Bacteriophage and Bacteria in a Flow Reactor

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Abstract The Levin-Stewart model of bacteriophage predation of bacteria in a chemostat is modified for a flow reactor in which bacteria are motile, phage diffuse, and advection brings fresh nutrient and removes medium, cells and phage. A fixed latent period for phage results in a system of delayed reaction-diffusion equations with non-local nonlinearities. Basic reproductive numbers are obtained for bacteria and for phage which predict survival of each in the bio-reactor. These are expressed in terms of physical and biological parameters. Persistence and extinction results are obtained for both bacteria and phage. Numerical simulations are in general agreement with those for the chemostat model.

Keywords Bacteriophage · Persistence

1 Introduction

Levin et al. (1977) and Lenski and Levin (1985) model phage (virus that attack bacteria) predation on a bacterial host which in turn consumes a limiting nutrient in a chemostat by the system

$$\begin{aligned}S'(t) &= D(S^0 - S(t)) - \gamma^{-1} f(S(t)) B(t) \\B'(t) &= (f(S(t)) - D) B(t) - k B(t) P(t) \\I'(t) &= k B(t) P(t) - D I(t) - e^{-D\tau} k B(t - \tau) P(t - \tau) \\P'(t) &= -D P(t) - k B(t) P(t) + \beta e^{-D\tau} k B(t - \tau) P(t - \tau),\end{aligned}\tag{1}$$

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where S is the resource supporting bacterial growth, B is for uninfected bacteria, I is phage-infected bacteria, and P is phage. S^0 is input nutrient concentration supplied to bacteria, D is the dilution rate of the chemostat, and $f(S)$ is the specific growth rate of bacteria at resource level S . The specific growth rate f is typically taken to be of Monod type:

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

where $m, a > 0$. However, we need only assume that $f : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ is C^1 and

$$f(0) = 0, \quad f'(S) > 0, \quad f(\infty) < \infty. \quad (2)$$

The yield constant γ converts nutrient to cells. We scale it out by setting $\tilde{B} = B/\gamma$, $\tilde{P} = P/\gamma$ and $\tilde{k} = k\gamma$. Henceforth, dropping the tildes on variables and parameters, we assume that

$$\gamma = 1. \quad (3)$$

Phage attach to the cell surface of a bacterium and inject their DNA into it. This causes the bacterium to begin to synthesize viral DNA and viral proteins in order to make new virus. After a time τ , called the latent period, this is complete and the bacterium lyses open releasing the new virus. Latent periods vary by bacterial type but are usually in the half hour to hour range. Denote by β the average number of progeny released when an infected cell lyses. The factor $e^{-D\tau}$ in the equations accounts for the fraction of infected bacteria that survive being washed out of the chemostat during the latent period. More generally, the probability of phage, nutrient, or bacteria avoiding washout in a time period of length t is e^{-Dt} .

Several important assumptions are made in formulating the model: (1) nutrient uptake by infected cells is negligible, (2) infected cells do not grow and divide, (3) phage binding to infected cells can be neglected, and (4) deactivation of phage can be neglected. We have scaled out the yield constant, a positive number multiplying $f(S)$ in the equation for S .

Nonnegative initial data for B and P must be prescribed on $[-\tau, 0]$ but only $S(0)$ need be prescribed. Initial data for I are constrained by those of B and P because

$$I(t) = \int_{t-\tau}^t e^{-D(t-s)} k B(s) P(s) ds, \quad t \geq 0 \quad (4)$$

(see Smith and Thieme 2010). The integral captures all cells infected from $t - \tau$ to t which have not washed out of the chemostat.

We assume that susceptible bacteria are viable in the absence of phage. By this we mean that the phage-free system

$$\begin{aligned} S'(t) &= D(S^0 - S(t)) - f(S(t))B(t) \\ B'(t) &= (f(S(t)) - D)B(t) \end{aligned} \quad (5)$$

has a unique positive equilibrium $(\bar{S}, \bar{B})$

$$\bar{S} = f^{-1}(D), \quad \bar{B} = S^0 - \bar{S}. \quad (6)$$

This is easily seen to be the case if and only if the basic reproductive number for bacteria, in the environment of the “washout equilibrium” $(S^0, 0)$, exceeds one:

$$R_0(B) = \frac{f(S^0)}{D} > 1. \quad (7)$$

It is well-known that this equilibrium attracts all solutions of (5) with $B(0) > 0$.

The corresponding equilibrium

$$E_B = (\bar{S}, \bar{B}, 0, 0)$$

of (1) will be called the virus-free equilibrium (VFE). Then the following can be proved. See Smith and Thieme (2011), Smith (2010) for the result below, and Beretta et al. (2002) for related results.

Proposition 1.1 *Let (7) hold. Then E_B is locally asymptotically stable for (1) if the phage reproductive number*

$$R_0(P) \equiv \frac{\beta e^{-D\tau} k \bar{B}}{D + k \bar{B}} \quad (8)$$

satisfies $R_0(P) < 1$ and unstable if $R_0(P) > 1$.

If $R_0(P) < 1$, then phage cannot survive:

$$P(t) \rightarrow 0.$$

If $R_0(P) > 1$, then phage and bacteria persist:

$$\exists \epsilon > 0, \quad \liminf_{t \rightarrow \infty} B(t) > \epsilon, \quad \liminf_{t \rightarrow \infty} P(t) > \epsilon$$

provided initial data for B, P are positive. An equilibrium (S^, B^*, I^*, P^*) with $S^*, B^*, I^*, P^* > 0$ exists if and only if $R_0(P) > 1$ and it is unique. It may undergo a Hopf bifurcation.*

The quantity $R_0(P)$ has a simple biological interpretation. Imagine adding a single hypothetical phage to the chemostat at the phage-free equilibrium E_B . Two possibilities can occur, the phage can washout before it can bind and infect a bacterium or it can bind and infect a bacterium. The probability of the latter is $\frac{k\bar{B}}{D+k\bar{B}}$. The probability that the resulting infected cell lyses before exiting the chemostat is $e^{-D\tau}$, and the number of virus progeny in that case is β . Therefore, the expected value of the number of progeny resulting from adding a single phage to the chemostat at equilibrium E_B is $R_0(P)$. It may be called the Phage Reproductive Number or Ratio.

Figure 1 depicts the various behaviors of solutions of (1) with $\beta = 5, 25, 50, 75$. Parameter values are $a = 0.04, m = 0.8, \tau = 0.5, D = 0.2, k = 0.023, S^0 = 1$, and Monod uptake was used. The yield constant has been used to scale variables as described in the introduction. P/b and B are plotted with initial data $S = 1, B = 1, P = 2$. For these parameters $R_0(P) \approx b/10$ so one expects virus elimination when $b < 10$ and virus persistence when $b > 10$. Virus elimination does occur at $b = 5$.

Fig. 1 Solutions of (1) with $\beta = 5, 25, 50, 75$

Both phages and bacteria persist for the other values of b , with solutions apparently converging to the coexistence equilibrium for $b = 25$ and for $b = 50$ although the approach to equilibrium appears to be oscillatory. The solution appears to be asymptotic to a periodic solution for $b = 75$. See Beretta et al. (2002) for a computation of the Hopf bifurcation.

Our interest in the present paper is to study the behavior of the analogous phage-bacteria model in a tubular flow reactor where spatial effects become important. The flow reactor has often figured in ecological modeling (Kung and Baltzis 1992; Ballyk et al. 1998; Smith 1995a, 1995b; Dung and Smith 1996) because it is one of the simplest spatially non-homogeneous environments featuring advection and diffusion. The flow reactor consists of the portion $0 \leq x \leq L$ of a tube with axis of symmetry along the x -axis through which liquid medium flows with constant velocity in the direction of increasing x . The fluid upstream of $x = 0$ brings nutrient at constant concentration into the reactor; unused nutrient and any contents of the reactor are carried out of the reactor at $x = L$ by the flow. We assume that bacteria and virus in the flow reactor undergo random diffusion as well as advecting with the flow. Bacterial chemotaxis is neglected in the current model, although we aim to consider it in the future.

For a flow reactor of length L , with flow velocity v , and diffusion coefficients d_i , $i = 0, 1, 2, 3$ for the constituents, and taking account of the scaling (3), the model

equations take the form:

$$\begin{aligned}
 S_t &= d_0 S_{xx} - v S_x - B f(S) \\
 B_t &= d_1 B_{xx} - v B_x + B f(S) - k B P \\
 I_t &= d_2 I_{xx} - v I_x + k B P - k \int_0^L G(\tau, x, y) B(t - \tau, y) P(t - \tau, y) dy \\
 P_t &= d_3 P_{xx} - v P_x - k B P + k \beta \int_0^L G(\tau, x, y) B(t - \tau, y) P(t - \tau, y) dy
 \end{aligned} \tag{9}$$

with Danckwerts boundary conditions (see Kung and Baltzis 1992; Ballyk et al. 1998):

$$\begin{aligned}
 d_0 S_x(t, 0) - v S(t, 0) &= -v S^0 \\
 d_1 B_x(t, 0) - v B(t, 0) &= 0 \\
 d_2 I_x(t, 0) - v I(t, 0) &= 0 \\
 d_3 P_x(t, 0) - v P(t, 0) &= 0 \\
 M_x(t, L) &= 0, \quad M = S, B, I, P,
 \end{aligned} \tag{10}$$

and where $G(t, x, y)$ is the probability density that an infected bacterium is at position x at time t given that at time $t = 0$ its position was y . It is the Green's function satisfying, as a function of (t, x) ,

$$G_t = d_2 G_{xx} - v G_x, \quad G(0, x, y) = \delta(x - y)$$

with boundary conditions as above for P , but with d_2 in place of d_3 , and where $y \in [0, L]$; δ denotes the Dirac “function”. See Karlin and Taylor (1981), Durrett (1996) for the connection between probability theory and Green's functions. Here, d_2 is the motility coefficient for infected cells, denoted by I , which may differ from uninfected cells denoted by B . The integral term in the P equation

$$k \int_0^L G(\tau, x, y) B(t - \tau, y) P(t - \tau, y) dy$$

gives the amount of infected cells which were infected at time $t - \tau$ at various positions $y \in [0, L]$ but at time t are at x where they lyse.

Initial data must be prescribed:

$$\begin{aligned}
 S(0, x) &= S^*(x) \\
 B(\theta, x) &= B^*(\theta, x), \quad (\theta, x) \in [-\tau, 0] \times [0, L] \\
 P(\theta, x) &= P^*(\theta, x).
 \end{aligned} \tag{11}$$

Later, we will see that initial conditions need only be prescribed at $t = 0$, no past history is required, but this requires a slightly different formulation. Analogous to (4),

infected cell density is given by

$$I(t, x) = \int_0^\tau \int_0^L G(a, x, y) k B(t - a, y) P(t - a, y) dy da, \quad (12)$$

where it is understood that (11) extend functions B and P for negative times. The integral captures all cells infected after time $t - \tau$ but before time t which are still in the reactor at time t .

Equations such as (9), containing non-local terms, were introduced by Marcati and Pozio (1980) in a vector-disease model and by Gourley and Britton (1996) and Thieme and Zhao (2001) for predator-prey models.

A more realistic model, assuming a three dimensional cylindrical reactor with a steady Poiseau flow, as in our previous work (Jones et al. 2002, 2003), could be formulated here as well. However, in order to keep the necessary eigenvalue computations as simple as possible, we restrict ourselves here to the simpler but cruder one-dimensional “thin-tube” approximation.

2 Preliminaries

Given $d > 0$, the eigenvalue problem

$$\begin{aligned} \lambda \phi &= d\phi'' - v\phi' \\ 0 &= d\phi'(0) - v\phi(0) = \phi'(L) \end{aligned} \quad (13)$$

is of critical importance here. The self-adjoint form of the differential equation

$$(de^{-(v/d)x} \phi')' = \lambda e^{-(v/d)x} \phi$$

reveals the weight function $e^{-(v/d)x}$ in the orthogonality relations. Eigenvalues of (13), $\{\lambda_n\}_{n \geq 1}$, ordered from largest to smallest, are negative and $\lambda_n \rightarrow -\infty$. When it is important to specify a value of d , we include it in our notation as $\lambda_n(d)$. Corresponding normalized eigenfunctions are denoted by $\{\phi_n(x)\}$:

$$\int_0^L \phi_n^2(x) e^{-(v/d)x} dx = 1, \quad n \geq 1.$$

Without loss of generality, we can take $\phi_1(x) > 0$, $0 \leq x \leq L$. The corresponding principal eigenvalue can be expressed as

$$\lambda_1 = -\frac{v}{L} \lambda^*(d/Lv), \quad (14)$$

where $\lambda^* : (0, \infty) \rightarrow (1, \infty)$ is strictly decreasing with $\lambda^*(0+) = \infty$ and $\lambda^*(\infty) = 1$. See Ballyk et al. (1998) and Fig. 2.

Fig. 2 Plot of $\lambda^*(d/Lv)$ versus d/Lv

The parabolic initial boundary value problem

$$\begin{aligned} U_t &= dU_{xx} - vU_x, \quad t > 0, \quad 0 \leq x \leq L \\ 0 &= dU_x(t, 0) - vU(t, 0) = U_x(t, L), \quad t > 0 \\ U(0, x) &= U_0(x), \quad 0 \leq x \leq L \end{aligned} \quad (15)$$

has the formal solution

$$U(t, x) = \int_0^L G(t, x, y) U_0(y) dy$$

in terms of the Green's function

$$G(t, x, y) = e^{-(v/d)y} \sum_{n \geq 1} e^{\lambda_n t} \phi_n(x) \phi_n(y). \quad (16)$$

The following result is classical (see Smith 1995a). If $\phi \in C([0, L], \mathbb{R})$, we write $\phi \geq 0$ if $\phi(x) \geq 0$ for all x , $\phi > 0$ if $\phi \geq 0$ and $\phi(x) > 0$ for some x , and $\phi \gg 0$ if $\phi(x) > 0$ for all x . All norms in this paper are supremum norms.

Proposition 2.1 *Define*

$$[T(t)\phi](x) = \int_0^L G(t, x, y) \phi(y) dy, \quad x \in [0, L], \quad t > 0.$$

Then $\{T(t)\}_{t \geq 0}$, with $T(0) = I$ the identity operator, defines a strongly continuous semigroup of bounded linear operators on $C([0, L], \mathbb{R})$. There exists $M > 0$ such that

$$\|T(t)\phi\| \leq M e^{\lambda_1 t} \|\phi\|, \quad t > 0, \quad \phi \in C([0, L], \mathbb{R}), \quad (17)$$

and $T(t)$ is a contraction. That is,

$$\|T(t)U_0\| \leq \|U_0\|, \quad t \geq 0. \quad (18)$$

Moreover, $T(t)$ is a compact operator for each $t > 0$ and it is strongly positive. That is,

$$\phi > 0, t > 0 \Rightarrow T(t)\phi \gg 0. \quad (19)$$

Indeed, $G(t, x, y) > 0$ for $t > 0$, $x, y \in [0, L]$. The unique solution of (15) is given by $U(t, x) = [T(t)U_0](x)$.

The operator $T(t)$ is also an L^1 contraction, which is important for interpreting our results:

$$\int_0^L \int_0^L G(t, x, y) U_0(y) dy dx \leq \int_0^L U_0(x) dx, \quad t \geq 0, U_0 \geq 0. \quad (20)$$

The inequality is strict if $U_0 \gg 0$. Indeed, (20) follows from the calculation

$$\frac{d}{dt} \int_0^L U(t, x) dx = dU_x(t, x) - vU(t, x) \Big|_{x=0}^{x=L} = -vU(t, L) \leq 0,$$

using the boundary conditions (15). Thus (20) and the positivity of G are consistent with our interpretation of $G(t, x, y)$ as the transition density, $\text{Prob}(x_t \in B | x_0 = y) = \int_B G(t, x, y) dx$, for an infected bacteria whose position at time t is the random variable x_t and B is a Borel set. (Here we take $d = d_2$ for our interpretation in terms of infected cell.) For this interpretation to be correct, given an initial density U_0 of newly infected cells, then $U(t, x) = \int_0^L G(t, x, y) U_0(y) dy$ represents those infected cells in the reactor at time t located at x and $\int_0^L U(t, x) dx / \int_0^L U_0 dx$ is the fraction still in the reactor at time t .

In the special case that $U_0 = \phi_1$, the positive principal eigenvector, $U(t, x) = e^{\lambda_1 t} \phi_1(x)$, and hence

$$\frac{\int_0^L \int_0^L G(t, x, y) \phi_1(y) dy dx}{\int_0^L \phi_1(x) dx} = e^{\lambda_1 t}.$$

For this reason, we regard

$$\frac{1}{-\lambda_1(d_2)} = \frac{L}{v} \cdot \frac{1}{\lambda^*} \quad (21)$$

as the mean residence time for infected cells in the reactor. By replacing d_2 by the other diffusion coefficients, we obtain residence times for uninfected cells, nutrient, and virus. It is appropriate here to point out a significant difference between the chemostat system (1) and the flow reactor system (9). Nutrient, bacteria and phages all have the same residence time in the chemostat, namely, $1/D$. This is not the case, however, for (9) because the diffusion coefficients of nutrient, bacteria and phages are different.

3 Main Results

In Smith (2011) it is shown that system (9)–(11) has a unique nonnegative solution defined for all $t \geq 0$ for all nonnegative continuous initial data given by (11). Indeed,

uniform bounds are obtained for solutions depending only on the uniform norm of the initial data; (9)–(11) generate an eventually compact semiflow having a compact global attractor. In this section, we focus on result of biological interest. Proofs of results are relegated to an appendix. Recall that I is determined by (12) so we can and do ignore the I equation in our analysis of (9)–(11).

We begin by reviewing known results for the virus-free system. Then we take up the question of whether the bacteria can survive predation by bacteriophage in the flow reactor. Finally, the more challenging question of persistence and extinction for the phage is addressed.

3.1 The Virus-Free System

The virus-free ($I = P = 0$) sub-model of (9)–(10) is

$$\begin{aligned} S_t &= d_0 S_{xx} - v S_x - Bf(S) \\ B_t &= d_1 B_{xx} - v B_x + Bf(S) \end{aligned} \quad (22)$$

with boundary conditions:

$$\begin{aligned} d_0 S_x(t, 0) - v S(t, 0) &= -v S^0 \\ d_1 B_x(t, 0) - v B(t, 0) &= 0 \\ B_x(L, t) = S_x(L, t) &= 0, \end{aligned} \quad (23)$$

and initial conditions

$$\begin{aligned} S(0, x) &= S^*(x) \\ B(0, x) &= B^*(x). \end{aligned} \quad (24)$$

The equations have been extensively studied (Ballyk et al. 1998; Dung and Smith 1996; Smith 1995a, 1995b). We briefly review the main findings of these works relevant for the current study.

The following result, except for its final assertion, is Theorem 3.1 in Ballyk et al. (1998). The final assertion is contained in Theorem 2.1 in Smith (1995a).

Theorem 3.1 *There is exactly one equilibrium of the form $S = S(x)$, $B = 0$, namely, $S = S^0$. If*

$$R_0(B) \equiv \frac{f(S^0)}{-\lambda_1(d_1)} < 1, \quad (25)$$

then $(S^0, 0)$ is locally asymptotically stable and every solution $(S(t, x), B(t, x))$ satisfies

$$S(t, x) \rightarrow S^0, \quad B(t, x) \rightarrow 0$$

as $t \rightarrow \infty$, uniformly in $x \in [0, L]$.

If

$$R_0(B) > 1, \quad (26)$$

then $(S^0, 0)$ is unstable and there exists $\epsilon > 0$ such that for every solution $(S(t, x), B(t, x))$ with $B^*(x)$ not identically zero, there exists $t_0 > 0$ such that

$$\min_{0 \leq x \leq L} B(t, x) \geq \epsilon, \quad t \geq t_0.$$

Furthermore, there exists a unique equilibrium solution $(\hat{S}(x), \hat{B}(x))$ with $\hat{B}$ not identically zero. $\hat{S}$ satisfies:

$$0 < \hat{S}(x) < S^0, \quad 0 \leq x \leq L, \quad \hat{S}'(x) < 0, \quad 0 \leq x < L \quad (27)$$

and $\hat{B}$ satisfies:

$$0 < \hat{B}(x), \quad 0 \leq x \leq L, \quad \hat{B}'(x) > 0, \quad 0 \leq x < L. \quad (28)$$

Finally, in the special case that $d_0 = d_1$, $(\hat{S}, \hat{B})$ is locally asymptotically stable and it attracts every solution with B^* not identically zero.

Extensive simulations of (22) with $d_0 \neq d_1$, reported in Ballyk et al. (1998), strongly suggest that $(\hat{S}, \hat{B})$ attracts all solutions with $B^*(0)$ not identically zero.

The quantity $R_0(B) = f(S^0)/(-\lambda_1(d_1))$, introduced in Theorem 3.1, like its analog (7) for the chemostat, should be viewed as the basic reproductive number for bacteria in the environment of the washout equilibrium $(S^0, 0)$. As $\frac{1}{-\lambda_1(d_1)}$ represents the residence time of a cell in the reactor and $f(S^0)$ its growth rate, their product is the amount of biomass (or cells) produced by a unit biomass (single cell) while in the reactor.

3.2 Persistence of Bacteria

In view of Theorem 3.1, the following result will not be surprising. The sign of $R_0(B) - 1$ determines the survival of bacteria in the presence of virus; bacteriophage cannot drive the bacteria to extinction.

Theorem 3.2 *If $R_0(B) < 1$, then bacteria and virus are eliminated from the reactor:*

$$S(t, x) \rightarrow S^0, \quad B(t, x), P(t, x) \rightarrow 0$$

uniformly in $x \in [0, L]$.

If $R_0(B) > 1$, then bacteria uniformly persist: $\exists \epsilon > 0$ such that $\forall (S^, B^*, P^*)$*

$$B^*(0, \cdot) > 0 \quad \Rightarrow \quad \exists t_0 > 0, \quad B(t, x) > \epsilon, \quad t > t_0, \quad 0 \leq x \leq L.$$

3.3 Persistence of Virus

Throughout this section, we assume without further mention that $R_0(B) > 1$. Virus cannot persist without bacteria. The equilibrium $S = \hat{S}$, $B = \hat{B}$, $I = P = 0$ is hereafter referred to as the Virus-free equilibrium, or VFE for short. Our immediate focus is on the stability of the VFE. The principle of linearized stability applies, see Theorem 4.1, Chap. 4 (Wu 1996), in the sense that VFE is locally asymptotically stable if the spectrum of its linearization is contained in the open left half-plane.

We consider only the P -component of the variational equation, the part that measures whether “ P can invade”, since it decouples from the other two components:

$$P_t = d_3 P_{xx} - v P_x - k \hat{B} P + k \beta \int_0^L G(\tau, x, y) \hat{B}(y) P(t - \tau, y) dy \quad (29)$$

with boundary conditions as above for P . Assuming that the VFE is locally asymptotically stable, when considered as an equilibrium of the virus-free system (22) (see Theorem 3.1 for sufficient conditions), any part of the spectrum of the variational equation with positive real part is due to the “invasion” part (29).

With the ansatz

$$P = P^0(x) e^{\mu t}$$

we arrive at the eigenvalue problem for μ and P^0 :

$$\mu P^0 = d_3 P_{xx}^0 - v P_x^0 - k \hat{B} P^0 + k \beta e^{-\mu \tau} \int_0^L G(\tau, x, y) \hat{B}(y) P^0(y) dy. \quad (30)$$

Note that P^0 must also satisfy the same boundary conditions as P in (10). By Theorem 2.2 (Thieme and Zhao 2001), the dominant eigenvalue μ is real with corresponding eigenfunction $P^0 \gg 0$. By dominant eigenvalue, we mean that all other eigenvalues have strictly smaller real parts and the sign of μ determines stability of VFE.

Let $\phi_1 \gg 0$ denote the normalized principal eigenfunction of (13) corresponding to $d = d_3$ and $\lambda_1 = \lambda_1(d_3) < 0$ be the largest eigenvalue. In order to avoid unsightly subscripts, in subsequent calculations we set $d = d_3$. We can choose P^0 such that

$$\int_0^L P^0(x) \phi_1(x) e^{-(v/d)x} dx = 1. \quad (31)$$

Multiplying (30) by $\phi_1(x) e^{-(v/d)x}$ and integrating, we have

$$\begin{aligned} \mu &= \int_0^L (d e^{-(v/d)x} P_{xx}^0)_x \phi_1 dx - \int_0^L k \hat{B} P^0 \phi_1 e^{-(v/d)x} dx \\ &\quad + k \beta e^{-\mu \tau} \int_0^L \int_0^L G(\tau, x, y) \hat{B}(y) P^0(y) dy \phi_1(x) e^{-(v/d)x} dx \\ &= \int_0^L (d e^{-(v/d)x} \phi_{1x})_x P^0 dx - \int_0^L k \hat{B} P^0 \phi_1 e^{-(v/d)x} dx \end{aligned}$$

$$\begin{aligned}
& + k\beta e^{-\mu\tau} \int_0^L \int_0^L G(\tau, x, y) \hat{B}(y) P^0(y) dy \phi_1(x) e^{-(v/d)x} dx \\
& = \lambda_1 - \int_0^L k \hat{B} P^0 \phi_1 e^{-(v/d)x} dx \\
& \quad + k\beta e^{-\mu\tau} \int_0^L \int_0^L G(\tau, x, y) \hat{B}(y) P^0(y) dy \phi_1(x) e^{-(v/d)x} dx.
\end{aligned}$$

Regarding the left and right hand side of this equation as functions of μ , a root corresponds to the intersection of their respective graphs. There is precisely one such intersection since the left side is increasing and unbounded whereas the right side is decreasing in μ and bounded. Clearly, the right hand side must be positive at $\mu = 0$ for a positive root to exist. Thus we see that there is exactly one positive root provided

$$\begin{aligned}
& k\beta \int_0^L \int_0^L G(\tau, x, y) \hat{B}(y) P^0(y) dy \phi_1(x) e^{-(v/d)x} dx \\
& > -\lambda_1 + \int_0^L k \hat{B} P^0 \phi_1 e^{-(v/d)x} dx
\end{aligned}$$

and no positive root when the inequality is reversed. This suggests that the basic reproductive number for phage in the environment of the virus-free equilibrium is

$$R_0(P) = \frac{k\beta \int_0^L \int_0^L G(\tau, x, y) \hat{B}(y) P^0(y) dy \phi_1(x; d_3) e^{-(v/d_3)x} dx}{-\lambda_1(d_3) + k \int_0^L \hat{B} P^0 \phi_1(x; d_3) e^{-(v/d_3)x} dx}, \quad (32)$$

where the appropriate value of d is indicated in the arguments of eigenfunctions, eigenvalues, and Green's functions. Formally, phage can invade the VFE if $R_0(P) > 1$ and cannot invade if the reverse holds. We seek a biological interpretation of it, guided by (8).

By virtue of (31), $P^0 \phi_1(x) e^{-(v/d_3)x} dx$ is a probability measure on $[0, L]$ so

$$[\hat{B}] \equiv \int_0^L \hat{B} P^0 \phi_1(x; d_3) e^{-(v/d_3)x} dx \quad (33)$$

represents an average value of $\hat{B}$.

The ratio

$$p(\tau) \equiv \frac{\int_0^L \int_0^L G(\tau, x, y) \hat{B}(y) P^0(y) dy \phi_1(x; d_3) e^{-(v/d_3)x} dx}{\int_0^L \hat{B} P^0 \phi_1(x; d_3) e^{-(v/d_3)x} dx} \quad (34)$$

satisfies $0 < p(\tau) < 1$ by (20). If we consider introducing an infinitesimal amount of virus into the VFE, say, distributed as ϵP^0 in the reactor, where $\epsilon > 0$ is small, then these virus will infect bacteria and $p(\tau)$ represents the fraction of those infected cells which remain in the reactor through the latent period and therefore are there to release progeny virus on lysis. Thus, we may express $R_0(P)$ as

$$R_0(P) = \beta p(\tau) \frac{k[\hat{B}]}{-\lambda_1(d_3) + k[\hat{B}]} . \quad (35)$$

The last fraction represents the probability that a virus introduced into the VFE will attach to a bacterium before being washed out of the reactor. Compare (35) with (8).

As for (8), (35) has a simple interpretation in terms of the expected number of progeny virus resulting from a hypothetical single virus inserted into the bio-reactor at the VFE equilibrium. Factor $\frac{k[\hat{B}]}{-\lambda_1 + k[\hat{B}]}$ is the probability that the virus attaches to a bacterium before it is washed out of the reactor; $p(\tau)$ is the probability that the resulting infected cell lyses before being washed out of the reactor; finally, β is the number of progeny that result on the lysis of the infected cell.

We have established the first assertion of the following result.

Proposition 3.1 *Let $R_0(P)$ be defined by (33)–(35). Then the sign of the principal eigenvalue μ of (30) is the same as the sign of $R_0(P) - 1$. Moreover, $p(\tau)$ satisfies $0 < p(\tau) < 1$ and $\tau \rightarrow p(\tau)$ is strictly decreasing.*

Proof Letting $h(x) = \phi_1(x; d_3)e^{-(v/d_3)x} > 0$, the difference between the numerator, N , and the denominator, D , of (34) can be expressed as

$$\begin{aligned} N - D &= \int_0^L \left(\int_0^L G(\tau, x, y) \hat{B} P^0 dy - \hat{B}(x) P^0(x) \right) h(x) dx \\ &= \int_0^L \left(\int_0^L G(\tau, x, y) \hat{B} P^0 dy - \hat{B}(x) P^0(x) \right) dx h(x_0) < 0, \end{aligned}$$

where we have used the mean value theorem for integrals in the second line (for some $x_0 \in [0, L]$) and (20) to obtain the final inequality. This proves the first assertion since $p(\tau) = (N - D)/D + 1$.

Similarly, if $0 < \tau_1 < \tau_2$ and $U(t, x) = \int_0^L G(t, x, y) \hat{B} P^0 dy$, then by the semi-group property $U(\tau_2, x) = \int_0^L G(s, x, y) U(\tau_1, y) dy$ where $s = \tau_2 - \tau_1$. Hence, by an argument similar to that above,

$$\begin{aligned} \int_0^L U(\tau_2, x) h(x) dx &= \int_0^L \int_0^L G(s, x, y) U(\tau_1, y) dy h(x) dx \\ &< \int_0^L U(\tau_1, x) h(x) dx. \end{aligned} \quad \square$$

The probability $p(\tau)$ can be made more explicit in case that

$$d_2 = d_3 = d.$$

In that case, by orthogonality of the ϕ_n with respect to weight function $e^{-(v/d)x}$, we have

$$\int_0^L G(\tau, x, y) \phi_1(x) e^{-(v/d)x} dx = e^{\lambda_1 \tau} e^{-(v/d)y} \phi_1(y).$$

Hence, the double integral in the numerator of expression of $p(\tau)$ is

$$\begin{aligned} & \int_0^L \int_0^L G(\tau, x, y) \phi_1(x) e^{-(v/d)x} dx \hat{B}(y) P^0(y) dy \\ &= e^{\lambda_1 \tau} \int_0^L e^{-(v/d)y} \phi_1(y) \hat{B}(y) P^0(y) dy. \end{aligned} \quad (36)$$

Therefore,

$$R_0(P) = \beta e^{\lambda_1 \tau} \frac{k[\hat{B}]}{-\lambda_1 + k[\hat{B}]}, \quad d_2 = d_3. \quad (37)$$

As noted in the previous section, extensive simulations of (22) strongly suggest that $(\hat{S}, \hat{B})$ attracts all solutions of (22) starting with some bacteria present. This in turn suggests, but does not prove, that $(\hat{S}, \hat{B})$ may be asymptotically stable in the linear approximation for the virus-free system (22). In this case, due to the above-mentioned decoupling of the variational equation, if $R_0(P) < 1$, then it would follow that VFE $(\hat{S}, \hat{B}, 0)$ is asymptotically stable for (9).

In contrast to the case of the chemostat, where the fact that residence times for nutrient, bacteria, and virus are all equal allows us to show that the virus goes extinct when $R_0(P) < 1$, here we are unable to establish this. One difficulty is obtaining an explicit asymptotic ($t \rightarrow \infty$) bound for $\|B(t, \bullet)\|$; as our system possesses a global attractor of bounded sets, such a bound exists. In a special, unrealistic case, we obtain the following extinction result.

Proposition 3.2 *Assume $d_2 = d_3$ and that $B_{\max} > 0$ satisfies*

$$\limsup_{t \rightarrow \infty} \|B(t, \bullet)\| \leq B_{\max} \quad (38)$$

holds for every solution. If

$$e^{\lambda_1(d_3)\tau} (\beta - 1) \frac{k B_{\max}}{-\lambda_1(d_3)} < 1, \quad (39)$$

then

$$\int_0^L (I(t, x) + P(t, x)) dx \rightarrow 0$$

If $d_0 = d_1$, then $B_{\max} \leq \|\hat{B}\| = \hat{B}(L)$.

It is not hard to see that the left side of (39) is smaller than $R_0(P)$ given in (37) under the hypotheses of Proposition 3.2. Recall that $-1/\lambda_1(d_3)$ is the residence time of virus in the flow reactor. As expected, virus go extinct if their latent period is too large, their burst size too small, their binding constant is too small, their residence time is too short, or their prey density B is too low.

An equilibrium (S_*, B_*, P_*) representing coexistence of bacteria and its phage must satisfy $B_*, P_* > 0$ and

$$\begin{aligned} 0 &= d_0 S_{xx} - v S_x - B f(S) \\ 0 &= d_1 B_{xx} - v B_x + B f(S) - k B P \\ 0 &= d_3 P_{xx} - v P_x - k B P + k \beta \int_0^L G(\tau, x, y) B(y) P(y) dy \end{aligned} \quad (40)$$

together with the boundary conditions.

The next result gives sufficient conditions for persistence of phage and for the existence of a coexistence equilibrium.

Theorem 3.3 *Suppose that $R_0(B) > 1$ and that the virus-free equilibrium is locally stable for the virus-free subsystem (22) and that it attracts all solutions of the virus-free subsystem with initial data (S^*, B^*) satisfying $B^*(\cdot) \neq 0$. If $R_0(P) > 1$ then the virus persists: $\exists \epsilon > 0$ such that $\forall (S^*, B^*, P^*)$ satisfying $B^*(0, \cdot) > 0$ and $B^* P^* > 0$, we have*

$$\exists t_0, \quad P(t, x) > \epsilon, \quad t > t_0, \quad 0 \leq x \leq L.$$

Moreover, there exists a coexistence equilibrium (S_*, B_*, P_*) with $B_*, P_* \gg 0$.

The hypothesis that VFE is locally and globally stable for the virus-free system is a strong one. It is satisfied when $d_0 = d_1$ by Theorem 3.1. If, in addition, VFE is asymptotically stable in the linear approximation, i.e. the principal eigenvalue is negative, for the virus-free subsystem (22), then the hypotheses continue to hold for $d_0 \approx d_1$ by Smith and Waltman (1999). Sufficient conditions for VFE to be asymptotically stable in the linear approximation are given in Theorem 3.2 (Ballyk et al. 1998).

4 Model Reformulation and Choice of Initial Data

The derivation of (9) is similar to that in Thieme and Zhao (2001) for a predator-prey system although we carry it a bit further in order to identify biologically important initial data for the model. The primary reason to focus on the derivation of the model is to seek a reformulation that requires only initial distributions of phages and bacteria but no past history as in (11). Experiments described in Levin et al. (1977), Lenski and Levin (1985) begin with adding phages to bacteria in the reactor such that there are no infected cells initially. This cannot be described by (11). Our reformulation will also facilitate our numerical simulations.

Let $N(t, a, x)$ be the density of infected cells of age a at position x at time t . Since infected cells lyse at age $a = \tau$, $I(t, x) = \int_0^\tau N(t, a, x) da$ and the equation for P is

$$P_t = d_3 P_{xx} - v P_x - k B P + \beta N(t, \tau, x).$$

We must calculate $N(t, \tau, x) : [0, \infty) \times [0, \tau] \times [0, L] \rightarrow [0, \infty)$. It satisfies

$$\begin{aligned} N_t + N_a &= d_2 N_{xx} - v N_x \\ -d_2 N_x(t, a, 0) + v N(t, a, 0) &= 0 = N_x(t, a, L) \\ N(t, a = 0, x) &= k B(t, x) P(t, x) \\ N(0, a, x) &= N^*(a, x), \end{aligned} \quad (41)$$

where $N^*(a, x)$ is the initial density of infected cells.

In order to solve for N we first fix t and a . There are two cases. If $t > a$, set $u(s, x) = N(t - a + s, s, x)$ for $0 \leq s \leq a$ and note that $u_s = N_t + N_a = d_2 u_{xx} - v u_x$ and $u(0, x) = N(t - a, 0, x) = k B(t - a, x) P(t - a, x)$. $u(s, x)$ also satisfies the I boundary conditions. Therefore,

$$u(s, x) = \int_0^L G(s, x, y) k B(t - a, y) P(t - a, y) dy,$$

and setting $s = a$, we find that

$$N(t, a, x) = u(a, x) = \int_0^L G(a, x, y) k B(t - a, y) P(t - a, y) dy, \quad a < t.$$

If $a > t$, let $u(s, x) = N(s, a - t + s, x)$ for $0 \leq s \leq t$. Again, u satisfies the same PDE as before but now $u(0, x) = N^*(a - t, x)$. So

$$u(s, x) = \int_0^L G(s, x, y) N^*(a - t, y) dy,$$

and setting $s = t$, we have

$$N(t, a, x) = \int_0^L G(t, x, y) N^*(a - t, y) dy, \quad a > t.$$

Therefore,

$$N(t, a, x) = \begin{pmatrix} \int_0^L G(a, x, y) k B(t - a, y) P(t - a, y) dy, & t > a \\ \int_0^L G(t, x, y) N^*(a - t, y) dy, & t < a \end{pmatrix}. \quad (42)$$

Putting $a = \tau$ into (42) to obtain $N(t, \tau, x)$, the equation for phage becomes

$$P_t = d_3 P_{xx} - v P_x - k B P + \beta \int_0^L G(t, x, y) N^*(\tau - t, y) dy, \quad 0 \leq t < \tau, \quad (43)$$

and

$$P_t = d_3 P_{xx} - v P_x - k B P + \beta \int_0^L G(\tau, x, y) k B(t - \tau, y) P(t - \tau, y) dy, \quad t > \tau \quad (44)$$

with boundary conditions as usual but the only initial data required are $P(0, \cdot)$.

Although we do not need the equation for $I(t, x)$, we can obtain it by integrating $N(t, a, x)$ from (42) with respect to the age variable. For $0 \leq t < \tau$ we have

$$\begin{aligned} I(t, x) &= \int_0^t N(t, a, x) da + \int_t^\tau N(t, a, x) da \\ &= \int_0^t \int_0^L G(a, x, y) k B(t-a, y) P(t-a, y) dy da \\ &\quad + \int_t^\tau \int_0^L G(t, x, y) N^*(a-t, y) dy da \end{aligned}$$

and for $t \geq \tau$ we have

$$I(t, x) = \int_{t-\tau}^t \int_0^L G(t-a, x, y) k B(a, y) P(a, y) dy da.$$

In summary, we have obtained a more general formulation of the problem than (9)–(11) consisting of the substrate and uninfected cell equations and boundary conditions from the latter but with P determined by (43) and (44) and with initial conditions at $t = 0$ prescribed by

$$\begin{aligned} S(0, x) &= S^*(x) \\ B(0, x) &= B^*(x) \\ N(0, a, x) &= N^*(a, x), \quad 0 \leq a \leq \tau, \quad 0 \leq x \leq L \\ P(0, x) &= P^*(x). \end{aligned} \tag{45}$$

In the special case that

$$N^*(a, x) = \int_0^L G(a, x, y) k B^*(-a, y) P^*(-a, y) dy, \tag{46}$$

where $B^*(\theta, x)$, $P^*(\theta, x)$, $(\theta, x) \in [-\tau, 0] \times [0, L]$ are as in (11), then

$$\begin{aligned} N(t, a, x) &= \int_0^L G(a, x, y) k B(t-a, y) P(t-a, y) dy, \\ (t, a, x) &\in [0, \infty) \times [0, \tau] \times [0, L] \\ I(t, x) &= \int_0^\tau \int_0^L G(a, x, y) k B(t-a, y) P(t-a, y) dy da, \\ (t, x) &\in [0, \infty) \times [0, L], \end{aligned}$$

where it is understood that P and B are extended by (11). In this case, we obtain the original system (9)–(11).

Table 1 Parameter values for the numerical model

Domain	$L = 1$ cm
Grid Resolution	$\Delta x = .01$ cm
Monod Uptake Function	$m = 0.8, a = .04$
Nutrient Diffusion	$d_0 = .025$ cm ² /hr
Uninfected Cell Diffusion	$d_1 = .02$ cm ² /hr
Infected Cell Diffusion	$d_2 = .02$ cm ² /hr
Virus Diffusion	$d_3 = .00012$ cm ² /hr
Latent Period	$\tau = .5$ hr
Phage Adsorption Rate	$k = .023$
Fluid Velocity	$v = .05$ cm/hr
Burst size	$\beta = 10\text{--}150$
Nutrient influx	$S^0 = 1$

4.1 Integration by the Method of Steps

Here we outline an approach to the solution of our model system based on (43) and (44). It is simplest if we assume that the initial conditions involve no infected cells: $N^*(a, x) \equiv 0$ and so $I^*(x) \equiv 0$. Laboratory experiments for the chemostat, reported in Levin et al. (1977), Lenski and Levin (1985), invariably begin by adding phages to a bacterial culture containing no infected cells. We can proceed by the familiar method of steps for delay equations.

For $0 \leq t \leq \tau$, solve

$$\begin{aligned}
 S_t &= d_0 S_{xx} - v S_x - Bf(S) \\
 B_t &= d_1 B_{xx} - v B_x + Bf(S) - kBP \\
 I_t &= d_2 I_{xx} - v I_x + kBP \\
 P_t &= d_3 P_{xx} - v P_x - kBP
 \end{aligned} \tag{47}$$

with appropriate boundary conditions from (10) and with initial data

$$\begin{aligned}
 S(0, x) &= S^*(x) \\
 B(0, x) &= B^*(x) \\
 I(0, x) &= 0 \\
 P(0, x) &= P^*(x).
 \end{aligned} \tag{48}$$

For $\tau \leq t \leq 2\tau$, solve

$$\begin{aligned}
 S_t &= d_0 S_{xx} - v S_x - Bf(S) \\
 B_t &= d_1 B_{xx} - v B_x + Bf(S) - kBP \\
 I_t &= d_2 I_{xx} - v I_x + kBP - N(t, x) \\
 P_t &= d_3 P_{xx} - v P_x - kBP + \beta N(t, x)
 \end{aligned} \tag{49}$$

Fig. 3 Virus-free steady state on the *left*; coexistence steady state for $\beta = 100$ on the *right*

Fig. 4 Average densities vs. time for $\beta = 10$ (*top left*), 50 (*top right*), 100 (*bottom left*), 175 (*bottom right*)

with appropriate boundary conditions from (10) and with initial data at $t = \tau$ taken from the previous step. Equations (49) require the input function $N(t, x) \equiv N(t, \tau, x)$, at least at grid points. If (t, x) is such a grid point, then $N(t, x) = u(\tau, x)$ where $u(s, x)$ is defined for $(s, x) \in [0, \tau] \times [0, L]$ by

$$u_s = d_2 u_{xx} - v u_x, \quad u(0, x) = k B(t - \tau, x) P(t - \tau, x) \quad (50)$$

with boundary conditions as for I in (10). Note that initial data for u are obtained from information obtained in the previous step. The argument $t - \tau$ in the initial data for u argues for a time-step mesh of width τ/N for some large integer N .

For $2\tau \leq t \leq 3\tau$, solve (49) with initial data at $t = 2\tau$ taken from the previous step. Again, the input function $N(t, x) \equiv N(t, \tau, x)$ must be computed from (50), which

Fig. 5 Space–Time dependence of B (top), I (middle), and P (bottom) for $\beta = 175$

requires initial data from the previous step. Continuing in this manner produces the solution.

5 Numerical Simulations

Equations (47)–(49) are discretized using a second-order finite difference scheme with a semi-implicit temporal discretization. To solve for S , B , I , or P on the boundary, the derivative on the boundary is approximated on the boundary using second-

order, one-sided differencing. By setting the discrete derivative to zero (Neumann boundary condition) or to the appropriate flux (Danckwerts boundary condition), (10), the value of S , B , I , or P on the boundary may be estimated. The treatment of the boundary conditions is described in detail in Jones et al. (2002).

Parameter values for the numerical simulations are given in Table 1. The bacteria and phage associated parameters are the same as for the chemostat except for the diffusivities. A diffusion coefficient for phage in the range of $0.5 \times 10^{-7} \text{ cm}^2/\text{sec}$ is taken from Dubin et al. (1970). Using these data, we can estimate the residence time of bacteria and virus in the flow reactor. We estimate $-\lambda_1(d_3/Lv) \approx 100$ and $-\lambda_1(d_2/Lv) \approx 1.45$. This leads to

$$\text{Mean Residence Time of Bacteria} \approx 13.8 \text{ hr.}$$

$$\text{Mean Residence Time of Virus} \approx 0.2 \text{ hr.}$$

The two order of magnitude difference in residence times reflect the two order of magnitude difference in diffusivities.

Figure 3 depicts the profiles of the virus-free equilibrium and the coexistence equilibrium with $\beta = 100$. The former corroborate (27) and (28). Notice that for the latter there are very few phages and infected cells at the upstream end of the reactor whereas phages and infected cell densities are high at the downstream end. The very low phage diffusivity does not allow significant upstream phage density.

Figure 4 can be compared with Fig. 1, at least qualitatively. In both, one sees that for sub-threshold values of β , the virus cannot survive, whereas for moderate but super-threshold values of β , virus attain equilibrium levels, and for still larger β we have first damped and then undamped oscillations.

Figure 5 depicts the space-time plots for uninfected bacteria B , infected bacteria B , and phages P corresponding to $\beta = 175$. Solutions appear to be periodic. Note that faster moving bacteria concentrate near the food at the upstream end of the reactor while sedentary virus are concentrated at the downstream end.

Appendix

Here we give proofs of our main results. We begin by reviewing some key results in Smith (2011). We showed that (9)–(11) generate a semiflow $\Phi : [0, \infty) \times \mathcal{C} \rightarrow \mathcal{C}$, defined by

$$\Phi(t, S^*, B^*, P^*) = (S(t), B_t, P_t),$$

where

$$\begin{aligned} \mathcal{C} = \{ (S^*, B^*, P^*) \in C([0, L], \mathbb{R}) \times C([-\tau, 0] \times [0, L], \mathbb{R}^2) : \\ 0 \leq S^* \leq S^0, 0 \leq B^*, P^* \}, \end{aligned}$$

and where $B_t \in C([-\tau, 0] \times [0, L], \mathbb{R})$ is defined by $B_t(\theta, x) = B(t + \theta, x)$. Note that I is determined by (12) and the other variables. Moreover, Φ has a compact global attractor of bounded sets, see Theorem 3.2 in Smith (2011). A key to this result is

the following. For $i = 0, 1, 2, 3$, let $e_i(x) = e^{-(v/d_i)x}$ and ϕ_{1i} denote the normalized principal eigenvector and λ_{1i} the corresponding principal eigenvalue of (13) with $d = d_i$.

Set

$$\begin{aligned}s(t) &= \int_0^L S(t, x) \phi_{10}(x) e_0(x) dx \\ b(t) &= \int_0^L B(t, x) \phi_{11}(x) e_1(x) dx \\ i(t) &= \int_0^L I(t, x) \phi_{12}(x) e_2(x) dx \\ p(t) &= \int_0^L P(t, x) \phi_{13}(x) e_3(x) dx.\end{aligned}$$

Then s is a measure of the total nutrient in the tube while b, i, p give totals for uninfected, infected cells, and virus, respectively. Multiplying (9) by appropriate $e_i \phi_{1i}$ and integrating gives

$$\begin{aligned}s' &= vS^0 \phi_{10}(0) + \lambda_{10}s - \int_0^L Bf(S) \phi_{10} e_0 dx \\ b' &= \lambda_{11}b + \int_0^L Bf(S) \phi_{11} e_1 dx - k \int_0^L BP \phi_{11} e_1 dx \\ i' &= \lambda_{12}i + k \int_0^L BP \phi_{12} e_2 dx - k \int_0^L \int_0^L GBP dy \phi_{12} e_2 dx \\ p' &= \lambda_{13}p - k \int_0^L BP \phi_{13} e_3 dx + k\beta \int_0^L \int_0^L GBP dy \phi_{13} e_3 dx,\end{aligned}\tag{51}$$

where we have dropped arguments in the last integrals for brevity. In Smith (2011) we showed that there are positive constants c_i , $i = 0, 1, 2, 3$ such that $u(t) = c_0s(t) + c_1b(t) + c_2i(t) + c_3p(t)$ satisfies the differential inequality $u' \leq K - Mu$ for positive constants M, K which can be obtained explicitly. Such an estimate leads to L^1 bounds on solutions. As the details are not needed here, we do not give them. See Smith (2011).

The following result provides sufficient conditions for positivity of B and P .

Proposition 6.1 *If $B^*(0, \cdot) \neq 0$, then $B(t) \gg 0$ for $t > 0$. If $P^*(0, \cdot) \neq 0$, then $P(t) \gg 0$ for $t > 0$. If $B^*P^* \neq 0$, then $P(t) \gg 0$ for $\tau \leq t$.*

Proof If $B^*(0, \cdot) \neq 0$, then $B(t) \gg 0$ for $0 < t < \sigma$ by standard comparison arguments (Pao 1992), taking $P(t)$ as a given continuous coefficient. If $P^*(0, \cdot) \neq 0$, then the assertion that $P(t) \gg 0$ for $t > 0$ can again be argued by the standard parabolic comparison principle on dropping the non-local term. Suppose now that $B^*P^* \neq 0$

and $P^*(0, \cdot) = 0$. P satisfies the linear inhomogeneous parabolic problem

$$\frac{\partial P}{\partial t} = d_3 \frac{\partial^2 P}{\partial x^2} - v \frac{\partial P}{\partial x} - a(t, x)P + f(t, x),$$

where $a(t, x) \equiv B(t, x)$ and $f(t, x) \equiv k\beta \int_0^L G(\tau, x, y)B(t - \tau, y)P(t - \tau, y)dy$, and where B and P are regarded as given nonnegative functions. Clearly, $f(t_0, \cdot) \gg 0$ for some $t_0 \in [0, \tau]$ since $B^*P^* > 0$. Standard comparison arguments imply the desired result. $\square$

Proof of Theorem 3.2 If $R_0(B) < 1$ solutions of the linear parabolic equation

$$b_t = d_1 b_{xx} - vb_x + f(S^0)b$$

with boundary conditions as for B , satisfy $b(t, x) \rightarrow 0$ uniformly in $x \in [0, L]$ because the dominant eigenvalue of the differential operators is negative.

Since $S(t, x) \leq S^0$, $B(t, x)$ satisfies

$$B_t \leq d_1 B_{xx} - vB_x + f(S^0)B.$$

Thus $B(t, x) \leq b(t, x)$, $t \geq t_0$ by the comparison principle, provided $b(0, \cdot) = B(0, \cdot)$. This proves $B(t, x) \rightarrow 0$ uniformly in x .

There exists $\gamma > 0$ such that solutions of the linear parabolic problem

$$p_t = d_3 p_{xx} - vp_x + \gamma p$$

satisfy $p(t, x) \rightarrow 0$ uniformly in x . As $B(t, x) \rightarrow 0$ uniformly in x and $G(\tau, x, y)$ is bounded, it follows that

$$P_t \leq d_3 P_{xx} - vP_x + \gamma P$$

for all large t and so by comparison with an appropriate solution p of the linear parabolic problem, we conclude that $P(t, x) \rightarrow 0$ uniformly in x . A comparison argument can be employed to show that $S(t, x) \rightarrow S^0$, using that $B(t, x) \rightarrow 0$.

Now suppose $R_0(B) > 1$. Our hypothesis $B^*(0, \cdot) > 0$ and the strong maximum principle implies that $B(t, x) > 0$ for $t > 0$ and all x . We employ the now standard acyclicity theorem for weak uniform persistence, see Theorem 7.17 (Smith and Thieme 2010), but first with the persistence functional $\rho : \mathcal{C} \rightarrow [0, \infty)$ given by $\rho(S, B, P) = \|B(0, \cdot)\|$. Consider the semiflow Φ restricted to the positively invariant set

$$\begin{aligned} Z_0 &\equiv \{(S, B, P) \in \mathcal{C} : \rho(\Phi(t, (S, B, P))) = 0, t \geq 0\} \\ &= \{(S, B, P) \in \mathcal{C} : B(0, \cdot) = 0\}. \end{aligned}$$

Without bacteria, $S \rightarrow S^0$ and $P \rightarrow 0$, uniformly in x , as simple comparison arguments show. Therefore, the equilibrium $M = (S^0, 0, 0)$ attracts all solutions in Z_0 . We aim to show that M is uniformly weakly ρ -repelling in the sense that there exists $\epsilon > 0$ such that if $(S^*, B^*, P^*) \in \mathcal{C}$ and $\rho(S^*, B^*, P^*) = \|B^*(0, \cdot)\| > 0$, then

$\limsup_{t \rightarrow \infty} d(\Phi(t, (S^*, B^*, P^*)), M) > \epsilon$, where $d(z, M)$ denotes distance of $z \in \mathcal{C}$ to M . Standard comparison arguments will be used again. As $R_0(B) > 1$, there exists $\delta > 0$ so small that the principal eigenvalue of

$$d_1 \phi'' - v \phi' + f(S^0 - \delta) \phi - \delta \phi = \lambda \phi,$$

with boundary conditions as for B , is positive. Denote by $\lambda_0 > 0$ this eigenvalue and let ϕ_0 be the corresponding positive eigenfunction. Then $e^{\lambda_0 t} \phi_0$ is an exponentially growing solution of the linear parabolic problem

$$b_t = d_1 b_{xx} - v b_x + f(S^0 - \delta) b - \delta b$$

with boundary conditions as for B . If M is not uniformly weakly ρ -repelling, then for arbitrarily small $\epsilon > 0$, there is $(S^*, B^*, P^*) \in \mathcal{C}$ with $\rho(S^*, B^*, P^*) = \|B^*(0, \cdot)\| > 0$ and $\limsup_{t \rightarrow \infty} d(\Phi(t, (S^*, B^*, P^*)), M) \leq \epsilon$. Thus, for some small $\epsilon > 0$, there is such a solution so that for large t , $S(t, \cdot) \geq S^0 - \delta$ and $kP(t, \cdot) < \delta$ so B satisfies

$$B_t \geq d_1 B_{xx} - v B_x + f(S^0 - \delta) B - \delta B$$

for large t , say $t > t_0$. As $B(t, \cdot) \gg 0$, $t > 0$ we find $c > 0$ such that $B(t_0, \cdot) \geq c \phi_0$ so by comparison with the linear parabolic problem we have $B(t, \cdot) \geq c e^{\lambda_0(t-t_0)} \phi_0$ for $t \geq t_0$. This contradicts the existence of a compact attractor. Having established that M is uniformly weakly ρ -repelling, we conclude that Φ is uniformly weakly ρ -persistent by Theorem 7.17 in Smith and Thieme (2010) and it is uniformly (strongly) ρ -persistent by Theorem 4.2 in Smith and Thieme (2010), where attracting compact set B of that result is the global attractor guaranteed by Theorem 3.2 in Smith (2011). In particular, there exists $\epsilon > 0$ such that

$$B^*(0, \cdot) > 0 \quad \Rightarrow \quad \liminf_{t \rightarrow \infty} \max_{x \in [0, L]} B(t, x) > \epsilon. \quad (52)$$

Now we go from “max” to “min” in (52) by employing Theorem 3.21 of Smith and Thieme (2010). In the notation of that result, attracting set $\tilde{C}$ will be the compact attractor and $\tilde{\rho}(S, B, P) = \min_{x \in [0, L]} B(0, \cdot)$, which is continuous on $\mathcal{C}$. It suffices to show that for every $\epsilon > 0$, $\tilde{C}_\epsilon = \{(S, B, P) \in \tilde{C} : \|B(0, \cdot)\| \geq \epsilon\}$ is compact and $\tilde{\rho}$ is positive on the largest invariant subset K of $\tilde{C}_\epsilon$. Compactness of $\tilde{C}_\epsilon$ follows from continuity of ρ . Positivity of $\tilde{\rho}$ at each point of C_ϵ follows from the strong maximum principle since $B(0, \cdot) > 0$ implies $B(0, \cdot) \gg 0$. The result now follows from Theorem 3.21 of Smith and Thieme (2010). $\square$

Proof of Proposition 3.2 If $d_2 = d_3$, then from (51) with $e_2 = e_3$, $\lambda_{12} = \lambda_{13}$, and $\phi_{12} = \phi_{13}$ we see that $v = i + p$ satisfies

$$v' = \lambda_{13} v + k(\beta - 1) \int_0^L \int_0^L G B P \, dy \, \phi_{13} e_3 \, dx.$$

On changing the order of integration in the final integral and using (16), it becomes

$$\int_0^L \int_0^L G B P \, dy \, \phi_{13} e_3 \, dx = e^{\lambda_{13} \tau} \int_0^L B(t - \tau, y) P(t - \tau, y) e_3(y) \phi_{13}(y) \, dy.$$

By our hypothesis, given $\delta > 0$ there exists $t_0 > 0$ such that $B(t, x) \leq B_{\max} + \delta$, $t \geq t_0$. Because $\beta > 1$, we can estimate the integral in the differential inequality as

$$v' \leq \lambda_{13}v + k(\beta - 1)(B_{\max} + \delta)e^{\lambda_{13}\tau}v(t - \tau), \quad t \geq t_0.$$

Hence, $v(t)$ can be compared to a solution $u(t)$ of the corresponding linear delay differential equality with the same initial data at $t = t_0$ by Theorem 3.6 (Smith 2010), that is, $v(t) \leq u(t)$, $t \geq t_0$. The roots of the characteristic equation corresponding to this linear delay differential equation have negative real parts if $\lambda_{13} + k(\beta - 1)(B_{\max} + \delta)e^{\lambda_{13}\tau} < 0$ by exercise 4.9 (Smith 2010). By virtue of (39), this will be the case provided δ is sufficiently small. Thus, $u(t) \rightarrow 0$ and $v(t) \rightarrow 0$ by comparison.

Suppose that $d_0 = d_1 = d$ and let $u = S + B$. Then (u, B) satisfy

$$\begin{aligned} u_t &\leq du_{xx} - vu_x \\ B_t &\leq dB_{xx} - vB_x + Bf(u - B). \end{aligned}$$

By monotonicity of f , the corresponding differential equality is a cooperative system of pdes, so by the comparison principle for weakly coupled parabolic systems, e.g. Theorem 3.4, Chap. 7 (Smith 1995b), $(u, B) \leq (\tilde{u}, \tilde{B})$ where $(\tilde{u}, \tilde{B})$ satisfies the pde equality and the same initial conditions and boundary conditions as (u, B) . As this pde is equivalent to (22) and $d_0 = d_1$, $B(t, x) \rightarrow \hat{B}(t, x)$ uniformly on $[0, L]$ as long as $B(0, x) > 0$ for some x . It follows that $B_{\max} \leq \|\hat{B}\|$. $\square$

Proof of Theorem 3.3 We employ the acyclicity theorem for weak uniform persistence, see Theorem 7.17 (Smith and Thieme 2010), but first with the persistence functional $\rho : \mathcal{C} \rightarrow [0, \infty)$ given by

$$\rho(S, B, P) = \min\{\|B(0, \cdot)\|, \|P(0, \cdot)\|\}.$$

Then ρ is continuous. Consider the semiflow Φ restricted to the closed positively invariant set $Z_0 \equiv \{(S, B, P) \in \mathcal{C} : \rho(\Phi(t, (S, B, P))) = 0, t \geq 0\}$. If $(S, B, P) \in Z_0$ there are two possibilities. Either $B(0, \cdot) = 0$ so $B(t, \cdot) = 0$, $t \geq 0$, which implies that $P(t, \cdot) \rightarrow 0$, or $B(0, \cdot) \neq 0$, which implies by Proposition 6.1 that $B(t, \cdot) \gg 0$, $t > 0$ and therefore that $P(t, \cdot) = 0$, $t \geq 0$. In the former case, $\Phi(t, (S, B, P)) \rightarrow M_0$ where $M_0 = (S^0, 0, 0)$ is the washout equilibrium; in the latter case, $\Phi(t, (S, B, P)) \rightarrow M_1$ where $M_1 = (\hat{S}, \hat{B}, 0)$ by our hypothesis that M_1 attracts all solutions of the virus-free subsystem. Hence, the asymptotic dynamics of Φ on Z_0 is covered by $M = M_0 \cup M_1$. We claim that there are no cycles among the invariant sets M_0 and M_1 contained in Z_0 . Clearly, there is no entire heteroclinic orbit connecting M_1 to M_0 in Z_0 , since this would require $P(t) \equiv 0$ and hence contradict our assumption that M_1 attracts all solutions of the virus-free subsystem. Thus, the only possibility of a cycle would be a non-constant entire orbit homoclinic to M_0 or to M_1 . Any such orbits would be bounded and hence contained in the compact attractor. An entire orbit homoclinic to M_0 in Z_0 must have $B(t) \equiv 0$ and therefore, $P(t) \equiv 0$ as well. So it must be the trivial constant entire orbit M_0 . An entire orbit homoclinic to

M_1 in Z_0 must have $P(t) \equiv 0$. Thus, it is an entire orbit for the virus-free system. But our assumption that M_1 is locally stable for the virus-free subsystem precludes non-constant entire orbits homoclinic to M_1 in Z_0 . This proves the acyclicity of M .

M_0 is an isolated invariant subset of Z_0 by our assumption that $R_0(B) > 1$ and by Theorem 3.1; it is a saddle point in Z_0 . In the notation of Theorem 7.17 (Smith and Thieme 2010), M_0 is uniformly weakly ρ -repelling by our assumption that $R_0(B) > 1$ and by Theorem 3.2.

M_1 is an isolated invariant subset of Z_0 by our local and global stability hypothesis of M_1 relative to the virus-free subsystem. We must show that it is uniformly weakly ρ -repelling. If this were false then for arbitrarily small $\epsilon > 0$ there exists $(S^*, B^*, P^*) \in \mathcal{C}$ with $B^*(0, \cdot) > 0$ and $P^* \gg 0$ such that $\|S(t) - \hat{S}\|, \|B(t) - \hat{B}\|, \|P(t)\| \leq \epsilon$ for all $t \geq 0$. Technically, this requires time-translation of a solution, which we assume has been performed. Consequently, P satisfies

$$P_t \geq d_3 P_{xx} - v P_x - k(\hat{B} + \epsilon)P + \beta k \int_0^L G(\tau, x, y)(\hat{B}(y) - \epsilon)P(t - \tau, y) dy.$$

If ϵ is chosen sufficiently small, then the dominant eigenvalue of

$$\mu P^0 = d_3 P_{xx}^0 - v P_x^0 - k(\hat{B} + \epsilon)P^0 + k\beta e^{-\mu\tau} \int_0^L G(\tau, x, y)(\hat{B}(y) - \epsilon)P^0(y) dy$$

with boundary conditions determined by P , satisfies $\mu > 0$ by our assumption that $R_0(P) > 1$, which implies that the dominant eigenvalue is positive with $\epsilon = 0$. Furthermore, there is a corresponding positive eigenvector $P_0 \gg 0$. Then $\tilde{P} = e^{\mu t} P_0$ is an exponentially growing solution of

$$\tilde{P}_t = d_3 \tilde{P}_{xx} - v \tilde{P}_x - k(\hat{B} + \epsilon)\tilde{P} + \beta k \int_0^L G(\tau, x, y)(\hat{B}(y) - \epsilon)\tilde{P}(t - \tau, y) dy.$$

Since $P^* \gg 0$, we can choose $c > 0$ such that $P^*(\theta, x) \geq c\tilde{P}(\theta, x)$, $(\theta, x) \in [-\tau, 0] \times [0, L]$. Then by comparison, see Proposition 3 in Martin and Smith (1990), we have $P(t) \geq c\tilde{P}(t)$, $t \geq 0$, contradicting that solutions are bounded. This contradiction proves that M_1 is uniformly weakly ρ -repelling. By Theorem 7.17 (Smith and Thieme 2010), Φ is weakly uniformly ρ -persistent and, as Φ has a global attractor, we may conclude that it is (strongly) uniformly ρ -persistent. Since we have shown that B persists in Theorem 3.2, we may conclude that there exists $\epsilon > 0$ such that for every $(S^*, B^*, P^*) \in \mathcal{C}$ with $B^*(0, \cdot) > 0$ and $P^*(0, \cdot) > 0$, we have

$$\liminf_{t \rightarrow \infty} \|P(t)\| \geq \epsilon.$$

In fact, it suffices to assume that $B^*(0, \cdot) > 0$ and $B^*P^* > 0$ by Proposition 6.1. A similar argument as in Theorem 3.2 shows that the maximum norm $\|P(t)\|$ can be replaced by $\min_{0 \leq x \leq L} P(t, x)$.

The proof of existence of a coexistence equilibrium is entirely similar to that in Theorem 2.3 of Thieme and Zhao (2001). $\square$

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