

# A Model of Microbial Growth in a Plug Flow Reactor with Wall Attachment

Mary Ballyk\* and Hal Smith<sup>†</sup>  
Department of Mathematics  
Arizona State University  
Tempe, AZ 85287-1804

August 29, 2002

## Abstract

A mathematical model of microbial growth for limiting nutrient in a plug flow reactor which accounts for the colonization of the reactor wall surface by the microbes is formulated and studied analytically and numerically. It can be viewed as a model of the large intestine or of the fouling of a commercial bio-reactor or pipe flow. Two steady state regimes are identified, namely, the complete washout of the microbes from the reactor and the successful colonization of both the wall and bulk fluid by the microbes. Only one steady state is stable for any particular set of parameter values. Sharp and explicit conditions are given for the stability of each, and for the long term persistence of the bacteria in the reactor.

Keywords: plug flow, bacterial wall growth, gut

## 1 Introduction

The standard models of microbial growth in laboratory bio-reactors such as the chemostat or the plug flow reactor [1, 2] do not account for the tendency of bacteria to adhere to surfaces and form biofilms. Yet wall growth can be a serious problem for bioreactors and fermenters as well as having fundamental implications for natural environments. See [3, 4, 5] for recent theoretical and experimental studies of biofilms. Simple chemostat models allowing for wall growth have been formulated by Topiwala and Hamer [6]

---

\*Gratefully acknowledges the support of NSERC

<sup>†</sup>Supported by NSF Grant DMS 9700910

and later by Baltzis and Fredrickson in [7]. A different model was recently studied by Pilyugin and Waltman [8].

Freter et al [9, 10, 11] have argued that wall growth plays a major role in the observed stability of the microflora of the mammalian large intestine to colonization by invading organisms. A mathematical model is formulated in [10], using the chemostat (CSTR) as a model of the gut, which incorporates wall growth. The introduction of a large dose of an invading strain into the chemostat at the resident strain's steady state is simulated numerically. The result is the near elimination of the invader, even though it is identical in every respect to the resident, because available wall sites are filled by the resident strain. See [12, 13, 14] for recent reviews of the ecology of the gut.

Motivated by Freter's work on the gut, we formulated a very general model of multi-strain competition for limiting nutrient and for limited wall colonization sites in [15]. Instead of the continuous culture as in Freter's work, we based our model on the plug flow reactor (PFR). Penry and Jumars [16] argue that the plug flow model is more appropriate for the human gut (and most other mammals):

“Development of the PFR model for animal guts, however, does more than confirm the obvious. It provides concrete physical and chemical reasons why animal guts should operate as PFR's. The PFR design represents the better method of accomplishing catalytic digestion because it maintains a gradient in reactant concentration, and therefore in reaction rate, from higher values near the reactor entrance to lower values near the exit. In contrast, the high reactant concentration entering a CSTR is diluted immediately to some lower, constant level by material recirculating in the reactor.”

In addition, the PFR model accounts for spatial heterogeneity and material flow neither of which can be considered in a chemostat environment. In the present paper, we analyze the single-strain case of the general model in [15].

We stress that while the model we study springs from Freter's work on the gut, the basic model may have other applications to commercial bio-reactors of plug flow type where wall growth is an issue. It also may serve as a simple model of bacterial fouling of flow through a pipe.

Two possible steady state regimes are identified: complete washout of the bacteria from the reactor and the successful colonization of the reactor by the bacterial strain. Exactly one of these regimes is stable for a given set of parameters. Our analysis focuses on determining the common boundary in parameter space separating regions of stability of each steady state regime. Sharp and explicit conditions are obtained for a single strain of bacteria to survive and persist indefinitely in the reactor and for the existence of steady state bacterial densities. These conditions depend on reactor operating conditions made up of physical variables (reactor length and flow velocity) and resource constraints (limiting nutrient concentration and diffusivity) as well as attributes of the bacterial strain (nutrient uptake rates, propensity for wall attachment, death rates and random motility coefficient).

Numerical simulations are used to illustrate the analytical results. We frame the numerics in a biologically reasonable context. Reactor dimensions (length, radius) are chosen in accordance with data on the large intestine, while the velocity of the medium is varied to reflect realistic transit times. The diffusivity and random motility coefficients are taken to approximate experimentally determined values. Finally, nutrient uptake functions, rates of adhesion and shedding, and the nutrient input concentration are as in Freter [10]. Our simulations, unlike those of Freter, suggest that wall growth is necessary for survival in the large intestine. Furthermore, lower growth rates for some microorganisms in the gut, quoted in [17, 18], lead to washout.

One may reasonably ask whether our results can be applied at all to the gut, in view of the fact that it is known to contain hundreds of strains of bacteria and many different nutrients may be limiting to one or more bacterial populations. Yet it is standard practice in many ecological studies to lump many species at the same trophic level into a single aggregate “population” ( e.g. phytoplankton and zooplankton in a marine setting) for modeling purposes. Thus, our “single strain” may be regarded as such an aggregate of the natural intestinal microflora. For example, it is generally accepted [12, 13, 14] that bacterial colonization of the lumen of the human small intestine is much less a factor than in the large intestine. The principal reason is that the more rapid distal movement of chyme caused by the stronger peristaltic motion experienced in the small bowel allows too little time for bacteria to grow. Thus microbial communities can establish in this region only if they can adhere to the gut wall. However, the more rapid turnover of epithelial cells lining the small bowel [12], may inhibit colonization of the gut wall by increasing the rate of slough-off of wall-attached cells. Our model can be used to quantify this prediction.

The model is described in the following section. Subsequent sections treat the stability of the washout steady state, the existence of a steady state representing survival of the population, the persistence of the population, and numerical simulations. We state our results in the form of theorems whose proofs are relegated to an appendix.

Both authors wish to acknowledge the Center for Systems Science at Arizona State University for sponsoring a workshop on microbial ecology which provided motivation for this research.

## 2 The Model

In this section we formulate the model, the basic ingredients of which are summarized in the table below. The model is essentially a synthesis of the chemostat-based model formulated by Freter et al [9, 10, 11] for microbial growth in the large intestine and the plug flow model of Kung and Baltzis [19] as modified by Ballyk et al [20]. It is the single-strain case of a multi-strain model introduced by the authors in [15].

symbol	description
$S(x, t)$	nutrient density
$u(x, t)$	free bacteria density
$w(x, t)$	wall-bound bacteria density
$w_\infty$	maximum wall bacterial density
$W(x, t)$	$w(x, t)/w_\infty$ , occupation fraction
$C$	circumference of tube
$A$	cross-sectional area of tube
$L$	tube length
$f(S)$	growth rate of free bacteria
$f_w(S)$	growth rate of wall-bound bacteria
$\gamma$	yield constant for free bacteria
$k$	death rate for free cells
$k_w$	death rate for wall-bound cells
$\delta$	$C/A$
$\alpha$	wall recruitment rate
$\beta$	wall slough-off rate
$G(W)$	fraction of daughter cells of wall-bound bacteria finding sites on wall
$d_0$	nutrient diffusivity
$d$	bacterial random motility coefficient
$v$	medium velocity
$S^0$	feed nutrient concentration
$u^0$	feed bacteria density

Consider a thin tube extending along the  $x$ -axis. The reactor occupies the portion of the tube from  $x = 0$  to  $x = L$ . It is fed with growth medium at a constant rate at  $x = 0$  by a laminar flow of fluid in the tube in the direction of increasing  $x$  and at velocity  $v$  (a constant). The external feed contains all nutrients in near optimal amounts except one, denoted by  $S$ , which is supplied in a constant, growth limiting concentration  $S^0$ . We allow the possibility that the feed contains bacteria at constant concentration  $u^0$ . The flow carries medium, depleted nutrients, cells, and their byproducts out of the reactor at  $x = L$ . Nutrient  $S$  is assumed to diffuse with diffusivity  $d_0$  while free microbial cells are assumed to be capable of random movement, modeled by diffusion with diffusivity (sometimes called random motility coefficient)  $d$ . Wall-attached bacteria are assumed to be immobile. We assume negligible variation of free bacteria and nutrient concentration transverse to the axial direction of the tube.

The model accounts for the density of free bacteria (bacteria suspended in the fluid)  $u(x, t)$ , the density of wall-attached bacteria  $w(x, t)$  and the density of nutrient  $S(x, t)$ .

The total free bacteria at time  $t$  is given by

$$A \int_0^L u(x, t) dx$$

and the total bacteria on the wall at time  $t$  is given by

$$C \int_0^L w(x, t) dx.$$

The quantities  $S, u, w$  satisfy the following system of equations.

$$\begin{aligned} S_t &= d_0 S_{xx} - v S_x - \gamma^{-1} u f(S) - \gamma^{-1} \delta w f_w(S) \\ u_t &= d u_{xx} - v u_x + u(f(S) - k) + \delta w f_w(S)(1 - G(W)) \\ &\quad - \alpha u(1 - W) + \delta \beta w \\ w_t &= w(f_w(S)G(W) - k_w - \beta) + \alpha \delta^{-1} u(1 - W), \end{aligned} \tag{2.1}$$

with boundary conditions

$$\begin{aligned} v S^0 &= -d_0 S_x(0, t) + v S(0, t), & S_x(L, t) &= 0 \\ v u^0 &= -d u_x(0, t) + v u(0, t), & u_x(L, t) &= 0, \end{aligned} \tag{2.2}$$

and initial conditions

$$S(x, 0) = S_0(x), \quad u(x, 0) = u_0(x), \quad w(x, 0) = w_0(x), \quad 0 \leq x \leq L. \tag{2.3}$$

The nutrient uptake rates for free and wall-attached bacteria are given by functions  $f$  and  $f_w$ , assumed to satisfy

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

A typical example is the Monod function

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

It is assumed that there is a finite upper bound  $w_\infty$  on the density of available wall sites for colonization. The fraction of daughter cells of wall-bound bacteria finding sites on the wall,  $G(W)$ , as a function of the occupancy fraction  $W = w/w_\infty$  is assumed to satisfy

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

Freter et al [9, 10, 11] use

$$G(W) = \frac{1 - W}{a + 1 - W}$$

where  $a$  is typically very small.

Free bacteria are attracted to the wall at a rate proportional (with constant  $\alpha$ ) to the product of the free cell density  $u$  and the fraction of available wall sites  $1 - W$ . Finally, we assume that wall-attached cells are sloughed off the wall by mechanical forces proportional (with constant  $\beta$ ) to their density. Except where explicitly mentioned, all parameters appearing in the model are assumed to be positive except possibly the cell death rates  $k \geq 0$  and  $k_w \geq 0$ , which are sometimes ignored. See [15] for further details on the modeling.

Suitable dimensionless variables and parameters are summarized below:

$$\begin{aligned}\bar{S} &= S/S^0, \quad \bar{u} = u/\gamma S^0, \quad \bar{u}^0 = u^0/\gamma S^0, \quad \bar{w} = W = w/w_\infty, \\ \bar{x} &= x/L, \quad \bar{t} = vt/L, \quad \bar{d} = d/Lv, \quad \bar{f}(\bar{S}) = (L/v)f(S^0\bar{S}), \\ \bar{f}_w(\bar{S}) &= (L/v)f_w(S^0\bar{S}), \quad \bar{\alpha} = (L/v)\alpha, \quad \bar{\beta} = (L/v)\beta \\ \bar{k} &= (L/v)k, \quad \bar{k}_w = (L/v)k_w, \quad \bar{d}_0 = d_0/Lv.\end{aligned}$$

Define

$$\epsilon = \frac{\delta w_\infty}{\gamma S^0}.$$

Then, in terms of these quantities, the model equations (2.1)-(2.2) become, on dropping the overbars:

$$\begin{aligned}S_t &= d_0 S_{xx} - S_x - u f(S) - \epsilon w f_w(S) \\ u_t &= du_{xx} - u_x + u(f(S) - k) + \epsilon w f_w(S)(1 - G(w)) \\ &\quad - \alpha u(1 - w) + \epsilon \beta w \\ w_t &= w(f_w(S)G(w) - k_w - \beta) + \epsilon^{-1} \alpha u(1 - w),\end{aligned}\tag{2.4}$$

with boundary conditions

$$\begin{aligned}1 &= -d_0 S_x(0, t) + S(0, t), \quad S_x(1, t) = 0 \\ u^0 &= -du_x(0, t) + u(0, t), \quad u_x(1, t) = 0\end{aligned}\tag{2.5}$$

and initial conditions

$$S(x, 0) = S_0(x), \quad u(x, 0) = u_0(x), \quad w(x, 0) = w_0(x), \quad 0 \leq x \leq 1.\tag{2.6}$$

The initial data are assumed to be continuous, that is, to belong to the set  $X = \{(S_0, u_0, w_0) \in C([0, 1], \mathbb{R})^3 : S_0 \geq 0, u_0 \geq 0, 0 \leq w_0 \leq 1\}$ . Our first result says that there is a finite upper bound on the biomass that can be supported in the reactor by the nutrient in the feed stream, independent of the initial data. If the initial density of organisms is larger than can be supported, then the excess will be washed out.

**Theorem 2.1** *The system (2.4)-(2.6) induces a semidynamical system on  $X$ . In particular,  $0 \leq w(x, t) \leq 1$  for all  $(x, t)$  with  $0 \leq x \leq 1$  and  $t > 0$ . Moreover, if  $\beta + k_w > 0$ , then there exists  $M > 0$ , independent of the initial conditions, such that for every solution of (2.4)-(2.6), we have*

$$\limsup_{t \rightarrow \infty} \int_0^1 u(x, t) dx \leq M.$$

Finally,

$$\limsup_{t \rightarrow \infty} \max_{0 \leq x \leq 1} S(x, t) \leq 1. \quad (2.7)$$

Of course, the ultimate bound (2.7) on  $S$  translates to  $\limsup S \leq S^0$  in the original unscaled variables; for large time, the reactor nutrient concentration ultimately cannot exceed the feed concentration. The quantity  $M$  obtained in our proof is not so illuminating other than it is linear in  $u^0$ , the bacteria concentration in the feed, but does not vanish with  $u^0$ .

The eigenvalue problem

$$\begin{aligned} \lambda \phi &= d\phi'' - \phi' \\ 0 &= -d\phi'(0) + \phi(0), \quad \phi'(1) = 0 \end{aligned} \quad (2.8)$$

plays a fundamental role here. Its eigenvalues,  $\{\lambda_n\}_{n \geq 0}$ , satisfy (see [20])  $\lambda_{n+1} < \lambda_n$ , and  $\lambda_0 < -1$ . In order to emphasize the dependence of  $\lambda_0$  on  $d$  and take account of its sign, we define  $\lambda_0 = -\lambda_d$ . As will be seen in the following sections,  $\lambda_d$  plays an important role in determining the behavior of the system. In terms of the original unscaled variables, the mean residence time of a free bacterial cell in the plug flow reactor in the absence of wall attachment is  $\frac{L}{v}(\lambda_d)^{-1}$  where  $\bar{d} = d/Lv$  (see [20]).

### 3 Stability of Washout Steady State

If there is no input of microorganisms from inflow, that is if  $u^0 = 0$ , which we assume throughout this section, then the system (2.4)-(2.6) has a trivial steady state

$$S \equiv 1, \quad u = w \equiv 0$$

which we refer to as the ‘washout steady state’ since no organisms are present. Our goal in this section is to examine the stability properties of this steady state. The reason for focusing on this uninteresting steady state is our expectation that when it is unstable, then a bacterial population can successfully colonize the reactor.

The linearization of (2.4)-(2.6) about the washout steady state is given by (we use the same variable names):

$$\begin{aligned}
S_t &= d_0 S_{xx} - S_x - u f(1) - \epsilon w f_w(1) \\
u_t &= d u_{xx} - u_x + u(f(1) - k) + \epsilon w f_w(1)(1 - G(0)) \\
&\quad - \alpha u + \epsilon \beta w \\
w_t &= w(f_w(1)G(0) - k_w - \beta) + \epsilon^{-1} \alpha u,
\end{aligned} \tag{3.1}$$

with the homogeneous boundary conditions:

$$\begin{aligned}
0 &= -d_0 S_x(0, t) + S(0, t), \quad S_x(1, t) = 0 \\
0 &= -d u_x(0, t) + u(0, t), \quad u_x(1, t) = 0.
\end{aligned}$$

Introducing  $(S, u, w) = \exp(\lambda t)(\bar{S}(x), \bar{u}(x), \bar{w}(x))$  into (3.1), we arrive at the eigenvalue problem relevant for the stability of the washout steady state

$$\begin{aligned}
\lambda \bar{S} &= d_0 \bar{S}'' - \bar{S}' - \bar{u} f(1) - \epsilon \bar{w} f_w(1) \\
\lambda \bar{u} &= d \bar{u}'' - \bar{u}' + \bar{u}(f(1) - k) + \epsilon \bar{w} f_w(1)(1 - G(0)) \\
&\quad - \alpha \bar{u} + \epsilon \beta \bar{w} \\
\lambda \bar{w} &= \bar{w}(f_w(1)G(0) - k_w - \beta) + \epsilon^{-1} \alpha \bar{u},
\end{aligned} \tag{3.2}$$

with

$$\begin{aligned}
0 &= -d_0 \bar{S}'(0) + \bar{S}(0), \quad \bar{S}'(1) = 0 \\
0 &= -d \bar{u}'(0) + \bar{u}(0), \quad \bar{u}'(1) = 0.
\end{aligned} \tag{3.3}$$

It turns out that the eigenvalues of (3.2)-(3.3) determine the stability of the washout steady state despite the fact that the spectrum of the differential-algebraic operator  $\mathbb{L}$ , appearing on the righthand side of (3.2), with the boundary conditions determining its domain, may not consist solely of eigenvalues.

**Theorem 3.1** *Let*

$$A = \begin{pmatrix} f(1) - k - \alpha - \lambda_d & \alpha \\ f_w(1)(1 - G(0)) + \beta & f_w(1)G(0) - k_w - \beta \end{pmatrix} \tag{3.4}$$

*and let  $s(A)$  be its stability modulus, i.e., the largest of the distinct real eigenvalues of matrix  $A$ . If  $s(A) < 0$  then all eigenvalues of (3.2) are negative and the washout steady state is asymptotically stable; the washout steady state is unstable whenever  $s(A) > 0$ .*

The mathematically inclined reader may appreciate the following remark concerning the spectrum of  $\mathbb{L}$ .

**Remark 3.1** *The eigenvalues of (3.2) (making up the point spectrum of  $L$ ) are countable in number and real. If  $\Lambda \equiv f_w(1)G(0) - k_w - \beta$  is an eigenvalue of (2.8) with  $d = d_0$ , then it is an eigenvalue of (3.2). Otherwise, it belongs to the continuous spectrum of  $L$ . In either case, the spectrum of  $L$  consists of the eigenvalues plus  $\Lambda$ .  $\Lambda < s(A)$  and if  $s(A) \geq 0$ , then  $s(A)$  is the largest eigenvalue of (3.2) and it is a simple eigenvalue.*

It may seem striking that stability boils down to the sign of the leading eigenvalue of a  $2 \times 2$  matrix. We would argue that it is quite natural on biological grounds. There are two habitats for the bacteria, the wall and the bulk fluid. To survive, the organism must be able to establish itself in at least one of the habitats sufficiently well to overcome the constant leakage to the other, possibly less suitable, habitat.

In order to interpret Theorem 3.1 biologically, we return to the unscaled parameters. In terms of the original parameters, the washout steady state is  $(S^0, 0, 0)$ . The matrix  $A$  is a scalar multiple of

$$\hat{A} = \begin{pmatrix} f(S^0) - k - \alpha - \lambda_{\bar{d}} \frac{v}{L} & \alpha \\ f_w(S^0)(1 - G(0)) + \beta & f_w(S^0)G(0) - k_w - \beta \end{pmatrix}. \quad (3.5)$$

The washout steady state is stable or unstable as  $s(\hat{A}) < 0$  or  $s(\hat{A}) > 0$ . The term  $\lambda_{\bar{d}} \frac{v}{L}$ , where  $\bar{d} = d/Lv$ , in the first row and first column of  $\hat{A}$  should be viewed as an effective washout or removal rate from the bio-reactor. Its inverse is a measure of the mean residence time of a free bacterial cell in the reactor. The factor  $\lambda_{\bar{d}}$  encodes the effect of the random cell motility on the washout rate. It decreases with increasing  $\bar{d}$ , approaching unity for very large  $\bar{d}$  and becoming unbounded as  $\bar{d}$  approaches zero (see [20]). The latter reference yields the useful bound for  $\lambda_{\bar{d}}$

$$\frac{1}{4\bar{d}} + \frac{\pi^2 \bar{d}}{4} < \lambda_{\bar{d}} < \frac{1}{4\bar{d}} + \pi^2 \bar{d}, \quad (3.6)$$

provided  $\bar{d} < 1/2\pi$ .

The Perron-Frobenius theory and the Gerschgorin circle theorem imply the estimates

$$\begin{aligned} & \max\{f(S^0) - k - \alpha - \lambda_{\bar{d}}(v/L), f_w(S^0)G(0) - k_w - \beta\} \\ & < s(\hat{A}) \leq \\ & \max\{f(S^0) - k - \lambda_{\bar{d}}(v/L), f_w(S^0) - k_w\}. \end{aligned} \quad (3.7)$$

The lower estimate follows by deleting the off-diagonal entries from  $\hat{A}$ , which decreases the stability modulus. The upper estimate follows immediately from the Gerschgorin circle theorem and the fact that the eigenvalues of  $\hat{A}$  are real. These estimates lead immediately to sufficient conditions for either stability or instability. For example, the washout steady state is **unstable** if either

$$f_w(S^0)G(0) - k_w - \beta > 0 \quad (3.8)$$

or

$$f(S^0) - k - \alpha - \lambda_{\bar{d}} \frac{v}{L} > 0. \quad (3.9)$$

The first condition says that the wall-attached organism's growth rate exceeds the sum of its death and slough-off rates when rare. The second condition says that the growth rate of free bacteria exceeds its death rate plus its loss rate due to recruitment to the wall plus its washout rate from the reactor. We expect that the former condition prevails more typically than the latter.

To begin, it is useful to keep in mind what happens in the absence of wall growth. If we set  $w_0 = 0$  and  $\alpha = 0$  in the model system (2.4), then  $w \equiv 0$  and we get a model for the growth of a single strain in the flow reactor without wall-growth. This model has been studied extensively in [20] where, among other things it has been shown that the washout steady state  $(S, u) = (S^0, 0)$  is asymptotically stable or unstable as  $f(S^0) - k - \lambda_{\bar{d}} \frac{v}{L}$  is negative or positive.

Consider the effect of increasing flow velocity on the stability of the washout steady state. As  $v$  increases,  $\frac{v}{L} \lambda_{\bar{d}}$  increases (without bound), from which it follows (by Perron-Frobenius theory or by direct calculation) that  $s(\hat{A})$  is strictly decreasing in  $v$ . Three possibilities emerge. Either  $s(\hat{A}) > 0$  for all  $v > 0$ , or  $s(\hat{A}) < 0$  for all  $v > 0$ , or there is a threshold value  $v^* > 0$  of  $v$  such that  $s(\hat{A}) > 0$  for  $v < v^*$  and  $s(\hat{A}) < 0$  for  $v > v^*$ . The first alternative occurs if and only if  $s(\hat{A}) > 0$  for all large  $v$  which is equivalent to  $f_w(S^0)G(0) - k_w - \beta \geq 0$ . The wall attached bacteria grow fast enough when rare and are immune to the negative effects of increasing  $v$ . The second case holds if and only if  $s(\hat{A}) \leq 0$  when  $v = 0$  ( $v = 0$  means  $\lambda_{\bar{d}} \frac{v}{L} = 0$ ). Thus the second case holds if and only if both diagonal entries are negative ( $f_w(S^0)G(0) - k_w - \beta < 0$  and  $f(S^0) - k - \alpha < 0$ ) and  $\det(\hat{A}) \geq 0$  when  $v = 0$ . Roughly, both habitats, the wall and the bulk fluid, must be unfavorable to the organism. The third case requires that  $s(\hat{A}) > 0$  when  $v = 0$  and  $s(\hat{A}) < 0$  when  $v$  is large. It holds if and only if  $f_w(S^0)G(0) - k_w - \beta < 0$  and  $\det(\hat{A}) < 0$  when  $v = 0$ . In particular, it holds when  $f(S^0) - k - \alpha > 0$  and  $f_w(S^0)G(0) - k_w - \beta < 0$ .

Two special cases are particularly revealing. In both, we assume that any daughter cell of a wall-attached bacteria remains on the wall when essentially all wall sites are free (i.e.  $G(0) = 1$ ). In the first, suppose that we can ignore slough-off from the wall (i.e.  $\beta = 0$ ). Then  $\hat{A}$  becomes upper triangular so we can conclude that

$$s(\hat{A}) = \max\{f(S^0) - k - \alpha - \lambda_{\bar{d}} \frac{v}{L}, f_w(S^0) - k_w\}.$$

Thus instability holds if either term is positive.

A second special case is when the growth and death rates of the organism are the same on the wall as in the fluid:  $f_w = f$  and  $k_w = k$ . Then

$$\hat{A} = (f(S^0) - k - \lambda_{\bar{d}} \frac{v}{L})I + \begin{pmatrix} -\alpha & \alpha \\ \beta & \lambda_{\bar{d}} \frac{v}{L} - \beta \end{pmatrix}.$$

Thus

$$s(\hat{A}) = f(S^0) - k - \lambda_d \frac{v}{L} + s$$

where  $s$  is the stability modulus of the quasi-positive matrix on the right. As its determinant is negative,  $s > 0$ , so  $f(S^0) - k > s(\hat{A}) > f(S^0) - k - \lambda_d \frac{v}{L}$ . As noted in a previous paragraph, free bacteria can survive in the flow reactor without wall growth, if and only if  $f(S^0) - k - \lambda_d \frac{v}{L} > 0$ . Thus, as expected, the capacity for wall growth gives the organism a better chance of survival in the reactor.

Considering parameters appropriate for the large (or small) intestine (see section 6), we find that  $\alpha = O(10^{-9})$  is much smaller than other parameters (e.g.  $\beta = O(10^{-1})$ ). Furthermore, as  $(\frac{2\pi d}{Lv})^2 \ll 1$  we conclude from (3.6) that

$$\frac{v}{L} \lambda_{d/Lv} \approx \frac{v^2}{4d} \quad (3.10)$$

is an excellent approximation. If  $f = f_w$ , then

$$s(\hat{A}) \approx \max\{f(S^0) - k - \frac{v^2}{4d}, f(S^0)G(0) - k_w - \beta\}. \quad (3.11)$$

We now return to the scaled parameters ( $S^0$  becomes unity). It is natural to conjecture, and we believe it to be true, that all organisms (free and wall-attached) are washed out of the reactor when  $s(A) < 0$ . In other words, the local asymptotic stability of the washout steady state, in this case, implies global asymptotic stability. We cannot prove this except under several different sets of additional conditions. One of these seems plausible on biological grounds in many cases:  $f_w(1) - k_w > f(1) - k - \lambda_d$ . It holds, for example, when  $f(1) \approx f_w(1)$  and  $k \approx k_w$ , since  $\lambda_d > 1$ .

**Theorem 3.2** *If either*

- (a)  $s(A) < 0$  and  $f_w(1) - k_w > f(1) - k - \lambda_d$ , or
- (b)  $f_w(1) - k_w < 0$  and  $f(1) - k - \lambda_d < 0$ , or
- (c)  $s(B) < 0$ ,

where

$$B = \begin{pmatrix} f(1) - k - \lambda_d & \alpha \\ f_w(1) + \beta & f_w(1)G(0) - k_w - \beta \end{pmatrix},$$

then

$$\int_0^1 [u(x, t) + w(x, t)] dx \rightarrow 0, \quad t \rightarrow \infty.$$

We note that as  $A < B$  it follows that  $s(A) < s(B)$ . Thus the hypothesis (c) of the Theorem 3.2 implies  $s(A) < 0$ . It is easy to see that (b) also implies  $s(A) < 0$ .

## 4 Population Steady State

We are interested in the existence of a steady state solution  $(S, u, w)$  with bacteria present, that is with  $u + w > 0$  at least for some  $x$ . A steady state solution must satisfy the boundary value problem

$$\begin{aligned}
 0 &= d_0 S'' - S' - u f(S) - \epsilon w f_w(S) \\
 0 &= du'' - u' + u(f(S) - k) + \epsilon w f_w(S)(1 - G(w)) \\
 &\quad - \alpha u(1 - w) + \epsilon \beta w \\
 0 &= w[f_w(S)G(w) - k_w - \beta] + \epsilon^{-1} \alpha u(1 - w),
 \end{aligned} \tag{4.1}$$

with boundary conditions

$$\begin{aligned}
 1 &= -d_0 S'(0) + S(0), \quad S'(1) = 0 \\
 u^0 &= -du'(0) + u(0), \quad u'(1) = 0.
 \end{aligned} \tag{4.2}$$

Hereafter, by a solution of (4.1) we always mean twice continuously differentiable functions  $S$  and  $u$  satisfying the equations and boundary conditions and satisfying  $0 \leq S(x), u(x), w(x)$  and  $w(x) \leq 1$  for all  $x$ .

There are two cases to consider. If no bacteria are present in the feed ( $u^0 = 0$ ), then the washout steady state is present, while if bacteria are present in the feed ( $u^0 > 0$ ), it is not. We establish that if  $u^0 = 0$ , if the washout steady state is unstable, and if a non-degeneracy condition holds, then there exists at least one steady state with microorganisms present both in the fluid and on the wall. If  $u^0 > 0$ , then no additional condition is required for the existence of such a steady state solution.

**Theorem 4.1** *Let  $u^0 = 0$ ,  $s(A) > 0$  and*

$$f_w(1)G(0) - k_w - \beta \neq 0,$$

*or let  $u^0 > 0$ . Then there exists a steady state solution  $(S, u, w)$  of (4.1) satisfying*

$$0 < S(x) < 1, \quad S'(x) < 0, \quad u(x) > 0, \text{ and } 0 < w(x) < 1, \quad 0 \leq x \leq 1.$$

As expected, nutrient concentration decreases as one moves down the reactor. Both free bacteria and wall-attached bacteria are present throughout the reactor. More information can be obtained from the numerically computed steady states. See figure 2 and 5 in section 6. From these, we see that essentially all the available wall sites are colonized ( $w \approx 1$ ) in the nutrient-rich upstream end of the reactor and as we move downstream, the wall colonization fraction monotonically decreases. The glut of wall-attached bacteria near  $x = 0$  acts as a source of free bacteria via slough-off and hence the free bacterial density monotonically increases from a very low level near  $x = 0$ , decreasing for larger  $x$  only when a significant cell death rate is assumed. We note that the uniqueness and stability properties of the steady states guaranteed by Theorem 4.1 have not been addressed.

## 5 Persistence of bacteria in the reactor

Our simulations, described in the next section, suggest that when the washout steady state is unstable (i.e.  $s(A) > 0$ , assuming  $u^0 = 0$ ) or when  $u^0 > 0$  then all solutions converge to the steady state described in Theorem 4.1. Proving that this happens is another matter. Instead we try to show that the microbial population persists indefinitely in the reactor. This is easy to do when the feed is a source of bacteria ( $u^0 > 0$ ), but much more difficult when it is not.

**Theorem 5.1** *Assume that  $u^0 > 0$ . Then there exist positive numbers  $K, a$ , independent of initial data, such that*

$$\int_0^1 [u(x, t) + \epsilon w(x, t)] dx = Ku^0 + O(e^{-at})$$

In the case  $u^0 = 0$  we expect that the microbial population persists when the washout steady state is unstable ( $s(A) > 0$ ). Unfortunately, we can only prove this by making additional assumptions and then, we are able to show only weak persistence (see [29]), that is, sufficient conditions are given for there to exist an ultimate lower bound, independent of initial data, on the uniform norm of  $u + w$ . In biological terms, there is a positive lower bound  $\delta$ , independent of the initial bacterial densities (so long as they aren't both zero), such that for all large times  $t$ , the sum of the microbial densities exceeds  $\delta$  somewhere in the reactor.

**Theorem 5.2** *Assume either*

- (a)  $s(A) > 0$  and  $f(1) - k - \lambda_d > f_w(1) - k_w$ , or
- (b)  $f(1) - k - \lambda_d > 0$  and  $f_w(1) - k_w > 0$ , or
- (c)  $f(1) - k - \lambda_d - \alpha > 0$ .

*Then there exists  $\delta > 0$ , independent of initial data provided  $u_0$  and  $w_0$  are not identically zero, such that*

$$\limsup_{t \rightarrow \infty} \max_{0 \leq x \leq 1} [u(x, t) + w(x, t)] > \delta.$$

It is worth stressing that  $\delta > 0$  does not depend on the initial data. The hypotheses (b) and (c) of the theorem imply that  $s(A) > 0$ .

## 6 Simulations and Applications to the Gut

In this section we report the results of numerical simulations which serve to illustrate some of the behaviors of system (2.1)-(2.3). We also indicate how the results of the previous sections can be used to predict the outcomes. We note that these simulations represent a small fraction of those run, and that all simulations performed resulted in convergence to an equilibrium. The bulk of the parameter values used in figures 1 through 6 are the same, so that certain behaviors and the effects of varying specific parameter values can be highlighted.

The spatial variable in the  $S$  and  $u$  equations of (2.1) is discretized using a second order finite difference scheme, while the boundary conditions (2.2) are approximated using a central difference scheme. A first order finite difference scheme is used for the  $w$  equation. The temporal variable in (2.1) is approximated using a Crank-Nicholson method. Steady state solutions and time series of the  $L^1$  norms of the components are reported. In the former, the dimensionless variables  $\bar{S} = S/S^0$ ,  $\bar{u} = u/\gamma S^0$ , and  $\bar{w} = w/w_\infty$  are plotted. In the latter, quantities are expressed as  $\log_{10}$  of the number of microorganisms. Steady states were obtained by solving the time-dependent problem for a suitably long time period until a steady state condition was observed. This was checked by doubling the integration time and checking for change.

We now describe our choice of parameters for figures 1 through 5. The basic dimensions of the reactor are chosen in accordance with data on the large intestine provided by Mitsuoka [22]. Thus, the length  $L = 150\text{cm}$  and the radius  $\rho = 2.5\text{cm}$ . The velocity of the medium is varied to approximate transit times between 12 and 48 hours [23]. It is maintained at  $v = 5.0\text{cm/hr}$  in figures 1 through 5. The random motility coefficient is taken to be  $d = 0.2\text{cm}^2/\text{hr}$  (see [24]), while the nutrient is assumed to diffuse with diffusivity  $d_0 = 0.0002\text{cm}^2/\text{hr}$  (see [25]). The nutrient uptake functions  $f$  and  $f_w$  are assumed to be identical and to satisfy Monod kinetics:

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

Thus, nutrient uptake is assumed to be the same for free bacteria as for wall-attached bacteria. The fraction of daughter cells of wall-bound bacteria finding sites on the wall  $G(W)$ , as a function of the occupancy fraction  $W = w/w_\infty$ , is taken to coincide with that of Freter et al [9]:

$$G(W) = \frac{1 - W}{1.01 - W}.$$

Other parameter values are chosen to coincide with those used by Freter in the chemostat model [10]:  $m = m_w = 1.66\text{hr}^{-1}$ ,  $\gamma = 0.5$ ,  $a = a_w = 9.0 \times 10^{-7}\text{g/ml}$ ,  $\beta = 0.1\text{hr}^{-1}$ , and  $S^0 = 2.09 \times 10^{-6}\text{g/ml}$ . In [10] the specific rate constant of adhesion is  $\alpha = 1 \times 10^{-7}\text{1/hr g}$ , with  $3 \times 10^7$  wall sites available for adhesion. Using the assumptions (see [10]) that 1g of bacterial mass contains  $1.8 \times 10^{12}$  cells and that the volume of the chemostat is

$V = 1\text{ml}$ , the values  $\alpha$  and  $w_\infty$  for the present model are obtained as follows:  $\alpha = (1 \times 10^{-7}\text{1/hr g})(3 \times 10^7\text{sites})/[(1.8 \times 10^{12}\text{cells/g})(1 \times 10^{-3}\text{l})] = 1.67 \times 10^{-9}\text{hr}^{-1}$  and  $w_\infty = [(3 \times 10^7\text{sites})/(1.8 \times 10^{12}\text{cells/g})]/(2\pi\rho L\text{cm}^2) = (1.67 \times 10^{-5})/(2\pi\rho L)\text{g/cm}^2$ .

Assume that the intrinsic death rate is insignificant ( $k = k_w = 0$ ) and that there is no bacterial input into the reactor ( $u^0 = 0$ ). The value of  $s(\hat{A})$  is approximated for the parameter values above using the estimates in section 3. First, using the approximation (3.10) we find that  $v\lambda_{\bar{d}}/L \approx v^2/4d = 31.25$ . Then, by (3.11),  $s(\hat{A}) \approx f(S^0)G(0) - k_w - \beta \approx 1.05$ . Since the washout equilibrium is unstable (see Theorem 3.1) and there exists a positive steady state solution of (4.1) (see Theorem 4.1), we do not expect to see washout. However,  $f(S^0) - k - v\lambda_{\bar{d}}/L \approx -30.09$  so that the washout equilibrium is globally attracting in the plug flow reactor without wall growth [20]. Thus, the bacterial population is not expected to survive when  $w_0(x) \equiv 0$  and  $\alpha = 0$ . Note that this is not in agreement with numerical simulations reported by Freter [10] in his investigation of the chemostat as a model of the gut.

In figures 1 through 3 the intrinsic death rates are considered insignificant ( $k = k_w = 0$ ). In the time series of figure 1(a),  $u_0(x) \equiv 1 \times 10^{-6}/(\pi\rho^2L)\text{g/ml}$  and  $u^0 = 0$ , so that no microorganisms are input into the reactor from the feed. In other words, the reactor is charged via the initial data. There is a period of adjustment early in the run. When free bacteria reach their equilibrium numbers they are lost via washout from the reactor and attachment to the wall. This results in a decline in their numbers and a corresponding increase in the number of wall-bound bacteria. Though not considered in the analysis of the previous sections, we also illustrate the consequences of allowing the reactor to be charged by a brief pulse of bacteria from the feed. In figure 1(b)  $u^0 = 1 \times 10^{-6}/(\pi\rho^2L)\text{g/ml}$  for  $0 \leq t \leq 10$  and  $u^0 = 0$  for  $t > 10$  with  $u_0(x) \equiv 0$ . Regardless of the manner in which the reactor is charged, solutions approach the steady state displayed in figure 2. The distribution of microorganisms is striking. The reactor is essentially divided into two regions, the upstream end consisting of the first 30cm or so and the downstream end consisting of the remainder. The wall-bound bacteria are concentrated in the upstream end at their maximum density  $w_\infty$ . Given that  $G(W) = 0$  here, all daughter cells of wall-bound bacteria are released into the lumen. Thus, the concentration of wall-bound bacteria at the inlet acts as a source of free bacteria, the concentration of which increases to a maximum along this length of the reactor. In addition, all nutrient entering the reactor is consumed here. In the downstream end of the reactor, the free bacteria dominate and the wall-bound bacteria are undetectable. With no resource available, the dynamics here are dominated by the effects of attachment and detachment, resulting in a balance between suspended and adherent bacteria. In the absence of wall growth ( $w_0(x) \equiv 0$  and  $\alpha = 0$ ), the bacterial population is washed out of the reactor (figure 3).

When bacteria are supplied to the reactor at a constant rate for all time ( $u^0 > 0$  for all  $t > 0$ ), the existence of a positive equilibrium is ensured by Theorem 4.1. In numerical simulations involving such inputs, a bacterial population was established both in the presence and absence of wall growth.

In figures 4 and 5 we allow for strain-specific death rates, taking  $k = k_w = 0.02$ . Here the time series of figure 4 exhibit the same behaviors as in the previous case. Solutions approach the steady state shown in figure 5. In this case, however, the dynamics in the downstream end of the reactor are dominated by cell death. Of course, in the absence of wall growth the bacterial population is again washed out of the reactor.

We now investigate the effect of increasing the flow velocity  $v$  on the stability of the washout steady state. Recall from section 3 that in order to exhibit a change in stability, a threshold value  $v^* > 0$  of  $v$  must exist such that  $s(\hat{A}) > 0$  for  $v < v^*$  and  $s(\hat{A}) < 0$  for  $v > v^*$ . This holds whenever  $f(S^0) - k - \alpha > 0$  and  $f_w(S^0)G(0) - k_w - \beta < 0$ . However,  $f_w(S^0)G(0) - k_w - \beta \approx 1.05$  in figure 1 and  $f_w(S^0)G(0) - k_w - \beta \approx 1.03$  in figure 4. Thus  $s(\hat{A}) > 0$  for all  $v > 0$ , so that the bacteria grow fast enough when rare and are immune to the negative effects of increasing  $v$ . We do not expect to see a change in the stability of the washout steady state via an increase in  $v$ . Maintaining insignificant death rates, the inequality  $f_w(S^0)G(0) - k_w - \beta < 0$  can be satisfied either by an increase in  $\beta$  or a decrease in  $f(S^0)$ . Increasing  $\beta$  alone seems biologically unrealistic, since we would require  $\beta > 1\text{hr}^{-1}$ . There is, however, some experimental evidence supporting a decrease in  $f(S^0)$  (see [18]). The value of  $f(S^0)$  in the above simulations corresponds to a doubling time of approximately 35.8 minutes. This is in keeping with values determined for *E. coli* in laboratory cultures [22]. However, Gibbons and Kapsimalis [18] determined that microorganisms in the large intestine of mice underwent only 2 to 3 divisions per day. Assuming a doubling time of approximately 8 hours we take  $f(S^0) = 0.08$ . Together with the growth parameters above, this corresponds to  $S^0 = 4.56 \times 10^{-8}\text{g/ml}$ . Note that both of the conditions  $f(S^0) - k - \alpha > 0$  and  $f_w(S^0)G(0) - k_w - \beta < 0$  are now met. To determine  $v^*$  we use the approximation of  $s(\hat{A})$  in (3.11) and solve the equation  $s(\hat{A}) \approx f(S^0) - k - v^2/4d = 0$  to find  $v^* \approx 0.25\text{cm/hr}$ . Thus, the bacterial population will be unable to survive in the flow reactor with wall growth for medium velocities corresponding to transit times between 12 and 48 hours. In figure 6(a) we again take  $v = 5.0\text{cm/hr} > v^*$ , and the bacterial population washes out of the reactor. In figure 6(b) we take  $v = 0.05\text{cm/hr} < v^*$  and the population survives.

We conclude this section with a discussion of the plug flow reactor as a model of the small intestine. In this case the length  $L = 600\text{cm}$ , the radius  $\rho = 1.5\text{cm}$  and the transit time is 4-6hr, corresponding to a medium velocity of  $v = 100\text{cm/hr}$  [22]. Maintaining  $d = 0.2\text{cm}^2/\text{hr}$  and using the estimate (3.10) we obtain  $v\lambda_{\bar{d}}/L \approx 12500$ . As bacteria can survive in the flow reactor without wall growth, if and only if  $f(S^0) - k > v\lambda_{\bar{d}}/L$  [20], survival in the lumen is not predicted by the model for any reasonable choice of growth parameters. However, allowing for wall growth and using the parameters of figure 1 we again have  $s(\hat{A}) > 0$  for all  $v > 0$ . Consequently, the survival of bacteria is assured for all  $v > 0$  with wall growth. When the parameters of figure 6 are used, a threshold velocity  $v^*$  exists, above which washout occurs. Since the approximation of  $v^*$  is independent of the physical parameters of the reactor, we again have  $v^* = 0.25\text{cm/hr}$ . Thus, as was the case in the large intestine, the bacterial population will be unable to survive in the flow reactor with wall growth for realistic medium velocities when  $f(S^0)$  corresponds

with a longer doubling time. However, bacterial populations are able to establish on the wall of both the large and small intestines [22]. Perhaps the warning issued by Savage [17] regarding the interpretation of experimental estimates of doubling times in the gastrointestinal tract is to be heeded.

## 7 Appendix

This section contains the proofs of our various theorems in order of their appearance. We begin with

**Proof of Theorem 2.1:** The existence of a unique nonnegative solution  $(S, u, w)$  of (2.4)-(2.6) defined for all  $t \geq 0$  and satisfying  $0 \leq w \leq 1$  is proved in [15].

Let  $\psi_d > 0$  be the principal eigenfunction of the Sturm-Liouville problem adjoint to (2.8)

$$\begin{aligned}\lambda\psi &= d\psi'' + \psi' \\ 0 &= d\psi'(1) + \psi(1), \quad \psi'(0) = 0\end{aligned}\tag{7.1}$$

corresponding to the eigenvalue  $-\lambda_d$ . We normalize  $\psi_{d_0}$  by requiring  $\psi_{d_0}(0) = 1$  and normalize  $\psi_d$  by requiring that  $\psi_d(x) \leq \psi_{d_0}(x)$ ,  $0 \leq x \leq 1$ , with equality holding for some  $x$ . Define

$$X = \int_0^1 S(x)\psi_{d_0}(x)dx, \quad Y = \int_0^1 u(x)\psi_d(x)dx, \quad Z = \int_0^1 w(x)\psi_d(x)dx.$$

Multiplying the first equation of (2.4) by  $\psi_{d_0}$  and the second and third by  $\psi_d$ , integrating and using the identity:

$$\int_0^1 [du'' - u']v = (-du'(0) + u(0))v(0) + \int_0^1 u[dv'' + v'],$$

where  $u$  satisfies  $u'(1) = 0$  and  $v$  satisfies the boundary conditions in (7.1), we get

$$\begin{aligned}X' &= 1 - \lambda_{d_0}X - \int_0^1 u\psi_{d_0}f - \epsilon \int_0^1 w\psi_{d_0}f_w \\ Y' &= u^0\psi_d(0) - (\lambda_d + k)Y + \int_0^1 u\psi_d f + \epsilon \int_0^1 w\psi_d f_w(1 - G) \\ &\quad - \alpha \int_0^1 u\psi_d(1 - w) + \epsilon\beta Z \\ Z' &= \int_0^1 w\psi_d f_w G - (k_w + \beta)Z + \epsilon^{-1}\alpha \int_0^1 u\psi_d(1 - w).\end{aligned}\tag{7.2}$$

If  $Q = X + mY + \epsilon Z$ , where  $m > 0$  is to be determined, then we get

$$\begin{aligned} Q' &\leq 1 + u^0 - \lambda_{d_0}X - (\lambda_d + k + \alpha - \alpha/m)mY - (k_w + \beta - m\beta)\epsilon Z \\ &\quad + \epsilon \int_0^1 w f_w [G\psi_d + m(1-G)\psi_d - \psi_{d_0}] \\ &\quad + \int_0^1 u f(m\psi_d - \psi_{d_0}) - \alpha(1-m) \int_0^1 uw\psi_d \end{aligned}$$

where we have used that  $\psi_d(0) \leq \psi_{d_0}(0) = 1$ . Putting  $m = \max\{1/2, \frac{\alpha}{\lambda_d/2+k+\alpha}\} < 1$ , then all the integral terms are negative so we get

$$Q' \leq 1 + u^0 - \delta Q$$

where  $\delta = \min\{\lambda_{d_0}, \lambda_d/2, k_w + \beta(1-m)\} > 0$ . Hence,  $\limsup_{t \rightarrow \infty} (X + mY + \epsilon Z) \leq \delta^{-1}(1 + u^0)$ , which, as  $m \geq 1/2$ , implies that  $\limsup_{t \rightarrow \infty} Y(t) \leq 2(1 + u^0)/\delta$ . This leads immediately to the conclusion that

$$\limsup_{t \rightarrow \infty} \int_0^1 u(x, t) dx \leq \frac{2(1 + u^0)}{\delta \min \psi_d}.$$

To get the ultimate boundedness of  $S$ , Observe that

$$S_t \leq d_0 S_{xx} - S_x$$

so, from a standard comparison principle, it follows that  $S(x, t) \leq \bar{S}(x, t)$ , where  $\bar{S}$  is the solution to the linear differential equality corresponding to the above inequality and satisfying the same boundary conditions and initial conditions as  $S$ . Since  $\bar{S}(x, t) = 1 + O(e^{-kt})$ , the conclusion follows.  $\blacksquare$

**Proof of Theorem 3.1:** We use the notation developed in section 3. Let  $Y = (S, u, w) \in E^3 = E \times E \times E$  where  $E$  denotes the Banach space of continuous functions on  $[0, 1]$  and where we have dropped the bars on  $S, u$  and  $w$ . Then the domain of  $\mathbb{L}$ ,  $D(\mathbb{L})$ , is the closure of

$$\{Y \in E^3 : S, u \text{ twice continuously differentiable and (3.3) holds}\}$$

in  $E^3$ .

We begin by considering the eigenvalues of  $\mathbb{L}$ . Note that if  $\bar{u} \equiv \bar{w} \equiv 0$  and  $\bar{S} \neq 0$  in (3.2), then we have the eigenvalue problem (2.8), with  $d = d_0$ , and the eigenvalues are negative as noted there. By the positivity of the coefficient of  $\bar{w}$  in the  $\bar{u}$  equation and the positivity of the coefficient of  $\bar{u}$  in the  $\bar{w}$  equation, it is easy to see that if  $\bar{u} \neq 0$  or  $\bar{w} \neq 0$  then neither can vanish identically. Similarly, one can see from the second and third equations of (3.2) that if  $\lambda = \Lambda$ , then  $\bar{u} \equiv \bar{w} \equiv 0$ , in which case either  $\bar{S} \equiv 0$  or

$\lambda = \Lambda$  is an eigenvalue of (2.8) with  $d = d_0$ . Assuming  $\lambda \neq \Lambda$ , solving for  $w$  in terms of  $u$  from the third equation, and substituting into the equation for  $u$  leads to

$$\lambda \bar{u} = d\bar{u}'' - \bar{u}' + \bar{u}[f(1) - k - \alpha - \frac{\alpha f_w(1)(1 - G(0)) + \alpha\beta}{\Lambda - \lambda}]$$

with boundary conditions as above. From (2.8), with  $d$ , we must have

$$\lambda - f(1) + k + \alpha + \frac{\alpha f_w(1)(1 - G(0)) + \alpha\beta}{\Lambda - \lambda} = \lambda_n,$$

for some  $n \geq 0$ , where  $\lambda_n$  are the eigenvalues of (2.8). Multiplying through by the denominator and collecting terms, we find that

$$\begin{aligned} 0 &= [f(1) - k - \alpha - \lambda + \lambda_n][\Lambda - \lambda] \\ &\quad - \alpha[f_w(1)(1 - G(0)) + \beta]. \end{aligned} \tag{7.3}$$

Thus, the eigenvalues of (3.2) consist of the eigenvalues of (2.8) with  $d = d_0$  plus possibly some of the roots of (7.3). (We show below that all roots of (7.3) are real.) Let  $\lambda$  be a root of (7.3), for some  $n$  and assume that  $\lambda$  is not an eigenvalue of (2.8) with  $d = d_0$ . We show that it is an eigenvalue of (3.2). Indeed, the corresponding eigenfunction  $\bar{u}$  is an eigenfunction of (2.8) corresponding to  $\lambda_n$  and  $\bar{w}$  is proportional to  $\bar{u}$  (from the third equation in (3.2)). Putting these into the first of equations (3.2) leads to the inhomogeneous boundary value problem

$$d_0 \bar{S}'' - \bar{S}' - \lambda \bar{S} = f(1)\bar{u} + \epsilon f_w(1)\bar{w}.$$

As  $\lambda$  is not an eigenvalue of the differential operator  $d_0 z'' - z'$  with the same boundary conditions as for  $\bar{S}$ , there is a unique solution of this problem. Hence, we have produced an eigenvector  $(\bar{S}, \bar{u}, \bar{w})$  corresponding to  $\lambda$ .

It is easy to see that  $\lambda$  is a solution of (7.3) if and only if it is an eigenvalue of the matrix

$$A_n = \begin{pmatrix} f(1) - k - \alpha + \lambda_n & \alpha \\ f_w(1)(1 - G(0)) + \beta & f_w(1)G(0) - k_w - \beta \end{pmatrix}.$$

The matrix  $A_n$  is quasi-positive (non-negative off-diagonal entries) and irreducible ( $\alpha > 0$  and  $f_w(1)(1 - G(0)) + \beta > 0$ ) so by the Perron-Frobenius Theorem ([21]), its eigenvalues are real and distinct. The largest we call the stability modulus of  $A_n$ . Furthermore, the stability modulus strictly increases with any entry (see [21]) so it follows ( $\lambda_n \leq \lambda_0$ ) that the maximal root of (7.3) is the stability modulus of  $A_0 \equiv A$ , where, according to our notation,  $\lambda_0 = -\lambda_d$ . Finally, note that if matrix  $B$  is obtained from  $A$  by setting  $\alpha = 0$  in the upper right corner of the matrix  $A$ , then the strict monotonicity of the stability modulus implies that

$$\Lambda \leq \max\{f(1) - k - \alpha - \lambda_d, \Lambda\} = s(B) < s(A).$$

We noted in the first paragraph of the proof that if  $\Lambda$  is not an eigenvalue of (2.8) with  $d = d_0$ , then the null space of  $\mathbb{L} - \Lambda$  is trivial. In this case, observe that

$$(\mathbb{L} - \Lambda)Y = F = (f_1, f_2, f_3) \in E^3$$

leads to

$$\begin{aligned} u &= \epsilon\alpha^{-1}f_3 \\ w &= p[f_2 - \epsilon\alpha^{-1}(P - \Lambda)f_3] \\ S &= (Q - \Lambda)^{-1}[f(1)u + \epsilon f_w(1)w] \end{aligned}$$

where  $p = [\epsilon f_w(1)(1 - G(0)) + \epsilon\beta]^{-1}$  and  $P$  and  $Q$  are the differential operators  $P = d\frac{d^2}{dx^2} - \frac{d}{dx} + (f(1) - k - \alpha)$  and  $Q = d_0\frac{d^2}{dx^2} - \frac{d}{dx}$ .  $(Q - \Lambda)^{-1}$  denotes the inverse operator to  $Q - \Lambda$ , incorporating appropriate boundary conditions, and is realized as an integral operator using a Green's function. It is easy to see from these formulae that the range of  $\mathbb{L} - \Lambda$  cannot be  $E^3$  ( $f_3$  must be smooth) and clearly  $(\mathbb{L} - \Lambda)^{-1}$  is not continuous because of the appearance of the unbounded operator  $P$  on the right side of the  $w$  equation. Thus,  $\Lambda$  belongs to the continuous spectrum of  $\mathbb{L}$  if it is not an eigenvalue of (2.8) with  $d = d_0$ .

It is a straightforward exercise to show that if  $\lambda \neq \Lambda$  and  $\lambda$  is not an eigenvalue of (3.2), then  $\mathbb{L} - \lambda$  has a bounded inverse defined on  $E^3$ . Indeed,  $(\mathbb{L} - \lambda)Y = F$  may be solved first for  $w$  in terms of  $u$  and  $f_3$ , the result inserted in the equation for  $u$  which is then solved for  $u$ . As the equation for  $S$  can be inverted once  $u$  and  $w$  are obtained, we are done.

The stability assertions of the Theorem follow from Theorem 4.2 in [26]. This completes our proof of Theorem 3.1. ■

**Remark 7.1** *The proof establishes that the eigenvalues of (3.2) consist of the eigenvalues of (2.8), with  $d = d_0$ , together with the roots of (7.3). The inequality  $\Lambda < s(A)$  is important because it implies that the stability of the washout steady state is determined by  $s(A)$ . Furthermore,  $s(A)$  is a simple eigenvalue of (3.2) when it does not coincide with an eigenvalue of (2.8) with  $d = d_0$ .*

**Proof of Theorem 3.2:** Given  $\delta > 0$ , we have that

$$S_t \leq d_0 S_{xx} - S_x$$

and hence, by a standard comparison result, conclude that  $S(x, t) \leq 1 + \delta$  for all  $x \in [0, 1]$  and all large  $t$ , say  $t \geq T$ . Letting  $Y$  and  $Z$  be as in the proof of Theorem 2.1 and arguing similarly (with  $u^0 = 0$ ), we find that for  $t \geq T$

$$\begin{aligned}
Y' &\leq [f(1+\delta) - k - \lambda_d - \alpha]Y + \epsilon[f_w(1+\delta)(1 - G(0)) + \beta]Z \\
&\quad + \epsilon f_w(1+\delta) \int_0^1 w\psi_d[G(0) - G(w)] + \alpha \int_0^1 u\psi_d w, \\
Z' &\leq [f_w(1+\delta)G(0) - k_w - \beta]Z + \epsilon^{-1}\alpha Y - \epsilon^{-1}\alpha \int_0^1 u\psi_d w \\
&\quad - f_w(1+\delta) \int_0^1 w\psi_d[G(0) - G(w)].
\end{aligned} \tag{7.4}$$

Suppose first that (a) holds. Setting

$$g(t) = \epsilon f_w(1+\delta) \int_0^1 w\psi_d[G(0) - G(w)] + \alpha \int_0^1 u\psi_d w \geq 0,$$

renaming  $Z = \epsilon Z$ , and putting  $V = (Y, Z)^t$  and  $E = (1, -1)^t$ , we find that

$$V' \leq A_* V + g(t)E. \tag{7.5}$$

Here  $A_*$  is identical to  $A^t$ , where  $A$  is as in (3.4), except that  $f(1), f_w(1)$  are replaced by  $f(1+\delta), f_w(1+\delta)$ . In view of our hypotheses, we can choose  $\delta > 0$  so small that  $q = s(A_*) < 0$  and  $f_w(1+\delta) - k_w > f(1+\delta) - k - \lambda_d$ . Exactly as in (3.7), we conclude that  $q \leq \max\{f(1+\delta) - k - \lambda_d, f_w(1+\delta) - k_w\}$ . Let  $P = (r, s)^t$  be a positive eigenvector ( $r, s > 0$ ) of  $A_*^t$  corresponding to eigenvalue  $q$ , which exists by the Perron-Frobenius theorem. Taking the scalar product of both sides of the differential inequality by  $P$  and setting  $B = V \cdot P = rY + sZ$ , we have

$$B' \leq qB + g(t)(r - s). \tag{7.6}$$

Clearly, if  $r \leq s$ , then, as  $g(t) \geq 0$ , it follows that  $B' \leq qB$  and hence  $B(t) \rightarrow 0$  as  $t \rightarrow \infty$ . We now show that  $r \leq s$ . The equation satisfied by  $r$  and  $s$  is

$$\begin{aligned}
0 &= [f(1+\delta) - k - \alpha - \lambda_d - q]r + \alpha s \\
0 &= [f_w(1+\delta)(1 - G(0)) + \beta]r + [f_w(1+\delta)G(0) - k_w - \beta - q]s,
\end{aligned} \tag{7.7}$$

By the second equation of (7.7), we get

$$\frac{r}{s} = \frac{k_w + q + \beta - f_w(1+\delta)G(0)}{f_w(1+\delta) + \beta - f_w(1+\delta)G(0)}.$$

As

$$q \leq \max\{f(1+\delta) - k - \lambda_d, f_w(1+\delta) - k_w\} = f_w(1+\delta) - k_w,$$

and the denominator in the expression for  $r/s$  is positive, it follows that  $r/s \leq 1$ .

Now suppose that (b) holds. Then the two inequalities in (b) continue to hold with  $1 + \delta$  in the arguments of  $f_w$  and  $f$  if  $\delta$  is small enough. Renaming  $Z = \epsilon Z$  and adding the two equations (7.4) gives

$$(Y + Z)' \leq [f(1 + \delta) - k - \lambda_d]Y + [f_w(1 + \delta) - k_w]Z \leq q(Y + Z)$$

where  $q = \max\{f(1 + \delta) - k - \lambda_d, f_w(1 + \delta) - k_w\} < 0$ . Again, we are done.

If (c) holds, then  $s(B^*) < 0$  where  $1 + \delta$  replaces 1 in the arguments of  $f, f_w$ . Notice that  $g(t) \leq \epsilon f_w(1 + \delta)G(0)Z + \alpha Y$ . Making use of this inequality in the first of equations (7.4) but dropping  $-g(t)$  from the second, and renaming  $Z = \epsilon Z$  leads to

$$V' \leq B^*V.$$

So  $V(t) \leq \exp(B^*t)V(0) \rightarrow 0$  as  $t \rightarrow \infty$ . ■

We now proceed towards the proof of Theorem 4.1. We have already noted in (2.7) that for any solution of (2.4)-(2.5)  $S$  is bounded so that  $S(x) \leq 1$  for all  $x$ . The next result gives an important a priori bound on  $\|u\|$ .

**Lemma 7.1** *For any solution  $(S, u, w)$  of (4.1)-(4.2), we have the estimate*

$$\|u\| \leq N \equiv u^0 + f(1)M + \epsilon f_w(1) \tag{7.8}$$

where  $M$  is as in Theorem 2.1.

**Proof:** The equation for  $w$  implies that  $\alpha u(1 - w) = -\epsilon w[f_w(S)G(w) - k_w - \beta]$  and substituting this expression into the  $u$  equation leads to

$$0 = du'' - u' + u[f(S) - k] + \epsilon w[f_w(S) - k_w].$$

Integrating this equation from 0 to  $x$  and using the boundary condition at  $x = 0$ , we get

$$0 = du'(x) - u(x) + u^0 + \int_0^x u[f(S) - k] + \epsilon w[f_w(S) - k_w].$$

Let  $u(x_m) = \|u\|$ . If  $x_m < 1$ , then  $u'(x_m) = 0$  and the same follows from the boundary conditions if  $x_m = 1$ . Putting  $x = x_m$  in the equation above, we get

$$\|u\| = u^0 + \int_0^{x_m} u[f(S) - k] + \epsilon w[f_w(S) - k_w].$$

Using  $S(x), w(x) \leq 1$ , we may estimate the right side as

$$\|u\| \leq u^0 + f(1) \int_0^1 u(x)dx + \epsilon f_w(1).$$

Theorem 2.1 may be used to estimate the integral, implying the estimate. ■

**Remark 7.2** Later, assuming  $u^0 = 0$ , we will need a **uniform** a priori bound for the one-parameter family, indexed by  $\lambda \geq 1$ , of boundary value problems (4.1) where  $k$  is replaced by  $k_\lambda = k + \alpha(1 - \lambda^{-1}) \geq k$ ,  $\alpha$  is replaced by  $\alpha/\lambda$ ,  $\epsilon$  is replaced by  $\epsilon/\lambda$ , and  $f$  is replaced by  $f/\lambda$  where  $\lambda \geq 1$ . That is, we want  $N$  to be independent of  $\lambda \geq 1$ . From the last line of the proof above, this holds if we can show that  $M$  is independent of  $\lambda$ . From the proof of Theorem 2.1, we find that the only quantity that need be considered is  $m = \max\{1/2, \frac{\alpha}{\lambda_d/2+k+\alpha}\}$ , which must be bounded away from unity (if  $k_w = 0$ ). But as  $\alpha/\lambda \leq \alpha$  and  $k_\lambda \geq k$ , this clearly holds.

We now examine the zero set of the third equation in (4.1).

**Lemma 7.2** *The equation*

$$H(S, u, w) \equiv w[f_w(S)G(w) - k_w - \beta] + \epsilon^{-1}\alpha u(1 - w) = 0 \quad (7.9)$$

has a unique solution  $w = h(S, u) \in (0, 1)$  for each  $u > 0$  and  $0 \leq S \leq 1$ . Moreover,  $h(S, u)$  is continuously differentiable with  $h_u > 0$  and  $h_S > 0$ . If  $f_w(1)G(0) - k_w - \beta < 0$ , then  $h(S, 0) \equiv 0$  extends  $h$  so that  $w = h(S, u)$  is the unique solution of (7.9),  $h$  is continuously differentiable and

$$h_u(1, 0) = \epsilon^{-1}\alpha[k_w + \beta - f_w(1)G(0)]^{-1}. \quad (7.10)$$

If  $f_w(1)G(0) - k_w - \beta > 0$ , let  $S^* \in (0, 1)$  be the unique root of  $f_w(S)G(0) - k_w - \beta = 0$ . Then  $H(S, 0, w) = 0$  has two branches of solutions,  $w = 0$ ,  $0 \leq S \leq 1$  and  $w = w_*(S) > 0$ ,  $S^* < S \leq 1$ . The function  $w_*$  is continuously differentiable and satisfies  $w_*(S^*) = 0$ ,  $w_*' > 0$ , and  $w_*(1) < 1$ . Extending  $w_*$  by defining  $w_*(S) = 0$  for  $0 \leq S \leq S^*$ , we obtain a continuous function, not differentiable at  $S = S^*$ , with the property that  $h(S, u) \rightarrow w_*(S)$  as  $u \rightarrow 0+$  and  $h(S, u) > w_*(S)$  for  $u > 0$ .

**Proof:** The solution set of  $H(S, 0, w) = 0$  is easily seen to be as described above using the strict monotonicity of  $f_w$  and  $G$ . Hereafter,  $S \rightarrow w_*(S)$  is the function defined for  $0 \leq S \leq 1$  as described above. In case  $f_w(1)G(0) - k_w - \beta < 0$  we define  $w_*(S) \equiv 0$  for  $0 \leq S \leq 1$ . The lemma essentially follows from a straightforward application of the intermediate value theorem and the implicit function theorem since  $H(S, u, 1) = -k_w - \beta < 0$ ,  $H(S, u, w_*(S)) > 0$  for  $0 \leq S \leq 1$  and  $u > 0$ , and  $H_w < 0$  for  $0 \leq S \leq 1$ ,  $u > 0$ ,  $w \geq w_*(S)$ . Implicit differentiation leads to  $h_S = -\frac{H_S}{H_w}$  and  $h_u = -\frac{H_u}{H_w}$  and it is easily checked that  $H_S, H_u > 0$ . ■

**Proof of Theorem 4.1:** We assume that  $u^0 = 0$ , later commenting on the easier case that  $u^0 > 0$ . It is convenient to make the change of variables  $v = 1 - S$  so that  $v$  satisfies homogeneous boundary conditions. We then have the system

$$\begin{aligned} -d_0 v'' + v' &= u f(1 - v) + \epsilon w f_w(1 - v) \\ -du'' + u' + (k + \alpha)u &= u f(1 - v) + \epsilon w f_w(1 - v)(1 - G(w)) \\ &\quad + \alpha u w + \epsilon \beta w \\ w &= h(1 - v, u) \end{aligned}$$

with boundary conditions

$$\begin{aligned} 0 &= -d_0 v'(0) + v(0), & v'(1) &= 0 \\ 0 &= -du'(0) + u(0), & u'(1) &= 0. \end{aligned} \tag{7.11}$$

We will always interpret  $1 - v$  as the positive part of it :  $(1 - v)_+$ . We can invert the differential operators on the left to express the boundary value problem as a fixed point problem:

$$\begin{aligned} v &= \int_0^1 K_0(x, \eta)[uf(1 - v) + \epsilon w f_w(1 - v)] \\ u &= \int_0^1 K(x, \eta)[uf(1 - v) + \epsilon w f_w(1 - v)(1 - G(w)) + \alpha u w + \epsilon \beta w] \\ w &= h(1 - v, u). \end{aligned} \tag{7.12}$$

The Green's functions  $K_0, K$  are positive (see e.g. Thm.4.2 of [27]). We view (7.12) as the fixed point equation

$$(v, u) = T(v, u)$$

where  $T : Y_+ \rightarrow Y_+$  is defined by the right side of (7.12) and  $Y_+$  is the positive cone in  $Y = E \times E$ , that is  $Y_+ = E_+ \times E_+$  with  $E_+ = C([0, 1], \mathbb{R}_+)$ . Obviously,  $T(0, 0) = (0, 0)$ , corresponding to the washout steady state, but we seek a nontrivial fixed point. It follows from well-known arguments that  $T$  is a completely continuous mapping on  $Y_+$ . We show that there exists  $R > 0$  such that  $T(v, u) \neq \lambda(v, u)$  for every  $(v, u) \in Y_+$  with  $\|v\| + \|u\| = R$  and  $\lambda \geq 1$ . Set  $R = N + 2$  where  $N$  is as in Remark 7.2. If  $T(v, u) = \lambda(v, u)$  for some  $\lambda \geq 1$  and  $(v, u) \in Y_+$ , then  $(v, u)$  must satisfy the boundary value problem

$$\begin{aligned} -d_0 v'' + v' &= u \lambda^{-1} f(1 - v) + \lambda^{-1} \epsilon w f_w(1 - v) \\ -du'' + u' + (k + \alpha)u &= u \lambda^{-1} f(1 - v) + \lambda^{-1} \epsilon w f_w(1 - v)(1 - G(w)) \\ &\quad + \lambda^{-1} \alpha u w + \lambda^{-1} \epsilon \beta w \\ w &= h(1 - v, u) \end{aligned}$$

with boundary conditions (7.11). Now  $v(x) \geq 0$  and we will show that  $v(x) \leq 1$  for all  $x$  (recall that  $1 - v$  is interpreted as  $(1 - v)_+$ ). Note that  $v(x) \geq 1$  cannot hold for all  $x \in [0, 1]$  since the right side of the first equation would vanish identically, implying  $v \equiv 0$ . Suppose that  $v(x) > 1$  for  $x \in I$ , where  $I$  is a nondegenerate interval, maximal with that property. Then  $d_0 v'' - v' = 0$  on  $I$  and at least one endpoint of  $I$  must be an interior point of  $[0, 1]$  where  $v = 1$ . Let  $a, b$  be the endpoints of  $I$  with  $a < b$ . Integrating the equation over  $I$  leads to

$$d_0 v'(b) - v(b) - d_0 v'(a) + v(a) = 0. \tag{7.13}$$

If  $a = 0$ , then  $b < 1$ ,  $v(b) = 1$ ,  $v'(b) \leq 0$  and using the boundary conditions, (7.13) becomes  $d_0 v'(b) - 1 = 0$ , a contradiction to  $v'(b) \leq 0$ . If  $0 < a < b < 1$ , (7.13) leads to  $v'(a) = v'(b) = 0$  since  $v(a) = v(b) = 1$ . Thus  $v \equiv 1$  on  $I$ , a contradiction. If  $0 < a < b = 1$ , (7.13) becomes  $1 - v(b) - d_0 v'(a) = 0$ , which, since  $v(b) \geq 1$  and  $v'(a) \geq 0$ , implies that  $v(b) = 1$  and  $v'(a) = 0$ . Again, we conclude that  $v \equiv 1$  on  $I$ , a contradiction. Hence,  $v(x) \leq 1$  for all  $x \in [0, 1]$  and so  $(1 - v(x))_+ = 1 - v(x)$ . Setting  $S = 1 - v \geq 0$ , in the first equation and rearranging, we find

$$\begin{aligned} 0 &= d_0 S'' - S' + u\lambda^{-1}f(S) + \lambda^{-1}\epsilon w f_w(S) \\ 0 &= du'' - u' + u[\lambda^{-1}f(S) + k_\lambda] + \lambda^{-1}\epsilon w f_w(S)(1 - G(w)) \\ &\quad + \lambda^{-1}\alpha u(1 - w) + \lambda^{-1}\epsilon\beta w \\ 0 &= w[f_w(S)G(w) - k_w - \beta] + (\lambda^{-1}\epsilon)^{-1}\lambda^{-1}\alpha u(1 - w) \end{aligned}$$

with boundary conditions (4.2). Thus,  $(S, u, w)$  satisfies equation (4.1) and (4.2) except that  $k_\lambda = k + \alpha(1 - \lambda^{-1})$ ,  $\alpha$  is replaced by  $\alpha/\lambda$ ,  $\epsilon$  is replaced by  $\epsilon/\lambda$ , and  $f$  is replaced by  $\lambda^{-1}f$ . According to Remark 7.2,  $\|u\| \leq N$ . Since  $0 \leq v \leq 1$ , we conclude that  $\|v\| + \|u\| < R$ . This establishes the assertion.

The remainder of the proof breaks down into two cases. We first suppose that

$$f_w(1)G(0) - k_w - \beta < 0. \tag{7.14}$$

In this case, we use Theorem 1.6 in [28] (see also Theorem 13.2 in [27]). A computation shows that  $T$  has a right derivative  $T'_+(0)$  and that

$$\begin{aligned} T'_+(0)(v, u) &= \left( \int_0^1 K_0 u [f(1) + \epsilon h_u(1, 0) f_w(1)], \right. \\ &\quad \left. \int_0^1 K u [f(1) + \epsilon h_u(1, 0) f_w(1)(1 - G(0)) + \epsilon\beta h_u(1, 0)] \right). \end{aligned}$$

If  $\lambda(v, u) = T'_+(0)(v, u)$  with  $(v, u) \neq (0, 0)$ , then we have

$$\begin{aligned} 0 &= d_0 v'' - v' + \lambda^{-1}u[f(1) + \epsilon h_u(1, 0) f_w(1)] \\ 0 &= du'' - u' - u(k + \alpha) + \lambda^{-1}u[f(1) + \epsilon h_u(1, 0) f_w(1)(1 - G(0)) + \epsilon\beta h_u(1, 0)] \end{aligned}$$

with boundary conditions (7.11). If  $u = 0$ , then  $v = 0$  so we conclude that  $u \neq 0$ . Inserting  $h_u(1, 0)$  from (7.10) into the second equation and rearranging, we get

$$0 = du'' - u' + u \left\{ \lambda^{-1} [f(1) + \frac{\alpha f_w(1)(1 - G(0)) + \alpha\beta}{\beta + k_w - f_w(1)G(0)}] - k - \alpha \right\}.$$

We conclude from (2.8) that

$$\lambda_n = -\lambda^{-1} \left[ f(1) + \frac{\alpha f_w(1)(1 - G(0)) + \alpha\beta}{\beta + k_w - f_w(1)G(0)} \right] + k + \alpha$$

for some  $n \geq 0$ . As we are interested in positive eigenvectors,  $n = 0$ , and, solving for  $\lambda$  we get

$$\lambda = \frac{f(1)[\beta + k_w - f_w(1)G(0)] + \alpha f_w(1)(1 - G(0)) + \alpha\beta}{f(1)[\beta + k_w - f_w(1)G(0)] + (k + \alpha + \lambda_d - f(1))(\beta + k_w - f_w(1)G(0))}.$$

From the definition of the matrix  $A$  in (3.4) we see that if  $s(A) > 0$  then either  $\det(A) < 0$  or  $\det(A) \geq 0$  and the trace of  $A$  is positive. As (7.14) holds, it follows that  $\det(A) < 0$  and this implies that  $\lambda > 1$ . Furthermore, corresponding to  $\lambda$ , there is a positive eigenfunction  $u = \phi_d$  since  $\lambda_0 = -\lambda_d$  is the largest eigenvalue of (2.8). We also have

$$v = \int_0^1 K_0 \lambda^{-1} u [f(1) + \epsilon g(1, 0) f_w(1)] > 0.$$

Thus, the eigenvector  $(v, u)$  is positive. But any positive eigenvector  $(v, u)$  for  $T_+^l(0)$  must satisfy  $u = c\phi_d$  for some  $c > 0$  and therefore must correspond to the eigenvalue  $\lambda > 1$  above. So there cannot be a positive eigenvector corresponding to the eigenvalue one. It follows from Theorem 13.2 of [27] or Theorem 1.6 in [28] that  $T$  has a fixed point  $(v, u) \in Y_+$  with  $0 < \|u\| + \|v\| < R$ . Now  $u \neq 0$  since this would imply that  $w = h(1-v, 0) = 0$  and, by (7.12), that  $v = 0$ . By the positivity of the Green's functions, we conclude from (7.12) that  $u(x) > 0$  for all  $x$ . This implies that  $1 > w(x) > 0$  for all  $x$  by Lemma 7.2.

Now suppose that

$$f_w(1)G(0) - k_w - \beta > 0 \tag{7.15}$$

holds. From Lemma 7.2 we conclude that  $S^* < 1$  and that  $w = h(S, u) \geq w_*(S)$ . We will use Theorem 12.3 in [27], which requires us to find  $0 < \delta < R$  such that  $T(v, u) \leq (v, u)$  does not hold for any  $(v, u) \in Y_+$  with  $\|v\| + \|u\| = \delta$ . (Actually, we could also use Corollary 12.4 in [27].) Suppose, for contradiction sake, that such a  $(v, u)$  exists. Then  $0 \leq v \leq \delta$  and from the definition of  $T$ , and monotonicity properties of the various functions, we have

$$\begin{aligned} v &\geq \int_0^1 K_0 [u f(1-v) + \epsilon w f_w(1-v)] \\ &\geq \epsilon \int_0^1 K_0 w f_w(1-v) \\ &\geq \epsilon f_w(1-\delta) \int_0^1 K_0 w \\ &\geq \epsilon f_w(1-\delta) w_*(1-\delta) \int_0^1 K_0. \end{aligned}$$

Recall that  $w = h(S, u) > w_*(S)$  and that  $w_*(S)$  is strictly increasing in  $S$  by Lemma 7.2. Thus we have

$$\delta \geq \epsilon C f_w(1-\delta) w_*(1-\delta)$$

where  $C > 0$  is the maximum value of  $\int_0^1 K_0(x, s) ds$ . Clearly by choosing  $\delta$  small enough we have a contradiction as  $f_w(1), w_*(1) > 0$ . Thus, by Theorem 12.3 of [27],  $T$  has a fixed point with  $\delta < \|v\| + \|u\| < R$ . If both  $u$  and  $w$  vanished identically, then  $v = 0$  by (7.12) so we conclude from (7.12) and the positivity of the Greens functions that  $u(x) > 0$  for all  $x$ . This and Lemma 7.2 implies that  $1 > w(x) > 0$  for all  $x$ .

The boundary conditions and nonnegativity of  $S$  implies  $S(0) > 0$ . Multiplying the equation for  $S$  in (4.1) by  $\exp(-x/d_0)$  and integrating, using the boundary conditions, leads to

$$S' = -d_0^{-1} \int_x^1 e^{(x-r)/d_0} u f(S) dr - \epsilon d_0^{-1} \int_x^1 e^{(x-r)/d_0} w f_w(S) dr.$$

Clearly,  $S' \leq 0$  and if  $S$  vanishes, then it vanishes on a (possibly degenerate) interval  $[x_0, 1]$ . If we write  $f(S) = Sg(S)$ ,  $f_w(S) = Sg_w(S)$ , then the first equation of (4.1) can be viewed as a linear equation for  $S$  with variable coefficients. Therefore, if  $S$  and its derivative vanish for some  $x$ , then it vanishes identitically. We conclude that  $S > 0$  and  $S' < 0$  for all  $x$ . ■

We have assumed that  $u^0 = 0$  in the proof of Theorem 4.1. In case  $u^0 > 0$ , the washout steady state does not exist to complicate matters. A simple application of the Schauder fixed point theorem establishes the existence of a solution of (4.1). The proof begins in a similar manner as Theorem 4.1 after replacing  $u$  by  $U = u - u^0$  to make the boundary conditions homogeneous.

**Proof of Theorem 5.1:** Again, we use the method of proof of Theorem 2.1, except that we normalize  $\psi_d$  so that  $\psi_d(0) = 1$ . Then, on adding the equation for  $Y$  to that for  $\epsilon Z$  in (7.2) and dropping all growth terms, we get

$$\begin{aligned} Y' + \epsilon Z' &\geq u^0 - (\lambda_d + k)Y - k_w \epsilon Z \\ &\geq u^0 - (\lambda_d + k + k_w)(Y + \epsilon Z). \end{aligned}$$

Consequently

$$Y + \epsilon Z \geq \frac{u^0}{\lambda_d + k + k_w} + [Y_0 + \epsilon Z_0 - \frac{u^0}{\lambda_d + k + k_w}] e^{-(\lambda_d + k + k_w)t}$$

proving the result. ■

**Proof of Theorem 5.2:** Suppose, for contradiction, that  $u(x, t) + w(x, t) \leq \delta$  for all  $(x, t) \in [0, 1] \times [t_0, \infty)$  for some  $t_0 > 0$  and where  $\delta < 1$  will be fixed later on. As  $\limsup \|S(\bullet, t)\| \leq 1$ , we may assume that  $S \leq 2$  for all  $x$  and  $t \geq t_0$ . Thus,  $f(S), \epsilon f_w(S) \leq m \equiv \max\{f(2), \epsilon f_w(2)\}$  for  $t \geq t_0$  and therefore

$$S_t \geq d_0 S_{xx} - S_x - m\delta, \quad t \geq t_0.$$

The associated differential equality, together with boundary conditions (2.5), has a globally attracting steady state given by

$$\begin{aligned}\hat{S}(x) &= 1 - m\delta[x + d_0(1 - \exp(-(1-x)/d_0))] \\ &\geq 1 - m\delta(1 + d_0) \equiv 1 - \eta/2.\end{aligned}$$

By a standard comparison theorem, we conclude that there exists  $t_1 > t_0$  such that  $S(x, t) \geq 1 - \eta$ ,  $t \geq t_1$ ,  $0 \leq x \leq 1$ .

Now we proceed as in the proof of Theorem 3.2 to obtain the differential inequality (compare with (7.4))

$$\begin{aligned}Y' &\geq [f(1 - \eta) - k - \lambda_d - \alpha]Y + [f_w(1 - \eta)(1 - G(0)) + \beta]Z \\ &\quad + \epsilon f_w(1 - \eta) \int_0^1 w\psi_d[G(0) - G(w)] + \alpha \int_0^1 u\psi_d w \\ Z' &\geq [f_w(1 - \eta)G(0) - k_w - \beta]Z + \alpha Y - \alpha \int_0^1 u\psi_d w \\ &\quad - \epsilon f_w(1 - \eta) \int_0^1 w\psi_d[G(0) - G(w)]\end{aligned}\tag{7.16}$$

for  $t \geq t_1$ , where, as usual, we have absorbed the  $\epsilon$  into  $Z$ .

Suppose first that (a) holds and define  $g(t), V, E$  and matrix  $A_*$  exactly as in Theorem 3.2 except for the matrix  $A_*$  and  $g(t)$  where  $1 - \eta$  appears in the argument of the growth functions  $f, f_w$ . We then have the following inequality (compare with (7.5))

$$V' \geq A_*V + g(t)E$$

which leads to (see (7.6))

$$B' \geq qB + g(t)(r - s).$$

If  $\eta$  is sufficiently small, then  $q$ , the stability modulus of  $A_*$ , is positive and  $f(1 - \eta) - k - \lambda_d > f_w(1 - \eta) - k_w$ . We will show that  $r \geq s$  by examining the first of equations (7.7):

$$\frac{r}{s} = \frac{\alpha}{\alpha + \lambda_d + k + q - f(1 - \eta)}.$$

Using (3.7) applied to  $A_*$ , we conclude that  $f(1 - \eta) - k - \alpha - \lambda_d < q \leq f(1 - \eta) - k - \lambda_d$  so the denominator is positive and  $r \geq s$  as asserted. Therefore,  $B' \geq qB$  so  $B \rightarrow \infty$  as  $t \rightarrow \infty$  ( $u_0 + w_0 \neq 0$ ). Now, recalling that

$$B = rY + sZ = r \int_0^1 u\psi_d + \epsilon s \int_0^1 w\psi_d,$$

we see that we have contradicted  $u + w \leq \delta$ . The proof is complete in this case.

Suppose that (b) holds. Then, as in the proof of case (b) of Theorem 3.2, we get

$$(Y + Z)' \geq [f(1 - \eta) - k - \lambda_d]Y + [f_w(1 - \eta) - k_w]Z.$$

Now, according to our hypotheses, we may choose  $\eta > 0$  so small that both terms in square brackets are positive. This leads to a contradiction as in the previous case.

If (c) holds, choose  $\eta > 0$  so small that  $f(1 - \eta) - k - \lambda_d - \alpha > 0$ . We may drop most of the first of equations (7.16) to obtain

$$Y' \geq [f(1 - \eta) - k - \lambda_d - \alpha]Y. \quad (7.17)$$

This leads to  $Y \rightarrow \infty$  as  $t \rightarrow \infty$ , a contradiction. ■

## References

- [1] H.L. Smith and P. Waltman, *The Theory of the Chemostat*, Cambridge Univ. Press, London, 1995.
- [2] J. Bailey and D. Ollis, *Biochemical Engineering Fundamentals*, 2nd ed., McGraw Hill, New York, 1986.
- [3] W.G. Characklis and K.C. Marshall (Eds.) *Biofilms*, Wiley Series in Ecological and Applied Microbiology, John Wiley & Sons, New York, 1990.
- [4] J.W. Costerton, Z. Lewandowski, D. DeBeer, D. Caldwell, D. Korber, G. James, Minireview: Biofilms, the customized microniche, *J. Bacteriology* 176 (1994) 2137-2142.
- [5] J.W. Costerton, Z. Lewandowski, D. Korber, H.M. Lappin-Scott, Microbial Biofilms, *Annual Review of Microbiology* 49 (1995) 711-745.
- [6] H. Topiwala and G. Hamer, Effect of wall growth in steady state continuous culture, *Biotech. and Bioeng.* 13 (1971) 919-922.
- [7] B.C. Baltzis, and A.G. Fredrickson, Competition of two microbial populations for a single resource in a chemostat when one of them exhibits wall attachment, *Biotechnology and Bioengineering* XXV (1983) 2419-2439.
- [8] S. Pilyugin and P. Waltman, Competition in a chemostat with wall growth, preprint.
- [9] R. Freter, H. Brickner, J. Fekete, M. Vickerman, K. Carey, Survival and implantation of E.Coli in the intestinal tract, *Infection and Immunity*, 39 (1983) 686-703.
- [10] R. Freter, Mechanisms that control the microflora in the large intestine, in: D.Hentges, (Ed.), *Human Intestinal Microflora in Health and Disease*, Academic Press, New York, 1983.

- [11] R. Freter, H. Brickner, S. Temme, An understanding of colonization resistance of the mammalian large intestine requires mathematical analysis, *Microecology and Therapy* 16 (1986) 147-155.
- [12] A. Lee, Neglected niches. The microbial ecology of the gastrointestinal tract, in: K.C. Marshall (Ed.), *Advances in Microbial Ecology*, Plenum Press, New York, 1985.
- [13] I. Hume, Fermentation in the hindgut of mammals, in: R.Mackie, B. White, (Eds.), *Gastrointestinal Microbiology*, vol 1, Chapman & Hall Microbiology Series, New York, 1997.
- [14] R. Rolfe, Colonization Resistance, in: R.Mackie, B. White, R. Isaacson,(Eds.), *Gastrointestinal Microbiology*, vol 2, Chapman & Hall Microbiology Series, New York, 1997.
- [15] M. Ballyk, H.L. Smith, A Flow Reactor with Wall Growth, preprint.
- [16] D. Penry and P. Jumars, Modeling animal guts as chemical reactors, *American Naturalist* 129 (1987) 69-96.
- [17] D.C. Savage, Microbial Ecology of the Gastrointestinal Tract, *Ann. Review Microbiol.* 31 (1977) 107-133.
- [18] R.J. Gibbons and B. Kapsimales, Estimates of the overall rate of growth of intestinal microflora of Hamsters, Guinea Pigs, and Mice, *J. Bacteriology* 93 (1967) 510-512.
- [19] C.-M. Kung and B.C. Baltzis, The growth of pure and simple microbial competitors in a moving and distributed medium, *Math. Biosci.* 111 (1992) 295-313.
- [20] M. Ballyk, D. Le, D. Jones, H.L. Smith, Effects of random motility on microbial growth and competition in a flow reactor, to appear, *SIAM J. Applied Math.*
- [21] A. Berman and R.J. Plemmons, *Nonnegative Matrices in the Mathematical Sciences*, Academic Press, New York, 1979.
- [22] T. Mitsuoka, *Intestinal Bacteria and Health*, Harcourt Brace Jovanovich, Tokyo, Japan, 1978.
- [23] H.D. Patton, A.F. Fuchs, B. Hille,A.M. Scher, R.Steiner, *Textbook of Physiology*, Vol 2, 21st edition, W.B. Saunders Co., Philadelpho, 1989.
- [24] L. Segel, *Modeling Dynamic Phenomena in Molecular and Cellular Biology*, Cambridge University Press, London, 1984.
- [25] H. Berg, *Random Walks in Biology*, Princeton University Press, Princeton N.J., 1983.

- [26] X. Mora, Semilinear Parabolic problems define semiflows on  $C^k$  spaces, Transactions of Amer. Math. Soc. 278 (1983) 21-55.
- [27] H. Amann, Fixed Point equations and nonlinear eigenvalue problems in ordered Banach Spaces, SIAM Rev. 18 (1976) 620-709.
- [28] J. Gatica and H.L. Smith, Fixed point techniques in a cone with applications, J. Math. Anal. Appl. 61 (1977) 58-71.
- [29] H. Thieme, Persistence under relaxed point-dissipativity (with application to an epidemic model), SIAM J. Math. Anal. 24 (1993) 407-435.
- [30] H.L. Smith, *Monotone Dynamical Systems: An introduction to the Theory of Competitive and Cooperative Systems* AMS Math. Surv.& Monographs, 41, Providence, R.I., 1995.

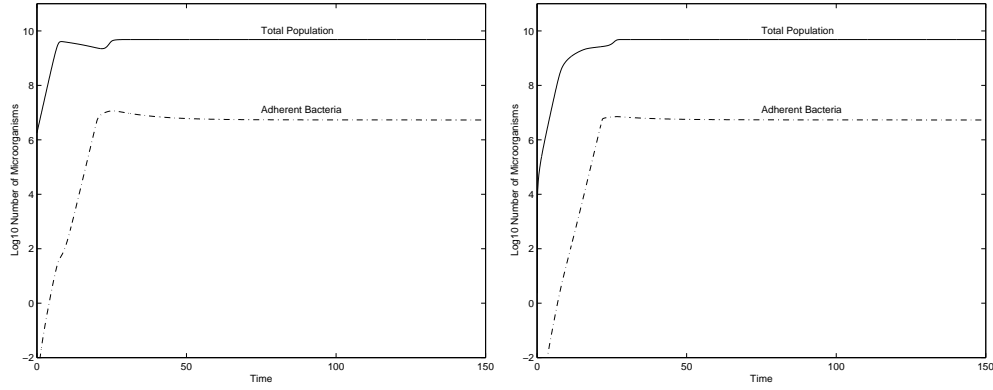


Figure 1: Time series for the case of insignificant death rates ( $k = k_w = 0$ ) with (a)  $u^0 = 0$  and  $u_0(x) \equiv 1 \times 10^{-6}/(\pi \rho^2 L)$ g/ml. (b)  $u^0 = 1 \times 10^{-6}/(\pi \rho^2 L)$ g/ml for  $0 \leq t \leq 10$  and  $u^0 = 0$  for  $t > 10$  with  $u_0(x) \equiv 0$ . All other parameter values are as in the text.

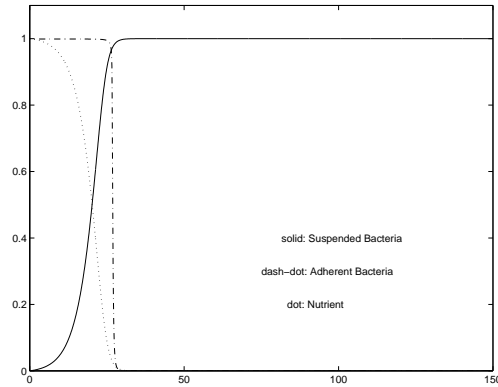


Figure 2: Steady state solution for  $k = k_w = 0$ .

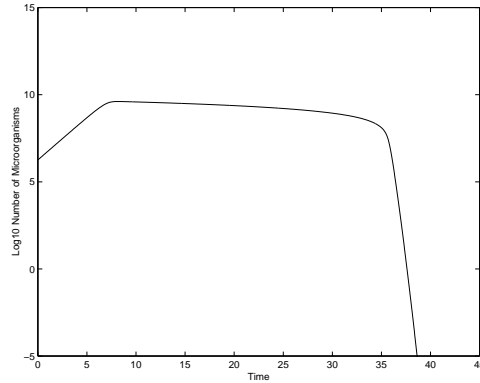


Figure 3: Time series for  $k = k_w = 0$  without wall growth. When the reactor is charged either via the initial conditions or via a brief pulse of microorganisms from the feed, the population washes out.

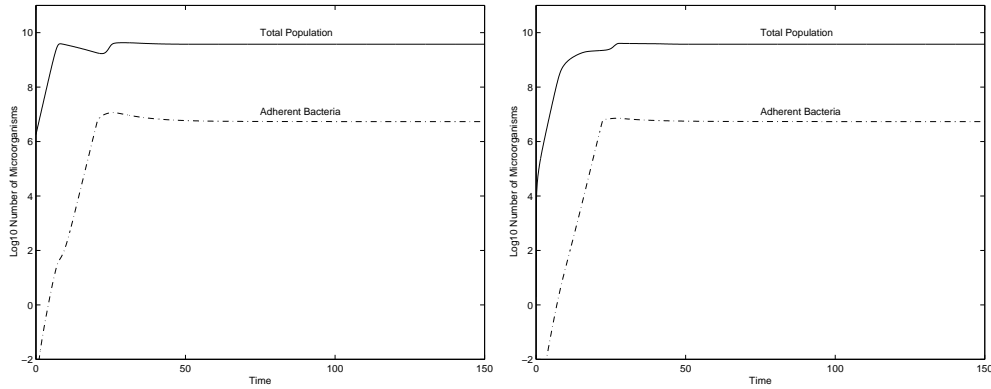


Figure 4: Time series for the case of significant death rates ( $k = k_w = 0.02$ ) with inputs as in figure 1. All other parameter values are as in the text.

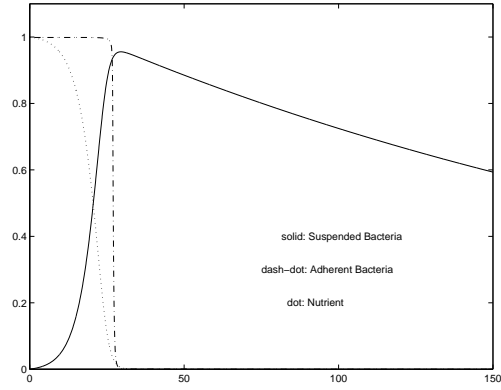


Figure 5: Steady state solution for  $k = k_w = 0.02$ .

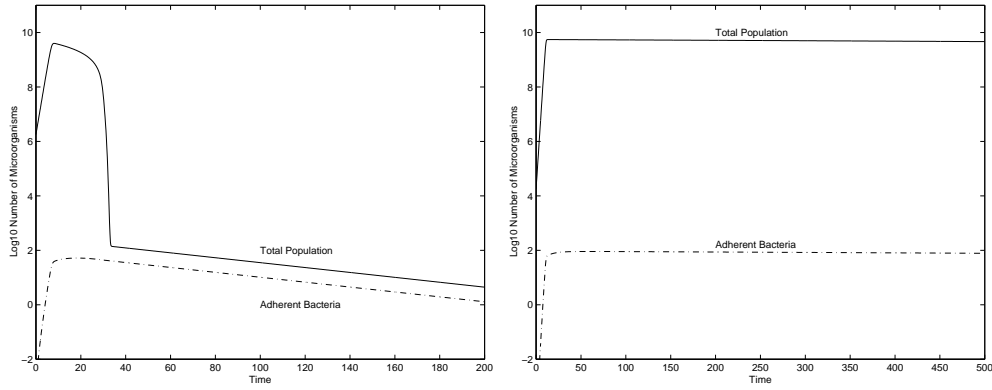


Figure 6: Time series for  $S^0 = 4.56 \times 10^{-8}$ g/ml with (a)  $v = 5.0$  (b)  $v = 0.05$  All other parameter values are as in figure 1.