SIAM J. APPL. MATH.
Vol. 61, No. 2, pp. 567–595

COMPETITION IN A CHEMOSTAT WITH WALL ATTACHMENT*

ERIC D. STEMMONS† AND HAL L. SMITH†

Abstract. A mathematical model of microbial competition for limiting nutrient and wall-attachment sites in a chemostat, formulated by Freter et al. in their study of the colonization resistance phenomena associated with the gut microflora, is mathematically analyzed. The model assumes that resident and invader bacterial strains can colonize the fluid environment of the vessel as well as its bounding surface, competing for a limited number of attachment sites on the latter. Although conditions for coexistence of the two strains are of interest, and are provided by some of our results, two bistable scenarios are of more relevance to the colonization resistance phenomena. In one case, each bacterial strain's single-population equilibrium, is stable against invasion by the other strain and there exists an unstable coexistence equilibrium, while in the second case the resident strain equilibrium is stable against invasion by the invader and yet a locally attracting coexistence equilibrium exists. Both scenarios imply that a threshold dose of invader is required to colonize the chemostat. Our analysis consists of finding equilibria, determining their stability properties, and establishing the persistence or extinction of the various strains.

Key words. chemostat, competition for wall-attachment sites, colonization resistance, uniform persistence

AMS subject classifications. 92A07, 92A15

PII. S0036139999358131

1. Introduction.

The well-known stability of the natural microflora of the gut of a mammal has important consequences for the health of the animal; see [22, 18, 21, 6]. Often referred to as colonization resistance, it refers to the difficulty for a nonindigenous bacterial strain to colonize the gut. In effect, the indigenous bacteria of the gut act as an immune system component by excluding potentially pathogenic invaders. Obviously, it is an important health concern to understand the reasons for this stability. Those most often cited are competition for limiting nutrients, a lag phase for growth of invaders in the gut, production of growth inhibitors by indigenous bacteria, and competition for gut-wall attachment sites. The evidence for the latter comes primarily from the numerical study of a mathematical model developed by Freter and his colleagues; see [10, 11, 12, 13, 14, 15]. Freter and his colleagues formulated their model, based on a chemostat or continuously stirred tank reactor (CSTR) model of the mouse gut, which allows for the attachment of the bacteria to the wall of the vessel. In an elegant set of numerical experiments, it was shown that a large initial influx of an invading strain, identical in every respect to an indigenous resident strain, introduced at the latter's equilibrium population, leads essentially to the washout of the invaders. As a control numerical experiment, it was shown that in the absence of the ability to attach to the wall of the vessel, the invader could establish in the chemostat, dominating the resident. Intuitively, with the possibility of wall growth and its attendant immunity from washout by the flow, an indigenous bacteria can monopolize the wall attachments sites excluding the invader, leaving it to the harsher environment of the bulk fluid and hence susceptible to washout.

*Received by the editors June 21, 1999; accepted for publication (in revised form) February 3, 2000; published electronically August 9, 2000. The research of the second author was supported by NSF grant DMS 9700910.
http://www.siam.org/journals/siap/61-2/35813.html
†Department of Mathematics, Arizona State University, Tempe, AZ 85287-1804 (halsmith@asu.edu).

These simulations are suggestive and warrant a more thorough analysis of the mathematical model, the intended purpose of the present paper. Obviously, competition between a resident strain and an invader which are identical in every respect, as assumed by Freter et al. [10, 11, 12, 14, 15], is a mathematically degenerate case. If we turn to the classical chemostat model (see [23]) for guidance, we find that there is a line segment (a continuum) of neutrally stable equilibria in case of competition between identical competitors. The ultimate outcome is extremely sensitive to initial data (and to noise!)—every solution approaches one of these equilibria, but a nearby solution may approach a different but nearby equilibrium. As it turns out, the same outcome holds for Freter's model. Clearly, there is a need to study more generic situations.

The model formulated by Freter is sufficiently general so that it may apply to the formation of a biofilm or the fouling of a bioreactor. Presently, there is a great interest in biofilms as it becomes clear that the more natural state of bacteria is as a member of a biofilm community rather than as an isolated planktonic cell in a fluid media and as the health implications of biofilms are becoming more wellknown. For example, antibiotics are less effective against bacteria in a biofilm community than they are for the planktonic form [9]. See various review articles by Costerton and his colleagues [7, 8, 9] and [5].

The Freter model has stimulated much research on an analogous model based on the plug flow tubular reactor; see [1, 2, 3, 17]. See [12, 19] for the use of CSTRs as experimental models in colon research.

The Freter model is not the only model of bacterial growth and competition with wall-attachment. Simple chemostat-based models have been formulated by Topiwala and Hamer [27] and later by Baltzis and Fredrickson [4]. A different model was formulated and studied recently by Pilyugin and Waltman [20]. The Freter model is distinguished from these earlier models by a number of factors. First and most importantly, it assumes a limited number of wall-attachment sites as opposed to an unlimited number. This difference has the effect of making the model more highly nonlinear. In fact, the attraction of bacteria to the wall is assumed to be given by a nonlinear mass-action rate rather than a linear rate assumed in other models. Finally, as the wall-attachment sites may fill up, the model must account for the daughter cells of wall-attached bacteria which cannot find attachment sites and consequently are sloughed off into the fluid environment. The bottom line is that the Freter model is highly nonlinear and difficult to fully analyze.

Aside from the obvious interest in the possibility of coexistence between two competing bacterial strains, which we show can occur for the Freter model, some other outcomes are also of biological interest. Perhaps of most interest is our finding that the bistable case may occur in which each strain's single-population equilibrium is stable in the linear approximation to invasion by the competing strain. In this case, there is an unstable coexistence equilibrium of saddle type, the stable manifold of which forms a separatrix surface in state space separating the basins of attraction of the two single-population equilibria. Viewing one population as representing the indigenous microflora of the gut and the other as an invading nonindigenous strain, we may consider Freter's experiment being carried out in this case. If a small dose of invaders is introduced with the resident population at its equilibrium, then the invaders will be washed out because the initial state belongs to the basin of attraction of the resident equilibrium. However, if the dose of invading strain is sufficiently high such that the initial state has crossed the separatrix surface into the domain of attraction of the invader equilibrium, then the invader will displace the resident strain with all the unwanted consequences for the health of the animal or human. The original use of the term "colonization resistance" in gut microbiology was as a measure of the oral dose of a bacterial strain required for colonization of the gut [18]. Mathematically, in the Freter model, it is represented by a separatrix manifold in state space.

The basic competition model is described in the next section and the single population growth model with wall attachment is fully analyzed in the subsequent section. Section 4 treats the case of competition between a resident strain able to colonize the wall of the vessel and an invader that lacks this ability. The full model treating competition between two bacterial strains capable of wall attachment is considered in section 5. Our main results are discussed in section 6 and illustrated by numerical simulations. An appendix contains the mathematical proofs of our results. All stability assertions of this paper are to be interpreted in a local sense unless explicitly indicated otherwise by the use of the adjective "global."

2. The model. We follow [12] in considering a two-strain model, referring to one strain as the resident strain and the other as the invading strain. See [12] for a thorough description of the model. Here, we simply outline its main features. Let $n_r(t)$ be the biomass concentration of planktonic resident bacteria, that is, resident bacteria in the fluid media of the chemostat and let $m_r(t)$ be the biomass of resident bacteria that are attached to the wall of the chemostat. We will refer to these cells as wall-attached cells. Similar designations are used for the planktonic invading strain biomass density $n_i(t)$ and wall-attached biomass density of invaders $m_i(t)$. We follow Freter in assuming that the specific growth rate of a microbe is the same whether the cell is in its planktonic state or its wall-attached state for a given value of the nutrient concentration. Recent evidence from work on biofilms suggest that this is not a good assumption [7, 8]. It is assumed here to simplify the algebra; however, based on previous work [2], it is not expected that the assumption of different specific growth rates for planktonic and wall-attached states will alter our results or add any new phenomena. We require that the specific growth rates f_r and f_i have the following properties:

$$f'(s) > 0, \quad f \in C^1, \quad f(0) = 0.$$

A common choice is the Monod function:

$$f(S) = \frac{mS}{a+S}.$$

The model assumes an upper bound A for the weighted biomass M of bacteria that can adhere to the wall of the chemostat. A fraction $G(M)$ of daughter cells of wall-attached cells are assumed to find wall-attachment sites, the fraction $1 - G(M)$ of daughter cells become planktonic cells. Here,

$$M = am_r + bm_i$$

is a weighted average of m_r and m_i (Freter assumes $a = 1$ and $b = 1$) and $G(M)$ is strictly decreasing, reflecting the idea that G is larger when wall-attachment sites are plentiful and small when they are scarce. We assume that $G(M)$ has the following properties:

$$G'(M) < 0, \quad G \in C^1, \quad 0 < G(0) \leq 1, \quad G(A) = 0.$$

Freter takes G to be

$$G(M) = \frac{A - M}{A + k - M},$$

where k is a small positive number, although he provides no justification for this particular form. We stress that, except for our numerical simulations, none of our results depend on the special forms of f or G.

Planktonic cells are attracted to the wall at a mass-action rate proportional to the product of n_r and $A - M$, the latter being a measure of the unoccupied wall attachment sites. Wall attached cells are sloughed off at a rate proportional to their density. Finally, we ignore cell death in the model.

The model parameters, all positive, are described in the following table.

Symbol	Description	Dimension
t	Time.	t
s	Concentration of limiting nutrient.	ml^{-3}
n_r	Biomass concentration of planktonic resident bacteria.	ml^{-3}
m_r	Biomass of wall-attached resident bacteria.	m
n_i	Biomass concentration of planktonic invading bacteria.	ml^{-3}
m_i	Biomass of wall-attached invading bacteria.	m
y_r	Yield constant of resident bacteria.	-
y_i	Yield constant of invading bacteria.	-
$f_r(s)$	Specific growth rate of resident bacteria.	t^{-1}
$f_i(s)$	Specific growth rate of invading bacteria.	t^{-1}
$G(M)$	Fraction of daughter cells of wall-attached cells that find wall sites.	-
ρ	Dilution rate of the chemostat.	t^{-1}
S_0	Concentration of the nutrient in the feed.	ml^{-3}
V	Volume of the chemostat.	l^{-3}
λ_r	Removal rate of wall-attached resident bacteria.	t^{-1}
λ_i	Removal rate of wall-attached invading bacteria.	t^{-1}
α_r	Specific rate constant of adhesion for resident bacteria.	$l^3t^{-1}m^{-1}$
α_i	Specific rate constant of adhesion for invading bacteria.	$l^3t^{-1}m^{-1}$
A	Maximum biomass of bacteria that can adhere to the wall.	m
M	Weighted total biomass of wall-attached bacteria.	m
a	Weighting constant for resident bacteria.	-
b	Weighting constant for invading bacteria.	-

The model equations then take the form:

$$\begin{aligned}
\dot{s} &= \rho(S_0 - s) - \frac{1}{y_r}\left(n_r + \frac{m_r}{V}\right) f_r(s) - \frac{1}{y_i}\left(n_i + \frac{m_i}{V}\right) f_i(s),\\
\dot{n}_r &= n_r(f_r(s) - \rho) + \frac{m_r\lambda_r}{V} + \frac{f_r(s)m_r[1 - G(M)]}{V} - \frac{\alpha_r n_r(A - M)}{V},\\
\dot{m}_r &= \alpha_r n_r(A - M) - \lambda_r m_r + f_r(s)m_r G(M), \qquad (2.1)\\
\dot{n}_i &= n_i(f_i(s) - \rho) + \frac{m_i\lambda_i}{V} + \frac{f_i(s)m_i[1 - G(M)]}{V} - \frac{\alpha_i n_i(A - M)}{V},\\
\dot{m}_i &= \alpha_i n_i(A - M) - \lambda_i m_i + f_i(s)m_i G(M).
\end{aligned}$$

The equations in (2.1) can be simplified by nondimensionalizing the parameters, and dependent and independent variables. Nondimensional quantities are indicated below with bars.

Symbol	Dimensionless quantity
$\bar{t}$	t/ρ
$\bar{n}_r$	$n_r Va/A$
$\bar{m}_r$	$m_r a/A$
$\bar{n}_i$	$n_i Vb/A$
$\bar{m}_i$	$m_i b/A$
$\bar{s}$	s/S_0
$\bar{f}_r(\bar{s})$	$f_r(S_0\bar{s})/\rho$
$\bar{f}_i(\bar{s})$	$f_i(S_0\bar{s})/\rho$
$\bar{\alpha}_r$	$\alpha_r A/(\rho V)$
$\bar{\alpha}_i$	$\alpha_i A/(\rho V)$
$\bar{\lambda}_r$	λ_r/ρ
$\bar{\lambda}_i$	λ_i/ρ
$\bar{G}(\bar{m}_r + \bar{m}_i)$	$G(A\bar{m}_r + A\bar{m}_i)$
$\bar{y}_r$	$aVs_0 y_r/A$
$\bar{y}_i$	$bVs_0 y_i/A$
$\bar{M}$	$m_r a/A + m_i b/A$

We drop the bars and return to the original notation:

$$\begin{aligned} \dot{s} &= 1 - s - \frac{1}{y_r}(n_r + m_r)f_r(s) - \frac{1}{y_i}(n_i + m_i)f_i(s), \\ \dot{n}_r &= n_r(f_r(s) - 1) + \lambda_r m_r + f_r(s)m_r[1 - G(M)] - \alpha_r n_r(1 - M), \\ \dot{m}_r &= \alpha_r n_r(1 - M) - \lambda_r m_r + f_r(s)m_r G(M), \\ \dot{n}_i &= n_i(f_i(s) - 1) + \lambda_i m_i + f_i(s)m_i[1 - G(M)] - \alpha_i n_i(1 - M), \\ \dot{m}_i &= \alpha_i n_i(1 - M) - \lambda_i m_i + f_i(s)m_i G(M). \end{aligned} \tag{2.2}$$

Note in particular that now

$$0 \le M = m_r + m_i \le 1,$$

and that $G : [0, 1] \to [0, 1]$ satisfies $G(1) = 0$. The biologically relevant domain for (2.2) is

$$\Omega = \{(s, n_r, m_r, n_i, m_i) \in \mathbb{R}^5_+ : m_r + m_i \le 1\}. \tag{2.3}$$

The system is well posed.

LEMMA 2.1. *The region Ω is positively invariant under the vector field* (2.2). *Furthermore, solutions starting there are unique, extend to $t \ge 0$, and are bounded.*

Proof. The vector field does not point out of the polygonal region Ω. For example, if $m_i + m_r = 1$, then

$$\dot{m}_r + \dot{m}_i = -\lambda_r m_r - \lambda_i m_i < 0.$$

Adding the five equations of (2.2) gives

$$\dot{s} + \frac{\dot{n}_r}{y_r} + \frac{\dot{m}_r}{y_r} + \frac{\dot{n}_i}{y_i} + \frac{\dot{m}_i}{y_i} = 1 - s - \frac{n_r}{y_r} - \frac{n_i}{y_i}.$$

Since $0 \le m_r \le 1$ and $0 \le m_i \le 1$, $b = s + \frac{n_r}{y_r} + \frac{n_i}{y_i} + \frac{m_r}{y_r} + \frac{m_i}{y_i}$ satisfies

$$\begin{aligned} \dot{b} &\le 1 - s - \frac{n_r}{y_r} - \frac{n_i}{y_i} + \left(\frac{1}{y_r} - \frac{m_r}{y_r}\right) + \left(\frac{1}{y_i} - \frac{m_i}{y_i}\right) \\ &= 1 + \frac{1}{y_r} + \frac{1}{y_i} - b, \end{aligned}$$

which immediately leads to the boundedness of solutions. ∎

3. Single-population-growth. We first consider single-population growth, the equations for which are the following:

$$\begin{aligned}\dot{s} &= 1 - s - \frac{1}{y_r}(n_r + m_r)f_r(s),\\ \dot{n}_r &= n_r(f_r(s) - 1) + \lambda_r m_r + f_r(s)m_r[1 - G(m_r)] - \alpha_r n_r(1 - m_r),\\ \dot{m}_r &= \alpha_r n_r(1 - m_r) - \lambda_r m_r + f_r(s)m_r G(m_r).\end{aligned} \tag{3.1}$$

The appropriate domain for (3.1) is

$$\Omega_0 = \{(s, n_r, m_r) \in \mathbb{R}^3_+ : m_r \leq 1\}$$

which is positively invariant. The washout equilibrium, uninteresting biologically, is denoted by

$$E_0 = (1, 0, 0),$$

and the variational matrix corresponding to it is given by

$$J(E_0) = \begin{pmatrix} -1 & -f_r(1)/y_r & -f_r(1)/y_r \\ 0 & f_r(1) - 1 - \alpha_r & f_r(1)[1 - G(0)] + \lambda_r \\ 0 & \alpha_r & f_r(1)G(0) - \lambda_r \end{pmatrix}.$$

The eigenvalues consist of -1 plus the eigenvalues of the following submatrix:

$$A_r = \begin{pmatrix} f_r(1) - 1 - \alpha_r & f_r(1)[1 - G(0)] + \lambda_r \\ \alpha_r & f_r(1)G(0) - \lambda_r \end{pmatrix}.$$

We denote by $SM(A_r)$, the stability modulus of A_r, which is just the maximum of the real parts of its eigenvalues. As for most matrices of interest in this paper, A_r has real eigenvalues so $SM(A_r)$ is simply the largest one.

Our main result follows.

THEOREM 3.1. *If $SM(A_r) < 0$, then E_0 is globally attracting in Ω_0. If $SM(A_r) > 0$, then E_0 is unstable and there exists a unique equilibrium $E_r = (s_r, n_r^*, m_r^*)$ with $m_r + n_r > 0$. In fact, $n_r^*, m_r^* > 0$ and E_r is asymptotically stable. Furthermore, if $SM(A_r) > 0$, there exists $\epsilon > 0$, independent of initial data, such that*

$$\liminf_{t\to\infty} n_r(t) > \epsilon,$$
$$\liminf_{t\to\infty} m_r(t) > \epsilon$$

for every solution of (3.1) *with $n_r(0) + m_r(0) > 0$.*

The bacterial population is washed out of the reactor if $SM(A_r) < 0$, or it can colonize the chemostat if the reverse inequality holds. In the latter case, there is a unique, locally attracting equilibrium with positive values for planktonic and wall-attached densities. Unfortunately, we are unable to show the latter is globally attracting, but at least we can show that both planktonic and wall-attached bacterial densities eventually exceed some positive lower bound which is independent of initial data.

Of course, the stability modulus may be computed explicitly and this leads to the conclusion that $SM(A_r) > 0$ if

$$f_r(1) > \frac{[\lambda_r + \alpha_r + G(0)] - \sqrt{[\lambda_r + \alpha_r + G(0)]^2 - 4G(0)\lambda_r}}{2G(0)}$$

and $SM(A_r) < 0$ if the reverse inequality holds. We note that the quantity on the right is strictly less than 1. This is an important observation since, in the absence of wall attachment a population can survive in the chemostat if and only if $f_r(1) > 1$ (see [23]). It stands to reason that the threshold growth rate should be lower when the organism can attach to the wall since then it is relatively less affected by washout.

We take a moment to defend a practice we will use throughout the paper. Rather than writing complicated inequalities resulting from the quadratic formula, as for the inequality immediately above, which reveals very little of the biology and which singles out for special attention the specific growth rate above all others, we choose to state conditions in terms of the stability modulus of various 2×2 matrices which have nonnegative off-diagonal entries. Matrices having nonnegative off-diagonal entries are called quasi-positive matrices here. Because the Perron–Frobenius theorem can be applied to the sum of a quasi-positive matrix and a suitable multiple of the identity matrix, quasi-positive matrices have nice spectral properties; see [23, 24]. This theory will find extensive application in our proofs.

The authors are indebted to Thieme for pointing out that a change of variables in (3.1) leads to a cooperative system under suitable conditions. A system is said to be cooperative if its Jacobian matrix is quasipositive in the region of interest and is irreducible if this Jacobian matrix is irreducible. See [24] for more on cooperative systems and monotone dynamics. In this special case, we can prove that E_r attracts all solutions with $n_r(0) + m_r(0) > 0$. Let

$$\begin{aligned} x &= \frac{n_r + m_r}{y_r}, \\ E &= s + x. \end{aligned}$$

Then (3.1) becomes

$$\begin{aligned} \dot{E} &= 1 - E + \frac{m_r}{y_r}, \\ \dot{x} &= x(f_r(E-x) - 1) + \frac{m_r}{y_r}, \\ \dot{m}_r &= \alpha_r(xy_r - m_r)(1 - m_r) - \lambda_r m_r + f_r\,(E-x)\,m_r G(m_r) \end{aligned} \tag{3.2}$$

on the positively invariant domain $\Lambda = \{(E, x, m_r) : 0 \le m_r \le 1, 0 \le x \le E\}$.

THEOREM 3.2. *If*

$$\alpha_r > \frac{1}{y_r}\left(\sup_{0\le s\le 1} f_r'(s)\right)\left(\sup_{0\le m_r\le 1} \frac{m_r G(m_r)}{1-m_r}\right) \tag{3.3}$$

holds then (3.2) *is a cooperative system in* Λ*, irreducible when* $x > 0$*. If, in addition,* $SM(A_r) > 0$*, then every trajectory of* (3.1) *with* $n_r(0) + m_r(0) > 0$ *converges to* E_r*.*

For example, if $G(M) = \frac{1-M}{1+k-M}$ and $f(S) = \frac{mS}{a+S}$, then (3.3) simplifies to $\alpha_r y_r ka > m$.

4. Wall-adhering residents versus nonadhering invaders.

We now consider competition between a resident strain, able to colonize the wall of the chemostat, and an invading strain which cannot colonize the wall. In this case, (2.2) reduces to the following system:

$$
\begin{aligned}
\dot{s} &= 1 - s - \frac{1}{y_r}(n_r + m_r) f_r(s) - \frac{n_i f_i(s)}{y_i}, \\
\dot{n}_r &= n_r(f_r(s) - 1) + \lambda_r m_r + f_r(s) m_r \left[1 - G(m_r)\right] - \alpha_r n_r (1 - m_r), \\
\dot{m}_r &= \alpha_r n_r (1 - m_r) - \lambda_r m_r + f_r(s) m_r G(m_r), \\
\dot{n}_i &= n_i(f_i(s) - 1).
\end{aligned} \tag{4.1}
$$

The washout equilibrium $E_0 = (1, 0, 0, 0)$ is always present. The resident-only equilibrium $E_r = (s_r, n_r^*, m_r^*, 0)$ exists if $SM(A_r) > 0$. An invader-only equilibrium exists if $f_i(1) > 1$. It is given by $E_i = (s_i, 0, 0, n_i^*) = (s_i, 0, 0, y_i\left[1 - s_i\right])$, where s_i is the unique solution of $f_i(s_i) = 1$. As noted in the previous section, the threshold growth rate for the invader-only equilibrium to exist is higher than that for the resident-only equilibrium to exist. A coexistence equilibrium $E_c = (\bar{s}, \bar{n}_r, \bar{m}_r, \bar{n}_i)$ is one for which $m_r + n_r > 0$ and $n_i > 0$. It is easy to see that in fact n_r and m_r must both be positive and $\bar{s} = s_i$.

Our first result summarizes the stability properties of the equilibria E_0, E_r, and E_i.

THEOREM 4.1. *We have the following stability conditions, assuming the equilibria in question exist:*

- *E_0 is asymptotically stable if $SM(A_r) < 0$ and $f_i(1) < 1$ and is unstable if either inequality is reversed.*
- *E_r is asymptotically stable if $f_i(s_r) < 1$ and unstable if $f_i(s_r) > 1$, in which case E_i exists and $s_i < s_r$.*
- *E_i is asymptotically stable if $SM(B) < 0$ and unstable if $SM(B) > 0$, in which case E_r must exist. Here, B is the quasipositive matrix given by*

$$
B = \begin{pmatrix} f_r(s_i) - 1 - \alpha_r & f_r(s_i)[1 - G(0)] + \lambda_r \\ \alpha_r & f_r(s_i)G(0) - \lambda_r \end{pmatrix}.
$$

Alternatively, E_i is asymptotically stable ($SM(B) < 0$) if

$$
f_r(s_i) < \frac{[\lambda_r + \alpha_r + G(0)] - \sqrt{[\lambda_r + \alpha_r + G(0)]^2 - 4G(0)\lambda_r}}{2G(0)}
$$

and unstable ($SM(B) > 0$) if the reverse inequality holds. The quantity on the right-hand side can be seen to be strictly less than 1 (see Remark 1). Therefore, as expected, the threshold growth rate for the invaders to successfully invade the resident strain equilibrium is higher than for the reverse invasion to occur. This reflects the lack of ability of the invaders to adhere to the wall.

It can be shown that if $SM(A_r) < 0$, then $n_r(t), m_r(t) \to 0$ as $t \to \infty$ for all solutions of (4.1). Similarly, if $f_i(1) < 1$, then $n_i(t) \to 0$ for every solution of (4.1). The proof follows that of Proposition 5.1.

If both E_r and E_i exist, then they cannot both be asymptotically stable in the linear approximation.

COROLLARY 4.2. *Suppose that both E_r and E_i exist. The condition $f_i(s_r) < 1$, which implies that E_r is asymptotically stable by Theorem* 4.1, *also implies that E_i is unstable; the condition $SM(B) < 0$, which by Theorem* 4.1 *implies that E_i is asymptotically stable, also implies that E_r is unstable.*

It is interesting that E_c can exist only when both E_r and E_i are unstable in the linear approximation. Thus, bistability cannot occur when one of the strains lacks the ability to attach to the wall of the vessel.

THEOREM 4.3. *A coexistence equilibrium E_c is unique if it exists. E_c exists if and only if E_r exists, E_i exists, $f_i(s_r) > 1$, and $SM(B) > 0$.*

While Theorem 4.3 completely settles the existence and uniqueness of E_c, it does not address its stability. We conjecture that E_c is asymptotically stable whenever it exists. This conjecture is based on a Maple calculation of the Routh–Hurwicz criterion reported in [25] which fills an entire page. Also see [25] for simulations demonstrating that E_c may exist.

We conclude this section by showing that if the resident and invader have the same nutrient uptake functions and if the resident can colonize the chemostat in the absence of the invader, then the resident excludes the invader.

THEOREM 4.4. *Let $f_r = f_i \equiv f$. If E_i exists, then E_r exists, and if E_r exists, then it is asymptotically stable and E_i is unstable if it exists. If $SM(A_r) < 0$, then $n_r + m_r + n_i \to 0$ as $t \to \infty$. If $SM(A_r) > 0$, i.e., if E_r exists, then there exists $\epsilon > 0$, independent of initial data, such that*

$$\liminf_{t\to\infty} n_r(t) > \epsilon,$$
$$\liminf_{t\to\infty} m_r(t) > \epsilon,$$
$$\lim_{t\to\infty} n_i(t) = 0$$

for every solution of (4.1) *with $n_r(0) + m_r(0) > 0$.*

5. Competition between two wall-adhering strains.

In this section we consider the full model (2.2) where both the resident and invader strains colonize the wall of the chemostat. In addition to the washout equilibrium $E_0 = (1, 0, 0, 0, 0)$ we have, from Theorem 3.1 and symmetry, that $E_r = (s_r, n_r^*, m_r^*, 0, 0)$ exists if and only if $SM(A_r) > 0$ and similarly $E_i = (s_i, 0, 0, n_i^*, m_i^*)$ exists if and only if $SM(A_i) > 0$. Properties of E_i and A_i are obtained from those of E_r and A_r. E_0 is asymptotically stable if both $SM(A_r) < 0$ and $SM(A_i) < 0$ and unstable if either inequality is reversed. These inequalities identify inadequate competitors as our first result shows.

PROPOSITION 5.1. *If $SM(A_r) < 0$, then $n_r(t), m_r(t) \to 0$ as $t \to \infty$ for every solution of* (2.2)*. If $SM(A_i) < 0$, then $n_i(t), m_i(t) \to 0$ as $t \to \infty$ for every solution of* (2.2)

It is traditional in population dynamics to discuss the stability of a single-population equilibrium in terms of whether or not it may be invaded by an infinitesimal inoculum of the other population. We wish to do that here as well but we caution the reader that our choice to use Freter's designation of the two strains as "resident" and "invader" strains now has an unfortunate consequence. In order to discuss the stability of the invader-only equilibrium E_i, we must determine whether or not the resident strain can or cannot successfully invade it. With this caution, we hope the reader will only be mildly annoyed with this language. The following theorem summarizes the stability properties of E_r and E_i.

THEOREM 5.2. *E_r is asymptotically stable if $SM(A_{ri}) < 0$ and unstable if $SM(A_{ri}) > 0$, where*

$$A_{ri} = \begin{pmatrix} f_i(s_r) - 1 - \alpha_i(1 - m_r^*) & f_i(s_r)[1 - G(m_r^*)] + \lambda_i \\ \alpha_i(1 - m_r^*) & f_i(s_r)G(m_r^*) - \lambda_i \end{pmatrix}.$$

E_i is asymptotically stable if $SM(A_{ir}) < 0$ and unstable if $SM(A_{ir}) > 0$, where A_{ir} is obtained from A_{ri} by interchanging r and i. If E_r is unstable, that is, if $SM(A_{ri}) > 0$, then E_i must exist and if E_i is unstable, that is, if $SM(A_{ir}) > 0$, then E_r must exist.

The invader strain can invade the resident strain equilibrium if $SM(A_{ri}) > 0$ and cannot if the reverse inequality holds. Note the mixing of subscripts "r" and "i" on quantities appearing in the matrix A_{ri} takes into account that the invading strain confronts the environment determined by the resident strain equilibrium.

It is reasonable that the invader cannot invade the resident strain equilibrium unless it can survive on its own in the chemostat (E_i exists) and similarly when invader and resident are interchanged.

An important question is under what circumstances can the invader strain successfully invade and establish itself in the chemostat. The following result addresses this issue.

THEOREM 5.3. *Suppose that E_r exists and that it attracts all solutions of* (2.2) *with $n_r(0) + m_r(0) > 0$ and $n_i(0) = m_i(0) = 0$. If $SM(A_{ri}) > 0$, then there exists $\epsilon > 0$, independent of initial data, such that*

$$\liminf_{t\to\infty} n_i(t) > \epsilon,$$
$$\liminf_{t\to\infty} m_i(t) > \epsilon$$

for every solution of (2.2) *with $n_i(0) + m_i(0) > 0$. A symmetric conclusion holds where i and r are interchanged.*

The result that the limit inferior of both n_i and m_i exceed some lower bound which is independent of initial data is termed uniform persistence or permanence in the population biology literature; see, e.g., [26].

A central issue is whether or not a coexistence equilibrium $E_c = (s_c, n_r^c, m_r^c, n_i^c, m_i^c)$, with $(n_r^c + m_r^c)(n_i^c + m_i^c) > 0$, exists. It's easily seen that all components of E_c must, in fact, be positive. E_c cannot exist unless both single-population equilibria exist; coexistence of the two strains would not be expected if either strain were unable to survive in the absence of competition.

LEMMA 5.4. *If an E_c exists, then both E_r and E_i must also exist.*

The question of the existence of E_c is algebraically difficult due to the many strong nonlinearities in the equations. We obtain a sufficient, but not necessary, condition for its existence. E_c exists if E_r and E_i are both unstable or if they are both stable in the linear approximation and an additional condition holds. The additional condition says, roughly, that although the invader cannot invade the resident-only equilibrium ($SM(A_{ri}) < 0$), it could invade if the nutrient level, instead of being $s = s_r$, were the higher value $s = 1$ which corresponds to the scaled input concentration from the nutrient reservoir ($SM(B_{ri}) > 0$), and similarly with resident and invader interchanged.

THEOREM 5.5. *Suppose that both E_r and E_i exist. If either*

$$SM(A_{ri}) > 0 \text{ and } SM(A_{ir}) > 0 \tag{5.1}$$

or

$$SM(A_{ri}) < 0 < SM(B_{ri}) \text{ and } SM(A_{ir}) < 0 < SM(B_{ir}), \tag{5.2}$$

where

$$B_{ri} = \begin{pmatrix} f_i(1) - 1 - \alpha_i(1 - m_r^*) & f_i(1)[1 - G(m_r^*)] + \lambda_i \\ \alpha_i(1 - m_r^*) & f_i(1)G(m_r^*) - \lambda_i \end{pmatrix}$$

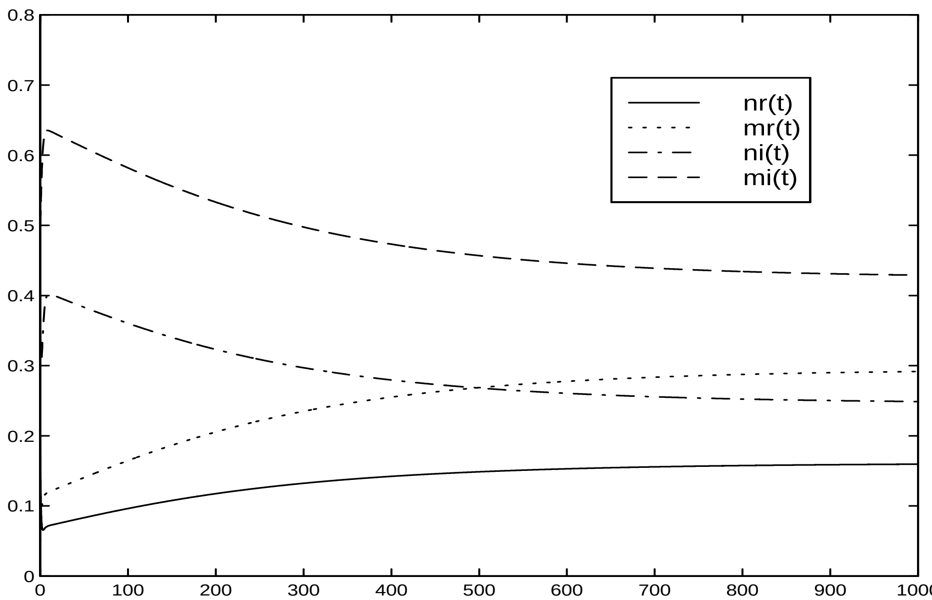

FIG. 1. *A plot of* $n_r(t), m_r(t), n_i(t)$, *and* $m_i(t)$ *versus time with parameters from Table* 3. E_c *is globally stable with* E_r *and* E_i *unstable.*

and B_{ir} *is obtained from* B_{ri} *by interchanging* i *and* r, *then there exists at least one coexistence equilibrium* E_c.

Both situations described in Theorem 5.5 occur. See Figure 1 for the case when both E_r and E_i are unstable to invasion by the other strain where an apparently stable E_c exists. Figures 2 and 3 show that E_c can exist in the bistable case where both E_r and E_i are asymptotically stable. In this case, E_c is unstable. E_c may be nonunique as Figures 4 and 5 attest. Here, one E_c is stable and another is unstable. See [25] for a bifurcation analysis which illuminates conditions under which E_c may bifurcate from E_r as the maximum growth rate of the invader is increased. Both supercritical and subcritical transcritical bifurcations may occur. Parameter values for simulations described in Figures 1–5 are provided in Tables 1,3, and 5; equilibrium locations and their stability are given in Tables 2, 4, and 6.

The existence of E_c does not ensure that the two strains can coexist. Below we establish conditions that do ensure that both populations survive in the long run. In the language of persistence theory, the two populations persist uniformly.

COROLLARY 5.6. *Suppose that* E_r *and* E_i *exist. Suppose also that* E_r *attracts all solutions of* (2.2) *with* $n_r(0) + m_r(0) > 0$ *and* $n_i(0) = m_i(0) = 0$, *and that* E_i *attracts all solutions of* (2.2) *with* $n_i(0) + m_i(0) > 0$ *and* $n_r(0) = m_r(0) = 0$. *If* $SM(A_{ri}) > 0$ *and* $SM(A_{ir}) > 0$, *then there exists* $\epsilon > 0$, *independent of initial data, such that, for* $u(t) = n_r(t), m_r(t), n_i(t)$, *or* $m_i(t)$, *we have*

$$\liminf_{t\to\infty} u(t) > \epsilon$$

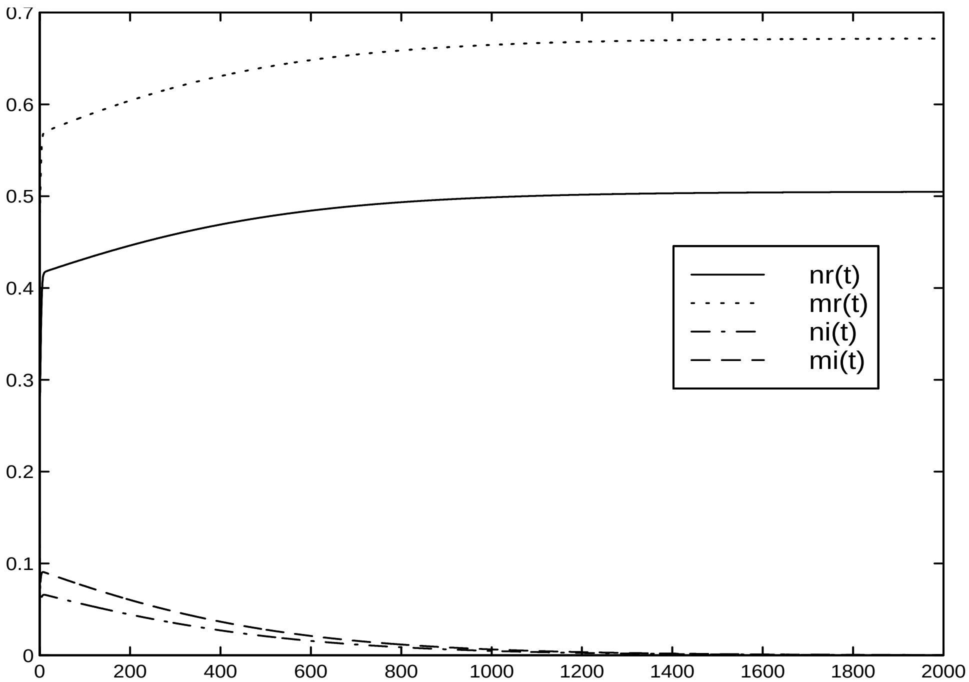

Fig. 2. *A plot of* $n_r(t), m_r(t), n_i(t)$, *and* $m_i(t)$ *versus time with parameters from Table* 1. *The residents win when they start at a relatively high density and the invaders start at a low density.* E_c *exists but is an unstable saddle.*

for all solutions of (2.2) *satisfying* $n_r(0) + m_r(0) > 0$ *and* $n_i(0) + m_i(0) > 0$.

We remark that in all simulations performed here and in [25], solutions converge to one of the equilibria.

A singular perturbation analysis is carried out in [25] when the dilution rate ρ is large, i.e., when the mean residence time of planktonic bacteria in the chemostat is small compared to other time scales of the problem. In this case, the densities of planktonic bacteria of each strain are in a quasi-steady state with the more slowly changing wall-attached densities allowing a reduction of the five-dimensional system (2.2) to a planar system for (m_r, m_i). In this regime, competitive exclusion is the generic outcome of competition.

6. Discussion. The ability of a bacterial strain, capable of wall attachment, to survive in the chemostat is shown to depend on whether the largest eigenvalue of a 2×2 quasi-positive matrix is positive or not. As there are two niches for bacteria, the planktonic niche and the wall-adherent niche, it seems entirely appropriate that its survival depends on whether it can grow sufficiently well in at least one of these two environments to offset possible losses to the other, perhaps less suitable, one. In terms of the original, unscaled parameters, a strain of bacteria can colonize the chemostat with dilution rate ρ and nutrient feed concentration S_0 if and only if the largest eigenvalue of the matrix

$$\begin{pmatrix} f_r(S_0) - \rho - \alpha_r \frac{A}{V} & \frac{f_r(S_0)[1-G(0)]}{V} + \frac{\lambda_r}{V} \\ \alpha_r A & f_r(S_0)G(0) - \lambda_r \end{pmatrix}$$

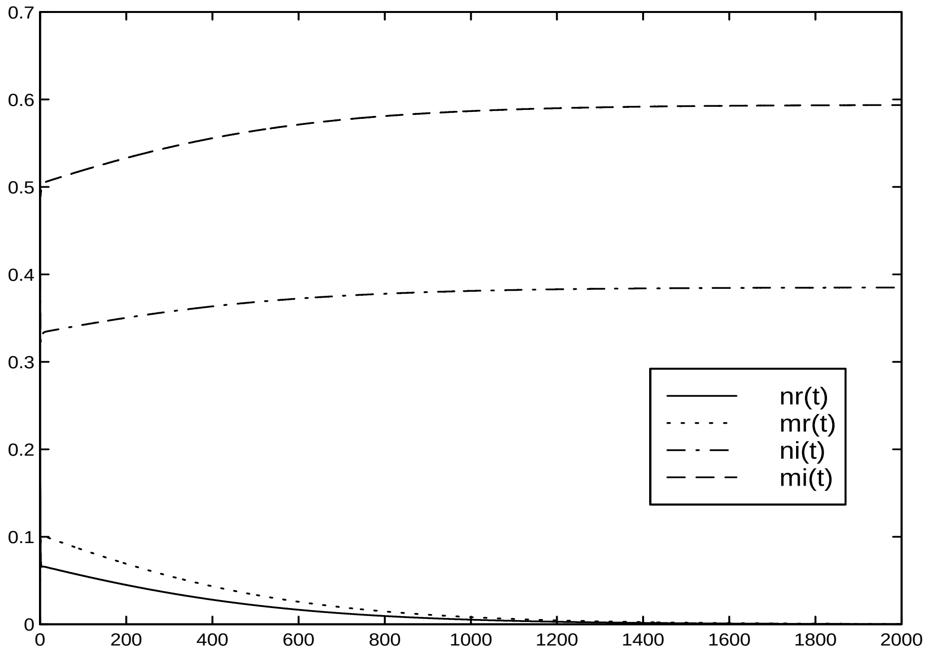

FIG. 3. *A plot of $n_r(t), m_r(t), n_i(t)$, and $m_i(t)$ versus time with parameters and initial conditions from Table* 1. *This time the invaders win when they start at relatively high density and the residents start at a low one.*

is positive, or equivalently, if

$$f_r(S_0) > \frac{[\lambda_r + \alpha_r \frac{A}{V} + G(0)\rho] - \sqrt{[\lambda_r + \alpha_r \frac{A}{V} + G(0)\rho]^2 - 4G(0)\lambda_r \rho}}{2G(0)}.$$

As the quantity on the right is complicated, it is useful to replace this inequality by slightly stronger inequalities which may better provide a biological interpretation. We offer two such below. The inequality above holds (see Remark 1) if either the wall-attached bacteria can grow fast enough to overcome loss due to slough-off of cells, i.e.,

$$f_r(S_0)G(0) - \lambda_r > 0,$$

or if the planktonic bacteria can grow fast enough to overcome washout, i.e,

$$f_r(S_0) - \rho > 0.$$

By way of contrast, the latter inequality gives the threshold for survival in the chemostat for planktonic cells in the absence of wall growth (see [23]). In simulations reported by Freter and his colleagues in [10, 12], $G(0) \approx 1$ and λ_r is much smaller than ρ, so the former inequality may more readily hold than the latter. Thus the ability to adhere to the wall of the chemostat provides a substantially greater chance for successful colonization.

Competition between a resident bacterial strain capable of wall attachment and an invader which lacks this competency is considered in section 4. We must again

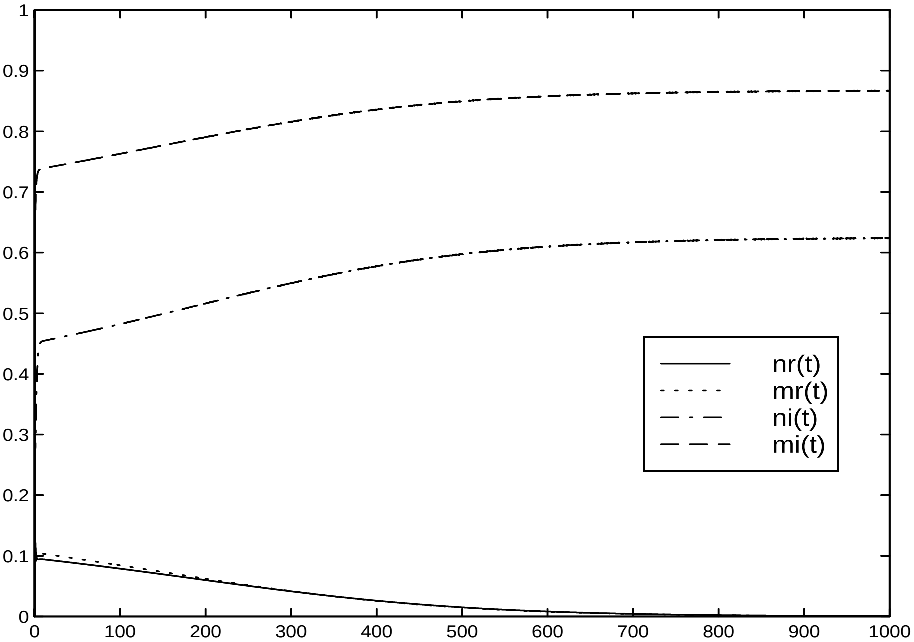

FIG. 4. *A plot of* $n_r(t), m_r(t), n_i(t)$, *and* $m_i(t)$ *versus time with parameters from Table* 5. *The residents win although there are two* E_c.

warn the reader here that by following Freter in designating "invader" and "resident" as the two bacterial strains, we make it awkward to employ the standard invasibility terminology in discussing the stability of each single-population equilibrium, particularly that of the invader-only equilibrium. Hopefully, this warning will prevent any misunderstandings.

As expected, it is more difficult for the invader to successfully invade the resident strain equilibrium than vice versa. Quantitatively, the invader can invade the resident strain equilibrium E_r only if

$$f_i(s_r) - \rho > 0,$$

while either of the inequalities (here, we make do with slightly stronger inequalities than required which allow a more transparent biological interpretation, using Remark 1)

$$f_r(s_i)G(0) - \lambda_r > 0$$

or

$$f_r(s_i) - \rho > 0$$

suffice to allow the resident strain to successfully invade the invader equilibrium E_i. Here, s_r and s_i denote the (unscaled) nutrient concentration at the resident or invader equilibrium, respectively. A unique coexistence equilibrium E_c is shown to exist if and only if each strain can successfully invade the other strain's equilibrium.

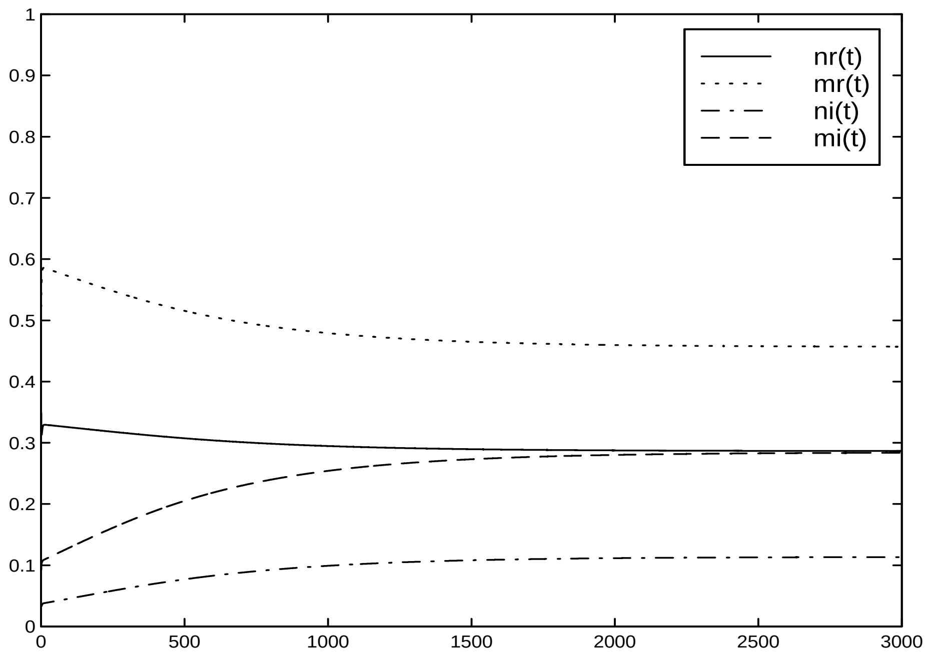

FIG. 5. *A plot of* $n_r(t), m_r(t), n_i(t)$, *and* $m_i(t)$ *versus time with parameters from Table* 5. *Coexistence occurs.*

As a special case, consider the competition between a resident strain, capable of wall attachment, and a mutant strain unable to colonize the wall, e.g., for lack of an appropriate receptor on its surface. Assuming the two strains have identical specific growth rates $f \equiv f_r = f_i$ and that the resident can colonize the chemostat in the absence of the mutant then Theorem 4.4 implies that the resident population drives the mutant to extinction.

Competition between two strains capable of wall attachment is considered in section 5. Sharp conditions for one strain to be able to successfully invade the other strain's equilibrium are given. Assuming that the resident strain equilibrium is globally attracting when only the resident strain is present (see Theorem 3.2 for sufficient conditions), it is proved that the above-mentioned invasion condition implies that the invader avoids extinction in the sense that both its planktonic and wall-attached densities ultimately exceed positive lower bounds which are independent of initial data.

A coexistence equilibrium exists when both resident and invader strains can invade each others' single-population equilibrium and when both resident and invader single-population equilibria are uninvadible by the rival strain. This is in contrast to the case of asymmetric competition between a resident capable of wall-attachment and a mutant lacking this ability where a coexistence equilibrium can only exist when both strains can invade each others equilibrium. We refer to this case where both E_r and E_i are asymptotically stable as the bistable case. We expect that E_c is an unstable saddle. (See Table 1 for parameter values leading to this case.) As noted in the introduction, this case may be particularly relevant to the phenomena of colonization resistance in the gut (see [18]). In the bistable case, ingestion of a subthreshold dose

TABLE 1

Parameter values that produce a unique unstable interior equilibrium, E_c.

Parameter	Value
λ_r	.6
λ_i	.5
α_r	1.1
α_i	.7
y_r	.8
y_i	.57
$f_r(s)$	$2s/(s+1.35)$
$f_i(s)$	$s/(s+.5)$

TABLE 2

Equilibrium values with parameters from Table 1. (Stable equilibria are indicated by superscript asterisk.)

Equilibrium	s	n_r	m_r	n_i	m_i
E_c	.34585	.21938	.31847	.27682	.31308
E_r^*	.36873	.50502	.67198	0	0
E_i^*	.32426	0	0	.38517	.59393

of a bacterial strain would lead to its being washed out of the gut over time (see Figure 2), while ingestion of a superthreshold dose would lead to it displacing the resident strain (see Figure 3) with potentially negative consequences for the health of the human or animal. For the parameter values of Table 1, we have determined the threshold inoculum of planktonic invaders n_i (we took $m_i = 0$) required to be introduced at the resident equilibrium to displace the resident as being approximately 7.53 times the equilibrium value n_i^* in the invader equilibrium E_i.

Also intriguing is the possibility for multiple coexistence equilibria. See Table 5 for parameter values which lead to two E_c, one stable and the other unstable. Figures 4 and 5 indicate some of the possible outcomes of such competition. The resident equilibrium E_r is asymptotically stable. If one perturbs it by introducing a small inoculum of planktonic invaders, the latter are washed out. However, a large dose of planktonic invaders results in the coexistence of the two strains at the asymptotically stable equilibrium E_{c_1}. The threshold inoculum of invading planktonic bacteria required to be introduced to the resident equilibrium to allow for coexistence was found to be 5.34 times the equilibrium value n_i^* of the invader equilibrium E_i. In contrast to the bistable case, successful invasion does not result in extinction but in coexistence.

Of course, the coexistence of two bacterial strains at a stable equilibrium is also of biological relevance given the great diversity of the gut ecosystem. See Figure 1 for a simulation in this case.

We make no claim that the parameter values used in our simulations are biologically reasonable. They have merely been chosen to illustrate the range of dynamical behavior inherent in the model.

It is interesting to compare our results with those in Pilyugin and Waltman [20]. As noted in the introduction, their model assumes unlimited wall-attachment sites so the only nonlinearities in the model are due to nutrient uptake. They do not assume that the specific growth rates of planktonic and wall-attached cells are equal. However, their results are most complete in this case, and since the general case is not treated we confine our comparisons to this case. They show that E_r is globally attracting for nontrivial initial data for the single-strain model. The main difference however is for the competition model. Their model gives competitive exclusion under

TABLE 3
Parameter values that produce a unique stable equilibrium, E_c.

Parameter	Value
λ_r	.375
λ_i	.4
α_r	.75
α_i	.8
y_r	.4
y_i	.8
$f_r(s)$	$2s/(s+1.35)$
$f_i(s)$	$s/(s+.5)$

TABLE 4
Equilibrium values with parameters from Table 3.

Equilibrium	s	n_r	m_r	n_i	m_i
E_c^*	.28958	.16111	.29499	.24612	.42497
E_r	.25514	.29794	.63927	0	0
E_i	.33535	0	0	.53172	.79279

the conditions described above. For n-competitors, they show that there is only one winner. The strain that can grow at the lowest nutrient concentration eliminates the others just as for the classical chemostat (see [23]).

Our results here complement those in [1, 2, 3] where the plug flow reactor was used instead of the chemostat. The simpler ordinary differential equations that result in the case of a chemostat allow for a more complete analysis to be given here.

Finally, our intention in this paper has been to give a reasonably complete mathematical analysis of an important model constructed by Freter and his colleaques in [10, 11, 12, 14, 15] to show that the ability of bacteria to adhere to the gut wall plays a role in the colonization resistance phenomena. These authors relied on a few numerical simulations, some of which were carried out in the mathematically degenerate case of identical resident and invader strains. Hopefully, our analysis provides a more balanced perspective on the generic dynamics inherent in this model system. Its dynamics are much richer than the classical chemostat competition model without wall-attachment where the generic outcome is competitive exclusion. Perhaps our most important contribution on the biological side has been to show the existence of various bistable phase portraits and to point out the relevance of these to colonization resistance. The associated separatrix surface, the stable manifold of an unstable coexistence equilibrium, implies a threshold dose of invading strain is required to overcome the advantages held by the resident strain. It is not clear that a separatrix can occur in the wall-growth model treated in [20].

7. Proofs.

7.1. Matrices. We begin by considering a family of quasi-positive matrices that have been encountered often. For $0 \le M \le 1$ and $x \ge 0$ define

$$P_r(x,M) = \begin{pmatrix} x-1-\alpha_r(1-M) & \lambda_r + x[1-G(M)] \\ \alpha_r(1-M) & G(M)x - \lambda_r \end{pmatrix},$$
$$H_r(x,M) = \det P_r(x,M) = (\lambda_r - G(M)x)(1-x) - x\alpha_r(1-M),$$
$$T_r(x,M) = \text{trace } P_r(x,M). \tag{7.1}$$

LEMMA 7.1. *The following hold for $0 \le M < 1$:*

TABLE 5
Parameter values that produce two coexistence equilibria.

Parameter	Value
λ_i	.4
λ_r	.62
α_i	.75
α_r	4
y_i	.4
y_r	.8
$f_i(s)$	$1.2s/(s+.3)$
$f_r(s)$	$3s/(s+1.35)$

TABLE 6
Equilibrium values with parameters from Table 5.

Equilibrium	s	n_r	m_r	n_i	m_i
$E^*_{c_1}$	.14198	.11361	.28436	.28640	.45658
E_{c_2}	.17938	.33871	.62392	.15889	.19497
E_i	.12157	0	0	.35137	.66403
E^*_r	.21896	.62483	.86758	0	0

1. *For $0 < x \leq 1$ we have $\frac{\partial H_r}{\partial M} > 0$.*
2. *For $0 \leq x < \min\{\frac{\lambda_r}{G(M)}, 1\}$ we have $\frac{\partial H_r}{\partial x} < 0$.*

Proof. The partial derivatives of H_r are given by

$$\begin{aligned} \frac{\partial H_r}{\partial M} &= x\left[\alpha_r - (1-x)G'(M)\right], \\ \frac{\partial H_r}{\partial x} &= -G(M)(1-x) - \left[\lambda_r - xG(M)\right] - \alpha_r(1-M). \end{aligned} \tag{7.2}$$

The results follow from $G' < 0$. ◻

LEMMA 7.2. *H_r and T_r have the following properties for fixed M, $0 \leq M < 1$:*

1. *The equation, $H_r(x, M) = 0$, has two real unequal positive solutions, denoted by $x_r(M)$ and $k_r(M)$. We define $x_r(M)$ to be the smaller of the two.*
2. *$H_r(x, M) < 0$ in the interval $x_r(M) < x < k_r(M)$ and $H_r(x, M) > 0$ for $0 \leq x < x_r(M)$ or $x > k_r(M)$.*
3. *There exists a unique solution to $T_r(x, M) = 0$, denoted by $p_r(M)$, such that $T_r(x, M) < 0$ for $0 \leq x < p_r(M)$ and $T_r(x, M) > 0$ for $x > p_r(M)$.*
4. *1, $\frac{\lambda_r}{G(M)}$, and $p_r(M)$ all lie within the open interval $(x_r(M), k_r(M))$.*

Proof. (1) and (2) follow directly from the quadratic formula or from the fact that $P_r(x, M)$ is a quasi-positive and irreducible matrix (see Appendix A of [23]). As such, it has a dominant real eigenvalue. The determinant in (7.1) has been factored so one sees that $H_r(0, M) > 0$, $H_r(1, M) < 0$, and $H_r(\lambda_r/G(M), M) < 0$. (3) The solution to $T_r(x, M) = 0$ is $x = p_r(M) \equiv \frac{\lambda_r + \alpha_r(1-M)+1}{1+G(M)}$. (4) We have

$$H_r(p_r(M), M) = \frac{\left[\lambda_r - G(M)\right]^2 + \alpha_r(1-M)\left[2\lambda_r + 1 + G(M)^2 + \alpha_r(1-M)\right]}{-\left[1+G(M)\right]^2} < 0.$$

The result follows. ◻

LEMMA 7.3. *For fixed M, $0 \leq M < 1$, we have the following:*

1. *$SM(P_r(x, M)) < 0$ for $0 \leq x < x_r(M)$.*
2. *$SM(P_r(x, M)) > 0$ for $x > x_r(M)$.*

3. *$SM(P_r(x,M)) = 0$ for $x = x_r(M)$.*

Proof. (1) If $0 \le x < x_r(M)$, then $\det P_r(x,M) > 0$ and $T_r(x,M) < 0$ by Lemma 7.2, thus both eigenvalues are negative and $SM(P_r(x,M)) < 0$.

(2) Now suppose $x > x_r(M)$. If $x_r(M) < x < k_r(M)$, we have $\det P_r(x,M) < 0$ by Lemma 7.2, which implies the eigenvalues have opposite sign giving $SM(P_r(x,M)) > 0$. If $k_r(M) \le x$, then $T_r(x,M) > 0$ and $\det(P_r(x,M)) \ge 0$ by Lemma 7.2, which implies that $SM(P_r(x,M)) > 0$.

(3) $\det P_r(x_r(M),M) = H_r(x_r(M),M) = 0$ and $T_r(x_r(M),M) < 0$ by Lemma 7.2. Thus one eigenvalue is 0 and the other negative so $SM(P_r(x_r(M),M)) = 0$. □

Remark 1. The inequalities $x_r(M) < 1$ and $x_r(M) < \lambda_r/G(M)$, established in Lemma 7.2 (4), lead to important biological consequences noted in previous sections. By Lemma 7.3, $SM(P_r(x,M)) > 0$ when $x > x_r(M)$ so $x_r(M)$ is the threshold for instability. In particular, $A_r = P(f_r(1),0)$ in section 3 is unstable when either $f_r(1) > \lambda_r/G(0)$ or when $f_r(1) > 1$. Similar results hold for $B = P_r(f_r(s_i),0)$ in section 4.

LEMMA 7.4. *If $0 \le M < 1$, then $\frac{dx_r}{dM} > 0$.*

Proof. We have $H_r(x_r(M),M) = 0$ from Lemma 7.2. Differentiating this equation implicitly and using Lemma 7.1 (2) and Lemma 7.2 (4) gives $\frac{dx_r}{dM} = -\frac{\partial H_r}{\partial M}/\frac{\partial H_r}{\partial x} > 0$. □

7.2. Equilibria. The equilibrium points of (2.2) are found by setting the functions on the right-hand side of (2.2) equal to zero and then solving the corresponding system of equations for solutions in Ω. The equations are:

$$
\begin{aligned}
0 &= 1 - s - \frac{1}{y_r}(n_r + m_r)f_r(s) - \frac{1}{y_i}(n_i + m_i)f_i(s),\\
0 &= n_r(f_r(s) - 1) + \lambda_r m_r + f_r(s)m_r(1 - G(M)) - \alpha_r n_r(1 - M),\\
0 &= \alpha_r n_r(1 - M) - \lambda_r m_r + f_r(s)m_r G(M),\\
0 &= n_i(f_i(s) - 1) + \lambda_i m_i + f_i(s)m_i(1 - G(M)) - \alpha_i n_i(1 - M),\\
0 &= \alpha_i n_i(1 - M), -\lambda_i m_i + f_i(s)m_i G(M).
\end{aligned}
$$

Adding the last two equations gives $n_i(f_i(s)-1)+f_i(s)m_i = 0$ so that $n_i = m_i\frac{f_i(s)}{1-f_i(s)}$. Using these relationships in the first equation yields $1 - s - \frac{n_r}{y_r} - \frac{n_i}{y_i} = 0$. Replacing n_i, n_r in the third and fifth equations yields the simplified equilibrium equations which have the same solutions as the preceding system:

$$
\begin{aligned}
0 &= (m_i + n_i)f_i(s) - n_i,\\
0 &= (m_r + n_r)f_r(s) - n_r,\\
0 &= 1 - s - \frac{n_r}{y_r} - \frac{n_i}{y_i},\\
0 &= \alpha_r m_r \frac{f_r(s)}{1 - f_r(s)}(1 - M) - m_r\left[\lambda_r - f_r(s)G(M)\right],\\
0 &= \alpha_i m_i \frac{f_i(s)}{1 - f_i(s)}(1 - M) - m_i\left[\lambda_i - f_i(s)G(M)\right].
\end{aligned}
\tag{7.3}
$$

If we are interested in solutions with nonzero m_r and m_i then we may divide through by these quantities in the last two equations and simplify to get

$$\begin{aligned} 0 &= (m_i + n_i) f_i(s) - n_i, \\ 0 &= (m_r + n_r) f_r(s) - n_r, \\ 0 &= 1 - s - \frac{n_r}{y_r} - \frac{n_i}{y_i}, \\ 0 &= H_r(f_r(s), M), \\ 0 &= H_i(f_i(s), M). \end{aligned} \tag{7.4}$$

The first two equations imply that $f_i(s), f_r(s) < 1$ so the last two equations are equivalent to

$$f_r(s) = x_r(M) \quad \text{and} \qquad f_i(s) = x_i(M).$$

7.3. Proofs in section 3. Now consider the resident equilibrium ($n_i = m_i = 0$, $M = m_r$). For $s > 0$, define

$$z_r(s) = \frac{(1-s)\left[1 - f_r(s)\right]}{f_r(s)}.$$

Solving the third equation for n_r in terms of s we have

$$\begin{aligned} n_r &= y_r(1-s), \\ m_r &= \frac{y_r(1-s)\left[1 - f_r(s)\right]}{f_r(s)}, \\ 0 &= H_r\left[f_r(s), y_r z_r(s)\right]. \end{aligned} \tag{7.5}$$

Define

$$\begin{aligned} h(s) &= H_r\left[f_r(s), y_r z_r(s)\right], \\ p(s) &= \frac{y_r(1-s),}{1 + y_r(1-s)}, \\ q(s) &= \lambda_r - f_r(s) G(y_r z_r(s)), \end{aligned} \tag{7.6}$$

and let

$$I = \{s \mid 0 < s < 1, p(s) < f_r(s) < 1, q(s) > 0\}.$$

If $E_r \in \Omega$, then $n_r > 0$, $0 < m_r < 1$, and $s > 0$. The first equation of (7.5) gives $s < 1$. The second equation gives $0 < y_r z_r(s) = m_r < 1$ and $f_r(s) < 1$. The constraint $y_r z_r(s) < 1$ leads to $p(s) < f_r(s)$. The fourth equation of (7.3) gives $q(s) > 0$. Thus s must be in I. If we have a solution to the last equation of (7.5) in I, then n_r^* and m_r^* are readily obtained from the first and second equations of (7.5). Thus E_r exists if and only if $h(s) = 0$ has a solution in I.

LEMMA 7.5. *I is a nonempty open interval, specifically $I = (s_1, \min\{1, f_r^{-1}(1), s_2\})$, where s_1 is the unique solution of $f_r(s_1) = p(s_1)$ and s_2 is the unique root of $q(s_2) = 0$ or $s_2 = \infty$ if no such root exists.*

Proof. We evaluate some derivatives below:

$$\begin{aligned} \frac{dz_r}{ds} &= -\left(\frac{1 - f_r(s)}{f_r(s)} + (1-s) \frac{f_r'(s)}{f_r^2(s)} \right) < 0, \\ \frac{dp}{ds} &= -\frac{y_r}{\left[1 + y_r(1-s)\right]^2} < 0, \end{aligned}$$

$$\frac{dq}{ds} = -f_r'(s)G(y_r z_r(s)) - f_r(s)G'(y_r z_r(s))y_r z_r'(s) < 0.$$

The equation $f_r(s) = p(s)$ has a unique root $s_1 \in (0,1)$ since $f_r \geq 0$ is strictly increasing with $f_r(0) = 0$ and $p(s) \geq 0$ is strictly decreasing with $p(1) = 0$. Furthermore, $f_r(s) > p(s)$ for $s_1 < s < 1$. Also the solution to $q(s) = 0$ is unique if it exists since $q'(s) < 0$. We have $q(s_1) = \lambda_r > 0$. Thus, $s_2 > s_1$ if s_2 exists. □

LEMMA 7.6. *$E_r = (s_r, n_r^*, m_r^*)$ exists and is unique if $SM(A_r) > 0$.*

Proof. Let $s^* = \min\{1, f_r^{-1}(1), s_2\}$. We have from Lemma 7.1 that for $s \in I$

$$\frac{dh}{ds} = \frac{\partial H_r}{\partial x}(f_r(s), y_r z_r(s))f_r'(s) + \frac{\partial H_r}{\partial M}(f_r(s), y_r z_r(s))y_r z_r'(s) < 0,$$

since $f_r(s) < 1$, $0 < y_r z_r(s) = m_r < 1$, $q(s) > 0$ for $s \in I$. Therefore, h is strictly decreasing in I so the solution s_r to $h(s) = 0$, if it exists, is unique. It follows (see (7.5)) that E_r is unique if it exists. Now, $h(s_1) = \lambda_r [1 - f_r(s_1)] > 0$ since $f_r(s_1) < 1$. By the intermediate value theorem $h(s) = 0$ has a solution , $s_r \in I$, if and only if $h(s^*) < 0$. Thus E_r exists if and only if $h(s^*) < 0$.

Now assume $SM(A_r) = SM(P_r(f_r(1), 0)) > 0$. We consider $h(s^*)$ for all three cases of $s^* = \min\{f_r^{-1}(1), 1, s_2\}$:

Case (i): If $s^* = 1$, then $f_r(1) \leq 1$ and $q(1) = \lambda_r - f_r(1)G(0) \geq 0$. $SM(P_r(f_r(1), 0)) > 0$, Lemma 7.3 and Lemma 7.2 ($x_r(0) < f_r(1) \leq 1 < k_r(0)$) imply $h(1) = H_r(f_r(1), 0) < 0$.

Case (ii): If $s^* = f_r^{-1}(1)$, then $h(s^*) = H_r(1, 0) = -\alpha_r < 0$.

Case (iii): If $s^* = s_2$, then $\lambda_r - f_r(s_2)G(y_r z_r(s_2)) = 0$ so (see (7.1))

$$h(s_2) = H_r(f_r(s_2), y_r z_r(s_2)) = -f_r(s_2)\alpha_r [1 - y_r z_r(s_2)] < 0,$$

where the last inequality holds since $y_r z_r(s_1) = 1$, $s_1 < s_2$, and $z_r'(s) < 0$ imply $y_r z_r(s_2) < 1$. □

PROPOSITION 7.7. *If $SM(A_r) > 0$, then E_r is asymptotically stable.*

Proof. The Jacobian matrix at E_r is given by

$$J_r = \begin{pmatrix} -1-\kappa & -\frac{f_r(s_r)}{y_r} & -\frac{f_r(s_r)}{y_r} \\ y_r\kappa - \kappa\,[1 - f_r(s_r)]\,G(m_r^*)y_r & f_r(s_r) - 1 - \left(\frac{1}{f_r(s_r)} - 1\right)\beta & f_r(s_r) + \phi + \beta \\ \kappa\,[1 - f_r(s_r)]\,G(m_r^*)y_r & \left(\frac{1}{f_r(s_r)} - 1\right)\beta & -\phi - \beta \end{pmatrix},$$

where $\beta \equiv \lambda_r - f_r(s_r)G(m_r^*) > 0, \phi \equiv \alpha_r n_r^* - f_r(s_r)m_r^* G'(m_r^*) > 0$, $\kappa \equiv \frac{f_r{}'(s_r)(n_r^* + m_r^*)}{y_r} > 0, \gamma \equiv 1 - f_r(s_r) + \kappa > \kappa$, and $\delta \equiv \phi + \frac{\beta}{f_r(s_r)} + 1 > 1$. The positivity of β follows from the second to last equation of (7.3). The characteristic polynomial of J_r is $p(x) = x^3 + A_1 x^2 + A_2 x + A_3$, where

$$\begin{aligned} A_1 &= \kappa + \frac{\beta}{f_r(s_r)} + \phi - f_r(s_r) + 2 = \gamma + \delta = -\text{trace } J_r, \\ A_2 &= \phi + \beta + \left(\phi + \frac{\beta}{f_r(s_r)} + 1\right)[\kappa + 1 - f_r(s_r)] = \gamma\delta + \phi + \beta, \\ A_3 &= [\phi + \kappa G(m_r^*) f_r(s_r)]\,[1 - f_r(s_r)] + \kappa(\phi + \beta) = -\det J_r. \end{aligned}$$

It is easily seen that A_1 and A_3 are positive since $f_r(s_r) < 1$. Now use the fact that $\delta > 1$, $\gamma > \kappa$, $f_r(s_r) < 1$, and $G(m_r^*) < 1$ to obtain

$$\begin{aligned} A_1 A_2 - A_3 = {} & (\gamma - \kappa)(\phi + \beta) + \gamma\,\delta\,(\delta + \gamma) + \phi\,(\delta - 1) + \delta\,\beta \\ & + f_r(s_r)\phi - \kappa G(m_r^*) f_r(s_r) + \kappa G(m_r^*) f_r(s_r)^2 \end{aligned}$$

$$> \kappa^2 + \beta + f\phi + \kappa\left[1 - f_r(s_r)G(m_r^*)\right] + \kappa f_r(s_r)^2 G(m_r^*)$$
$$> 0.$$

The Routh–Hurwitz theorem completes the proof. ∎

PROPOSITION 7.8. *If $SM(A_r) < 0$, then E_0 is globally attracting.*

Proof. Rewrite the last two equations in (3.1) to get

$$\begin{aligned}\dot{n}_r =& n_r\left(f_r(s) - 1 - \alpha_r\right) + \lambda_r m_r + f_r(s)m_r[1 - G(0)]\\ &+ f_r(s)m_r[G(0) - G(m_r)] + \alpha_r n_r m_r\\ \dot{m}_r =& \alpha_r n_r + m_r[f_r(s)G(0) - \lambda_r] - m_r[f_r(s)(G(0) - G(m_r)] - \alpha_r n_r m_r.\end{aligned}$$

Using the fact that

$$\limsup_{t\to\infty} s(t) \le 1,$$

which follows from the first of equations (3.1), we find that n_r and m_r satisfy the following differential inequality

$$\begin{aligned}\dot{n}_r &\le n_r(f_r(1+\delta) - 1 - \alpha_r) + m_r[f_r(1+\delta)(1 - G(0)) + \lambda_r] + g(t),\\ \dot{m}_r &\le \alpha_r n_r + m_r[f_r(1+\delta)G(0) - \lambda_r] - g(t)\end{aligned}$$

for large values of t, where

$$g(t) = f_r(s)m_r[G(0) - G(m_r)] + \alpha_r n_r m_r > 0,$$

and for arbitrary $\delta > 0$ which will be chosen below. If we define $V = (n_r, m_r)^t$, $E = (1, -1)^t$, and $C = P_r(f_r(1+\delta), 0)$, then the system above takes the form

$$\dot{V} \le CV + g(t)E.$$

As $SM(A_r) = SM(P_r(f_r(1), 0)) < 0$, we may choose $\delta > 0$ so small that $q \equiv SM(C) < 0$. By the Perron–Frobenius theorem, corresponding to $q = SM(C)$, there exists an eigenvector $W = (u, v)^t$, with $u, v > 0$, such that $C^t W = qW$. The ratio of the components of V is easily seen to satisfy

$$\frac{u}{v} = \frac{q + \lambda_r - f_r(1+\delta)G(0)}{f_r(1+\delta) + \lambda_r - f_r(1+\delta)G(0)}.$$

As the denominator is positive so must be the numerator, since $u, v > 0$, so $q < 0 < f_r(1+\delta)$ implies that $u < v$. Taking the inner product of both sides of the differential inequality satisfied by V with the positive vector W, we get

$$\frac{d}{dt}(V \cdot W) \le q(V \cdot W) + g(t)(u - v) \le q(V \cdot W).$$

As $q < 0$, $V \cdot W = un_r(t) + vm_r(t) \to 0$ as $t \to \infty$. ∎

PROPOSITION 7.9. *If $SM(A_r) > 0$, then there exists $\epsilon > 0$ such that*

$$\liminf_{t\to\infty} n_r(t) > \epsilon,$$
$$\liminf_{t\to\infty} m_r(t) > \epsilon$$

for every solution of (3.1) *with $n_r(0) + m_r(0) > 0$.*

Proof. We apply Theorem 4.6 in [26]. Using the notation of that result, we set $X = \Omega_0$, $X_2 = \{(s, n_r, m_r) \in \Omega_0 : n_r = 0 \text{ or } m_r = 0\}$, and $X_1 = X \setminus X_2$. We wish to show that solutions starting in X_1 ultimately stay away from X_2. The notation $x(t) = (s(t), n_r(t), m_r(t))$ for a solution of (3.1) will be used. The set $Y_2 = \{x(0) \in X_2 : x(t) \in X_2, t \geq 0\} = \{(s, 0, 0) : s \geq 0\}$ and Ω_2, defined to be the union of the omega limit sets of solutions starting in Y_2, consists of the equilibrium E_0. Obviously, the set $M = \{E_0\}$ is an acyclic covering of Ω_2 in X_2. We must show that M is an isolated compact invariant set in X and that it is weak repellor for X_1: $\limsup_{t\to\infty} d(x(t), M) > 0$ for all $x(0) \in X_1$, where $d(x, M)$ is the distance from x to M. Suppose M is not a weak repellor for X_1. Then there exists $x(0) \in X_1$ such that $x(t) \to E_0$ as $t \to \infty$, i.e., $x(0)$ belongs to the stable manifold of E_0. If we let $V = (n_r, m_r)^t$, then we may write the last two equations of (3.1) as

$$\dot{V} = P_r(f_r(1), 0)V + [P_r(f_r(s), m_r) - P_r(f_r(1), 0)]V.$$

The Perron–Frobenius theorem implies the existence of an eigenvector $W = (u, v)^t$ for $P_r(f_r(1), 0)$ corresponding to the dominant eigenvalue $q \equiv SM(P_r(f_r(1), 0)) > 0$ with $u, v > 0$. Taking the inner product of both sides of the differential equation with W leads to

$$\frac{d}{dt}(un_r + vm_r) = q(un_r + vm_r) + o(|n_r| + |m_r|).$$

For all large t, we have

$$\frac{d}{dt}(un_r + vm_r) \geq q/2(un_r + vm_r),$$

implying that $un_r + vm_r \to \infty$ as $t \to \infty$. This contradiction to $x(t) \to E_0$ shows that M is a weak repellor for X_1. A similar argument also establishes that M is isolated in X. Theorem 4.6 in [26] implies the desired result. ☐

Proof of Theorem 3.2. The off-diagonal entries of the Jacobian matrix of the vector field (3.2) are displayed below

$$J = \begin{pmatrix} * & 0 & y_r^{-1} \\ xf_r'(E - x) & * & y_r^{-1} \\ f_r'(E - x)m_rG(m_r) & \beta & * \end{pmatrix},$$

where $\beta = \alpha_r y_r(1 - m_r) - f_r'(E - x)\, m_rG(m_r)$. The quantity β is positive if (3.3) holds, in which case (3.2) is cooperative. It is easily checked that J is irreducible when $x > 0$.

In the new coordinates $E_0 = (E, x, m_r) = (1, 0, 0)$ and

$$E_r = (E^*, x^*, m_r^*) = \left(s_r + \frac{n_r^*}{y_r} + \frac{m_r^*}{y_r}, \frac{n_r^*}{y_r} + \frac{m_r^*}{y_r}, m_r^*\right).$$

By Theorem 3.1 and $SM(A_r) > 0$, an omega limit point (E, x, m_r) of any trajectory with $x(0) > 0$ satisfies $x > \epsilon/y_r$. No such solution can converge to E_0. By Theorem 1.4.3 of [24] there exists a dense set of initial data that corresponds to trajectories that converge to an equilibrium. Let $w(0) = (E(0), x(0), m_r(0))$ be an arbitrary initial condition in Λ with $x(0) > 0$. Let $\mu > 0$ be small enough so that the ball B of radius μ containing $w(0)$ contains only points with x-component positive. Then there exist initial conditions $z(0)$ and $p(0)$ in B such that $z(t)$ and $p(t)$ converge to E_r and

$z(0) \leq w(0) \leq p(0)$. Since (3.2) is a monotone system we have $z(t) \leq w(t) \leq p(t)$ for $t > 0$. Thus $w(t)$ also converges to E_r. Since $w(0)$ was chosen arbitrarily, we have all trajectories with initial conditions in Λ off of the E-axis converge to E_r. We can conclude that all of the trajectories with initial conditions in Ω off of the s-axis converge to E_r. ◻

7.4. Proofs in section 4.

Proof of Theorem 4.1. The Jacobian of (4.1) evaluated at $E_0 = (1, 0, 0, 0)$ is

$$J(E_0) = \begin{pmatrix} -1 & -f_r(1)/y_r & -f_r(1)/y_r & -f_i(1)/y_i \\ 0 & P_r(f_r(1), 0) & & 0 \\ 0 & & & 0 \\ 0 & 0 & 0 & f_i(1) - 1 \end{pmatrix},$$

where $P_r(f_r(1), 0)$ is the central 2×2 block. It is apparent that $SM(J(E_0)) < 0$ when $SM(P_r(f_r(1), 0)) = SM(A_r) < 0$ and $f_i(1) < 1$ and $SM(J(E_0)) > 0$ if either inequality is reversed. Thus E_0 is asymptotically stable if $SM(A_r) < 0$ and $f_i(1) < 1$ and unstable if one of these is reversed.

The Jacobian evaluated at E_r is the block matrix

$$J(E_r) = \begin{pmatrix} & & & -f_i(s_r)/y_i \\ & J_r & & 0 \\ & & & 0 \\ 0 & 0 & 0 & f_i(s_r) - 1 \end{pmatrix},$$

where J_r is given in the proof of Proposition 7.7. As shown there, $SM(J_r) < 0$ so $SM(J(E_r)) < 0$ when $f_i(s_r) < 1$ and $SM(J(E_r)) > 0$ when $f_i(s_r) > 1$. If the latter holds, then $s_r < 1$ implies that $f_i(1) > 1$ so E_i exists and $s_i < s_r$ as $f_i(s_i) = 1$.

The Jacobian evaluated at $E_i = (s_i, 0, 0, n_i^*)$ is

$$J(E_i) = \begin{pmatrix} -1 - \frac{f_i'(s_i) n_i^*}{y_i} & \frac{-f_r(s_i)}{y_r} & \frac{-f_r(s_i)}{y_r} & -\frac{1}{y_i} \\ 0 & P_r(f_r(s_i), 0) & & 0 \\ 0 & & & 0 \\ f_i'(s_i) n_i^* & 0 & 0 & 0 \end{pmatrix}.$$

The characteristic polynomial of $J(E_i)$ is

$$p(\mu) = \left[\mu^2 - T_r(f_r(s_i), 0)\mu + H_r(f_r(s_i), 0)\right] (\mu + 1) \left(\mu + \frac{f_i'(s_i) n_i^*}{y_i}\right).$$

Two eigenvalues are -1 and $\frac{-f_i'(s_i) n_i^*}{y_i}$. The polynomial

$$\mu^2 - T_r(f_r(s_i), 0)\mu + H_r(f_r(s_i), 0)$$

is the characteristic polynomial of $P_r(f_r(s_i), 0) = B$. Thus $SM(J(E_i)) < 0$ when $SM(B) < 0$ and $SM(J(E_i)) > 0$ when $SM(B) > 0$. If the latter holds, then as $s_i < 1$ we have $B < A_r$ so $SM(A_r) > SM(B) > 0$ and E_r exists. ◻

Proof of Corollary 4.2. The differential equation for $V \equiv (n_r, m_r)^t$, the second and third equations in (4.1), can be written as $\dot{V} = P_r(f_r(s), m_r)V$, and hence $V^* = (n_r^*, m_r^*)^t$ is a positive vector satisfying $P_r(f_r(s_r), m_r^*)V^* = 0$ since E_r exists. Obviously then $H_r(f_r(s_r), m_r^*) = 0$ and by Lemma 7.1 we may conclude that

$H_r(f_r(s_r),0) < 0$. But this implies that $SM(P_r(f_r(s_r),0) > 0$ since $P \equiv P_r(f_r(s_r),0)$ has eigenvalues of opposite sign.

Now, if $f_i(s_r) < 1 = f_i(s_i)$, then $s_i > s_r$ so $B = P_r(f_r(s_i),0) > P_r(f_r(s_r),0)$. Consequently, $SM(B) > SM(P_r(f_r(s_r),0))$ by the Perron–Frobenius theorem (see Theorem A.5 of Appendix A of [23]). But $SM(P_r(f_r(s_r),0)) > 0$ from above. Thus, $SM(B) > 0$ and E_i is unstable. On the other hand, if $SM(B) = SM(P_r(f_r(s_i),0) < 0$, then the fact that E_r exists implies that $SM(P_r(f_r(s_r),0)) > 0$ so $s_i < s_r$ by the last assertion of Theorem A.5 of [23], so $f_i(s_r) > f_i(s_i) = 1$. Thus E_r is unstable. ∎

Proof of Theorem 4.3. The s-component of E_c is s_i. After some simplification of the equilibrium equations similar to that of (7.4) we obtain the relations

$$\begin{aligned} \bar{n}_i &= \left(1 - s_i - \frac{\bar{n}_r}{y_r}\right) y_i, \\ \bar{n}_r &= \frac{f_r(s_i)\bar{m}_r}{1 - f_r(s_i)}, \\ 0 &= H_r(f_r(s_i), \bar{m}_r). \end{aligned} \tag{7.7}$$

The uniqueness of E_c follows immediately from the last equation and Lemma 7.1.

Assume that $E_c = (s_i, \bar{n}_r, \bar{m}_r, \bar{n}_i)$ exists. The existence of E_i is trivial since $s_i < 1$. It follows from Lemma 7.1 that $H_r(f_r(s_i),0) < 0$ so $SM(P_r(f_r(s_i),0)) > 0$. But $B = P_r(f_r(s_i),0)$ so $SM(B) > 0$, implying by Theorem 4.1 that E_i is unstable and E_r exists. Lemma 7.6 and its proof imply that $s = s_r$ is the unique root of $h(s_r) = H_r(f_r(s_r), y_r z_r(s_r)) = 0$ in I. Now, $\bar{n}_r > 0$ implies that $f_r(s_i) < 1$ and

$$\bar{n}_i/y_i = 1 - s_i - \frac{\bar{n}_r}{y_r} = 1 - s_i - \frac{f_r(s_i)\bar{m}_r}{y_r\,[1 - f_r(s_i)]} > 0$$

yields that $\bar{m}_r < y_r z_r(s_i)$ and $s_i < 1$. If $y_r z_r(s_i) \geq 1$ (recall that $1 > y_r z_r(s_r) = m_r^*$), then it follows that $s_i < s_r$ since $\frac{dz_r}{ds} < 0$ (see proof of Lemma 7.5). In this case, $f_i(s_r) > f_i(s_i) = 1$, and we are done since E_r is unstable. If $y_r z_r(s_i) < 1$, by Lemma 7.1 and the third of equations (7.7), we have $h(s_i) = H_r(f_r(s_i), y_r z_r(s_i)) > 0$. Furthermore, $p(s_i) < f_r(s_i)$ is a consequence of $y_r z_r(s_i) < 1$. Since $f_r(s_i) < 1 < k_r(y_r z_r(s_i))$, by Lemma 7.2 we conclude that $f_r(s_i) < x_r(y_r z_r(s_i)) < \lambda_r/G(y_r z_r(s_i))$. Thus $q(s_i) > 0$. Therefore, $s_i \in I$. By Lemma 7.6, h is strictly decreasing in I, from which it follows that $s_i < s_r$ and consequently $f_i(s_r) > f_i(s_i) = 1$.

If E_r and E_i are both unstable, then by Theorem 4.1 we have $f_i(s_r) > 1$, implying that $s_i < s_r < 1$, and we have $SM(B) > 0$, implying that $f_r(s_i) > x_r(0)$ by Lemma 7.3. Therefore, $x_r(0) < f_r(s_i) < f_r(s_r) < 1 < k_r(0)$, so by Lemma 7.2 we have $H_r(f_r(s_i),0) < 0$. Since E_r exists, we have $H(f_r(s_r), m_r^*) = 0$. Furthermore, $\lambda_r - f_r(s_r)G(m_r^*) > 0$ implies $\lambda_r - f_r(s_i)G(m_r^*) > 0$ so, by Lemma 7.1, we conclude that $H(f_r(s_i), m_r^*) > 0$. By the intermediate value theorem there exists a $\bar{m}_r \in (0, m_r^*)$ such that $H(f_r(s_i), \bar{m}_r) = 0$. Now, $\bar{n}_r > 0$ is determined from the second of equations (7.7). Since $\bar{m}_r < m_r^* = y_r z_r(s_r) < y_r z_r(s_i)$ we have

$$\bar{n}_i/y_i = 1 - s_i - \frac{\bar{n}_r}{y_r} = 1 - s_i - \frac{f_r(s_i)\bar{m}_r}{y_r\,[1 - f_r(s_i)]} > 0.$$

Thus E_c exists. ∎

Proof of Theorem 4.4. If E_i exists, then $f(1) > 1$ which implies $SM(A_r) > 0$ by the inequality immediately below Theorem 3.1. Thus E_r exists. If E_r exists, then $f(s_r) < 1$ (see the second of equations (7.4)) so E_r is asymptotically stable by Theorem 4.1 and E_i is unstable, if it exists, by Corollary 4.2.

If $SM(A_r) < 0$, then $f(1) < 1$ by the inequality immediately below Theorem 3.1. Thus, as already noted below Theorem 4.1, both $n_r + m_r \to 0$ and $n_i \to 0$ as $t \to \infty$.

Hereafter, we assume that $SM(A_r) > 0$, so E_r exists. We will first establish that the resident population persists, employing arguments similar to those used in the proof of Proposition 7.9. We use the notation of the latter result, indicating the important changes. In our case, $X_2 = \{(s, n_r, m_r, n_i) \in \Omega : n_r = 0 \text{ or } m_r = 0\}$ and $X_1 = \Omega \setminus X_2$. We note that X_1 is open and positively invariant. We will use the notation $x(t)$ for a solution of (4.1). The set $Y_2 = \{x(0) : x(t) \in X_2, t \geq 0\} = \{x(0) \in \Omega : n_r(0) + m_r(0) = 0\}$ is the (s, n_i)-plane and the set Ω_2 is either $\{E_0\}$ if E_i doesn't exist or is $\{E_0, E_i\}$ if E_i exists by standard results for single population growth in a chemostat (see [23]). An acyclic covering of Ω_2 is given by $M_1 = \{E_0\}$ or by $M = M_1 \cup M_2$, where $M_2 = \{E_i\}$. Suppose M_2 is not a weak repeller for X_1 (the case for M_1 is simpler). Then there exists $x(0) \in X_1$ such that $x(t) \to E_i$ as $t \to \infty$. In particular, $s(t) - s_i \to 0$ and $n_r(t) + m_r(t) \to 0$ as $t \to \infty$. Now $W = (n_r, m_r)^t$ satisfies $\dot{W} = P_r(f(s), m_r)W$. Since $SM(A_r) > 0$, $A_r = P_r(f(1), 0)$ and $f(s) \to f(s_i) = 1$, $m_r \to 0$, we may apply the same argument as in the proof of Proposition 7.9 to obtain a contradiction. Thus, M_2 is a weak repeller and a similar argument implies that it is an isolated compact invariant set in Ω. Theorem 4.6 in [26] implies that there is an $\epsilon > 0$ such that every solution of (4.1) with $x(0) \in X_1$ satisfies $\liminf n_r(t) > \epsilon$ and $\liminf m_r(t) > \epsilon$.

Let $V = \frac{n_i}{n_r + m_r}$ and note that $\dot{V} = -(\frac{m_r}{n_r + m_r})V$ along any solution $x(t)$ starting in X_1. Thus V decreases along solutions of (4.1). $\dot{V} = 0$ only when $m_r = 0$ or $n_i = 0$, but solutions starting in X_1 are bounded away from the coordinate hyperplane $m_r = 0$. Since $\dot{V} = 0$ on the omega limit set (see Theorem X.1.3 in [16], and keep in mind the previous paragraph), it follows that $n_i \to 0$ as $t \to \infty$. □

7.5. Proofs in section 5.

Proof of Proposition 5.1. The proof is similar to that of Proposition 7.8. □

Proof of Theorem 5.2. The Jacobian evaluated at E_r is the block matrix

$$J(E_r) = \begin{pmatrix} J_r & D \\ 0 & P_i(f_i(s_r), m_r^*) \end{pmatrix},$$

where J_r is the 3×3 block described in Proposition 7.7 and D is a 3×2 matrix whose entries are irrelevant to the stability of E_r. The eigenvalues of $J(E_r)$ are given by the eigenvalues of J_r and the eigenvalues of $P_i(f_i(s_r), m_r^*)$. As $SM(J_r) < 0$ by Proposition 7.7 and $A_{ri} = P_i(f_i(s_r), m_r^*)$, we conclude that E_r is asymptotically stable when $SM(A_{ri}) < 0$ and unstable if the reverse inequality holds.

If $SM(A_{ri}) = SM(P_i(f_i(s_r), m_r^*)) > 0$, then $f_i(s_r) > x_i(m_r^*)$ by Lemma 7.3. By Lemma 7.4 and $s_r < 1$ we have

$$f_i(1) > f_i(s_r) > x_i(m_r^*) > x_i(0).$$

This gives $SM(A_i) > 0$ so E_i exists. □

Proof of Theorem 5.3. We apply Theorem 4.6 in [26]. Using the notation of that result, we set $X = \Omega$, $X_2 = \{(s, n_r, m_r, n_i, m_i) \in \Omega : n_i = 0 \text{ or } m_i = 0\}$, and $X_1 = X \setminus X_2$. We want to show that solutions which start in X_1 are eventually bounded away from X_2. Using the notation $x(t) = (s(t), n_r(t), m_r(t), n_i(t), m_i(t))$ for a solution of (2.2),

$$Y_2 = \{x(0) \in X_2 : x(t) \in X_2, t \geq 0\} = \{(s, n_r, m_r, 0, 0) \in X : s, n_r \geq 0,\ 0 \leq m_r \leq 1\},$$

and Ω_2, the union of omega limit sets of solutions starting in X_2, is, by our hypotheses, the set $\{E_0, E_r\}$. We will show that if $M_1 = \{E_0\}$ and $M_2 = \{E_r\}$, then M_1, M_2 is an isolated acyclic covering of Ω_2 in Y_2 and each M_i is a weak repellor. All solutions starting in Y_2 but not on the s-axis converge to E_r while those on the axis converge to E_0. E_r, being locally asymptotically stable cannot belong to the alpha limit set of any full orbit in Y_2 different from E_r itself. Similarly for E_0. Thus M_1, M_2 is an acyclic covering of Ω_2.

If M_2 were not a weak repellor for X_1, there would exist an $x(0) \in X_1$ such that $x(t) \to E_r$ as $t \to \infty$. Letting $V = (n_i, m_i)^t$, we may write the equations satisfied by V as

$$\dot{V} = P_i(f_i(s_r), m_r^*)V + [P_i(f_i(s), M) - P_i(f_i(s_r), m_r^*)]V.$$

If $P_i(f_i(s_r), m_r^*)^t W = qW$, where $q = SM(P_i(f_i(s_r), m_r^*)) = SM(A_{ri}) > 0$ and $W = (u, v)^t$ with $u, v > 0$ is the Perron–Frobenius eigenvector, then on taking the dot product of both sides of the differential equation by W and using that $s(t) \to s_r$ and $M(t) \to m_r^*$, we have

$$\frac{d}{dt}(un_i + vm_i) \geq q/2(un_i + vm_i)$$

for all large t. But this leads to the contradiction to $x(t) \to E_r$, namely that $un_i(t) + vm_i(t) \to \infty$ as $t \to \infty$. Thus M_2 is a weak repellor and a similar argument shows that it is an isolated compact invariant set in X. An argument similar to that given in the proof of Proposition 7.9 shows that E_0 is a weak repellor and an isolated compact invariant set in X. Therefore, Theorem 4.6 in [26] implies our result. □

Proof of Lemma 5.4. If an interior equilibrium point, $E_c = (s_c, n_r^c, m_r^c, n_i^c, m_i^c)$, exists, then (7.4) has a solution. Thus, $s_c < 1$, $f_r(s_c) < 1$, and $M^c = m_r^c + m_i^c < 1$. From the penultimate equation and Lemma 7.2 we have $f_r(s_c) = x_r(M^c)$. Therefore, $f_r(1) > f_r(s_c) = x_r(M^c) > x_r(0)$, where we used Lemma 7.6 for the last inequality. But $f_r(1) > x_r(0)$ implies E_r exists. Similarly for E_i. □

Proof of Theorem 5.5. Consider the system of equations (7.4). Given that we must have $f_i(s) < 1 < k_i(M)$, and similarly for $f_r(s)$ the last two equations are equivalent to $f_r(s) = x_r(M)$ and $f_i(s) = x_i(M)$, respectively, so $s = f_r^{-1}(x_r(M)) = f_i^{-1}(x_i(M))$. Thus we are motivated to seek a solution of

$$Z(M) \equiv f_r^{-1}(x_r(M)) - f_i^{-1}(x_i(M)) = 0.$$

If $SM(A_{ri}) > 0$ and $SM(A_{ir}) > 0$, then $f_i(s_r) > x_i(m_r^*)$ and $f_r(s_i) > x_r(m_i^*)$ (these are equivalent). The existence of E_r implies that $f_r(s_r) = x_r(m_r^*)$ and the existence of E_i implies that $f_i(s_i) = x_i(m_i^*)$. It follows that $x_i(m_r^*)$ belongs to the range of f_i and $x_r(m_i^*)$ belongs to the range of f_r so Z is defined on the closed interval with endpoints m_r^* and m_i^*. We calculate

$$\begin{aligned} Z(m_r^*) &= f_r^{-1}(x_r(m_r^*)) - f_i^{-1}(x_i(m_r^*)) \\ &= s_r - f_i^{-1}(x_i(m_r^*)) > 0. \end{aligned}$$

Similarly,

$$\begin{aligned} Z(m_i^*) &= f_r^{-1}(x_r(m_i^*)) - f_i^{-1}(x_i(m_i^*)) \\ &= f_r^{-1}(x_r(m_i^*)) - s_i < 0. \end{aligned}$$

If (5.2) holds, then $f_i(s_r) < x_i(m_r^*) < f_i(1)$ and $f_r(s_i) < x_r(m_i^*) < f_r(1)$. It follows that $x_i(m_r^*)$ belongs to the range of f_i and $x_r(m_i^*)$ belongs to the range of f_r so Z is defined on the closed interval with endpoints m_r^* and m_i^*. But now the inequalities above are reversed.

In either case, there is a solution M^c between m_r^* and m_i^* of $Z(M) = 0$ and $m_i^* \neq m_r^*$. We assume $m_r^* < m_i^*$, the other case may be treated similarly. Define $s_c = f_i^{-1}(x_i(M^c)) = f_r^{-1}(x_r(M^c))$. As $m_r^* < M^c < m_i^*$ and using Lemma 7.4,

$$s_r = f_r^{-1}(x_r(m_r^*)) < s_c < f_i^{-1}(x_i(m_i^*)) = s_i < 1,$$

$f_i(s_c) = x_i(M^c) < 1$, and $f_r(s_c) = x_r(M^c) < 1$. From the first two of equations (7.4) we have

$$\frac{m_i^c}{n_i^c} = \frac{1}{f_i(s_c)} - 1 \quad \text{and} \quad \frac{m_r^c}{n_r^c} = \frac{1}{f_r(s_c)} - 1.$$

Finally, m_r^c and m_i^c are determined by the third of equations (7.4):

$$\begin{aligned} M^c &= m_r^c + m_i^c, \\ 1 - s_c &= \frac{f_r(s_c)}{y_r[1 - f_r(s_c)]} m_r^c + \frac{f_i(s_c)}{y_i[1 - f_i(s_c)]} m_i^c. \end{aligned}$$

The second line intersects the m_r-axis at $m_r = y_r z_r(s_c)$ and intersects the m_i-axis at $m_i = y_i z_i(s_c)$. Consequently, there is a unique intersection point (m_r^c, m_i^c) of the two lines if and only if $y_r z_r(s_c) < M^c < y_i z_i(s_c)$ or $y_i z_i(s_c) < M^c < y_r z_r(s_c)$. But from (7.5), $z_i' < 0$ and $z_r' < 0$, and the relations above, we have

$$y_i z_i(s_c) > y_i z_i(s_i) = m_i^* > M^c > m_r^* = y_r z_r(s_r) > y_r z_r(s_c).$$

Therefore, E_c exists. □

Proof of Corollary 5.6. The result follows immediately by applying Theorem 7.9 to E_i as well as to E_r. □

REFERENCES

[1] M. Ballyk and H. L. Smith, *A flow reactor with wall growth*, in Mathematical Models in Medical and Health Sciences, M. Horn, G. Simonett, and G. Webb, eds., Vanderbilt University Press, Nashville, TN, 1998.

[2] M. Ballyk and H. L. Smith, *A model of microbial growth in a plug flow reactor with wall attachment*, Math. Biosci., 158 (1999), pp. 95–126.

[3] M. Ballyk, D. Le, D. Jones, and H. L. Smith, *Effects of random motility on microbial growth and competition in a flow reactor*, SIAM J. Appl. Math., 59 (1998), pp. 573–596.

[4] B. Baltzis and A. Frederickson, *Competition of two microbial populations for a single resource in a chemostat when one of them exhibits wall attachment*, Biotechnology and Bioengineering, 25 (1983), pp. 2419–2439.

[5] W. G. Characklis and K. C. Marshall, eds., *Biofilms*, Wiley Series in Ecological and Applied Microbiology, John Wiley and Sons, New York, 1990.

[6] P. L. Conway, *Microbial ecology of the human large intestine*, in Human Colonic Bacteria, Role in Nutrition, Physiology, and Pathology, G. R. Gibson and G. T. Macfarlane, eds., CRC Press, Boca Raton, FL, 1995.

[7] J. Costerton, Z. Lewandowski, D. Debeer, D. Caldwell, D. Korber, and G. James, *Biofilms, the customized microniche*, J. Bacteriology, 176 (1994), pp. 2137–2142.

[8] J. Costerton, Z. Lewandowski, D. Caldwell, D. Korber, and H. Lappin-Scott, *Microbial biofilms*, Ann. Rev. Microbiology, 49 (1995), pp. 711–745.

[9] J. Costerton, P. Stewart, and E. Greenberg *Bacterial biofilms: A common cause of persistent infections*, Science, 284 (1999), pp. 1318–1322.

[10] R. Freter, E. Stauffer, E. Cleven, L. Holdeman, and W. Moore, *Continuous-flow cultures as in vitro models of the ecology of large intestinal flora*, Infection and Immunity, 39 (1983), pp. 666–675.

[11] R. Freter, H. Brickner, J. Fekete, M. Vickerman, and K. Carey, *Survival and implantation of Escherichia coli in the intestinal tract*, Infection and Immunity, 39 (1983), pp. 686–703.

[12] R. Freter, *Mechanisms that control the microflora in the large intestine*, in Human Intestinal Microflora in Health and Disease, D. Hentges, ed., Academic Press, New York, 1983.

[13] R. Freter, *The need for mathematical models in understanding colonization and plasmid transfers in the mammalian intestine*, Banbury Report, 24 (1983), pp. 81–93.

[14] R. Freter, *Interdependence of mechanisms that control bacterial colonization of the large intestine*, Microecology and Therapy, 14 (1984), pp. 89–96.

[15] R. Freter, H. Brickner, and S. Temme, *An understanding of colonization resistance of the mammalian large intestine requires mathematical analysis*, Microecology and Therapy, 16 (1986), pp. 147–155.

[16] J. K. Hale, *Ordinary Differential Equations*, Krieger Publishing, Malabar, FL, 1980.

[17] D. Jones and H. L. Smith, *Microbial competition for nutrient and wall sites in plug flow*, SIAM J. Appl. Math., 60 (2000), pp. 1576–2000.

[18] A. Lee, *Neglected Niches: The Microbial Ecology of the Gastrointestinal Tract,* in Advances in Microbial Ecology, K. C. Marshall, ed., Plenum Press, New York, 1985.

[19] G. T. Macfarlane, S. Macfarlane, and G. R. Gibson, *Validation of a three-stage compound continuous culture system for investigating the effect of retention time in the ecology and metabolism of bacteria in the human colon*, Microbial Ecology, 35 (1998), pp. 180–187.

[20] S. Pilyugin and P. Waltman, *The simple chemostat with wall growth*, SIAM J. Appl. Math., 59 (1999), pp. 1552–1572.

[21] R. Rolfe, *Colonization resistance*, in Gastrointestinal Microbiology, Vol 2, R. Mackie, B. White, R. Isaacson, eds., Chapman and Hall Microbiology Series, Chapman and Hall, New York, 1997.

[22] D. C. Savage, *Microbial ecology of the gastrointestinal tract*, Ann. Rev. Microbiology, 31 (1977), pp. 107–133.

[23] H. L. Smith and P. Waltman, *The Theory of the Chemostat*, Cambridge University Press, Cambridge, UK, 1995.

[24] H. L. Smith, *Monotone Dynamical Systems, an Introduction to the Theory of Competitive and Cooperative Systems*, Math. Surveys Monogr. 41, Amer. Math. Soc., Providence, RI, 1995.

[25] E. D. Stemmons, *Competition in a Chemostat with Wall Growth*, Ph.D. thesis, Arizona State University, Tempe, AZ, 1999.

[26] H. Thieme. *Persistence under relaxed point-dissipativity (with application to an endemic model)*, SIAM J. Math. Anal., 24 (1993), pp. 407–435.

[27] H. Topiwala and G. Hamer, *Effect of wall growth in steady-state continuous cultures*, Biotechnology and Bioengineering, 13 (1971), pp. 919–922.