NONLINEAR POPULATION DYNAMICS IN THE CHEMOSTAT

The author describes the chemostat, a device used to study bacterial populations under nutrient-limited conditions. This article shows that a simple criterion can help predict which species survive in the long run, an example of the principle of mutual exclusion.

The chemostat, also known as the continuous stirred tank bioreactor, was independently invented by Jacques Monod[1] and by Aaron Novick and Leo Szilard,[2,3] who also coined the term *chemostat*. Its inventors conceived that this device provided a convenient way to study a bacterial population in the steady state, letting the experimenter adjust growth rate and external parameters, such as temperature or pH level. Novick and Szilard were mostly interested in the effects of mutations on a population's long-range behavior, while Monod's interest centered on the regulation mechanisms operating within the cells under nutrient-limited conditions.

Since its invention, the chemostat has become a ubiquitous tool for studying microbial physiology and metabolism.[4] Over the years, researchers have come to appreciate that chemostat theory could apply to studies of microbial ecology and, more generally, of population dynamics.[5] Early formulations used time-invariant differential equations to model the chemostat. More recently, the models have expanded to include delayed nutrient recycling, as could occur in a lake where slow sediment decomposition takes place.[6,7]

In this article, I wish to give an elementary account of the chemostat, introduce the model's equations, and describe some typical cases of population dynamics. Although the chemostat does not enjoy the Lotka–Volterra predator–prey model's widespread popularity, this system is worthy of the interest of science educators. I've used it for several years as a theme for a computational physics project.

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Basic relations

Figure 1 shows the chemostat's basic principle—it is a well-stirred, constant-level reactor. Microorganisms reside in the vessel at a density x (organisms per unit volume or grams of biomass per unit volume) in a culture volume v. We assume that these bacteria depend for their continued existence on a single nutrient, which we call the *substrate*. A pump (not shown) delivers sterile growth medium, which contains the substrate at concentration s_R to the chemostat at a constant flow rate f (volume per unit time). The culture medium, containing bacteria, unused substrate, and possible secondary products of metabolism, is discharged from the constant-volume reactor at an identical rate f.

We define the dilution rate $D = f/v$; it is the number of complete volume renewals per unit time. Because the tank is well stirred, a culture particle (nutrient molecule or bacterium) has probability D of leaving the chemostat during the unit time. Conversely, such a particle's average residence time in the reactor is $1/D$, where D is the system's main control parameter. Therefore, the washout rate for organisms is

$$\left.\frac{dx}{dt}\right|_w = -Dx \quad . \tag{1}$$

Bacterial population growth by cell division is governed by an exponential law or, equivalently, by the differential equation

$$\left.\frac{dx}{dt}\right|_g = \mu x \tag{2}$$

where μ is the specific growth rate (measured in units of inverse time; usual values fall in the range 0.1 to 1 h^{-1}). It is related to the population-doubling time t_d by $t_d = \ln(2)/\mu$. We can obtain the complete equation for the number density of organisms in the chemostat (or the biomass concentration) by adding the two previous contributions:

$$\frac{dx}{dt} = (\mu - D)x \, . \tag{3}$$

The substrate concentration in the reaction volume s (grams or moles per unit volume) evolves because of inflow, washout, and consumption by the organisms. The first two contributions are described by an equation similar to Equation 2:

$$\left.\frac{ds}{dt}\right|_{flow} = D(s_R - s) \, . \tag{4}$$

Monod showed that bacterial growth rate and substrate utilization are usually proportional to each other, at least when we use a single nutrient.[1] We write this in differential form as

$$\left.\frac{dx}{dt}\right|_g = -Y\left.\frac{ds}{dt}\right|_g \, . \tag{5}$$

The parameter Y is known as the yield constant; it is dimensionless, and the minus sign accounts for the fact that the substrate is consumed during growth. Most microorganisms have Y values between 0.05 and 0.2. Adding the two contributions to ds/dt leads to

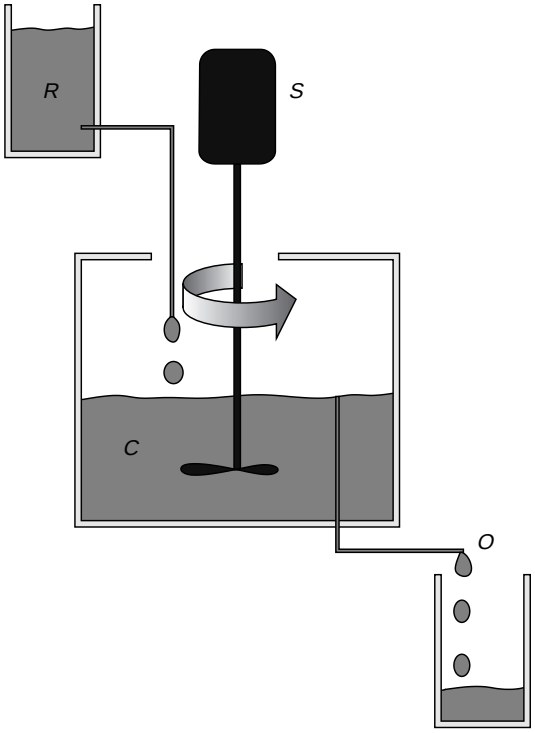

Figure 1. The chemostat in schematic outline. *R* stands for reservoir; *S* for stirrer; *C* for chemostat or reactor, and *O* for overflow. The flow rate in and out of *C* is constant.

$$\frac{ds}{dt} = D(s_R - s) - \frac{\mu x}{Y} \, . \tag{6}$$

Equations 3 and 6 would form a simple system of coupled linear differential equations were it not for the quantity μ, which depends on the substrate concentration and introduces a nonlinear coupling. Following Monod,[8] we assume that for a single substrate

$$\mu = \mu_m \frac{s}{k + s} \tag{7}$$

where μ_m is the maximum possible value of μ reached at infinite nutrient concentration (μ_m depends on the medium's physical parameters such as temperature and pH). k is what we call a saturation constant, and it is equal to that value of s for which μ is one-half its maximal value. k is generally found in the range 10^{-4} to 10^{-3} gl^{-1} (where gl^{-1} represents grams per liter). Equation 7 is a transposition of the well-known Michaelis–Menten law for enzyme kinetics.[9] (In their model of an enzyme-catalyzed reaction, Leonor Michaelis and

Maude Menten proposed that when a substrate (or reagent) molecule S encounters an enzyme molecule E, a complex ES is formed; both formation and dissociation of ES back to $E + S$ are fast processes. However, the complex sometimes dissociates by a different route to enzyme + product P; this reaction is slow. Simple kinetic theory then shows that in the steady state, the overall rate of formation of P depends on the substrate concentration, just as it does in Equation 7.) There is little direct experimental justification for Equation 7, but the precise form of the growth rate–substrate concentration relationship is not important, provided μ is a monotonous increasing function of s, with a limiting value.

A steady-state bacterial population can be established given a suitable dilution rate.

Equations 1 through 7 completely describe the behavior of a single-species, single-substrate chemostat, where μ_m, k, and Y are constants characteristic of the organism (for given external parameters); the experimenter can adjust s_0 and D.

The steady state

Setting $dx/dt = ds/dt = 0$ and denoting with a tilde steady-state quantities, we derive the relations (disregarding the trivial case $x = 0$, $s = s_R$):

$$\tilde{s} = k\frac{D}{\mu_m - D}, \tag{8}$$

$$\tilde{x} = Y(s_R - \tilde{s}), \tag{9}$$

$$\tilde{\mu} = \frac{\mu_m \tilde{s}}{k + \tilde{s}} = D. \tag{10}$$

As the dilution rate D increases from zero, the steady-state nutrient concentration in the chemostat increases, while the concentration of organisms falls until D reaches the critical value D_c, for which the substrate concentration is s_R and the biomass concentration vanishes. We find from Equation 8

$$D_c = \frac{s_R \mu_m}{k + s_R}. \tag{11}$$

At all higher values of D, bacteria are washed out of the reactor faster than they can multiply, and we can't establish a steady state with a nonvanishing bacterial population, whatever the initial conditions. It might also happen that we can't maintain a valid steady state, characterized by s, x, and μ, because the independent quantity s_R is too small. We must therefore also require that $s_R > s$.

A special limiting case

Let's investigate the special case of vanishing inflow and outflow, $D = 0$. The two governing equations now read

$$\frac{dx}{dt} = \mu_m \frac{sx}{k + s} \quad \text{and} \quad \frac{ds}{dt} = -\frac{\mu_m}{Y}\frac{sx}{k + s}. \tag{12}$$

We observe first that s and x are linked by the simple relation $(d/dt)(x + Ys) = 0$, or introducing the initial values of the concentrations in the reactor, x_0 and s_0:

$$x + Ys = x_0 + Ys_0 \equiv C_0. \tag{13}$$

This relation expresses a simple conservation law: the bacteria uses any organic matter that disappears to make microbes, albeit with the yield Y.

Assume further that the substrate concentration is far from saturating or that s is small compared to k. The equation for x is then

$$\frac{dx}{dt} = \frac{\mu_m}{kY} x(C_0 - x) \tag{14}$$

a form of the well-known logistic equation,[10] with a growth parameter $\mu_m C_0/kY$ and a carrying capacity C_0. (Attributed to Pierre Verhulst, this model of population growth states that at low density, growth rate is proportional to population, leading to an exponential growth. However, food will become scarce and the habitat overcrowded. This effect is conventionally modeled by the factor $C_0 - x$. Growth stops when x reaches C_0, the carrying capacity of that particular habitat.) There are again two fixed points: the trivial case $x = 0$ and the steady state $x = C_0$.

The general case

Because we need to examine, without restrictions, the properties of the solutions of the chemostat Equations 1 through 7, it's more

convenient to switch to dimensionless variables. Previous works have proposed various choices of variables, but we have found Hal Smith and Paul Waltman's[11] scheme to be especially convenient—it also decreases to a minimum the number of independent parameters. Smith and Waltman use $1/D$ as the time unit and s_R as the concentration unit. More precisely, we can define reduced variables

$$T = Dt\ ;\ S = s/s_R\ ;\ X = x/Ys_R \tag{15}$$

and recast the differential equations as

$$S' = \frac{dS}{dT} = 1 - S - \frac{MSX}{K+S} \equiv F(S, X), \tag{16}$$

$$X' = \frac{dX}{dT} = \frac{MSX}{K+S} - X \equiv G(S, X). \tag{17}$$

This introduces the reduced parameters $M = \mu_m/D$ and $K = k/s_R$ and defines, for further reference, the right-hand sides of Equations 16 and 17 as F and G.

We first notice that a conservation law, similar to that used in the previous paragraph, is still operative in the general case. Adding Equations 16 and 17, we get $S' + X' = 1 - S - X$. We can write the solution as

$$S + X = (S_0 + X_0 - 1)e^{-t} + 1. \tag{18}$$

This result defines the asymptotic behavior of the solutions as $\lim_{t\to\infty}(S + X) = 1$.

The system in Equations 16 and 17 has two fixed points: $\{X_1 = 0, S_1 = 1\}$ and

$$\tilde{S}_2 = \frac{K}{M-1}\ \ ;\ \ \tilde{X}_2 = 1 - \frac{K}{M-1} \tag{19}$$

which are the translation, in terms of dimensionless variables, of Equations 8 through 10. The role of D is now taken up by M. Because concentrations are positive, $M > 1$ (or $D < \mu_m$). If this condition is violated, no steady state with a finite bacterial population is possible; this is the washout I already described. We must also have $K < M - 1$. This is the condition on s_R I already mentioned, which we can verify using the definitions of M and K.

Stability of the fixed points

To investigate the stability of the fixed points, we form the Jacobian matrix

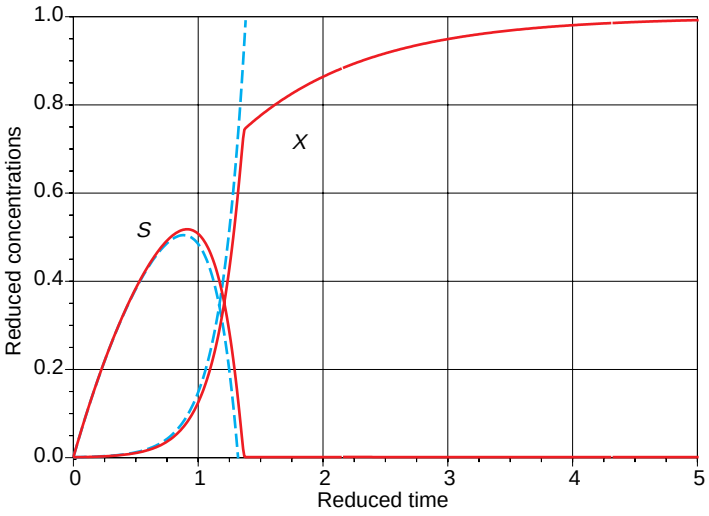

Figure 2. Concentrations versus time computed according to Equations 16 and 17 (full line) or Equations 22 and 23 (dashed line). *S* denotes substrate and *X* microbes.

$$\mathbf{J} = \begin{bmatrix} \frac{\partial F}{\partial S} & \frac{\partial F}{\partial X} \\ \frac{\partial G}{\partial S} & \frac{\partial G}{\partial X} \end{bmatrix} = \begin{bmatrix} -1 - \frac{XMK}{(K+S)^2} & -\frac{MS}{K+S} \\ \frac{XMK}{(K+S)^2} & -1 + \frac{MS}{K+S} \end{bmatrix} \tag{20}$$

and for the steady state, we find

$$\mathbf{J}_2 = \begin{bmatrix} -1-\alpha & -1 \\ \alpha & 0 \end{bmatrix}\ \ ;\ \ \alpha = \frac{M-1}{M}\left(\frac{M-1}{K} - 1\right). \tag{21}$$

The eigenvalues and eigenvectors are $\lambda_1 = -1$, $\mathbf{v}_1 = [1, -\alpha]^T$ and $\lambda_2 = -\alpha$, $\mathbf{v}_2 = [1, -1]^T$. According to the previous paragraph, $M > 1$ and $M - 1 > K$; thus, α is a positive quantity, and both eigenvalues are negative. This fixed point is therefore a stable node.

Numerical simulations of the simple chemostat

It is straightforward to numerically solve the system in Equations 16 and 17 of two coupled, first-order differential equations, given a set of initial values. We used the free software Scilab (see www-rocq.inria.fr/scilab), which incorporates sophisticated subroutines from the Netlib collection (lsoda, a predictor–corrector Adams method from the Odepack package, is the default choice, but many others are available). Figure 2 shows a typical time course corresponding

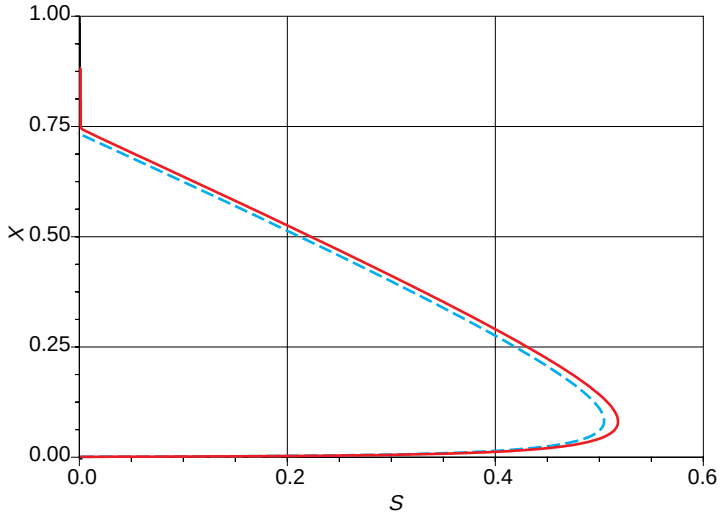

Figure 3. A phase plane display of Figure 2's data. The dashed line refers to the approximate Equations 22 and 23.

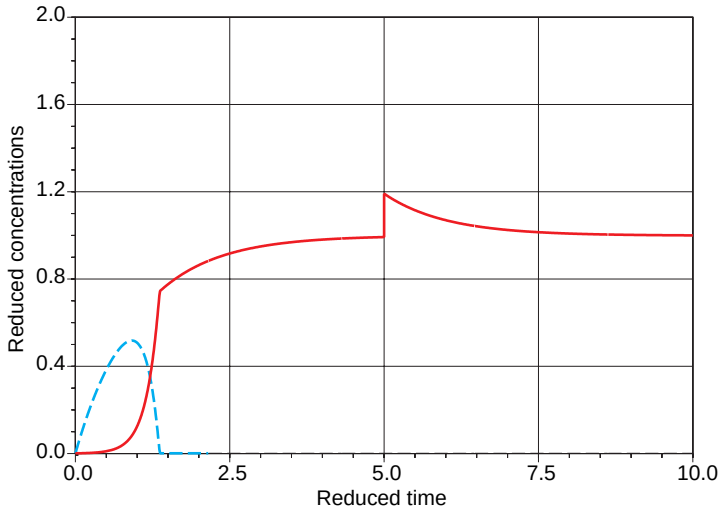

Figure 4. The effect of a 20% decrease of the substrate feed concentration. The full line represents bacterial concentration, and the dashed line represents substrate.

to the parameter values in a previous study (Y = 0.53, μ_m= 0.85 h^{-1}, k = 0.0123 gl^{-1}, s_R = 2.5 gl^{-1}).[4] It is also convenient to use a phase plane (X versus S) display, as in Figure 3.

We observe similar patterns for all realistic parameter choices. The cell density increases almost exponentially and then rather suddenly levels off, while the substrate concentration goes through a maximum and falls to a small value. This characteristic behavior suggests that we can derive a simple approximation that could simulate the early stages of biomass development.

Assuming that $S >> K$, we find that Equations 16 and 17 become almost uncoupled:

$$S' = 1 - S - MX \tag{22}$$

$$X' = MX - X. \tag{23}$$

Solutions for these simplified equations are plotted as dashed lines in Figures 2 and 3. They provide rather good approximations while S is large compared to K.

We can also check the steady state's stability numerically. We integrate Equations 16 and 17 for a time span sufficient for the system to be close to the steady state, and then we suddenly apply a perturbation—for instance, a 20% decrease of s_R (due to our choice of s_R as the concentration unit, this is equivalent to a 20% increase of X, S, and K). Figure 4 shows that the system exponentially returns to its previous state. We observe a similar behavior after a jump of D.

Comparison with experiment

The model I presented earlier in Equations 1 through 7 describes the Monod–Novick–Szilard experiment's gross features.[4] However, more detailed investigations have shown that for some operating conditions, the chemostat can display phenomena typical of nonlinear systems: oscillations and hysteresis. It would take us too far afield to describe the numerous and complex mechanisms that we could invoke to explain these observations. However, I will mention two simple modifications of the basic Equations 16 and 17 that might lead to oscillations for some values of the parameters.

The concept of maintenance energy was introduced[12] to take into account the fact that, quite apart from growth, cells will consume energy and thus substrate to maintain ion gradients across the membrane, to move, and so forth. Formally, we write

$$\frac{ds}{dt} = \left.\frac{ds}{dt}\right|_{flow} + \left.\frac{ds}{dt}\right|_{g} + \left.\frac{ds}{dt}\right|_{m} \equiv D(s_R - s) - \frac{\mu x}{Y} - nx. \tag{24}$$

Generally accepted values of the maintenance coefficient n are in the range 0.01 to 0.05 h^{-1}. Equation 23 is replaced with

$$S' = \frac{dS}{dT} = 1 - S - \frac{MSX}{K+S} - NX \equiv F(S, X) \qquad (25)$$

where $N = nY/D$. The Jacobian matrix's eigenvalues become complicated expressions in N, M, and K—it would be tedious to give an analytical discussion of the maintenance energy's effect on population dynamics. On the other hand, it is a simple matter to numerically solve the modified equations. The result (not shown) for all reasonable values of N is the appearance of a slight overshoot in S and X just before reaching the steady state, indicating that the eigenvalues λ_1 and λ_2 now have a small imaginary part.

As another simple modification of the model, it has been suggested[13,14] that the yield Y should depend on the substrate concentration s in the reactor. A simple linear law, $Y = a + bs$, is usually assumed. For some ranges of values of a and b, oscillations about the steady state can occur. Figure 5 shows the result of a numerical simulation. The dimensionless variable $X = x/s_R Y$ defined in the previous section is inconvenient here; better choices are $X^* = x/x_R$ or the use of dimensioned variables. Figure 5 shows that substrate and microbe concentrations undergo oscillations reminiscent of the nonlinear van der Pol oscillator.

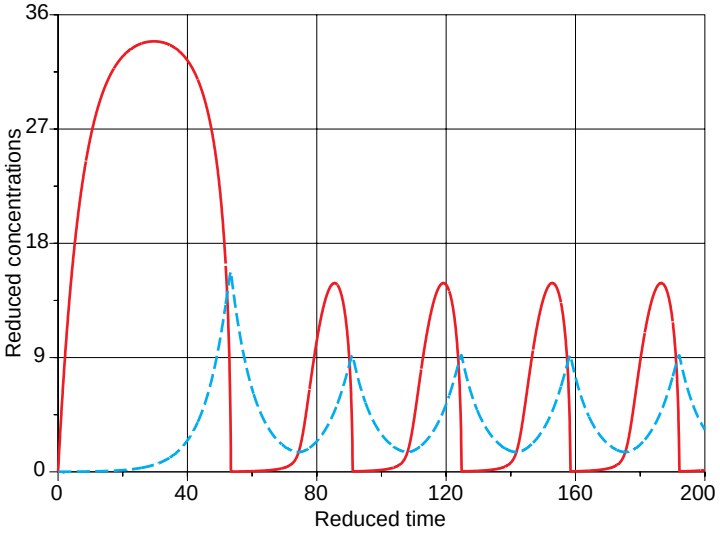

Figure 5. Oscillating concentrations when the yield depends on the substrate concentration: $Y = 0.01 + 0.03s$. Other parameters are $D = 0.14\ h^{-1}$; $\mu_m = 0.3\ h^{-1}$; $k = 1.75\ gl^{-1}$; and $s_R = 35\ gl^{-1}$. The full line refers to the substrate and the dashed line to bacteria.

Competition in the chemostat

Although in practice the chemostat is rarely seeded with several microbial species, chemostat theory that is generalized to account for more than one population has received much attention as a convenient model with which to study competition among species that feed on renewable resources. For the case of closed ecosystems, Vito Volterra and many others[15] established the principle of competitive exclusion: the number of species cannot exceed the number of resources (substrates). This principle is also valid for the chemostat.[11] Let's examine the rather simple case of two species competing for a single limited substrate.

We consider a constant-level, continuously stirred reactor harboring two distinct microbial species, at concentrations $x_1(t)$ and $x_2(t)$ that both feed on the same substrate whose concentration is $s(t)$. A pump delivers substrate to the reactor at concentration s_R at a constant rate. We assume a simple additive model for microbial growth and substrate utilization, as the following equations show:

$$\dot{x}_1 = (\mu_1 - D)x_1; \qquad (26a)$$

$$\dot{x}_2 = (\mu_2 - D)x_2; \qquad (26b)$$

$$\dot{s} = (s_R - s)D - \frac{\mu_1 x_1}{Y_1} - \frac{\mu_2 x_2}{Y_2}. \qquad (26c)$$

Each growth constant μ_i (i = 1,2) depends on s and on two specific parameters $\mu_{m,i}$ and k_i through the Monod relationship

$$\mu_i = \frac{\mu_{m,i} s}{k_i + s}. \qquad (27)$$

We proceed as in the previous simulation to dedimensionalize Equation 26. We set $X_i = x_i/s_R Y_i$, $S = s/s_R$, $T = Dt$, $M_i = \mu_{m,i}/D$, and $K_i = k_i/s_R$ so that the governing equations are

$$S' = 1 - s - \frac{M_1 S X_1}{K_1 + S} - \frac{M_2 S X_2}{K_2 + S} \equiv F(S, X_1, X_2) \qquad (28)$$

$$X'_1 = \frac{M_1 S X_1}{K_1 + S} - X_1 \equiv G(S, X_1, X_2) \qquad (29)$$

$$X'_2 = \frac{M_2 S X_2}{K_2 + S} - X_2 \equiv H(S, X_1, X_2) \qquad (30)$$

where a prime denotes derivation with respect

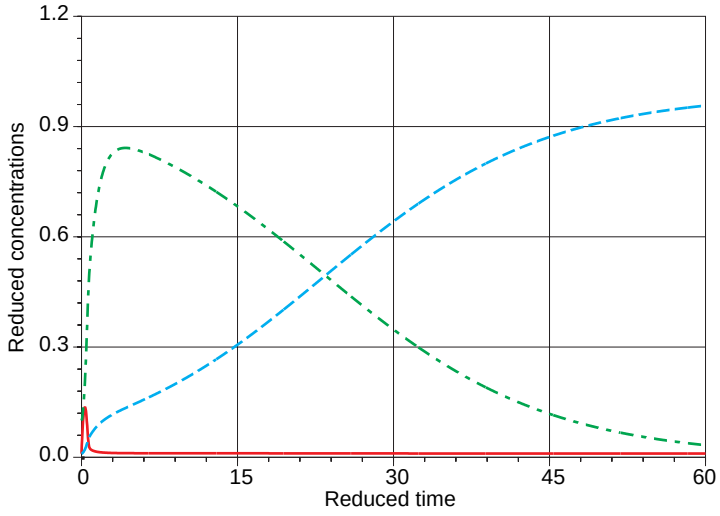

Figure 6. A time course for the concentrations of substrate (full line)—species 1 is the dashed line, and species 2 is the dot and dashed line.

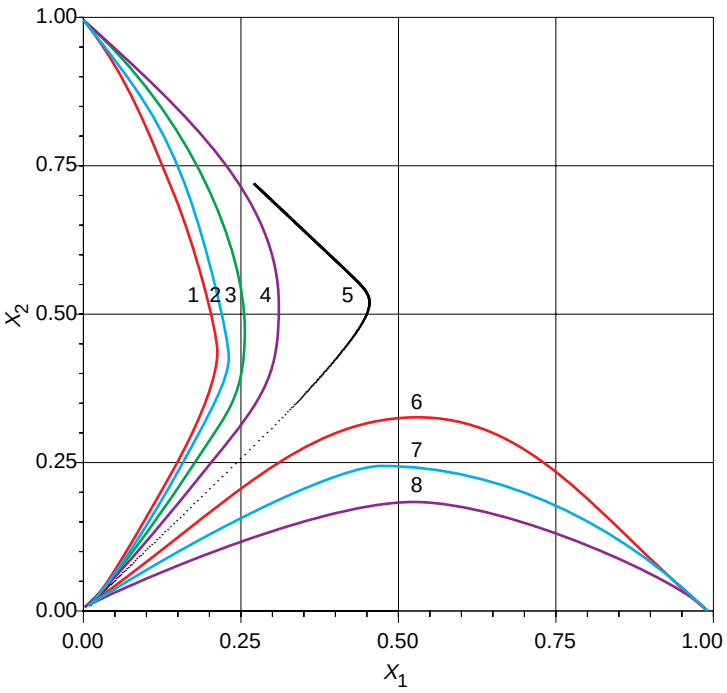

Figure 7. A phase plane representation of the competition between similar species. R_1 = 0.01 at all times. R_2 increases for each successive trajectory, with values (1): 0.0025; (2): 0.0035; (3): 0.0049; (4): 0.00686; (5): 0.0096; (6): 0.01345; (7): 0.0188; (8): 2.635.

to T, and we define functions F, G, and H for later reference.

The steady state is defined by setting the three time derivatives equal to zero. We see that no steady state exists with both populations different from zero, because S would have to satisfy two incompatible equations, $G = 0$ and $H = 0$. There are nonetheless three different steady states. Introducing the quantities $R_i = K_i/(M_i - 1)$, $i = 1,2$ (with $0 < R_i < 1$), we find that one of the following three sets of conditions must hold:

$$X_1 = X_2 = 0; S = 1, \tag{31a}$$

$$\tilde{X}_1 = 0 \;;\; \tilde{S} = R_2 \;;\; \tilde{X}_2 = 1 - R_2, \tag{31b}$$

$$\tilde{X}_2 = 0 \;;\; \tilde{S} = R_1 \;;\; \tilde{X}_1 = 1 - R_1. \tag{31c}$$

We can investigate the stability of these states by first forming the Jacobian matrix of all partial derivatives of F, G, and H and then computing the eigenvalues. From the condition in Equation 31a, we derive the three eigenvalues:

$$\lambda_1 = -1 \;;\; \lambda_2 = \frac{M_1}{K_1 + 1} - 1 \;;\; \lambda_3 = \frac{M_2}{K_2 + 1} - 1. \tag{32a}$$

The last two are positive, implying that the trivial steady state is a saddle point. Starting from Equation 31b, we get

$$\lambda_1 = -1 \;;\; \lambda_2 = \frac{R_2 - R_1}{R_1 + \frac{R_2}{M_1 - 1}} - 1 \;;\; \lambda_3 = \frac{(M_2 - 1)^2}{K_2 M_2}(1 - R_1) \tag{32b}$$

where λ_1 and λ_3 are negative. The steady state's stability depends on the sign of λ_2, more precisely on the sign of its numerator. If the condition

$$R_2 = \frac{K_2}{M_2 - 1} < \frac{K_1}{M_1 - 1} = R_1 \tag{33}$$

holds, then all three eigenvalues are negative, and the steady state defined by Equation 31b is a stable node. A similar analysis would show that the condition $X_2 = 0$ corresponds to an unstable state. Should the inequality in Equation 33 be reversed, then the previous conclusions must also be reversed: Equation 31c is the stable steady state and 31b is unstable.

We have thus shown that a single species survives in the long run—that with the smallest $K/(M - 1)$ ratio. This conclusion is an example of the competitive-exclusion principle as applied to a continuous culture. Smith and Waltman offer a much more general and rigorous proof, ex-

tended to any number of competing species.[11] According to these authors, coexistence is possible in the improbable case that $R_1 = R_2$.

Numerical simulations of competition processes

Figure 6 displays the substrate's time dependence and microorganism concentrations in the case of species with similar parameters: $M_1 = 5$, $K_1 = 0.04$, $R_1 = 0.01$, $M_2 = 5$, $K_2 = 0.045$, and $R_2 = 0.01125$. X_2 starts very strongly, but goes through a maximum and finally heads for oblivion. Figure 7 shows the behavior of several similar systems plotted in the phase plane (X_1, X_2). Parameter R_1 is fixed at 0.01 ($R_1 = 0.0025$). The full line trace on the left corresponds to $K_2 = 0.01$ ($R_2 = 0.0025$) and increases by a factor of 1.4 for each successive curve. Species 2 survives in the long run as long as $R_2 < R_1$ (first five traces) and then X_1 takes over (last three curves).

I have described the behavior of microbial species in a chemostat, under simple hypotheses. Such studies offer interesting examples of nonlinear dynamics, and although the device is 50 years old, it is still the subject of active research that could also be of interest to scientists and engineers.

In further studies, we could modify or generalize the previous simple models in this article in many ways. We could introduce more complex dependencies of μ or Y on the substrate concentration. We could make the supply of limiting substrate time-dependent, thus simulating seasonal variations. We could consider several species and/or several limiting substrates. Moreover, other types of interactions between species are possible. For instance, one strain could be assumed to produce the substrate for another (commensalism). Under another hypothesis (mutualism), the shared compound, although essential for life of the second species, is not responsible for its growth. Analogous to the Lotka–Volterra model, one or several predator species can be introduced, and we could model multistage chemostats in which the overflow of stage k feeds stage $k + 1$. Finally, we could abandon the well-stirred hypothesis, introducing spatial dependencies in the system.

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