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ON SPREAD OF PHAGE INFECTION OF BACTERIA IN A PETRI DISH*

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Abstract. A reaction diffusion system with time delay is proposed for virus spread on bacteria immobilized on an agar-coated plate. The delay explicitly accounts for a virus latent period of fixed duration. An interval of possible spreading speeds for virus infection is established, and traveling wave solutions are shown to exist. Linear determinacy of spreading speed breaks down for some parameter values.

Key words. virus plaque, virus spread, traveling wave solution, speed of spread, linear determinacy

AMS subject classifications. 92B05, 35C07

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1. Introduction.

When liquid agar containing a very small quantity of virus, together with susceptible host bacteria, is evenly spread on a plate of solid agar, a number of "plaques" are eventually visible, each initiated from a single virus infection of a host cell. This happens as follows: A free virus diffuses in the agar, adsorbs to a bacterial host cell, and injects its DNA into the cell. After a time, called the latent period, during which the protein synthesis machinery of the infected host is diverted to producing and assembling new virus particles, the host cell lyses, releasing the newly made virus progeny. Of course, the progeny viruses repeat the process.

A plaque is a clear, disk-shaped region of lysed cells surrounded by unlysed host cells. It can be observed to spread at a well-characterized speed, typically of the order of less than a millimeter per hour, which, along with its shape and clarity, can serve to identify the virus.

There is a large literature devoted to predicting the speed of spread of these viral plaques. Koch [10] estimated that the speed of spread is proportional to $\sqrt{d/\tau}$, where d is the diffusion constant of a virus particle in agar, and τ is the length of the latent period. Yin and McCaskill [24] constructed a reaction diffusion system modeling the spread of virus and infected host cells, identified the growing plaque with a putative traveling wave solution of this system, and, through formal arguments, obtained various improved approximations for the speed of spread. You and Yin [25] reported numerical simulations supporting the conclusion that traveling wave solutions exist for the system described in [24]. However, the model of Yin and McCaskill assumes that the length of the latent period is exponentially distributed. In fact, the length of the latent period is remarkably constant for given environmental conditions [6]. An exponentially distributed latent period implies that a relatively

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large fraction of cells lyse sooner than average, which should lead to an overestimate of the wave speed. Yin and McCaskill's estimated wave speed exceeds the observed speed by a factor of 20; You and Yin's estimate is five times larger than observed.

Lee and Yin [12] used computer-assisted digital imaging to obtain hourly images of plaque size over a 24 hour period, allowing the determination of average spread speed throughout the period. They found significant transient effects in spreading speed before a constant speed was achieved. The period of observation was long enough for faster growing strains to emerge.

Fort and Méndez [8] claim to account for a time delay for the latent period by deriving a "hyperbolic approximation to the full time-delayed evolution equation." In their derivation, the time interval during which viruses do not move is identified with the latent period. The result is a damped wave equation whose terms may have a mathematical interpretation but are nonintuitive from the biological viewpoint; the latent period appears explicitly, but not in the usual sense, as a delay in the argument of a dependent variable. However, their computed wave speeds can be fit to the observed ones. A later work by Ortega-Cejas et al. [15] based on the model proposed in [8] obtains some approximate but explicit formulas for the wave speed.

Abedon and Culler [1, 2] provide a readable review and synthesis of known results on plaque spread. They note that when several virus strains compete by exploiting a common host, the faster spreading strain is the winner, and therefore the speed of plaque spread can be viewed as a measure of virus fitness.

None of the works cited above gives a mathematical proof of the existence of traveling wave solutions of the models considered.

In this paper, a reaction diffusion system with time delay is proposed for plaque spread. The delay explicitly accounts for a latent period of fixed duration, representing an approximation of a more realistic latent period distribution having a small coefficient of variation about the mean. Employing time delays to account for the phage latent period is standard practice in phage modeling since Campbell [3] and Levin, Stewart, and Chao [13]. It is also a common assumption for the within-host parasite maturation period in other host-parasite systems [7].

We show the existence of an interval, $c^* < c < c^0$, of potential spreading speeds, c, for solutions of our model system on the infinite spatial domain for the idealized case where the initial bacterial density is spatially uniform and the initial virus density is nonzero on a nonempty bounded set. The meaning of this result is as follows. If $0 < c < c^*$, then $\sup_{|x|\leq ct} B(t,x) \to 0$ as $t \to \infty$, where $B(t,x)$ denotes bacterial density at position x and time t. On the other hand, if $c > c^0$, then $\sup_{|x|\geq ct} |B(t,x) - B_0| \to 0$ as $t \to \infty$, where $B(0,x) = B_0$. Intuitively, if we start at the origin at $t = 0$ and move with speed $c < c^*$ in any direction, then eventually we will find no bacteria because it has been lysed by virus; however, if we travel at speed $c > c^0$, we find that the bacteria is unperturbed from its initial density. A somewhat less transparent spreading result is given for the virus density $V(t,x)$. In fact, the key to all of the results in this paper is that the quantity $u(t,x) = \int_0^t V(s,x)ds$, which can be viewed as the accumulated exposure to virus of a bacterium located at position x, satisfies a scalar reaction diffusion equation with time delay. This fact allows us to make use of the theory developed by Thieme [18, 19] and Thieme and Zhao [21] on asymptotic speed of spread for certain integral equations. We show that $\inf_{|x|\leq ct} u(t,x) \to \infty$ as $t \to \infty$ if $c < c^*$, and $\sup_{|x|\geq ct} u(t,x) \to 0$ as $t \to \infty$ if $c > c^0$. We conjecture that there is a positive constant, namely $V_\infty = (\beta - 1)B_0$, such that for $c < c^*$, $\sup_{|x|\leq ct} |V(t,x) - V_\infty| \to 0$ as $t \to \infty$, and for $c > c^0$, $\sup_{|x|\geq ct} V(t,x) \to 0$ as $t \to \infty$, where $\beta > 1$ is the burst size, described below. Our results for u are consistent with this conjecture. If a certain technical condition holds, it is shown that $c^* = c^0$; in this case, c^* is the asymptotic spreading speed for our system.

The speed c^* is determined by the usual linearization about the virus-free state $B = B_0$, $V = 0$. A characteristic equation couples the speed c and a wave "shape parameter" λ, and c^* corresponds to a double root λ^* of this equation, which also depends on model parameters. Our numerical simulations show that solutions spread with speed close to c^* for some, but not all, parameter values. In particular, as a suitably scaled virus adsorption constant increases, c^* increases to a maximum and then decreases. Simulations show that solutions spread with speed near c^* as long as the adsorption constant is less than the critical value corresponding to the maximum of c^*; for values of the adsorption constant exceeding the critical value, as c^* decreases, numerically computed solutions spread faster than c^* but slower than c^0, reflecting a failure of linear determinacy of the spreading speed (cf. [14, 23] and the references therein).

We show the existence of traveling wave solutions of our model system in one space dimension for any wave speed exceeding c^0. As above, if a certain technical condition holds, then traveling wave solutions exist for $c > c^*$. The traveling wave profile for virus connects the virus-free state to $V_0 = (\beta-1)B_0$; the profile for bacteria connects the virus-free value B_0 to zero.

In summary, to the best of our knowledge, our results provide the first mathematically rigorous results concerning the asymptotic speed of spread of virus plaques.

2. The model. Following Yin and McCaskill [24] and You and Yin [25], we assume that host bacteria in agar do not grow or diffuse and that virus particles do not decay. However, we replace their assumption of an exponentially distributed latent period for the virus by the assumption that the latent period is exactly τ units of time: a host cell infected at time t lyses at time $t+\tau$. As in [24, 25], we assume that on average $\beta > 0$ viruses are released when an infected host cell lyses; β is called the "burst size" or "yield." Viruses diffuse and adsorb to host bacteria, creating infected cells.

Let virus density be denoted by V, let virus-susceptible bacteria density be denoted by B, and let infected bacteria density be denoted by I. Our model is essentially captured by the schematic

$$B + V \xrightarrow{k} I \rightarrow \beta V,$$

where a cell remains in the infected I-compartment exactly τ units of time and k is the virus adsorption rate.

Imagine that at $t = 0$ the initial density of infected cells is $I^0(s, x)$, where $s \in [0, \tau]$ denotes age-of-infection. Roughly, $I^0(s, x)$ denotes the number of cells at position x at time $t = 0$ that were infected s units of time in the past. More precisely,

$$\int_{[a,b]} \int_A I^0(s, x) dx ds$$

gives the number of cells located at position $x \in A$ and having infection-age $s \in [a, b]$.

Then, over the first latent period, new viruses can be produced only by the lysing of the initial cohort I^0 of infected cells:

$$
\begin{aligned}
V_t &= d\Delta V - kBV + \beta I^0(\tau - t, x),\\
B_t &= -kBV, \qquad x \in D,\ 0 \le t \le \tau,\\
I_t &= kBV - I^0(\tau - t, x).
\end{aligned} \tag{2.1}
$$

An infected cell from the initial cohort must have infection-age $\tau - t$ at time $t = 0$ in order to be of infection-age τ, and hence lyse, at time t.

After the first latent period, the initial cohort of infected cells have all lysed, so a new virus is produced by infections created after $t = 0$:

$$
\begin{aligned}
V_t &= d\Delta V - kB(t,x)V(t,x) + \beta kB(t-\tau,x)V(t-\tau,x),\\
B_t &= -kB(t,x)V(t,x), \qquad x \in D,\ t > \tau,\\
I_t &= kB(t,x)V(t,x) - kB(t-\tau,x)V(t-\tau,x).
\end{aligned} \tag{2.2}
$$

In (2.1) and (2.2), k is the adsorption constant and d is the effective diffusion constant for phage. Note that virus adsorption to already infected cells is neglected. D denotes the domain, which, typically in applications, is a disk in the plane $\mathbb{R}^2$. However, we may also consider D as the entire plane or the real line. The Laplacian is $\Delta V = \sum_i V_{x_i x_i}$. Here and above, a subscripted variable denotes partial derivative with respect to that variable.

The infected cells can be obtained directly by an integration; they do not affect the dynamics of the virus and uninfected cells:

$$
\begin{aligned}
I(t,x) &= \int_0^t kB(\nu,x)V(\nu,x)d\nu + \int_0^{\tau-t} I^0(s,x)ds\\
&= B(0,x) - B(t,x) + \int_0^{\tau-t} I^0(s,x)ds, \quad 0 < t \le \tau,\\
I(t,x) &= \int_{t-\tau}^t kB(\nu,x)V(\nu,x)d\nu = B(t-\tau,x) - B(t,x), \qquad t > \tau.
\end{aligned} \tag{2.3}
$$

Initial data for V and B at $t = 0$ must be prescribed, as well as boundary conditions for V (e.g., no flux condition). As our primary interest is in the spread of a single plaque, we assume that D is the entire plane or real line. Initial data appropriate for a spreading plaque in an initially homogeneous "lawn" of bacteria might contain no infected cells, e.g.,

$$B(0,x) = B^0 > 0, \quad V(0,x) = V^0\delta(x), \quad I^0 = 0,$$

where δ is the Dirac delta distribution concentrated at $x = 0$, an idealized version of placing a single virion at $x = 0$. Alternatively, we might preadsorb the virus to bacteria,

$$B(0,x) = B^0 > 0, \quad V(0,x) = 0, \quad I^0(s,x) = \iota^0\delta(s)\delta(x),$$

where $\iota^0 > 0$. This represents an idealized version of placing a single newly infected host at $x = 0$. In either case, these initial data should induce an outward traveling wave of virus infection. However, for mathematical simplicity, we restrict our attention to smoother initial data, as noted below.

Solutions of our system exist, and are unique and nonnegative, globally in time. The following result is stated for $D = \mathbb{R}^n$, but a parallel result holds for a bounded domain D with Neumann boundary conditions.

THEOREM 2.1. *Let $B(0,\cdot)$ and $V(0,\cdot)$ be nonnegative, bounded, and continuous on $\mathbb{R}^n$. Assume that I^0 is bounded and continuous on $[0,\tau]\times\mathbb{R}^n$, has compact support, is continuously differentiable with respect to t, and is twice continuously differentiable in x.*

Then there exists a unique nonnegative solution (V,B) satisfying (2.1) on $(0,\tau]\times\mathbb{R}^n$ and (2.2) on $(\tau,\infty)\times\mathbb{R}^n$. (V,B) is bounded on $[0,T]\times\mathbb{R}^n$ for each $T>0$.

Proof. We proceed by the method of steps to obtain a solution on $[j\tau,(j+1)\tau]$ for $j\geq 0$. Notice that on each such interval, the equation for V takes the form

$$V_t = d\triangle V - kBV + f_j(t,x),$$

where $f_j(t,x)$ is already known. For example, $f_0(t,x) = \beta I^0(\tau - t, x)$ and $f_j(t,x) = \beta k B(t-\tau,x)V(t-\tau,x)$, $j\geq 1$. In fact, we will show that f_j and B are nonnegative, bounded, and continuous on $Q_j \equiv [j\tau,(j+1)\tau]\times\mathbb{R}^n$. Assuming that $B(t,x)\geq 0$ on Q_j, it follows that V satisfies the differential inequality

$$V_t \leq d\triangle V + F_j, \quad (t,x)\in Q_j,$$

where $F_j = \sup_{(t,x)\in Q_j} f_j(t,x)$. This leads to an a priori bound for (V,B). Assuming (V,B) exists and is nonnegative and bounded on $[0,j\tau]\times\mathbb{R}^n$, then

$$0\leq V(t,x)\leq v_j(t,x) + F_j(t-j\tau), \quad 0\leq B(t,x)\leq B_0(x), \quad (t,x)\in Q_j,$$

where $v_j(t,x)$ satisfies $u_t = d\triangle u$, $t\geq j\tau$, $u(j\tau,x) = V(j\tau,x)$. These a priori bounds suffice to show that local solutions, obtained by the contraction mapping theorem (see below) on subintervals of $[j\tau,(j+1)\tau]$, cover the entire interval.

Consider the first latent period interval $[0,\tau]$. Let $\Phi_\alpha(t,x)$ denote the fundamental solution of $u_t = d\triangle u - \alpha u$ [9, Chap. V]. Then $V(t,x)$ satisfies the integral equation

$$\begin{aligned} V(t,x) &= \int_{\mathbb{R}^n}\Phi_\alpha(t,x-y)V(0,y)dy + \int_0^t\int_{\mathbb{R}^n}\Phi_\alpha(t-s,x-y)\beta I^0(\tau-s,y)dyds \\ &\quad + \int_0^t\int_{\mathbb{R}^n}\Phi_\alpha(t-s,x-y)(\alpha - kB(s,y))V(s,y)dyds \\ &= v^0(t,x) + \int_0^t\int_{\mathbb{R}^n}\Phi_\alpha(t-s,x-y)(\alpha - kB(s,y))V(s,y)dyds, \end{aligned}$$

where $\alpha > k\|B_0\|_\infty$ and where $B(t,x)$ satisfies

$$B(t,x) = B_0(x)e^{-k\int_0^t V(s,x)ds}. \tag{2.4}$$

Note that the hypotheses on I^0 are sufficient for the second integral term in the expression for V to be a classical solution if $u_t = d\triangle u - \alpha u + \beta I^0(\tau - t, x)$ for $0 < t \leq \tau$.

This suggests the following fixed point problem. Given $0<\sigma\leq\tau$ and a function $V:[0,\sigma]\times\mathbb{R}^n\to\mathbb{R}$ satisfying $0\leq V(t,x)\leq 2M$, where $M = \sup_{Q_0} v_0 + F_0\tau$, define $B(t,x)$ as in (2.4) and $S(V):[0,\sigma]\times\mathbb{R}^n\to\mathbb{R}$ by the right-hand side of the integral equation for V above. Then $S(V)$ is nonnegative, bounded, and continuous and satisfies $S(V)\leq M + 2M(1-e^{-\alpha\sigma})\leq 2M$ (note that $v^0(t,x)\leq M$) if σ is small enough. It is easy to see that S is a contraction mapping on the set of continuous functions on $[0,\sigma]\times\mathbb{R}^n$ with range in $[0,2M]$ if σ is chosen small enough. We find that $\|S(V_1)-S(V_2)\|_\infty \le \kappa\|V_1-V_2\|_\infty$, where $\kappa=(1-e^{-\alpha\sigma})\left(\alpha+k\|B_0\|_\infty+2Mk^2\|B_0\|_\infty\sigma\right)$. Therefore, S has a unique fixed point $S(V)=V$, and (V,B) satisfies (2.1) for $0<t\le\sigma$ where B is given by (2.4). This solution satisfies the a priori estimates above so we may extend the solution by a finite number of steps until we have a solution on Q_0. This argument may be repeated to extend the solution to Q_j by an induction argument. ∎

3. Reduction to a single diffusion equation. We proceed as in [4, 5, 17] for epidemic models in the late 1970s to reduce the system (2.1)–(2.2) to a single scalar equation (see also [16] and [20, Chap. 20]). Define

$$u(t,x)=\int_0^t V(s,x)ds=(\ln B_0(x)-\ln B(t,x))/k. \tag{3.1}$$

The last equality follows from the differential equation for B in (2.2). Now, solve for B to get

$$B(t,x)=B_0(x)e^{-ku(t,x)}. \tag{3.2}$$

In view of (3.2), $u(t,x)$ can be viewed as the accumulated exposure to viruses of a bacterium located at position x.

We substitute the differential equation for B into the first two equations in (2.1)–(2.2),

$$\begin{aligned} V_t &= d\Delta V + B_t - \beta B_t(t-\tau,x), && t>\tau,\\ V_t &= d\Delta V + B_t + \beta I^0(\tau-t,x), && 0<t<\tau. \end{aligned}$$

Now, integrate from τ to $t\ge\tau$ and from 0 to $t\le\tau$, respectively,

$$\begin{aligned} V(t,x)-V(\tau,x) &= d\Delta(u(t,x)-u(\tau,x)) + B(t,x) - B(\tau,x)\\ &\quad + \beta[B_0(x)-B(t-\tau,x)], \qquad t>\tau,\\ V(t,x)-V(0,x) &= d\Delta u(t,x) + B(t,x) - B_0(x)\\ &\quad + \beta\int_0^t I^0(\tau-s,x)ds, \qquad 0\le t\le\tau. \end{aligned}$$

Add the second equation, with $t=\tau$, to the first, and use $V=u_t$ and (3.2) to obtain

$$\begin{aligned} u_t(t,x) &= d\Delta u(t,x) + \hat{V}_0(t,x) - \mu(x)f(u(t,x))\\ &\quad + \nu(x)f(u(t-\tau,x)), \qquad t>0,\\ u(t,x) &= 0, \qquad t\le 0, \end{aligned} \tag{3.3}$$

with

$$\mu(x)=B_0(x)k, \qquad \nu(x)=\beta\mu(x), \tag{3.4}$$

and

$$\hat{V}_0(t,x)=V_0(x)+\beta\int_0^{\min\{\tau,t\}} I^0(\tau-s,x)ds, \tag{3.5}$$

and

$$f(u)=\frac{1-e^{-ku}}{k}. \tag{3.6}$$

Notice that the delay term in (3.3) is absent during the initial latent period $0 < t < \tau$ because $u = 0$ for $t < 0$.

Also note that

$$f(0) = 0, \qquad f'(0) = 1. \tag{3.7}$$

It is possible to rewrite this with a monotone increasing nonlinearity. Notice that

$$\begin{aligned} -f(u) &= -u + g(u), \\ g(u) &= u - f(u). \end{aligned} \tag{3.8}$$

$g(u)$ is an increasing function of u. Unfortunately, it is not dominated by its derivative at 0, $g'(0) = 0$.

Notice that, via (3.2), all results for u, the cumulative phage density, can be rephrased in terms of the density of susceptible bacteria.

Finally, we note that $u(t, x)$ grows at most linearly with t.

LEMMA 3.1. *Let D be a smooth bounded domain with Neumann boundary conditions or $D = \mathbb{R}^n$, and let V_0, B_0 be continuous, nonnegative, and bounded. Then there exists $M > 0$ such that*

$$0 \le u(t, x) \le Mt, \quad t \ge 0, \quad x \in D.$$

Proof. By Theorem 2.1, $u \ge 0$ is a classical solution of (3.3) for $t > 0$, and it is bounded on $[0, T] \times \mathbb{R}^n$ for each $T > 0$. If $M \ge 0$ is sufficiently large, then $w = u - Mt$ satisfies $w_t - \Delta w \le 0$ for $t \ge 0$, $x \in D$ because B_0, V_0, and f are bounded, and $w(0, x) = 0$, $x \in D$. Therefore, $w \le 0$ by the comparison principle; see, e.g., [11, Theorem 8.1.4]. ∎

As a consequence of Lemma 3.1, the time-average of V, $\frac{1}{t}\int_0^t V(s, x)ds$ is uniformly bounded, as expected, if $V(t, x)$ asymptotically approaches a constant value.

4. Spreading speeds. We assume that $B_0(x) = B_0$ is constant and positive on the domain $\mathbb{R}^n$. By a comparison argument, $u(t, x) \ge v(t, x)$, where

$$\begin{aligned} v_t(t, x) &= d\Delta v(t, x) + \hat{V}_0(t, x) - \mu v(t, x) + \nu f(v(t - \tau, x)), \\ &\qquad t > 0, \\ v(t, x) &= 0, \qquad t \le 0, \end{aligned} \tag{4.1}$$

with

$$\nu = \beta\mu. \tag{4.2}$$

Let $\Gamma(t, x)$ be the fundamental solution of $\partial_t - d\Delta$ [9, Chap. V]. Then

$$v(t, x) = v_0(t, x) + \int_0^t \int_{\mathbb{R}^n} e^{-\mu s}\Gamma(s, y)\nu f(v(t - s - \tau, x - y))dsdy \tag{4.3}$$

with

$$v_0(t, x) = \int_0^t \int_{\mathbb{R}^n} e^{-\mu s}\Gamma(s, y)\hat{V}_0(t - s, x - y)dyds. \tag{4.4}$$

After a substitution,

$$v(t, x) = v_0(t, x) + \int_0^t \int_{\mathbb{R}^n} G(s, y)\nu f(v(t - s, x - y))dsdy \tag{4.5}$$

with

$$G(s,y) = \begin{cases} e^{\mu(\tau-s)}\Gamma(s-\tau,y), & s>\tau, \\ 0, & 0\le s\le\tau. \end{cases} \tag{4.6}$$

The spreading speed (aka asymptotic speed of spread) for this equation, c^*, equals the minimum wave speed and equals

$$c^* = \inf\{c\ge 0; \exists\lambda>0 : \mathcal{G}(c,\lambda)<1\}, \tag{4.7}$$

where

$$\mathcal{G}(c,\lambda) = \int_0^\infty \int_{\mathbb{R}^n} e^{-\lambda(cs+y_1)}\nu G(s,y)dyds. \tag{4.8}$$

See [18] and [21, sect. 2]. By (4.6),

$$\begin{aligned} \mathcal{G}(c,\lambda) &= \nu\int_\tau^\infty \int_{\mathbb{R}^n} e^{-\lambda(cs+y_1)}e^{\mu(\tau-s)}\Gamma(s-\tau,y)dyds \\ &= \nu\int_0^\infty \int_{\mathbb{R}^n} e^{-\lambda(c[s+\tau]+y_1)}e^{-\mu s}\Gamma(s,y)dyds \\ &= \nu e^{-\lambda c\tau}\int_0^\infty e^{-[\lambda c+\mu]s}ds \int_{\mathbb{R}^n} e^{-\lambda y_1}\Gamma(s,y)dy. \end{aligned}$$

Set

$$\psi(s) = \int_{\mathbb{R}^n} e^{-\lambda y_1}\Gamma(s,y)dy.$$

Then $\psi(0+)=1$ and

$$\psi'(s) = \int_{\mathbb{R}^n} e^{-\lambda y_1} d\Delta_y\Gamma(s,y)dy = d\lambda^2\psi(s).$$

Hence $\psi(s)=e^{d\lambda^2 s}$. We substitute this into the formula for $\mathcal{G}$ and obtain

$$\mathcal{G}(c,\lambda) = \frac{\nu e^{-\lambda c\tau}}{\lambda c+\mu-d\lambda^2}, \qquad 0\le\lambda<\lambda^\sharp(c), \tag{4.9}$$

where $\lambda^\sharp(c)$ is the unique $\lambda>0$ with $\lambda c+\mu-d\lambda^2=0$. By [18] (see also [21, Prop. 2.3]), the spreading speed for (4.1), c^*, is determined by the unique solution (c^*,λ^*) of

$$\mathcal{G}(c,\lambda)=1, \qquad \frac{d}{d\lambda}\mathcal{G}(c,\lambda)=0. \tag{4.10}$$

Note that (c^*,λ^*) exists if and only if $\beta>1$.

This means (c^*,λ^*) is the unique solution of

$$\nu e^{-\lambda c\tau} = \lambda c+\mu-d\lambda^2, \qquad -c\tau(\lambda c+\mu-d\lambda^2)-c+2d\lambda=0. \tag{4.11}$$

The next result follows from Theorem 2.8 in [18] and Theorem 2.2 in [21]. The existence of a solution v of (4.1) for all $t\ge 0$, which is bounded on $[0,T]\times\mathbb{R}^n$ for each $T>0$, follows as a special case from general existence results for integral equations established in [18].

PROPOSITION 4.1. *Let $\beta > 1$, i.e., $\mu < \nu$, and $c^* > 0$ be the unique solution of (4.11). Further let v^* be the unique positive solution of $v^* = \frac{\nu}{\mu} f(v^*)$. Then, for every $c \in (0, c^*)$,*

$$\liminf_{t\to\infty} \inf_{|x|\le ct} v(t,x) \ge v^*$$

for all solutions v of (4.1), where $\hat{V}_0(\tau, x)$ is Borel measurable, nonnegative, and not zero almost everywhere (a.e.).

Since $u(t,x) \ge v(t,x)$, we will prove the following result.

THEOREM 4.2. *Let $\beta > 1$ and $c^* > 0$ be the unique solution of (4.11). Then, for every $c \in (0, c^*)$,*

$$\inf_{|x|\le ct} u(t,x) \to \infty, \qquad t \to \infty,$$

for all solutions u of (3.3), where $\hat{V}_0(\tau, x)$ is measurable, nonnegative, and not zero a.e.

Proof. Recall that (3.3) can be rewritten as

$$\begin{aligned} u_t(t,x) &= d\Delta u(t,x) + \hat{V}_0(t,x) - \mu u(t,x) + \mu g(u(t,x)) + \nu f(u(t-\tau,x)), \\ &\qquad t > 0, \\ u(t,x) &= 0, \qquad t \le 0, \end{aligned}$$

where both f and g are increasing functions. Equivalently, with v_0 from (4.4),

$$\begin{aligned} u(t,x) = v_0(t,x) &+ \int_0^t \int_{\mathbb{R}^n} e^{-\mu s}\Gamma(s,y)\mu g(u(t-s,x-y))dyds \\ &+ \int_0^t \int_{\mathbb{R}^n} e^{-\mu s}\Gamma(s,y)\nu f(u(t-s-\tau,x-y))dyds. \end{aligned} \tag{4.12}$$

We proceed as in [19, sect. 3.9] and [21, Thm. 2.4]. Define

$$u_\infty(c) = \liminf_{t\to\infty} \inf_{|x|\le ct} u(t,x) = \lim_{t\to\infty} \inf\{u(s,x);\ s \ge t, |x| \le cs\}.$$

Notice that $u_\infty(c) \in [0,\infty]$ and is decreasing as a function of c. Let $c < c^*$, and assume that $u_\infty(c) < \infty$. Let $c < \gamma < \theta < c^*$. Choose a sequence $t_j \to \infty$ and $(x_j) \in \mathbb{R}^n$ such that $u(t_j, x_j) \to u_\infty(\gamma) \le u_\infty(c) < \infty$. By Fatou's lemma,

$$\begin{aligned} u_\infty(\gamma) \ge &\int_0^\infty \int_{\mathbb{R}^n} \mu e^{-\mu s}\Gamma(s,y) \liminf_{j\to\infty} g(u(t_j - s, x_j - y))dyds \\ &+ \int_0^\infty \int_{\mathbb{R}^n} e^{-\mu s}\Gamma(s,y)\nu \liminf_{j\to\infty} f(u(t_j - s - \tau, x_j - y))dyds. \end{aligned}$$

Since f and g are increasing and continuous,

$$\begin{aligned} u_\infty(\gamma) \ge &\int_0^\infty \int_{\mathbb{R}^n} \mu e^{-\mu s}\Gamma(s,y)\ g\Big(\liminf_{j\to\infty} u(t_j - s, x_j - y)\Big)dyds \\ &+ \int_0^\infty \int_{\mathbb{R}^n} e^{-\mu s}\Gamma(s,y)\nu\ f\Big(\liminf_{j\to\infty} u(t_j - s - \tau, x_j - y)\Big)dyds. \end{aligned}$$

For all $s \ge 0$ and $y \in \mathbb{R}^n$, since $|x_j| \le \gamma t_j$ and $\gamma < \theta$,

$$\liminf_{j\to\infty} u(t_j - s - \tau, x_j - y) \ge u_\infty(\theta),$$

and so, since g and f are increasing,

$$\begin{aligned} u_\infty(\gamma) &\ge \int_0^\infty \int_{\mathbb{R}^n} \mu e^{-\mu s}\Gamma(s,y) g(u_\infty(\theta)) dy ds \\ &\quad + \int_0^\infty \int_{\mathbb{R}^n} e^{-\mu s}\Gamma(s,y)\nu f(u_\infty(\theta)) dy ds \\ &= g(u_\infty(\theta)) + \frac{\nu}{\mu} f(u_\infty(\theta)) = u_\infty(\theta) + \frac{\nu-\mu}{\mu} f(u_\infty(\theta)). \end{aligned}$$

By Proposition 4.1, since $u(t,x) \ge v(t,x)$, we have $u_\infty(\theta) \ge v^* > 0$, and thus

$$u_\infty(\gamma) \ge u_\infty(\theta) + \frac{\nu-\mu}{\mu} f(v^*).$$

For $0 < c < \tilde{c} < c^*$ define $u_* = \inf_{c<\gamma<\tilde{c}} u_\infty(\gamma)$. Then $u_* < u_\infty(c) < \infty$ and

$$u_* \ge u_* + \frac{\nu-\mu}{\mu} f(v^*),$$

a contradiction. ∎

THEOREM 4.3. *Let $c^* > 0$ and $\lambda^* > 0$ be the unique solution of* (4.11) *and*

$$\beta e^{-2\lambda^* c^* \tau} \ge 1. \tag{4.13}$$

Then c^* is the spreading speed; i.e., in addition to the result of Theorem 4.2 *we have for any $c > c^*$ that*

$$\limsup_{t\to\infty} \sup_{|x|\ge ct} u(t,x) = 0$$

for all solutions of (3.3), *where $\hat{V}_0(\tau,x) \le \eta e^{-\lambda^*|x|}$ for all $x \in \mathbb{R}^n$ with some constant $\eta > 0$.*

Proof. We look for a supersolution of

$$\begin{aligned} u_t(t,x) = d\Delta u(t,x) + \hat{V}_0(t,x) - \mu f(u(t,x)) + \nu f(u(t-\tau,x)), \\ t > 0,\ x \in \mathbb{R}^n, \end{aligned} \tag{4.14}$$

in the form

$$u(t,x) = \eta e^{\lambda(ct + x\cdot z)} = w(t,x), \tag{4.15}$$

where $z \in \mathbb{R}^n$, $|z| = 1$.

Let $c > c^*$, with c^* being the spreading speed, and let λ^* be the unique number determined by (4.11). Choose $\lambda = \frac{\lambda^* c^*}{c}$. Then $\lambda c = \lambda^* c^*$ and $\lambda < \lambda^*$. Thus $\beta e^{-2\lambda c\tau} \ge 1$, i.e., $\nu e^{-2\lambda c \tau} \ge \mu$, and

$$\nu e^{-\lambda c\tau} < \lambda c + \mu - d\lambda^2. \tag{4.16}$$

Since $w(t-\tau,x) = e^{-\lambda c\tau} w(t,x)$,

$$\begin{aligned}(4.17)\qquad &-\partial_t w(t,x) + d\Delta w(t,x) + \hat{V}_0(t,x) - \mu f(w(t,x)) + \nu f(w(t-\tau,x)) \\ &= (-\lambda c + d\lambda^2 |z|^2) w(t,x) + \hat{V}_0(t,x) + h(w(t,x))\end{aligned}$$

with

$$(4.18)\qquad h(w) = \nu f(e^{-\lambda c\tau} w) - \mu f(w).$$

By Taylor's formula, since $f(0) = h(0) = 0$,

$$h(w) = h'(0)w + \frac{1}{2} h''(\tilde{w}) w^2$$

with

$$\begin{aligned} h'(w) &= \nu e^{-\lambda c\tau} f'(e^{-\lambda c\tau} w) - \mu f'(w), \\ h''(w) &= \nu e^{-2\lambda c\tau} f''(e^{-\lambda c\tau} w) - \mu f''(w), \end{aligned}$$

and

$$f'(w) = e^{-kw}, \qquad f''(w) = -k e^{-kw}.$$

Thus

$$h''(\tilde{w}) \le (\nu e^{-2\lambda c\tau} - \mu) f''(\tilde{w}).$$

This implies that $h''(\tilde{w}) \le 0$ because $\nu e^{-2\lambda c\tau} \ge \mu$. Thus

$$h(w) \le h'(0) w = (\nu e^{-\lambda c\tau} - \mu) w.$$

We substitute this inequality into (4.17),

$$\begin{aligned} &-\partial_t w(t,x) + d\Delta w(t,x) + \hat{V}_0(t,x) - \mu f(w(t,x)) + \nu f(w(t-\tau,x)) \\ &\le (-\lambda c + d\lambda^2 + \nu e^{-\lambda c\tau} - \mu) w(t,x) + \hat{V}_0(\tau,x). \end{aligned}$$

By (4.16), the factor multiplying $w(t,x)$ is negative. So the right-hand side is negative if $\hat{V}_0(\tau,x) \le \eta_0 e^{-\lambda|x|}$ for some $\eta_0 > 0$ and $\eta > 0$ is chosen large enough. By a comparison principle, $u(t,x) \le \eta w(t,x)$. Notice that the choice of η does not depend on $z \in \mathbb{R}^n$, $|z| = 1$. With $z = -|x|^{-1} x$, we obtain

$$u(t,x) \le \eta e^{\lambda(ct - |x|)}.$$

Let $\tilde{c} > c$, and choose $c \in (c^*, \tilde{c})$ close enough to c^*. Then

$$\sup_{|x| \ge \tilde{c}t} u(t,x) \le \eta e^{\lambda(c-\tilde{c})t} \to 0, \qquad t \to \infty. \qquad \square$$

REMARK 4.1. *Let $c > c^*$. Then there exist $\lambda_2 > \lambda_1 > 0$ (which depend on c) such that $\nu e^{-\lambda c\tau} < \lambda c + \mu - d\lambda^2$ for all $\lambda \in (\lambda_1, \lambda_2)$ and $\nu e^{-\lambda_1 c\tau} = \lambda_1 c + \mu - d\lambda_1^2$. λ_1 is uniquely determined, and $\nu e^{-\lambda c\tau} > \lambda c + \mu - d\lambda^2$ for all $\lambda \in [0, \lambda_1)$. This implies $\lambda_1 < \lambda^*$, and it can be seen that $\lambda_1 c < c^* \lambda^*$. Hence, if $\beta e^{-2\lambda^* c^* \tau} \ge 1$, then $\beta e^{-2\lambda_1 c\tau} > 1$. Define*

$$(4.19)\qquad w_1(t,x) = \eta e^{\lambda_1(ct + x\cdot z)}.$$

The same argument as in the proof of Theorem 4.3 shows that for all $t \in \mathbb{R}$, $x \in \mathbb{R}^n$,

$$\partial_t w_1(t,x) \geq d\Delta w_1(t,x) - \mu f(w_1(t,x)) + \nu f(w_1(t-\tau,x)). \tag{4.20}$$

If $\beta e^{-2\lambda^* c^* \tau} < 1$, one can still find an upper spreading speed. By a comparison argument, $u(t,x) \leq w(t,x)$, where

$$\begin{aligned} &w_t(t,x) = d\Delta w(t,x) + \hat{V}_0(\tau,x) + \nu w(t-\tau,x), \qquad t > 0,\\ &w(t,x) = 0, \qquad t \leq 0,\ x \in \mathbb{R}^n. \end{aligned} \tag{4.21}$$

Let $c^0 = c$ be determined by the unique solution (c^0, λ^0) of

$$\nu e^{-\lambda c \tau} = \lambda c - d\lambda^2, \qquad -c\tau(\lambda c - d\lambda^2) - c + 2d\lambda = 0. \tag{4.22}$$

A proof similar to that of Theorem 4.3, with $\mu = 0$, provides the following result.

THEOREM 4.4. *For any $c > c^0$,*

$$\limsup_{t\to\infty} \sup_{|x|\geq ct} u(t,x) = 0$$

for all solutions u of (3.3), where $\hat{V}_0(\tau,x) \leq \eta e^{-\lambda^*|x|}$, $x \in \mathbb{R}^n$, with some constant $\eta > 0$.

Now we aim to translate the results of Theorems 4.3 and 4.4 into results for our system (2.1)–(2.2). Recall (3.2) and (2.3):

$$\begin{aligned} I(t,x) &= B(t-\tau,x) - B(t,x), \quad t > \tau,\\ B(t,x) &= B_0 e^{-ku(t,x)}, \quad t > 0. \end{aligned} \tag{4.23}$$

Using (4.23) and the previous results, we have the following corollary.

COROLLARY 4.1. *Let $\beta > 1$ and let (V, B) be a solution of (2.1)–(2.2) with the initial data $I^0(s,x) \geq 0$, $V(0,x) = V_0(x) \geq 0$, and $B(0,\cdot) \equiv B_0 > 0$, where $\hat{V}_0(\tau,x)$ is measurable and not zero a.e. Let (c^*, λ^*) be the unique solution of (4.11). Then, for every $c \in (0, c^*)$,*

$$\lim_{t\to\infty, |x|\leq ct} B(t,x) = 0, \quad \lim_{t\to\infty, |x|\leq ct} I(t,x) = 0. \tag{4.24}$$

In addition, assume that $\hat{V}_0(\tau,x) \leq \eta e^{-\lambda^*|x|}$, $x \in \mathbb{R}^n$, for some $\eta > 0$ and that one of the following holds:

(1) *$c > c^*$ and $\beta e^{-2\lambda^* c^* \tau} \geq 1$, or*

(2) *$c > c^0$, with c^0 determined by (4.22).*

Then

$$\lim_{t\to\infty, |x|\geq ct} B(t,x) = B_0, \quad \lim_{t\to\infty, |x|\geq ct} I(t,x) = 0. \tag{4.25}$$

Proof. The B limit in (4.24) follows from (4.23) and the blow-up of u described in Theorem 4.2. Similarly, the I limit uses (4.23) and the blow-up of u.

The B limit (4.25) follows from (4.23), the inequality $B(t,x) \leq B_0$, Theorem 4.3, and Theorem 4.4. The I limit uses (4.23). ∎

5. Traveling waves. In this section we seek traveling wave solutions of (3.3) in one space dimension. A traveling wave solution is defined for all $t, x \in \mathbb{R}$, with $\hat{V}_0 \equiv 0$ and with homogeneous initial bacterial density B_0, satisfying the differential equation for all $t \in \mathbb{R}$, and is of the form $u(t, x) = U(ct + x)$ with $U(y) \to 0$ as $y \to -\infty$.

THEOREM 5.1. *Assume one of the following holds:*
(1) $c > c^*$, *with* (c^*, λ^*) *determined by* (4.11) *and* $\beta e^{-2\lambda^* c^* \tau} \geq 1$, *or*
(2) $c > c^0$, *with* c^0 *determined by* (4.22).
Then there exists a solution $u(t, x) = U(ct + x)$ *of the equation*

$$u_t(t, x) = d\partial_x^2 u(t, x) - \mu f(u(t, x)) + \nu f(u(t - \tau, x)), \qquad t, x \in \mathbb{R}, \tag{5.1}$$

with an increasing continuous $U : \mathbb{R} \to \mathbb{R}_+$, $U(\xi) \to 0$ *as* $\xi \to -\infty$ *and* $U(\xi) \to \infty$ *as* $\xi \to \infty$. *Moreover, there exist* $M, N > 0$ *such that* $U(\xi) \leq M[\xi]_+ + N$, $\xi \in \mathbb{R}$.

Proof. Equivalently,

$$\begin{aligned} u(t, x) = &\int_0^\infty \int_{\mathbb{R}} e^{-\mu s}\Gamma(s, y)\mu g(u(t - s, x - y))dyds \\ &+ \int_0^\infty \int_{\mathbb{R}} e^{-\mu s}\Gamma(s, y)\nu f(u(t - s - \tau, x - y))dyds. \end{aligned}$$

This can be brought to the form of (3.1) in [21] with

$$F(u, s, y) = e^{-\mu s}\Gamma(s, y)\mu g(u) + G(s, y)\nu f(u).$$

However, [21, Thm. 3.3] does not apply directly because F cannot be majorized by a linear operator in the same way as there. But the proof, which goes back to Diekmann [5] and Weinberger [22], who, independently, introduced the method of upper and lower solutions to prove the existence of traveling waves, can be modified.

We substitute $u(t, x) = U(ct + x)$ into the integral equation yielding

$$\begin{aligned} U(ct + x) = &\int_0^\infty \int_{\mathbb{R}} e^{-\mu s}\Gamma(s, y)\mu g(U(c(t - s) + x - y))dyds \\ &+ \int_0^\infty \int_{\mathbb{R}} e^{-\mu s}\Gamma(s, y)\nu f(U(c(t - s - \tau) + x - y))dyds. \end{aligned}$$

We set $\xi = ct + x$,

$$\begin{aligned} U(\xi) = &\int_0^\infty \int_{\mathbb{R}} e^{-\mu s}\Gamma(s, y)\mu g(U(\xi - cs - y))dyds \\ &+ \int_0^\infty \int_{\mathbb{R}} e^{-\mu s}\Gamma(s, y)\nu f(U(\xi - c(s + \tau) - y))dyds = F(U)(\xi). \end{aligned}$$

At this point, we consider F as a map from $\mathcal{M}(\mathbb{R}, \mathbb{R}_+)$ to $\mathcal{M}(\mathbb{R}, \bar{\mathbb{R}}_+)$ with $\bar{\mathbb{R}}_+ = [0, \infty]$, with $\mathcal{M}$ denoting the measurable functions on $\mathbb{R}$ with values in $\mathbb{R}_+$ and $\bar{\mathbb{R}}_+$, respectively.

Assume hypothesis (1) holds. Notice that w in (4.19), with $z = 1$, is of the form $w(t, x) = W(ct + x)$ with $W(\xi) = \eta e^{\lambda_1 \xi}$. It follows from Remark 4.1, (4.20), that $F(W) \leq W$ for arbitrary $\eta > 0$.

Now $F(U) \geq F_0(U)$, where

$$F_0(U)(\xi) = \int_0^\infty \int_{\mathbb{R}} e^{-\mu s}\Gamma(s, y)\nu f(U(\xi - c(s + \tau) - y))dyds. \tag{5.2}$$

For the same function ϕ as in the proof of [21, Thm. 3.3],

$$\phi(\xi) = \max\{0, \delta(1 - Me^{\epsilon\xi})e^{\lambda_1\xi}\}, \qquad \xi \in \mathbb{R},$$

with sufficiently small $\delta, \epsilon > 0$, we have $\phi \le F_0(\phi) \le F(\phi)$.

If $\eta > 0$ is chosen large enough, $\phi \le W$ on $\mathbb{R}$.

Since f and g are increasing, F is an increasing map on the order interval $[\phi, W]$ of measurable functions between ϕ and W. Notice that F maps increasing functions on increasing functions. The iteration $W_{n+1} = F(W_n)$, $W_0 = W$, provides a decreasing sequence of increasing functions which have a pointwise limit U, which is also increasing, $U \ge \phi$. By the dominated convergence theorem, $F(U) = \lim_{n\to\infty} F(W_n) = \lim_{n\to\infty} W_{n+1} = U$, where the limit is pointwise. After a substitution,

$$\begin{aligned} U(\xi) = &\int_0^\infty \int_{\mathbb{R}} e^{-\mu s}\Gamma(s, y+\xi)\mu g(U(-cs - y))dyds \\ &+ \int_0^\infty \int_{\mathbb{R}} e^{-\mu s}\Gamma(s, y+\xi)\nu f(U(-c(s+\tau) - y))dyds. \end{aligned}$$

The continuity properties of Γ imply that U is continuous.

Let $U_\infty = \lim_{\xi\to\infty} U(\xi)$. Then $U_\infty > 0$. Suppose that $U_\infty < \infty$. By Beppo Levi's monotone convergence theorem,

$$\begin{aligned} U(\infty) = &\int_0^\infty \int_{\mathbb{R}} e^{-\mu s}\Gamma(s, y)\mu g(U(\infty))dyds \\ &+ \int_0^\infty \int_{\mathbb{R}} e^{-\mu s}\Gamma(s, y)\nu f(U(\infty))dyds \\ &= g(U(\infty)) + \frac{\nu f(U(\infty))}{\mu} = U(\infty) - f(U(\infty)) + \frac{\nu f(U(\infty))}{\mu}. \end{aligned}$$

Since $\nu > \mu$, this is a contradiction. This completes the proof when assumption (1) holds.

If assumption (2) holds, the upper solution $W(\xi) = \eta e^{\lambda\xi}$ can be chosen as above except that $c\lambda = c^0\lambda^0$, where (c^0, λ^0) is determined by (4.22).

Finally, the estimate $U(\xi) \le M[\xi]_+ + N$, $\xi \in \mathbb{R}$, follows from the comparison principle and monotonicity of U since $W = U - Mt - N$ satisfies $W_t - dW_{xx} \le 0$ for $t \ge 0$ and $W(0, x) \le 0$. ☐

REMARK 5.1. *Theorem* 5.1 *implicitly assumes that* $\beta > 1$. *It is easy to see that* (5.1) *cannot have a traveling wave satisfying the properties mentioned if* $\beta \le 1$. *One need only compare solutions of* (5.1) *with solutions of the scalar delay equation* $y'(t) = -\mu f(y(t)) + \mu f(y(t-\tau))$. *Every value of* y *is an equilibrium for this equation. If* $U : \mathbb{R} \to \mathbb{R}_+$ *is a solution of* (5.1) *satisfying* $U(-\infty) = 0$, *then by comparison with any constant solution* $y > 0$, *it follows that* $U(t) \le y$, $t \in \mathbb{R}$, *and we conclude that* U *vanishes identically on* $\mathbb{R}$.

Now our focus turns to showing the existence of traveling waves for our original system under the same conditions as in Theorem 5.1. It is useful to work with the delay differential equation satisfied by $U(s)$:

$$dU''(s) - cU'(s) - \mu f(U(s)) + \beta\mu f(U(s - c\tau)) = 0. \tag{5.3}$$

LEMMA 5.2. *Let* U *be a traveling wave solution of* (5.1) *described in Theorem* 5.1. *Then* U' *satisfies*

$$U'(-\infty) = 0, \quad U'(+\infty) = (\beta - 1)B_0/c. \tag{5.4}$$

Proof. By virtue of (5.3), $V = U'$ satisfies the linear inhomogeneous differential equation

$$dV' - cV = H(s),$$

where $H(s) = \mu f(U(s)) - \beta\mu f(U(s - c\tau)$ is bounded on $\mathbb{R}$, and

$$H(-\infty) = 0, \quad H(+\infty) = -(\beta - 1)B_0.$$

By the Fredholm alternative, this linear ODE has a unique solution $\tilde{V}(s)$ which is bounded on $\mathbb{R}$, and it is given by

$$\tilde{V}(s) = -\int_0^\infty d^{-1}H(s + r)e^{-cr/d}dr.$$

Furthermore, taking limits as $s \to \pm\infty$, we find that

$$\tilde{V}(-\infty) = 0, \quad \tilde{V}(+\infty) = B_0(\beta - 1)/c.$$

By superposition, $V(s) = U'(s) = \tilde{V}(s) + ae^{cs/d}$ for some real a; we will show $a = 0$. Since $U' \geq 0$ and $\tilde{V}$ is bounded, $a \geq 0$. Suppose $a > 0$. Note that

$$U(s) = \int_{-\infty}^s U'(t)dt = U_0(s) + (da/c)e^{cs/d},$$

where $U_0(s) = \int_{-\infty}^s \tilde{V}(t)dt$.

The solution U of (5.1) satisfies $U(t, x) \leq Mt + N$, $t \geq 0$, for some positive constants M, N as noted in Theorem 5.1. This implies that $a = 0$. ∎

THEOREM 5.3. *Assume one of the following holds:*

(1) $c > c^*$, *with* (c^*, λ^*) *determined by* (4.11) *and* $\beta e^{-2\lambda^* c^* \tau} \geq 1$, *or*

(2) $c > c^0$, *with* c^0 *determined by* (4.22).

Then there exist traveling wave solutions $V(x + ct)$ *and* $B(x + ct)$ *of*

$$\begin{aligned} V_t &= dV_{xx} - kBV + \beta kB(t - \tau, x)V(t - \tau, x), \\ B_t &= -kBV \end{aligned} \tag{5.5}$$

satisfying

$$B(-\infty) = B_0,\ B(+\infty) = 0,\ V(-\infty) = 0,\ V(+\infty) = B_0(\beta - 1). \tag{5.6}$$

Proof. Let U be a traveling wave solution of (5.1) described in Theorem 5.1, which also satisfies (5.3). Define B and V as follows:

$$V(s) = U'(s)c, \quad B(s) = B_0e^{-kU(s)}. \tag{5.7}$$

Differentiating (5.3) and multiplying by c, we obtain

$$dV''(s) - cV'(s) - kB_0e^{-kU(s)}V(s) + \beta kB_0e^{-kU(s-c\tau)}V(s - c\tau) = 0.$$

In view of (5.7), this becomes

$$dV''(s) - cV'(s) - kB(s)V(s) + \beta kB(s - c\tau)V(s - c\tau) = 0,$$

and, by (5.4), V has the limits in (5.6). B satisfies

$$B'(s) = -kB(s)V(s)/c.$$

Obviously, B is monotone decreasing, and the limiting values of U imply that B has the limits in (5.6). It follows that B and V satisfy (5.5). ∎

6. Numerical solutions and computation of spreading speed.

6.1. Scaling. It is important to pass to nondimensional quantities for numerical solutions. We first scale time and space,

$$\bar{t} = t/\tau, \quad \bar{x} = x/L,$$

where L will be chosen below. We also scale dependent variables,

$$v = V/(\beta - 1)B_0, \quad b = B/B_0,$$

where $B_0 \equiv B(0, x)$ denotes the constant initial bacterial density in all of our simulations. Then $v(\bar{t}, \bar{x}) = V(t, x)/(\beta - 1)B_0$ and $b(\bar{t}, \bar{x}) = B(t, x)/B_0$ satisfy

$$\begin{aligned} v_{\bar{t}} &= v_{\bar{x}\bar{x}} - \bar{k}bv + \beta\bar{k}bv(\bar{t} - 1, \bar{x}), \\ b_{\bar{t}} &= -\bar{k}(\beta - 1)bv, \quad \bar{t} > 1, \end{aligned} \tag{6.1}$$

where L is chosen such that the new virus diffusion constant $\bar{d} = d\tau L^{-2} = 1$ and

$$\bar{k} = kB_0\tau. \tag{6.2}$$

In relating the spread speed of the scaled system to that of the unscaled system, we must keep in mind the relation

$$\frac{dx}{dt} = \sqrt{\frac{d}{\tau}}\frac{d\bar{x}}{d\bar{t}}. \tag{6.3}$$

Yin and McCaskill [24] take $d = 4 \times 10^{-8} cm^2/s$ and $\tau \approx 20\ min$ leading to the estimate

$$\sqrt{\frac{d}{\tau}} \approx\ 0.2\ mm/hr. \tag{6.4}$$

They observe that host bacteria are at initial concentrations of 10^7–$10^8/ml$. We take this as a measure of B_0. They take $k \approx 10^{-9} ml/min$, $\tau = 20\ min$. This results in

$$\bar{k} \approx 10^{-9} \times (10^7\text{–}10^8) \times 20 \in (0.2, 2).$$

6.2. Scaling the characteristic equations. It will prove useful to rescale the characteristic equations (4.11) and (4.22) to reflect the nondimensional quantities (6.2) and (6.3). Let

$$\bar{\lambda} = \lambda c\tau, \quad \bar{c}^2 = c^2\frac{\tau}{d}. \tag{6.5}$$

Then (4.11) becomes

$$\beta\bar{k}e^{-\bar{\lambda}} = \bar{\lambda} + \bar{k} - \bar{\lambda}^2/\bar{c}^2, \qquad -\beta\bar{k}e^{-\bar{\lambda}} - 1 + 2\bar{\lambda}/\bar{c}^2 = 0. \tag{6.6}$$

The two equations can be used to eliminate $\bar{c}^2$ to obtain an equation for $\bar{\lambda}$:

$$\bar{\lambda} + 2\bar{k} - \bar{k}\beta e^{-\bar{\lambda}}(2 + \bar{\lambda}) = 0. \tag{6.7}$$

Then, $\bar{c}$ is determined by the unique solution $\bar{\lambda} > 0$ of (6.7) by

$$\bar{c}^2 = \frac{2\bar{\lambda}}{1 + \bar{k}\beta e^{-\bar{\lambda}}}. \tag{6.8}$$

Observe that (6.7) implies that

$$\beta e^{-\bar{\lambda}} = \frac{\bar{\lambda} + 2\bar{k}}{\bar{\lambda}\bar{k} + 2\bar{k}} \leq 1, \qquad \bar{k} \geq 1.$$

Therefore, the extra condition (4.13), which becomes

$$\beta e^{-2\bar{\lambda}} \geq 1, \tag{6.9}$$

cannot hold if $\bar{k} \geq 1$.

Similarly, (4.22) becomes

$$\beta \bar{k} e^{-\bar{\lambda}} = \bar{\lambda} - \bar{\lambda}^2/\bar{c}^2, \qquad -\beta \bar{k} e^{-\bar{\lambda}} - 1 + 2\bar{\lambda}/\bar{c}^2 = 0. \tag{6.10}$$

The corresponding version of (6.7) is obtained by dropping the $2\bar{k}$ term from (6.7), and the corresponding equation for the upper spread speed is the same as (6.8).

Below, the bars will be dropped; all variables and parameters are the scaled ones.

6.3. Numerical simulations. We consider the scaled equations on a finite interval of length L_D and on a disk of radius R_D with homogeneous Neumann boundary conditions. We consider only radially symmetric solutions on the disk. The systems to be discretized are

$$\begin{aligned} v_t &= v_{xx} - kbv + \beta kbv(t-1, x), \\ b_t &= -k(\beta - 1)bv, \quad t > 1,\ 0 < x < L_D, \end{aligned} \tag{6.11}$$

and

$$\begin{aligned} v_t &= v_{rr} + \frac{1}{r}v_r - kbv + \beta kbv(t-1, r), \\ b_t &= -k(\beta - 1)bv, \quad t > 1,\ 0 < r < R_D. \end{aligned}$$

In practice we see only small changes in the numerical solutions for L_D, $R_D > 80$. Throughout we use $L_D = R_D = 100$. For the tube, the initial data is placed at $L_D/2$ and is symmetric about this point. Specifically, we set $v = 1$ and $b = 0$ on $(L_D/2 - 2, L_D/2 + 2)$, and $v = 0$, $b = 1$ on the remaining domain for the tube. For the disk, the data is placed at the origin. We set $v = 1$ and $b = 0$ on $0 \leq r \leq 2$, and $v = 0$, $b = 1$ on the remaining part of the disk.

To discretize either system we use a uniform spatial grid with 400 grid points with the usual second-order centered-in-space discretization for the Laplacian. The time grid is uniform as well, and we use a second-order Adams–Bashforth scheme for the time integration. We first integrate the equations on the interval $0 \leq t \leq 1$, where we assume the term $bv(t-1, x)$ is zero. On this interval, equations (6.11) are easily integrated as described. The quantity bv is simultaneously stored during the integration on $0 \leq t \leq 1$. On the next time interval, $1 \leq t \leq 2$, the equations can be integrated in the manner described since $bv(t-1, x)$ is known discretely. Again bv is stored for use on the next interval $2 \leq t \leq 3$. The numerical scheme continues in this way.

Figure 6.1 plots the (scaled) spread speed c^* and the upper spread speed c^0 as a function of the (scaled) adsorption constant $\bar{k}$ (top) and β (bottom), obtained using Newton's method. Also included are numerically computed spread speeds for both one- and two-dimensional domains. The speed of the wave is found by tracking, in

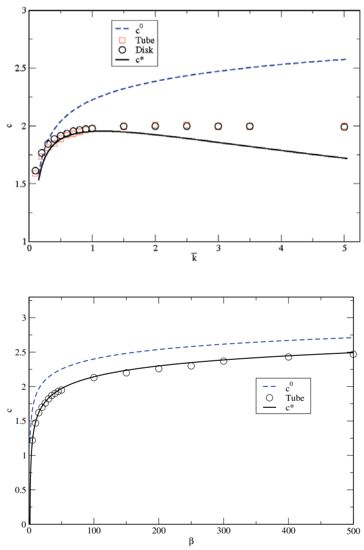

FIG. 6.1. *Top: spread dependence on* $\bar{k}$ *with* $\beta = 50$. *Bottom: spread speed dependence on* β *with* $\bar{k} = 1$.

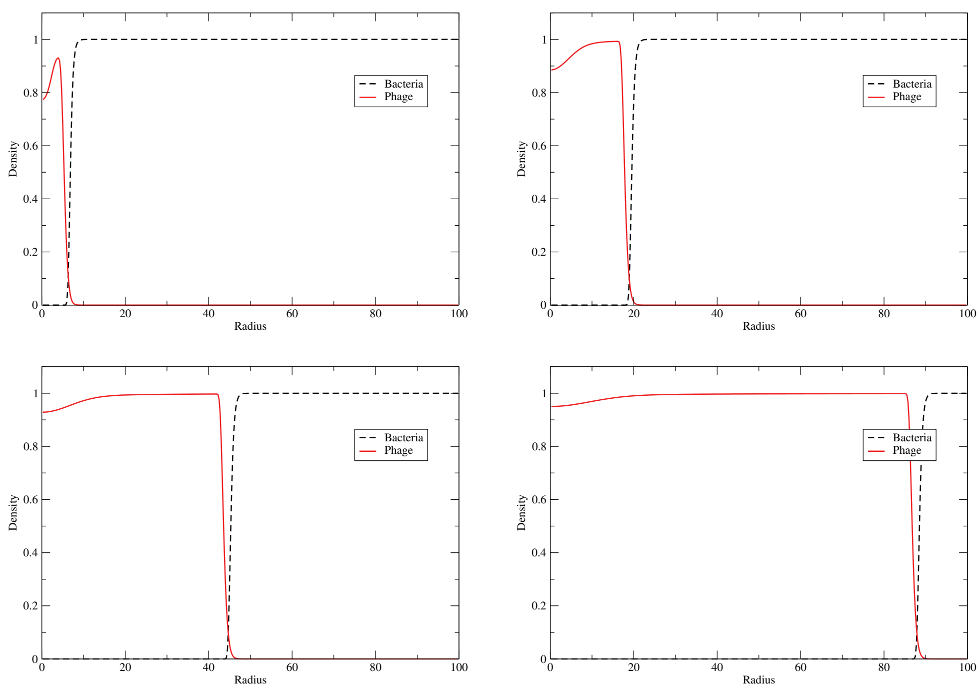

FIG. 6.2. *Time evolution of phages and bacteria for a disk. The upper left shows a slice of the solution at* $t = 2$, *upper right at* $t = 8$, *lower left at* $t = 20$, *and lower right at* $t = 40$. *Here* $\beta = 100$ *and* $\bar{k} = 1$.

time, a point on the wave at a fixed height. We note that the wave form does not change much as it evolves, as Figure 6.2 shows. We also note that the extra condition, (4.13), fails to hold for a substantial portion of the entire range of $\bar{k}$ (containing the interval $1 \leq \bar{k} < \infty$). Figure 6.1(top) shows that solutions spread with speed close to c^* for some, but not all, values of $\bar{k}$. In particular, as the scaled virus adsorption constant $\bar{k}$ increases, c^* increases to a maximum and then decreases. Solutions spread with speed near c^* as long as $\bar{k}$ is less than the critical value corresponding to the maximum of c^*; for values of $\bar{k}$ exceeding the critical value, while c^* decreases, numerically computed solutions spread faster than c^* but slower than c^0, reflecting a failure of linear determinacy of the spreading speed (cf. [14, 23] and the references therein).

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