Mathematical Models of Microbial Growth

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The Basic Model for Microbial Growth (Monod and others, 1940s-50s)

- Hypotheses
  - Microbial growth rate is determined by the concentration of a single growth-limiting substrate (nutrient) in the growth medium.
  - The growth rate adjusts itself instantaneously in response to changes in the substrate concentration.

$s(t) =$ concentration of substrate at time t

$x(t) =$ concentration of microorganism at time t

$\frac{x'(t)}{x(t)}$ is called the specific growth rate of the colony.

Monod hypothesized that

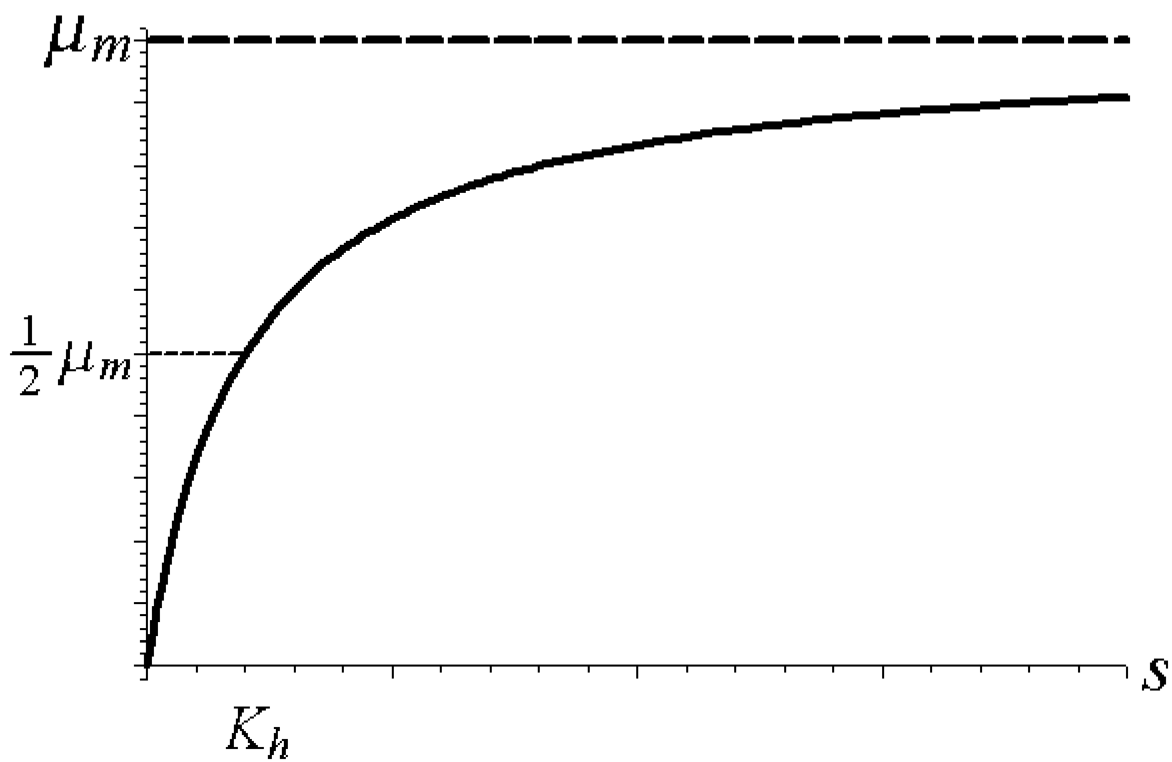
$$\frac{x'(t)}{x(t)} = \mu(s(t))$$

where μ is a continuous and increasing function that satisfies $\mu(0) = 0$ and $\lim_{s\to\infty} \mu(s) = \mu_m$ where $\mu_m < \infty$ is called the maximal specific growth rate.

Specifically, Monod hypothesized that μ has the form

$$\mu(s) = \frac{\mu_m s}{K_h + s}$$

where μ_m is the *maximal specific growth rate* and K_h is called the *half-saturation constant* (because it is the value of s for which $\mu(s) = \mu_m/2$).



One more hypothesis is:
The rate of decrease of substrate is instantaneously proportional to the rate of increase of microorganism.
Thus

$$x'(t) = -Ys'(t)$$

where

$$Y = \frac{\text{mass of organism formed}}{\text{mass of substrate consumed}}$$

is called the *yield constant*.

By combining all of our modelling hypotheses, we obtain:

The Monod Model for Microbial Growth in Batch Culture

$$s'(t) = -\frac{1}{Y}\frac{\mu_m s(t)}{K_h + s(t)}x(t), \qquad s(0) = s_0 > 0$$

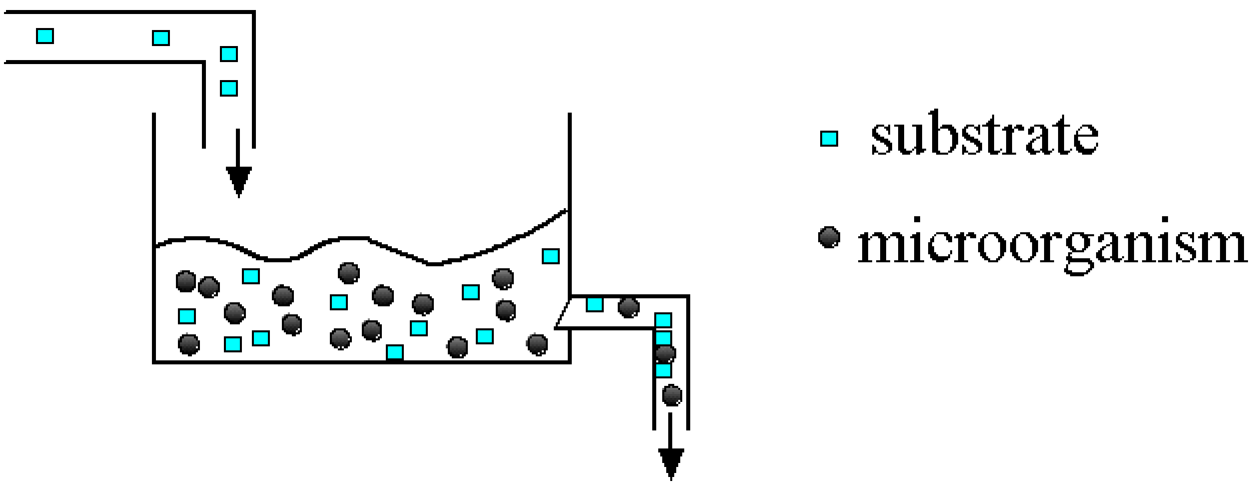
$$x'(t) = \frac{\mu_m s(t)}{K_h + s(t)}x(t), \qquad x(0) = x_0 > 0$$

This solutions of this model are in agreement with what would be expected based on the modelling hypotheses: The substrate decreases. The microbe increases (as an increasingly slower rate as substrate becomes depleted) and

$$\lim_{t\to\infty} s(t) = 0, \qquad \lim_{t\to\infty} x(t) = x_0 + Ys_0.$$

Continuous Culture

A chemostat (also called a continuous culture device or a CSTR) is a device that allows us to continuously refresh the culture medium and simultaneously remove the contents of the culture vessel (at the same rate - so that the volume of the culture vessel remains constant at all times).



The Basic Continuous Culture Model

F = flow rate (volume/time)

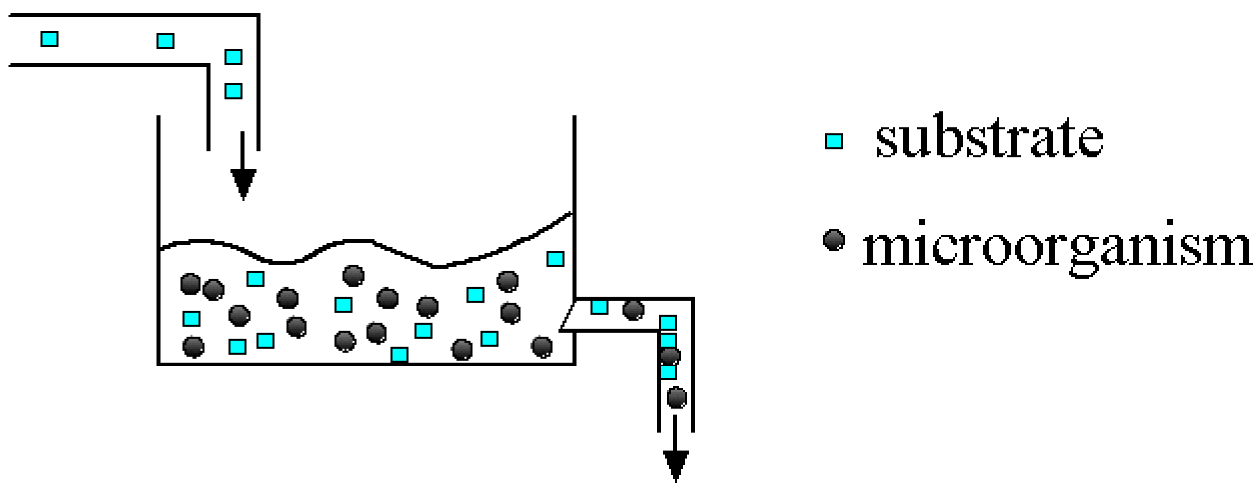
V = volume

$D = F/V$

s_f = substrate concentration in the influent fresh medium

$$s'(t) = Ds_f - \frac{1}{Y}\mu(s(t))x(t) - Ds(t), \qquad s(0) = s_0 > 0$$

$$x'(t) = \mu(s(t))x(t) - Dx(t), \qquad x(0) = x_0 > 0$$



Equilibria

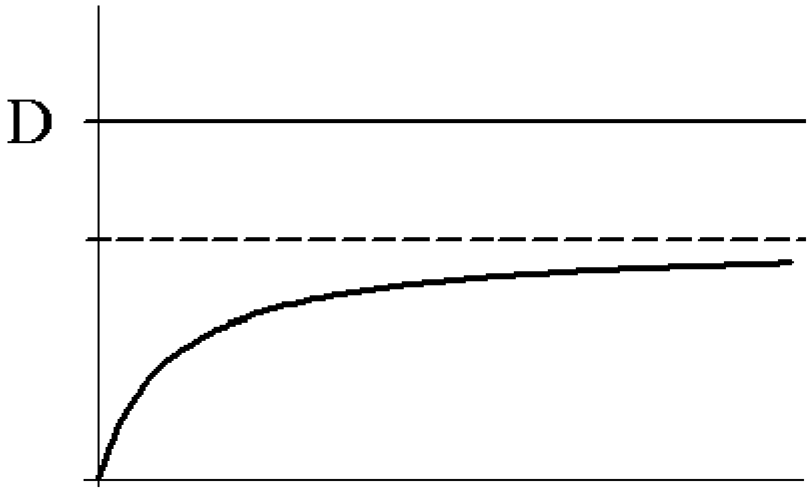
$$s'(t) = Ds_f - \frac{1}{Y}\mu(s(t))x(t) - Ds(t), \qquad s(0) = s_0 > 0$$

$$x'(t) = \mu(s(t))x(t) - Dx(t), \qquad x(0) = x_0 > 0$$

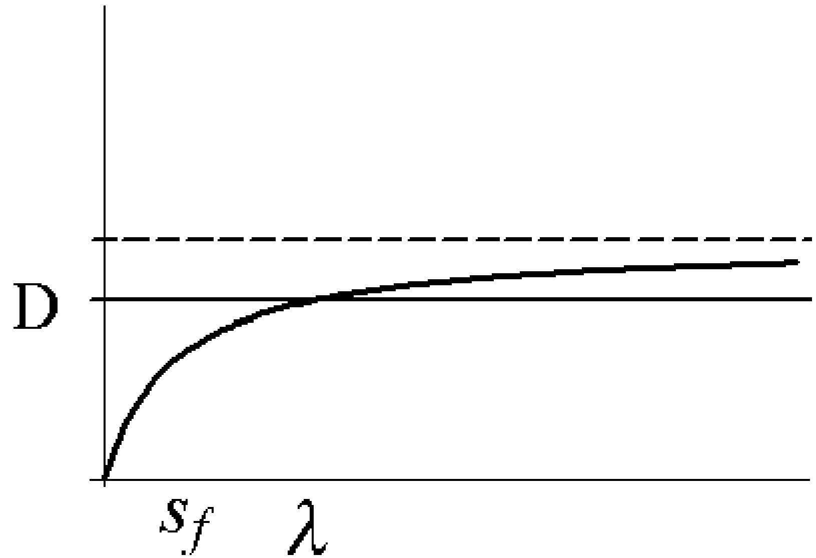
One equilibrium point is $E_0 = (s_f, 0)$. This is the equilibrium that would be achieved if there were no microbes in the growth vessel.

Assuming that there is a value, λ, such that $\mu(\lambda) = D$, there is another equilibrium point: $E_1 = (\lambda, Y(s_f - \lambda))$. This equilibrium point is meaningful only if $\lambda < s_f$.

Three Scenarios

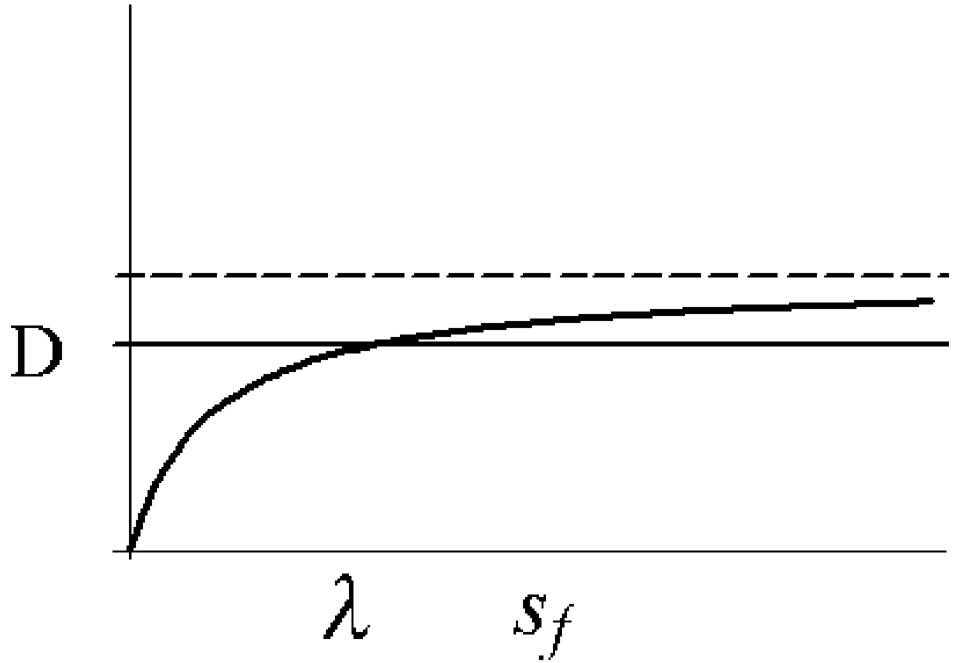


Washout rate too high



Food input concentration too low

E_1 does not exist in either of these scenarios.



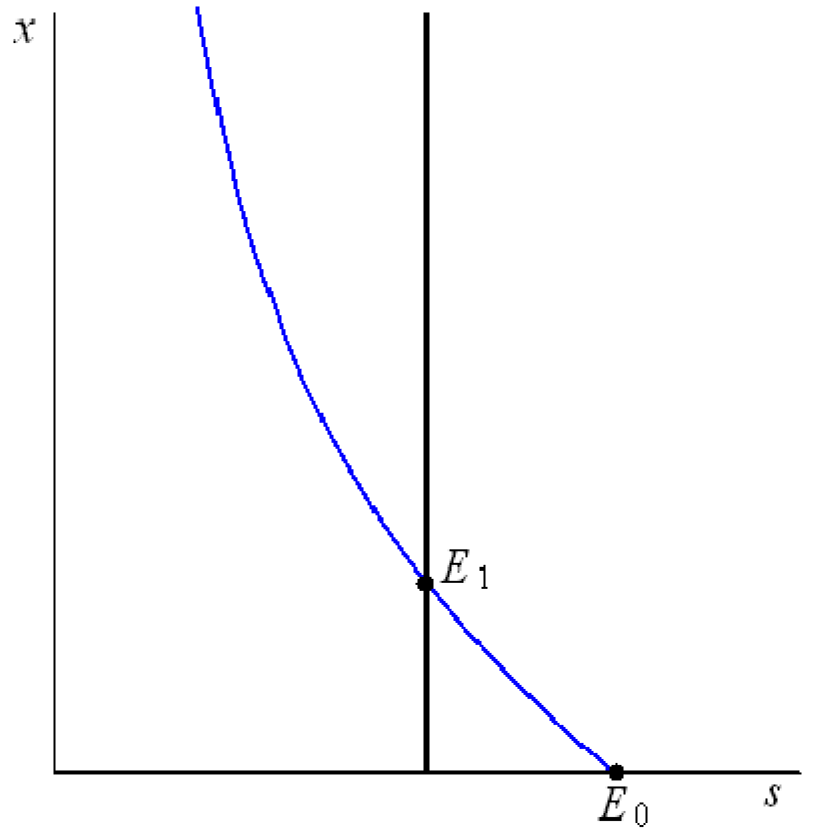
$E_1 = (\lambda, Y(s_f - \lambda))$ does exist in this scenario because $\mu_m > D$ (meaning that λ exists) and also $s_f > \lambda$.

We will now analyze what happens (using graphical methods) when E_1 exists ($\mu_m > D$ and $s_f > \lambda$).

For simplicity, we will assume that $Y = 1$.

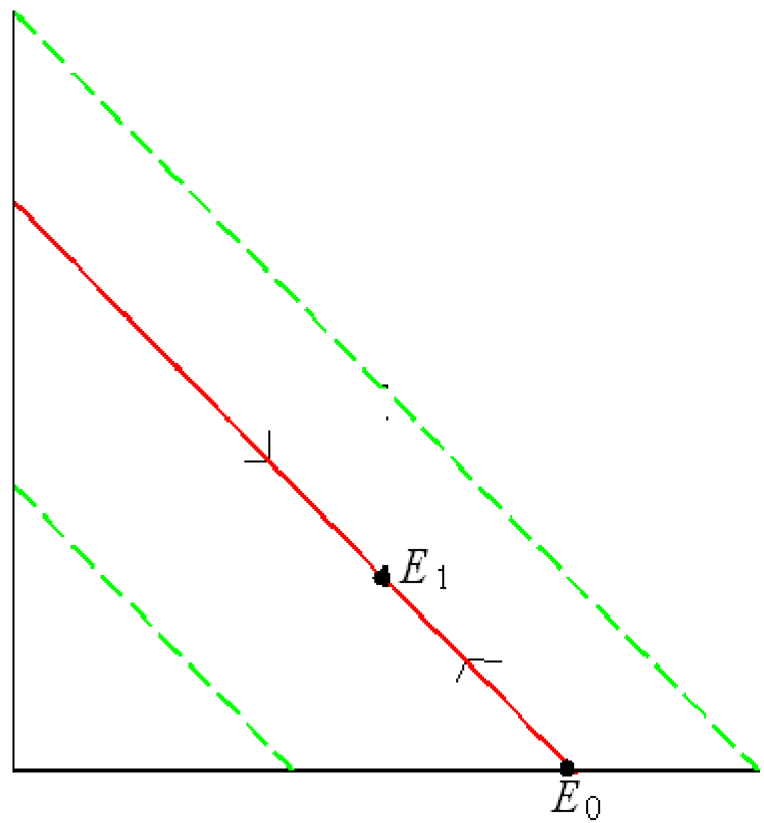
Thus $E_0 = (s_f, 0)$ and $E_1 = (\lambda, s_f - \lambda)$.

The nullclines in this case are pictured below.

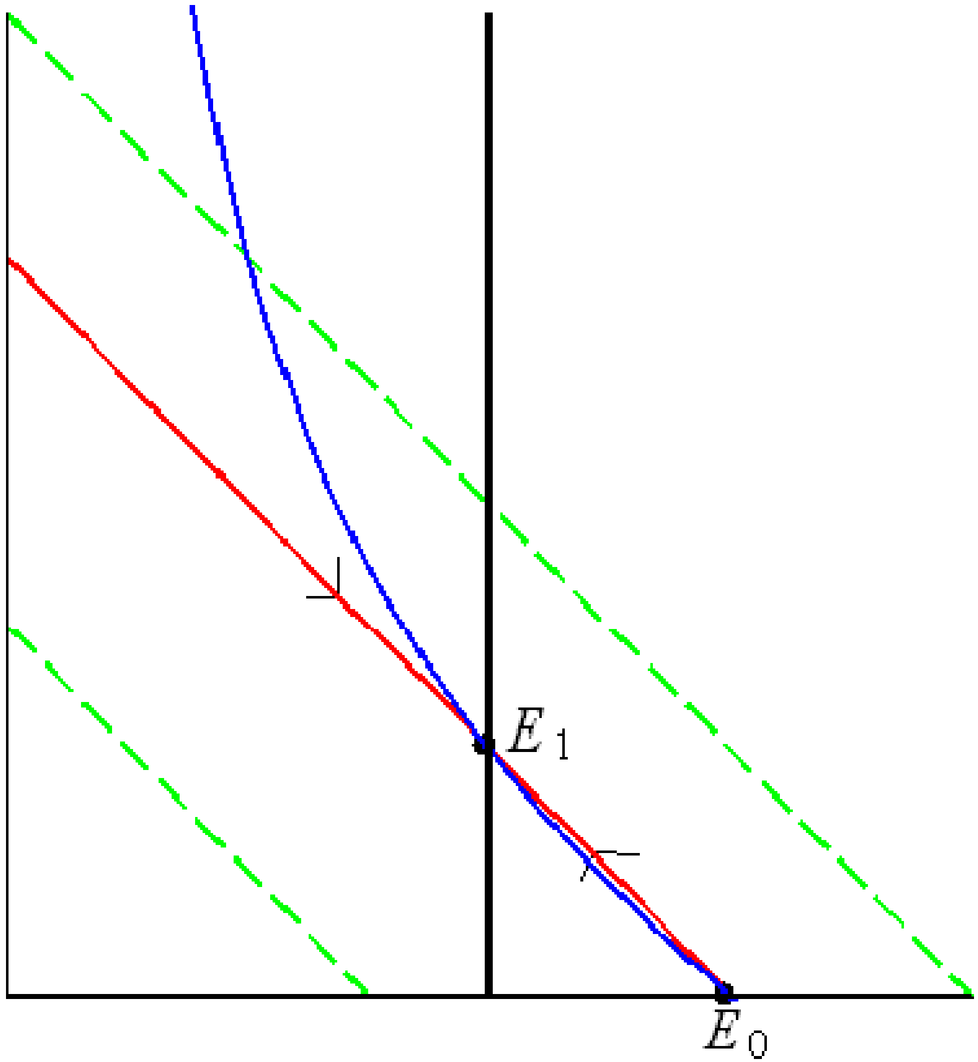


Observe that our system also satisfies a “conservation law”.

$$s(t) + x(t) = s_f + (s_f - (s_0 + x_0))e^{-Dt}.$$



When we put these two pictures together, we see



Conclusion

If either $D > \mu_m$ or ($D < \mu_m$ and $s_f < \lambda$),
then the microoranism becomes extinct in the growth vessel:

$$\lim_{t\to\infty} s(t) = s_f \quad \text{and} \quad \lim_{t\to\infty} x(t) = 0.$$

If $D < \mu_m$ and $s_f > \lambda$ (and $x_0 > 0$), then the microogranism and substrate equilibrate to positive values.

$$\lim_{t\to\infty} s(t) = \lambda \quad \text{and} \quad \lim_{t\to\infty} x(t) = s_f - \lambda.$$

The latter case illustrates why this culture device is called a *chemostat*. It allows us to maintain a bacterial culture at a constant level for an indefinitely long period of time. Furthermore, the level can be adjusted by adjusting the operating parameters of the chemostat (the flow rate and substrate input concentration).

Competition Between Two Species

For two different microbial species competing for the same resource in a chemostat, the model is

$$s'(t) = D(s_f - s(t)) - \mu_1(s(t))x_1(t) - \mu_2(s(t))x_2(t)$$

$$x_1'(t) = \mu_1(s(t))x_1(t) - Dx_1(t)$$

$$x_2'(t) = \mu_2(s(t))x_2(t) - Dx_2(t)$$

where μ_1 and μ_2 are both assumed to be Monod functions (which are different for each species).

We assume that each competitor is “adequate", meaning that each would survive (not become extinct) in the absense of the other. Thus we assume that

$$\mu_{1m} > D, \quad \mu_{2m} > D, \quad s_f > \lambda_1, \quad s_f > \lambda_2.$$

Equilibria

The equilibria of this system are

$$
\begin{aligned}
E_0 &= (s_f, 0, 0) \\
E_1 &= (\lambda_1, s_f - \lambda_1, 0) \\
E_2 &= (\lambda_2, 0, s_f - \lambda_2).
\end{aligned}
$$

There is no possibility of coexistence of the species at equilibrium. The questions to ask are thus:

1) Can the two species both persist in the culture vessel?

2) If not, then will both or only one of the species persist?

We will seek guidance on this issue by linearizing the system at each of the equilibria.

The Jacobian matrix of the right hand side of the system

$$
\begin{aligned}
s'(t) &= D(s_f - s(t)) - \mu_1(s(t))x_1(t) - \mu_2(s(t))x_2(t) \\
x_1'(t) &= \mu_1(s(t))x_1(t) - Dx_1(t) \\
x_2'(t) &= \mu_2(s(t))x_2(t) - Dx_2(t)
\end{aligned}
$$

is

$$
J = \begin{bmatrix} -D - \mu_1'(s)x_1 - \mu_2'(s)x_2 & -\mu_1(s) & -\mu_2(s) \\ \mu_1'(s)x_1 & \mu_1(s) - D & 0 \\ \mu_2'(s)x_2 & 0 & \mu_2(s) - D \end{bmatrix}
$$

At $E_0 = (s_f, 0, 0)$, we have

$$J = \begin{bmatrix} -D & -\mu_1(s_f) & -\mu_2(s_f) \\ 0 & \mu_1(s_f) - D & 0 \\ 0 & 0 & \mu_2(s_f) - D \end{bmatrix}$$

Since two of the eigenvalues of J are positive, we conclude that E_0 is unstable. Solutions that begin near E_0 will move away from E_0 as time increases.

At $E_1 = (\lambda_1, s_f - \lambda_1, 0)$, we have

$$J = \begin{bmatrix} -D - \mu_1'(\lambda_1)(s_f - \lambda_1) & -D & -\mu_2(\lambda_1) \\ \mu_1'(\lambda_1)(s_f - \lambda_1) & \mu_1(\lambda_1) - D & 0 \\ 0 & 0 & \mu_2(\lambda_1) - D \end{bmatrix}$$

In this case, the eigenvalues of J are

$$\eta_1 = -D < 0$$

$$\eta_2 = -\mu_1'(\lambda_1)(s_f - \lambda_1) < 0$$

$$\eta_3 = \mu_2(\lambda_1) - D.$$

Thus all eigenvalues of J have negative real parts (and hence J_1 is asymptotically stable) if and only if $\mu_2(\lambda_1) < D$. This will be true if and only if $\lambda_1 < \lambda_2$.

Analysis of the equilibrium point E_2 is similar.

Conclusion

Assuming that

$$\mu_{1m} > D, \quad \mu_{2m} > D, \quad s_f > \lambda_1, \quad s_f > \lambda_2$$

and assuming that $\lambda_1 \neq \lambda_2$, only one of the competitors (the one with the smaller λ value) can persist in the growth vessel. The other competitor becomes extinct. Thus, for example, if $\lambda_1 < \lambda_2$ (and $x_{10} > 0$), then

$$\lim_{t\to\infty} s(t) = \lambda_1$$

$$\lim_{t\to\infty} x_1(t) = s_f - \lambda_1$$

$$\lim_{t\to\infty} x_2(t) = 0.$$

Some Questions to Consider

1) Recalling that

$$\mu_i(s) = \frac{\mu_{mi} s}{K_{hi} + s},$$

and that λ_i is defined to be the value such that $\mu_i(\lambda_i) = D$, how do we express the condition $\lambda_1 < \lambda_2$ (which is necessary for the species x_1 to be the dominant competitor) in terms of the parameters μ_{mi} and K_{hi}?

2) Is it possible that $\lambda_1 = \lambda_2$? If so, what happens in the competition?!