bar{N}$ ) and critical nutrient concentration ( $\bar{C}$ ) as functions of the flow-rate parameter  $q$  [see equations (13) and (14)].

$$C_1/M - C_1 q > qK,$$

or

$$q < q^*, \quad \text{where } q^* = \frac{M}{1 + (K/C_1)}. \quad (14)$$

Note that  $q^* < M$ , so that if  $\bar{N} > 0$ , then certainly  $\bar{C} > 0$ .

Figure 5.5 depicts graphs of the steady-state nutrient concentration  $\bar{C}$  and bacteria number  $\bar{N}$  as functions of the flow parameter  $q$ . It is seen that as  $q$  increases toward  $q^*$ ,  $\bar{C}$  increases to its maximum possible value  $C_1$ , while  $\bar{N}$  decreases toward zero.

If the chemostat is regarded as a factory for producing bacteria, then it is natural to inquire as to its optimum output. One possible quantity to maximize is the bacterial production rate  $q\bar{N}$ . This is zero when  $q = 0$ , and also when  $q = q^*$  (and  $\bar{N} = 0$ ). There must be an optimum intermediate flow rate.

**Problem:** Find the flow rate  $q$  that maximizes  $q\bar{N}$ .

**Solution:** From (13b),

$$q\bar{N} = Y\left(qC_1 - \frac{q^2K}{M-q}\right).$$

The derivative  $d(q\bar{N})/dq$  vanishes when

$$C_1 - \frac{(M-q)(2qK) + q^2K}{(M-q)^2} = 0. \quad (15)$$

Simplifying, we observe that (15) holds if

$$q^2(C_1 + K) - 2Mq(C_1 + K) + M^2C_1 = 0. \quad (16)$$

It is an important observation that (16) can be further simplified if we divide through by  $C_1 + K$  and use (14), yielding

$$q^2 - 2Mq + Mq^* = 0. \tag{17}$$

On solving (17), we find that

$$q = M - [M(M - q^*)]^{1/2}. \tag{18}$$

Because  $q^* < M$ , the quantity whose root must be extracted is positive. We have not written a plus sign before the square-root term, because the plus sign corresponds to the value of  $q$  that is larger than  $M$  and is therefore of no biological interest. But we must verify that the other root is not only less than  $M$  but also less than  $q^*$ .

$$\begin{aligned} \text{Is } M - [M(M - q^*)]^{1/2} < q^*? \quad \text{I.e., is } M - q^* < [M(M - q^*)]^{1/2}? \\ \text{Is } (M - q^*)^2 < M(M - q^*)? \quad \text{Is } M - q^* < M? \quad \text{Yes.} \end{aligned} \tag{19}$$

The maximum flow rate is not the only possible optimization that may be sought. For example, we might wish to maximize profit, given certain prices to be paid for nutrient and to be received for bacteria (Exercise 7).

### Dimensionless variables

At some stage in the examination of a nontrivial mathematical model it is often wise to introduce dimensionless variables, if only to simplify the notation by the consolidation of some parameters (see Appendix 7). We must divide the existing variables by parameters of the same dimensions. A way in which this can be done in the present case is to measure time in multiples of  $1/q = V/Q$ , the time it takes to fill (or empty) the chemostat at rate  $Q$ . The first term of (9a) will simplify, if we define a dimensionless concentration  $c$  by  $C(t) = Kc(t)$ , that is, if we measure concentration in units of the half-saturation constant  $K$ . And it is natural to measure  $N$  in terms of the initial inoculant size  $N_0$ . With the dimensionless variables

$$\tau = tq, \quad c = C/K, \quad n = N/N_0, \tag{20a, b, c}$$

the system (9) becomes [Exercise 1(a)]

$$\frac{dn}{d\tau} = \frac{\mu n c}{1+c} - n, \quad \frac{dc}{d\tau} = \xi - c - \frac{\mu n c}{1+c}, \tag{21a, b}$$

$$n(0) = 1, \quad c(0) = c_0. \tag{21c, d}$$

Instead of the eight parameters of (9), the dimensionless equations (21) contain the four dimensionless parameters

$$\mu = M/q, \quad \xi = C_1/K, \quad \nu = N_0/YKV, \quad c_0 = C_0/K. \tag{22a-d}$$

The dimensionless steady solutions satisfy

$$\bar{n} = 0, \quad \bar{c} = \xi, \tag{23a, b}$$

or

$$\frac{\mu \bar{c}}{1+\bar{c}} = 1, \quad \xi - \bar{c} - \frac{\nu \mu \bar{n} \bar{c}}{1+\bar{c}} = 0, \tag{24a, b}$$

so that [Exercise 1(b)]

$$\bar{n} = \frac{\xi}{\nu} - \frac{1}{\nu(\mu-1)}, \quad \bar{c} = \frac{1}{\mu-1}. \tag{25a, b}$$

The positivity of the solutions in (25) is assured by the following dimensionless version of (14):

$$\mu > 1 + \xi^{-1}. \tag{26}$$

### Stability of the steady states

Under certain conditions we have two possible steady states: (23) and (25). To which of these, if either, will the system tend? This is not an easy question to answer in general, but we can answer it rather simply for solutions that start near one of the steady states. The required "stability analysis" is always worthwhile as part of an attempt to understand the behavior of a system of ordinary differential equations (see Appendix 5). Our calculations will be facilitated by the relatively uncluttered form of the dimensionless equations (21), but except for slightly increased algebraic complication, they could just as well have been carried out on the original equations (9) (Exercise 3). The given equations (21) have the form

$$dn/d\tau = f(n, c), \quad dc/d\tau = g(n, c), \tag{27a, b}$$

where

$$f(n, c) = \frac{\mu n c}{1+c} - n, \quad g(n, c) = \xi - c - \frac{\nu \mu n c}{1+c}.$$

As is discussed in Appendix 5, the procedure is to introduce deviations  $n'(t)$  and  $c'(t)$  from a given steady state  $(\bar{n}, \bar{c})$  by

$$n = \bar{n} + n', \quad c = \bar{c} + c'. \tag{28a, b}$$

Assuming that the quantities  $n'$  and  $c'$  are small, we can utilize the Taylor approximation (A2.8) to obtain the approximate (linear) equations

$$dn'/dt = An' + Bc', \quad dc'/dt = Cn' + Dc', \quad (29a, b)$$

where

$$A \equiv \left. \frac{\partial f(n, c)}{\partial n} \right|_{n=\bar{n}, c=\bar{c}} = \frac{\mu\bar{c}}{1+\bar{c}} - 1, \quad B = \left. \frac{\partial f(n, c)}{\partial c} \right|_{n=\bar{n}, c=\bar{c}} = \frac{\mu\bar{n}}{(1+\bar{c})^2}, \quad (30a, b)$$

$$C = \left. \frac{\partial g(n, c)}{\partial n} \right|_{n=\bar{n}, c=\bar{c}} = -\frac{\nu\mu\bar{c}}{1+\bar{c}}, \quad D = \left. \frac{\partial g(n, c)}{\partial c} \right|_{n=\bar{n}, c=\bar{c}} = -1 - \frac{\nu\mu\bar{n}}{(1+\bar{c})^2}. \quad (30c, d)$$

Let us first consider the steady-state point (25). Using (24a) for preliminary simplification of the expressions in (30) (not an essential step, but one that makes calculations easier), we find (Exercise 4) that

$$A = 0, \quad B = \theta, \quad C = -\nu, \quad D = -1 - \nu\theta. \quad (31)$$

Here,

$$\theta = \frac{(\mu-1)^2}{\mu\nu} \left( \xi - \frac{1}{\mu-1} \right) \quad (32)$$

is a positive constant, by (26). From (A5.16), the next step is to calculate  $\beta$  and  $\gamma$ :

$$\beta = -(A+D) = 1 + \nu\theta, \quad \gamma = AD - BC = \nu\theta. \quad (33)$$

Because

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

we see from Figure A5.9 that the steady-state point (25) is a stable node. Suppose that circumstances are such that the steady state in question exists [i.e., (26) holds]. Then our stability result implies that if the chemostat starts near this steady state, conditions in the chemostat will automatically adjust themselves so that steady-state conditions (with a non-zero bacterial population) will be approached even more closely. (This is a homeostatic property that is typical of biological systems. The investigation of homeostasis mandates stability analyses in many biological problems.)

Having examined (25), we turn our attention to the other steady state (23), wherein there are no bacteria in the chemostat. Here (Exercise 4),

$$A = \frac{\mu\xi}{1+\xi} - 1, \quad B = 0, \quad C = -\frac{\nu\mu\xi}{1+\xi}, \quad D = -1, \quad (34)$$

$$\beta = 2 - \frac{\mu\xi}{1+\xi}, \quad \gamma = 1 - \frac{\mu\xi}{1+\xi}.$$

Perusal of Figure A5.9 leads us to conclude that there are two possibilities. If

$$1 < \frac{\mu\xi}{1+\xi}, \quad \text{so that } \gamma < 0, \quad (35a, b)$$

then (23) is a saddle point. Alternatively, if (35a) is reversed, then  $\gamma > 0$ ,  $\beta > 0$ ,  $\beta^2 - 4\gamma = (\gamma + 1)^2 - 4\gamma = (\gamma - 1)^2 > 0$ ,

and (23) is a stable node.

We must now relate the conditions just obtained to the other inequalities that we have derived. In doing so, we observe that (35a) is in fact identical with (26). Consequently, either there is a single stable steady state (with no bacteria) or there are two steady states – one with no bacteria, and one in which the chemostat is operating properly. In the latter case, the steady state (25) with bacteria is stable, and the no-bacteria state (23) is unstable.

#### Qualitative behavior and the phase plane

Determination of steady states and their stability is a relatively straightforward task that it is almost always worth carrying out for any dynamic model (i.e., for any set of time-varying equations). Accomplishment of this task is a major step toward the objective of ascertaining the model's qualitative behavior for all possible sets of parameters and initial conditions.

For the present problem, for every (biologically meaningful) parameter value there is exactly one stable steady state. Thus, it is natural to conjecture that the chemostat will approach this state from all initial conditions. This would mean, from (14), that if the flow rate  $q$  were larger than the critical value  $q^*$ , then in whatever manner the chemostat was started, all the bacteria would eventually disappear. But if  $q < q^*$ , there would be a strong homeostatic tendency. No matter how far the chemostat was started from its steady-state operating conditions, the "proper" steady state would be approached as time passed.

of the chemostat is quite reasonable, and it is possible to terminate our theoretical investigation at this point. But additional effort will make the conjecture firm, in the face of such questions as Could there be an oscillatory solution as well as a steady state? Further light will be shed on the operation of the system, and we shall obtain valuable practice in thinking about the phase plane.

Let us follow the steps suggested in Appendix 5 to conjecture the behavior of the various trajectories in the phase plane. We shall plot the bacterial population  $n$  on the ordinate (vertical axis) and the critical substrate concentration  $c$  on the abscissa (horizontal axis), in deference to the tendency to view the bacterial population as a function of its nutrient supply. (In fact, it is wise to keep firmly in mind that  $n$  and  $c$  are mutually interdependent.)

Horizontal tangents in the governing system (21a,b) occur when

$$\frac{dn}{dt} = 0, \text{ i.e., when } n \left( \frac{\mu c}{1+c} - 1 \right) = 0.$$

Thus, **horizontal nullclines** are the straight lines  $n = 0$  and  $c = (\mu - 1)^{-1}$ . The **vertical nullcline** (where  $dc/dt = 0$ ) is the curve

$$\xi - c - \frac{\mu n c}{1+c} = 0, \text{ i.e., } n = \frac{(\xi - c)(1+c)}{\mu c}.$$

This curve approaches  $+\infty$  as  $c$  decreases to zero, and it cuts the  $c$  axis when  $c = \xi$ . In checking for intersections of vertical and horizontal nullclines (the steady-state points), we observe that there are two cases, depending on the relation between  $\xi$  and  $(\mu - 1)^{-1}$ . This is shown in Figure 5.6, where we have also indicated the directions of the trajectories on the nullclines, as well as their directions on the vertical axis (Exercise 8).

Knowing the information we do, it is now possible to sketch the trajectories of Figure 5.7 with quite good confidence, for there seem to be no other reasonable alternatives.

Note how the typical trajectory labeled *A* moves upward and to the left in the beginning, because the initially large nutrient supply permits rapid growth. This, in turn, leads to ever more rapid depletion of bacterial nutrient. Eventually a time is reached at which the population begins to decline; at that time, bacterial density is maximal, at a point of horizontal tangency.

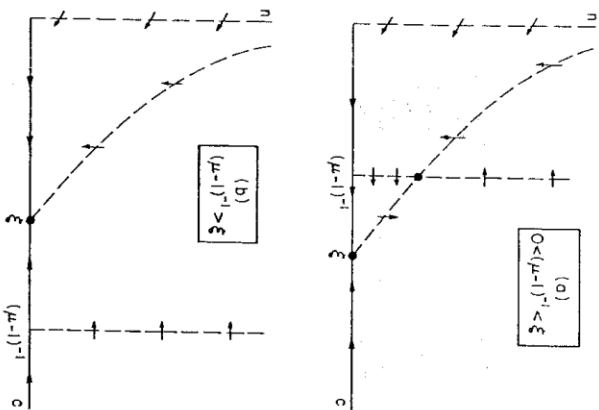


Figure 5.6. Nullclines of the system (21a,b) with the intersections of vertical and horizontal nullclines (steady-state points) marked by heavy dots. Arrows indicate the directions of trajectories on the nullclines and on the axes.

It is a recurrent theme of this book that dynamic systems should be analyzed by examining steady-state points and their stability, conjecturing qualitative behavior, and testing the conjectures by means of computer simulations. For the difference equations of Chapters 2 and 3, such simulations were relatively easy to carry out. They are more difficult for differential equations, but preprogrammed "packages" are becoming available that make phase-plane analysis easier and easier. One such package has been written by Professor G. Odell, of the Department of Mathematical Sciences, Rensselaer Polytechnic Institute, and



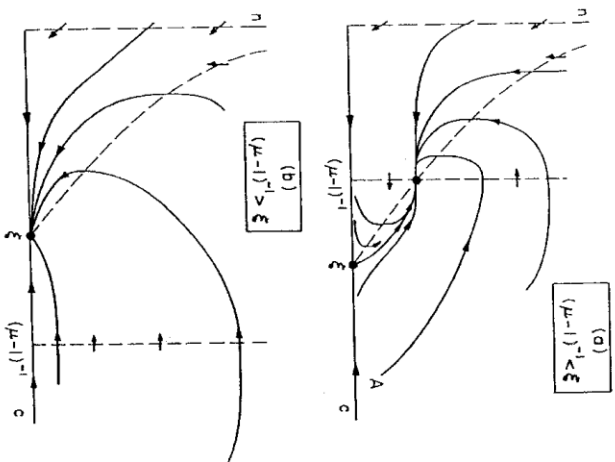


Figure 5.7. Trajectories consistent with the information of Figure 5.6. The trajectory marked A is discussed in the text.

was kindly used by him to produce Figure 5.8. This figure provides gratifying verification of the qualitative behavior that was sketched in Figure 5.7.<sup>1</sup>

The author is not expert with the computer. In an hour of need, he has been able to induce Professor Odell to produce some desired computer simulations. Similarly, when in need of assistance, the reader can doubtless enlist the services of a sympathetic computer virtuoso.

<sup>1</sup> Results of an honest test are being reported. Figure 5.7 was sketched *before* Figure 5.8 was constructed.

### Final remarks

We have answered the various questions we posed concerning the qualitative behavior of the chemostat. Our calculations give strong evidence that the chemostat always approaches a steady state. The approach is nonoscillatory, because steady-state points are never foci.

Although eight parameters appear in our model (9), we have seen that the major qualitative features of the system depend on whether or not the two dimensionless parameters  $\mu$  and  $\xi$  obey inequality (26). Figure 5.9 sums up the situation. In this figure we have chosen to present the results in terms of  $\mu^{-1}$ , not  $\mu$ , because the former is proportional to the most easily adjustable parameter, the flow rate  $Q$ .

In terms of the original parameters, the condition of Figure 5.9 for the final state to contain no bacteria becomes the following constraint on the flow parameter  $q \equiv Q/V$  [see equation (14)]:

$$q > MC_1/(K + C_1). \quad (36)$$

To interpret this condition, consider the (dimensional) bacteria equation (9a):

$$dN/dt = MMC(t)/(K + C(t)) - qN.$$

In this equation, the flow parameter  $q$  can be regarded as playing the role of a death rate, and  $MC(t)/(K + C(t))$  is a nutrient-dependent birthrate. The largest birthrate that can occur in the chemostat is when the nutrient concentration  $C$  takes on its maximum possible value of  $C_1$ . If and only if this maximum birthrate exceeds the "death rate"  $q$  will a nonzero population eventually emerge.

None of our major conclusions may seem surprising in retrospect, but few are generally able to predict our findings without mathematical analysis. Indeed, the chemostat field began with the fundamental theoretical papers of Novick and Szilard (1950) and Monod (1950). The theory has become more necessary as biologists use the chemostat to study more complicated matters, such as competition between different organisms (Slobodkin, 1961) (see Exercise 10) and the effects of temporally varying conditions (Frisch and Gotham, 1977; Smith, 1981).

Experiments have indicated that the basic theory can indeed capture the main features of the experimental phenomena (Rubinow, 1975; Section 1.7), but, as outlined in Exercise 13, recent measurements have provided surprises that require extensions of the analysis.

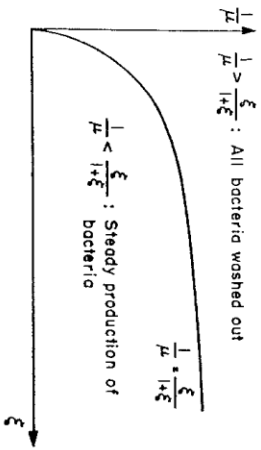


Figure 5.9. Parameter plane indicating domains of different qualitative behaviors of solutions to (21). As in (22),  $\mu^{-1} = \frac{1}{\mu} = \frac{1}{C_0} + \frac{1}{C}$  and  $\xi = \frac{C_0}{C}$ .

Exercises

- (a) Verify equation (21).  
 (b) Verify equations (23)–(26) both by proceeding directly from (21) and by translating earlier formulas into dimensionless variables.  
 (c) Verify that the graphs of  $\bar{N}$  and  $\bar{C}$  are respectively concave down and concave up, as depicted in Figure 5.5.
- Instead of equation (20), introduce the variables  $r = IM$ ,  $c = C/C_0$ ,  $n = N/N_0$ .  
 (Note that these variables are dimensionless.) Find the equations corresponding to (21) in terms of the dimensionless parameters  $\alpha = \mu q/M$ ,  $\beta = K/C_0$ ,  $\gamma = N_0 \gamma'/C_0$ , and  $\delta = C_0/C_1$ . Express  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  in terms of the dimensionless parameters of (22), and thereby show that the latter could still be used to characterize the problem.  
 For practice, repeat the stability calculations of the text using the original equations (9) rather than the dimensionless version (21). Show that the results of the two approaches are the same.
- For practice, repeat the stability calculations of the text using the original equations (31) and (34).
- Show that assumption (5) is “usually” appropriate, at least for sufficiently small values of  $C$ . Describe circumstances, using a specific example, under which (5) would not be a valid approximation, even for small  $C$ .
- Consider the case in which assumption (5), that  $k$  and  $r$  are proportional, is not made.  
 (a) Show that there is essentially no change in the steady states.  
 (b) Discuss the stability of the steady states.  
 (c) Describe the effect of this generalization, if any, on the qualitative behavior.
- How should the chemostat be run to maximize profit if a certain sum is received per bacterium, taking into account the cost of critical nutrient? Consider two cases:

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- (a) In the first case, no nutrient that enters the chemostat is recoverable.  
 (b) In the second case, all nutrient that leaves the chemostat can be recycled.
- Carry out the remaining analysis necessary to obtain Figure 5.6.
- (a) Find the general solution of the linear system given by (29) and (31).  
 (b) Keeping in mind that  $\exp(-qt)$  decays appreciably in a time of order  $q^{-1}$  [see equation (4.20)], show that if  $(1+\theta)^{-1} < 4\theta^2$ , then  $(1+\theta)/2q$  estimates the time for the chemostat to approach nontrivial steady conditions, provided that the system is not started too far from such conditions.  
 (c) Show that if  $(1+\theta)^2 > 4\theta^2$ , then the corresponding time is  $\max(m_1 q^{-1}, m_2 q^{-1})$ , where  $-m_1$  and  $-m_2$  are the roots of  $m^2 + (1+\theta)m + \theta = 0$ .
- This problem concerns the competition between two species in a chemostat (or, equivalently, two species subject to indiscriminate predation or harvesting). Let  $N_1(t)$  and  $N_2(t)$  be the number of individuals in the chemostat.  
 (a) We shall employ the equations  $\frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{N_1 + \alpha_{12} N_2}{K_1}\right) - q N_1$ ,  $\frac{dN_2}{dt} = r_2 N_2 \left(1 - \frac{N_2 + \alpha_{21} N_1}{K_2}\right) - q N_2$ .  
 Discuss the assumptions that are implicit in these equations.  
 (b) Show that coexistence of the two species is possible (Slobodkin, 1961) if  $K_1 \left(1 - \frac{q}{r_1}\right) > \alpha_{12} K_2 \left(1 - \frac{q}{r_2}\right)$ ,  $K_2 \left(1 - \frac{q}{r_2}\right) > \alpha_{21} K_1 \left(1 - \frac{q}{r_1}\right)$ , where  $q < r_1$ ,  $q < r_2$ .  
 (c) Show that, if  $q = 0$ , then species 1 will always win in competition if  $K_1 > \alpha_{12} K_2$ ,  $K_2 > \alpha_{21} K_1$ .  
 (d) Given that  $\alpha_{12} \alpha_{21} < 1$ ,  $r_1 < r_2$ , show that, in spite of the intrinsic superiority of species 1, if  $\frac{K_1 - \alpha_{12} K_2}{K_1 r_1 - \alpha_{12} K_2 r_1} < q < \frac{\alpha_{21} K_1 - K_2}{\alpha_{21} K_1 r_1 - K_2 r_1}$ , then coexistence is possible. (Ecologically speaking, this shows that indiscriminate predation can enhance the possibilities of species coexistence.)  
 (e) Find conditions permitting coexistence when  $q = 0$  but not when  $q > 0$ .
- An extremely simple model for the number of bacteria  $N(t)$  in some natural environment is  $\frac{dN}{dt} = \frac{MCN}{C+k} - DN$ ,  $\frac{dC}{dt} = -\frac{MCN}{Y(C+k)} + I$ , where  $M$ ,  $k$ ,  $d$ ,  $y$ , and  $I$  are positive constants.