

## SPREAD OF VIRAL INFECTION OF IMMOBILIZED BACTERIA

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**ABSTRACT.** A reaction diffusion system with a distributed time delay is proposed for virus spread on bacteria immobilized on an agar-coated plate. A distributed delay explicitly accounts for a virus latent period of variable duration. The model allows the number of virus progeny released when an infected cell lyses to depend on the duration of the latent period. A unique spreading speed for virus infection is established and traveling wave solutions are shown to exist.

**1. Introduction.** Bacteriophages are viruses which parasitize bacteria. They adsorb to a bacterial surface receptor and inject their DNA into the bacterial cell thereby turning the protein making machinery of the bacterial cell into a virus-making factory. When virus progeny have been assembled, the bacterial cell wall lyses and releases the virus progeny. These then diffuse until they reach another bacterium where the cycle is continued. The latent period is defined as the time from virus adsorption to the bacteria until the subsequent release of progeny viruses on bacterial lysis.

A standard experimental protocol for the study of bacteriophages and their bacterial hosts is the plaque assay. Liquid agar containing a very small quantity of virus together with host bacteria is evenly spread on a plate of solid agar. After some time has passed, a number of “plaques” become visible, each initiated from a single virus infection of a host cell. The plaque is a clear, disk-shaped, region of lysed cells surrounded by un-lysed bacteria. It spreads 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.

In a recent paper [9], the authors together with G. Röst, developed a mathematical model of the spread of virus infection on their bacterial hosts, creating an expanding plaque on an agar plate. In addition, we gave the first mathematically rigorous proof of the spreading of the plaque, identifying an interval of possible spreading speeds. Traveling wave solutions were also shown to exist for the model. Our model assumed, following standard practice in the mathematical modeling of virus and host-cell interaction [3, 1, 12, 17], that the latent period duration is a fixed constant. We also assumed that the burst size, the number of viral progeny released at cell lysis, is a fixed constant. Furthermore, we did not include any loss or

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degradation of viruses in our model other than adsorption of viruses to uninfected cells leading to their infection. Therefore, the spread of virus infection results in converting a once homogeneous “lawn” of bacteria into a plaque devoid of bacteria and occupied by a homogeneous density of virus.

Here, we generalize our earlier model by allowing for a variable latent period distribution and for the burst size to depend on the timing of bacterial lysis. We counter this added generality by simplifying the viral loss term, replacing a nonlinear one by a constant loss rate that is assumed to account for loss of virus due to adsorption to host cells, whether uninfected or uninfected, and due to the degradation of free virus. The simplification of the viral loss term, often made in mathematical models of virus interaction with their target cells [14, 16, 1, 4], results in a significant improvement in mathematical tractability of the spreading problem. It also changes the character of the spreading plaque such that virus is plentiful only immediately behind the moving front and decays away behind the front instead of remaining at high levels. Thus the interior of a plaque has very low levels of both bacteria and viruses.

Finally we briefly summarize the literature of this problem. 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  $\tau$  is the length of the latent period. Yin and McCaskill [24] were the first to construct a mathematical model of virus spread, a reaction diffusion system, and they identified the growing plaque with a traveling wave solution of their system, although they did not give a proof of its existence. Yin and You [25] reported numerical simulations supporting the conclusion that traveling wave solutions exist for the system described in [24]. 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 [7]. Fort and Méndez [8] account for a time-delay for the latent period by deriving a “hyperbolic approximation to the full time-delayed evolution equation”, a damped wave equation. Later work by Ortega-Cejas et al. [15] based on the model proposed in [8] obtains some approximate but explicit formula for the wave speed. None of the works cited here give a mathematical proof of the existence of traveling wave solutions of the models considered.

Following the description of our model below, we prove the existence of a uniquely determined spreading speed  $c^*$  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 non-zero on a non-empty bounded set. Following [9], the key to the results of this paper is that the accumulated virus density at position  $x$ ,  $u(t, x) = \int_0^t V(s, x) ds$ , satisfies a scalar reaction diffusion equation with distributed time delay. This fact allows us to make use of the theory developed by Thieme [19, 20] and by Thieme and Zhao [22] on asymptotic speed of spread for certain integral equations. We show that  $\inf_{|x| \leq ct} u(t, x) > u^* > 0$  for large  $t$  if  $c < c^*$  and  $\sup_{|x| \geq ct} u(t, x) \rightarrow 0$  as  $t \rightarrow \infty$  if  $c > c^*$ . The speed  $c^*$  is determined by the usual linearization about the virus-free state. A characteristic equation couples the speed  $c$  and a wave “shape parameter”  $\lambda$  and  $c^*$  corresponds to a double root  $\lambda^*$  of this equation, which also depends on model parameters. Thus, different from [9], linear determinacy of the spreading speed (cf. [13, 23] and the references therein) holds for our system. We show that the spreading speed  $c^*$  is also the minimum wave speed: Traveling wave solutions of our model system in one-space dimension exist for any wave speed exceeding  $c > c^*$  and do not exist for  $c < c^*$ . The traveling

wave profile for viruses is pulse-like, virus levels are low well in front of the wave and well behind the wave. The profile for bacteria connects the virus-free value to a significantly lower one.

**2. The model.** Following [24, 25], we assume that host bacteria in agar do not grow or diffuse. Viruses diffuse and adsorb to host bacteria creating infected cells. Following many authors [14, 16, 1, 4], we assume a constant virus loss rate  $\alpha$ . Viruses are lost in several ways. They are lost when they adsorb to either susceptible bacteria, to already infected bacteria, and to bacterial fragments left after cell lysis. Viruses also naturally degrade over time. We combine all these loss rates into a single loss rate.

Let virus density be denoted by  $V$ , virus-susceptible bacteria density be denoted by  $B$ , and infected bacteria density be denoted by  $I$ . Let  $\mathfrak{F}(a)$  be the probability that an infected bacterium has not yet lysed  $a$  time units after infection. There exists a unique Lebesgue-Stieltjes probability measure  $\nu$  on the Borel sets of  $\mathbb{R}_+$  such that  $\mathfrak{F}(a) - \mathfrak{F}(\tilde{a}) = \nu([a, \tilde{a}])$  whenever  $0 \leq a \leq \tilde{a}$  and  $\mathfrak{F}$  is continuous at  $a$  and  $\tilde{a}$ . We note that if  $\mathfrak{F}$  is differentiable, then  $-\mathcal{F}'(a)da = d\nu(a)$ . See [17] for further details.

Let  $b(a)$  denote the average number of progeny released when an infected cell lyses  $a$  time units after infection. We assume that  $b : \mathbb{R}_+ \rightarrow \mathbb{R}_+$  is bounded and continuous. Viruses are assumed to adsorb to bacteria with adsorption constant  $k$ , and  $d$  is the effective diffusion constant for phages. Bacteria are immobile in the agar. The spatial density of infected bacteria is described by

$$I(t, x) = \int_0^\infty i(t, a, x) da$$

where  $i(t, a, x)$  denotes the density of infected bacteria with respect to age and space.

The model is given by the following system,

$$\begin{aligned} V_t &= d\Delta V - \alpha V + \int_0^\infty b(a)i(t, a, x)\mathfrak{F}(a)^{-1}d\nu(a) \\ B_t &= -kB V, \quad x \in D, t > 0. \end{aligned} \quad (1)$$

The integral represents the rate at which viruses are shed by infected bacteria of all age-since-infection at position  $x$  and at time  $t$ .

At  $t = 0$ , the initial density of infected bacteria is  $i(0, a, x) = i_0(a, x)$ , where  $a \in [0, \infty)$  denotes age-of-infection. As infected bacteria are immobile, we have that

$$i(t, a, x) = \begin{cases} kB(t-a, x)V(t-a, x)\mathfrak{F}(a), & t > a \geq 0 \\ i_0(a-t, x)\frac{\mathfrak{F}(a)}{\mathfrak{F}(a-t)}, & 0 \leq t < a \end{cases}. \quad (2)$$

Indeed, for  $t > a$ , the infected bacteria with infection age  $a$  are those that have been infected at time  $t-a$  (at rate  $kB(t-a, x)V(t-a, x)$ ) and have not yet lysed. For  $t < a$ , they are those bacteria that were in the infected stage already at time 0, when they had infection age  $a-t$ , and have not yet lysed at time  $t$ , with the conditional probability  $\mathfrak{F}(a)/\mathfrak{F}(a-t)$ .

Inserting (2) into the definition of  $I(t, x)$  above, we find that

$$I(t, x) = \int_0^t kB(t-a, x)V(t-a, x)\mathfrak{F}(a)da + \int_t^\infty i_0(a-t, x)\frac{\mathfrak{F}(a)}{\mathfrak{F}(a-t)}da \quad (3)$$

$D$  denotes the domain, typically in applications, 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.

Inserting (2) into (1), we obtain

$$V_t = d\Delta V - \alpha V + J(t, x) + k \int_0^t b(a)B(t-a, x)V(t-a, x)d\nu(a) \quad (4)$$

where

$$J(t, x) = \int_t^\infty b(a) \frac{i_0(a-t, x)}{\mathfrak{F}(a-t)} d\nu(a). \quad (5)$$

If there are no infected bacteria at  $t = 0$ , i.e., if  $i_0 = 0$ , then  $J = 0$ .

Initial data for  $V$  and  $B$  at  $t = 0$  must be prescribed:

$$B(0, x) = B_0(x), \quad V(0, x) = V_0(x), \quad x \in \mathbb{R}^n$$

We will assume that  $B_0$  is some positive constant, to model a homogeneous ‘‘lawn’’ of bacteria;  $V_0 \geq 0$  is expected to have compact (very small) support to model a drop containing viruses.

It may be useful to introduce the density of lysed bacteria  $L(t, x)$ . Clearly,

$$B_0(x) = B(t, x) + I(t, x) + L(t, x), \quad t \geq 0, \quad (6)$$

since bacteria are immobile and are either susceptible, infected, or lysed.

**3. Reduction to a single diffusion equation.** We proceed as in [9] to reduce the system (1) to a single scalar equation. Define the accumulated density of viruses,

$$u(t, x) = \int_0^t V(s, x)ds = (\ln B_0(x) - \ln B(t, x))/k. \quad (7)$$

The last equality follows from the differential equation for  $B$  in (1). Now, solve for  $B$  to get

$$B(t, x) = B_0(x)e^{-ku(t, x)}. \quad (8)$$

In view of (8),  $e^{-ku(t, x)}$  can be viewed as the probability of a bacterium located at position  $x$  to be still uninfected at time  $t$ .

We substitute the differential equation for  $B$  into (4),

$$V_t = d\Delta V - \alpha V + J(t, x) - \int_0^t b(a)B_t(t-a, x)d\nu(a)$$

Integrating from  $t = 0$  to  $t = t$ ,

$$V(t, x) - V_0(x) = d\Delta u - \alpha u + \int_0^t J(s, x)ds - \int_0^t \int_0^s b(a)B_t(s-a, x)d\nu(a)ds$$

Setting  $V = u_t$  and interchanging order of integration, we find that

$$u_t = d\Delta u - \alpha u + \hat{V}_0(t, x) + \int_0^t b(a)[B_0(x) - B(t-a, x)]d\nu(a)$$

where

$$\hat{V}_0(t, x) = V_0(x) + \int_0^t J(s, x)ds$$

We note that

$$\int_0^\infty J(s, x)ds = \int_0^\infty b(a) \int_0^a \frac{i_0(r, x)}{\mathfrak{F}(r)} dr d\nu(a). \quad (9)$$

In particular, if  $V_0$  and  $i_0(r, x)$  vanish for  $|x| \geq \eta$  and all  $r \geq 0$ , then so does  $\hat{V}_0$  vanish for  $|x| \geq \eta$  and all  $t \geq 0$ . We assume that  $\hat{V}^0(t, x)$  is bounded.

Finally, making use of (8), we have

$$u_t = d\Delta u - \alpha u + \hat{V}_0(t, x) + kB_0(x) \int_0^t b(a)f(u(t-a, x))d\nu(a) \quad (10)$$

where

$$f(u) = \frac{1 - e^{-ku}}{k}. \quad (11)$$

Note that  $f$  is bounded and  $f(0) = 0$ ,  $f'(0) = 1$ , and  $f(u) < u$  for all  $u > 0$ .

Notice that, via (8), all results for  $u$ , the cumulative phage density, can be rephrased in terms of the density of susceptible bacteria.

We assume that  $B_0(x) = B_0$  is constant and positive on the domain  $\mathbb{R}^n$ . Since the phage loss rate  $\alpha > 0$  includes adsorption by susceptible bacteria,  $\alpha \geq kB_0$ .

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

$$\begin{aligned} u(t, x) &= u_0(t, x) \\ &+ \int_0^t \int_{\mathbb{R}^n} e^{-\alpha s} \Gamma(s, y) \int_0^{t-s} kB_0 b(a) f(u(t-s-a, x-y)) d\nu(a) dy ds \end{aligned} \quad (12)$$

with

$$u_0(t, x) = \int_0^t \int_{\mathbb{R}^n} e^{-\alpha s} \Gamma(s, y) \hat{V}_0(t-s, x-y) dy ds. \quad (13)$$

The boundedness of  $\hat{V}_0$  implies that  $u_0$  is bounded. Furthermore, if  $\hat{V}_0$  is bounded and vanishes for  $|x| \geq \eta$  and all  $t \geq 0$ , then an estimate yields that

$$u_0(t, x) \leq Ce^{-\left(\frac{|x|^2 - 2\eta|x|}{4dt}\right)}, \quad |x| > 2\eta. \quad (14)$$

This implies the overall assumption (21) made in [19]. It also implies that  $u_0$  is admissible in the sense of [22, (2.11)].

Interchanging the order of space and time integration in (12), we may focus on the two time integrations as follows:

$$\begin{aligned} & \int_0^t e^{-\alpha s} \Gamma(s, y) \int_0^{t-s} b(a) f(u(t-s-a, x-y)) d\nu(a) ds \\ &= \int_0^t \int_0^{t-a} e^{-\alpha s} \Gamma(s, y) b(a) f(u(t-s-a, x-y)) ds d\nu(a) \\ &= \int_0^t \int_a^t e^{-\alpha(r-a)} \Gamma(r-a, y) b(a) f(u(t-r, x-y)) dr d\nu(a) \\ &= \int_0^t \Phi(r, y) f(u(t-r, x-y)) dr \end{aligned}$$

where

$$\Phi(r, y) = \int_0^r e^{-\alpha(r-a)} \Gamma(r-a, y) b(a) d\nu(a). \quad (15)$$

Therefore, (12) may be rewritten as

$$u(t, x) = u_0(t, x) + kB_0 \int_0^t \int_{\mathbb{R}^n} \Phi(r, y) f(u(t-r, x-y)) dr dy. \quad (16)$$

**Proposition 1.** *Assume that  $\hat{V}_0$  is bounded and continuous. Then (16) has a unique solution  $u : [0, \infty) \times \mathbb{R}^n \rightarrow [0, \infty)$  which is continuous and bounded on  $[0, r] \times \mathbb{R}^n$  for each  $r > 0$ . In fact,  $u$  is bounded on  $[0, \infty) \times \mathbb{R}^n$ .*

*Proof.* This follows immediately from Theorem 2.1 in [22] and the boundedness of  $f$ .  $\square$

The spatial density of infected bacteria may also be rewritten in terms of  $u(t, x)$ , starting from (3) as follows:

$$\begin{aligned} I(t, x) &= \int_0^t \frac{\partial}{\partial a} B(t-a, x) \mathfrak{F}(a) da + \hat{J}(t, x) \\ &= \mathfrak{F}(t) B_0 - B(t, x) + \int_0^t B(t-a, x) d\nu(a) + \hat{J}(t, x) \\ &= \mathfrak{F}(t) B_0 - B_0 e^{-ku(t, x)} + \int_0^t B_0 e^{-ku(t-a, x)} d\nu(a) + \hat{J}(t, x) \end{aligned} \quad (17)$$

where

$$\hat{J}(t, x) = \int_t^\infty i_0(a-t, x) \frac{\mathfrak{F}(a)}{\mathfrak{F}(a-t)} da$$

Thus, we see from (8) and (17) that  $B$  and  $I$  are determined by  $u$ . We also get a formula for the lysed cell density from (6):

$$L(t, x) = B_0 \int_0^t \left(1 - e^{-ku(t-a, x)}\right) d\nu(a) - \hat{J}(t, x) \quad (18)$$

Like  $u(t, x)$ , it must be monotone nondecreasing in  $t$ .

**4. Spreading speeds.** The spreading speed (aka asymptotic speed of spread) for this equation,  $c^*$ , equals the minimum wave speed and is given by

$$c^* = \inf\{c \geq 0; \exists \lambda > 0 : \mathcal{G}(c, \lambda) < 1\} \quad (19)$$

where  $\mathcal{G}$  is the transform of  $kB_0\Phi$ :

$$\mathcal{G}(c, \lambda) = kB_0 \int_0^\infty \int_{\mathbb{R}^n} e^{-\lambda(cs+y_1)} \Phi(s, y) dy ds. \quad (20)$$

See [19] and [22, Sec.2].

We first show that  $c^*$  is proportional to  $\sigma = \sqrt{d}$ . Let  $\Phi_1$  the kernel  $\Phi$  associated with  $d = 1$ . Since  $\Phi(s, y) = \sigma^{-n} \Phi_1(s, y/\sigma)$ ,

$$\mathcal{G}(c, \lambda) = kB_0 \int_0^\infty \int_{\mathbb{R}^n} e^{-\lambda(cs+\sigma y_1)} \Phi_1(s, y) dy ds = \mathcal{G}_1(c/\sigma, \lambda\sigma),$$

where  $\mathcal{G}_1$  is  $\mathcal{G}$  associated with  $d = 1$ . So

$$\begin{aligned} c^*/\sigma &= \inf\{c/\sigma; c \geq 0, \exists \lambda > 0 : \mathcal{G}_1(c/\sigma, \lambda\sigma) < 1\} \\ &= \inf\{r \geq 0; \exists \mu > 0 : \mathcal{G}_1(r, \mu) < 1\} =: c_1. \end{aligned}$$

Changing the order of integration and [22, Prop.4.2] yield

$$\mathcal{G}_1(c, \lambda) = \frac{kB_0 \Psi(\lambda c)}{\lambda c + \alpha - \lambda^2}, \quad 0 \leq \lambda < \lambda^\#(c), \quad (21)$$

where  $\lambda^\#(c)$  is the unique  $\lambda > 0$  with  $\lambda c + \alpha - \lambda^2 = 0$  and

$$\Psi(s) = \int_0^\infty e^{-s\tau} b(\tau) d\nu(\tau). \quad (22)$$

For all  $c \geq 0$ ,

$$\mathcal{G}_1(c, 0) = \frac{kB_0}{\alpha} \int_0^\infty b(a) d\nu(a) =: \mathcal{R}_0. \quad (23)$$

$\mathcal{R}_0$  will turn out to be a crucial threshold parameter. Notice that  $c^* = 0 = c_1$  if and only if  $\mathcal{R}_0 \leq 1$ .  $\mathcal{R}_0$  has the interpretation of a basic phage reproduction number. Consider one phage that is introduced into a bacteria “lawn” of constant density  $B_0$ . Then  $\frac{1}{kB_0}$  is the average time it takes until it is adsorbed while  $1/\alpha$  is the average time available for adsorption. Recall that, at time 0,  $kB_0$  is the per phage rate of being adsorbed by susceptible bacteria and  $\alpha$  is the per phage loss rate including adsorption,  $\alpha \geq kB_0$ . So  $\frac{kB_0}{\alpha} \leq 1$  is the average probability that the phage manages to infect a bacterium while  $\int_0^\infty b(a)d\nu(a)$  is the average amount of viruses that are released when the bacterium eventually lyses.

The following alternative formula for  $c_1$  is inspired by [2]. The following chain of equivalences holds for  $c > 0$  provided that  $c^* > 0$ :

$$\begin{aligned} c \leq c_1 &\iff \forall \lambda > 0 : G_1(c, \lambda) \geq 1 \\ &\iff \forall \lambda > 0 : kB_0\Psi(\lambda c) \geq \lambda c + \alpha - \lambda^2 \\ &\iff \forall s > 0 : kB_0\Psi(s) \geq s + \alpha - \frac{s^2}{c^2} \\ &\iff \forall s > 0 : \frac{1}{c^2} \geq \frac{s + \alpha - kB_0\Psi(s)}{s^2} \end{aligned}$$

So

$$c_1 = \frac{1}{\sqrt{\Theta}}, \quad \Theta = \sup_{s>0} \frac{s + \alpha - kB_0\Psi(s)}{s^2}. \quad (24)$$

This equation shows that the spreading speed is an increasing function of  $kB_0$  and, via  $\Psi$ , on the virus release rate  $b$ . It is a decreasing function of  $\alpha$ . If  $\mathcal{R}_0 > 1$ , by [19] (see also [22, Prop.2.3]), the spreading speed for (16),  $c^* = \sqrt{d}c_1$ , can be determined from the unique solution  $(c_1, \lambda_1)$  of

$$\mathcal{G}_1(c, \lambda) = 1, \quad \frac{d}{d\lambda}\mathcal{G}_1(c, \lambda) = 0. \quad (25)$$

Equivalently, with  $\Psi$  in (22),

$$\begin{aligned} kB_0\Psi(c\lambda) &= \lambda c + \alpha - \lambda^2 \\ c\Psi'(c\lambda)(\lambda c + \alpha - \lambda^2) &= (c - 2\lambda)\Psi(c\lambda). \end{aligned} \quad (26)$$

The next result follows from Theorem 2.8 in [19] and Theorems 2.1 and 2.2 in [22]. It says that  $c^*$  is the spreading speed for (16).

**Theorem 4.1.** *Assume that  $\hat{V}_0$  is bounded and continuous, vanishes for  $|x| \geq \eta$  and all  $t \geq 0$ , and is not identically zero. Let  $\mathcal{R}_0 > 1$ , and  $c^* > 0$  be the unique solution of (19).*

*Then the unique solution of (16) satisfies*

$$\lim_{t \rightarrow \infty, |x| \geq ct} u(t, x) = 0 \quad (27)$$

for  $c > c^*$ .

Further let  $u^*$  be the unique positive solution of  $u^* = \mathcal{R}_0 f(u^*)$ . Then, for every  $c \in (0, c^*)$ ,

$$\liminf_{t \rightarrow \infty, |x| \leq ct} u(t, x) \geq u^* \quad (28)$$

**Remark 1.** We have followed the notation of [22] in (27) and (28). The former means that for every  $\epsilon > 0$ , there exists  $t > 0$  such that  $|u(s, x)| < \epsilon$  for  $s \geq t$ ,  $|x| \geq cs$ . (28) has the meaning:

$$\liminf_{t \rightarrow \infty, |x| \leq ct} u(t, x) = \sup_{t \geq 0} \inf \{u(s, x) : s \geq t, |x| \leq cs\}.$$

We now leverage Theorem 4.1 to obtain information about  $B, I$  and  $L$ . (27), (28), and (8) give

$$\lim_{t \rightarrow \infty, |x| \geq ct} B(t, x) = B_0, \quad c > c^*,$$

and

$$\limsup_{t \rightarrow \infty, |x| \leq ct} B(t, x) \leq B_0 e^{-ku^*}, \quad 0 < c < c^*.$$

Note that the first integral in the expression (3) is dominated by  $kB_0 u(t, x)$  and  $\hat{J}(t, x)$  has compact support in  $x$  uniformly in  $t$  if  $i_0$  does, so in this case we have

$$\lim_{t \rightarrow \infty, |x| \geq ct} I(t, x) = 0, \quad c > c^*.$$

(27) implies that for  $c > c^*$  we have

$$\lim_{t \rightarrow \infty, |x| \geq ct} \int_0^t e^{-ku(t-a, x)} d\nu(a) = \int_0^\infty d\nu(a) = 1$$

which implies, via (18) that

$$\lim_{t \rightarrow \infty, |x| \geq ct} L(t, x) = 0, \quad c > c^*$$

Also, by (6) and the expression above for  $B$ , we have

$$\liminf_{t \rightarrow \infty, |x| \leq ct} I(t, x) + L(t, x) \geq B_0(1 - e^{-ku^*}), \quad 0 < c < c^*.$$

For completeness, we add that no substantial spread occurs in the subthreshold case  $\mathcal{R}_0 \leq 1$ . Then  $\mathcal{R}_0 f(u) < u$  for all  $u > 0$  and [19, Thm.2.6] applies.

**Theorem 4.2.** *Assume that  $\hat{V}_0$  is bounded and continuous and vanishes for  $|x| \geq \eta$  and all  $t \geq 0$ . Let  $\mathcal{R}_0 \leq 1$ .*

*Then the unique solution of (16) satisfies*

$$u(t, x) \rightarrow 0, \quad |x| \rightarrow \infty, \quad \text{uniformly in } t \geq 0.$$

**5. Traveling waves.** In this section we seek traveling wave solutions of the asymptotic form of (10) 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 has the form  $u(t, x) = U(ct + x)$  with  $U(s) \rightarrow 0$  as  $s \rightarrow -\infty$ . Equivalently,

$$U(ct + x) = kB_0 \int_0^\infty \int_{\mathbb{R}} \Phi(r, y) f(U(c(t-r) + x - y)) dy dr$$

Set  $s = ct + x$  to obtain

$$U(s) = kB_0 \int_0^\infty \int_{\mathbb{R}} \Phi(r, y) f(U(s - cr - y)) dy dr. \quad (29)$$

Observe that the translate of a traveling wave solution is also a traveling wave solution.

We obtain the following results from Theorem 3.1, 3.2, 3.4, and 3.5 in [22] which are based on results in [5] and [6].



**Theorem 5.1.** *Let  $\mathcal{R}_0 > 1$  and  $c \geq c^*$ . Then there exists a solution  $u(t, x) = U(ct + x)$  of the equation*

$$u_t(t, x) = d\partial_x^2 u(t, x) - \alpha u(t, x) + kB_0 \int_0^\infty b(a)f(u(t-a, x))d\nu(a), \quad t, x \in \mathbb{R}, \quad (30)$$

with an increasing continuous  $U : \mathbb{R} \rightarrow \mathbb{R}_+$  satisfying  $U(s) \rightarrow 0$  as  $s \rightarrow -\infty$  and  $U(s) \rightarrow u^*$  as  $s \rightarrow \infty$ .

For  $c > c^*$ , such solutions are unique up to translation.

If  $c \in (0, c^*)$ , no traveling wave solutions exists.

We observe that a traveling wave solution  $U(s)$  of (30) satisfies the delay differential equation:

$$dU''(s) - cU'(s) - \alpha U(s) + kB_0 \int_0^\infty b(a)f(U(s-ca))d\nu(a) = 0. \quad (31)$$

The threshold condition  $\mathcal{R}_0 > 1$  is necessary for the existence of traveling wave solutions.

**Remark 2.** If  $\mathcal{R}_0 \leq 1$ , there exists no nontrivial bounded nonnegative solution of (29).

*Proof.* Suppose it does. Set  $\bar{U} = \sup U$ . Since  $f$  is nondecreasing,  $\bar{U} \leq \mathcal{R}_0 f(\bar{U})$ . If  $\bar{U} > 0$ , this implies  $\bar{U} < \bar{U}$ .  $\square$

Now our focus turns to showing the existence of traveling waves for the asymptotic form of our original system under the same conditions as in Theorem 5.1.

**Theorem 5.2.** *Let  $\mathcal{R}_0 > 1$  and  $c \geq c^*$ . Then there exists traveling wave solutions  $V(x + ct)$  and  $B(x + ct)$  of*

$$\begin{aligned} V_t &= dV_{xx} - \alpha V + k \int_0^\infty b(a)B(t-a, x)V(t-a, x)d\nu(a) \\ B_t &= -kB V \end{aligned} \quad (32)$$

satisfying

$$B(-\infty) = B_0, \quad B(+\infty) = B_0 e^{-ku^*}, \quad V(\pm\infty) = 0. \quad (33)$$

$B$  and  $V$  are positive and  $B$  is strictly decreasing. Moreover,  $V \in L^1(\mathbb{R})$  and the total amount of virus in the wave is given by

$$\int_{\mathbb{R}} V(s)ds = cu^* = c\mathcal{R}_0 f(u^*). \quad (34)$$

*Proof.* Let  $U$  be a traveling wave solution of (30) described in Theorem 5.1, which also satisfies (31). Define  $B$  and  $V$  as follows:

$$V(s) = U'(s)c, \quad B(s) = B_0 e^{-kU(s)}. \quad (35)$$

Differentiating (31) and multiplying by  $c$ , we obtain

$$dV''(s) - cV'(s) - \alpha V(s) + k \int_0^\infty b(a)B_0 e^{-kU(s-ca)} V(s-ca)d\nu(a) = 0.$$

In view of (35), this becomes

$$dV''(s) - cV'(s) - \alpha V(s) + k \int_0^\infty b(a)B(s-ca)V(s-ca)d\nu(a) = 0. \quad (36)$$

As  $U(s)$  is bounded on  $\mathbb{R}$  with finite limits at  $\pm\infty$  and  $U'(s) \geq 0$ , it follows that  $U'(\pm\infty) = 0$ .

$B$  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 (33). It follows that  $B$  and  $V$  satisfy (32).

Finally, we note that  $B'$  is integrable on  $\mathbb{R}$ , implying that  $BV$  is as well, and since  $B$  is bounded from below, we conclude that  $V$  is integrable. (34) is obtained by integrating (36) and changing the order of integration.  $\square$

**6. Special examples.** Two important special cases of the general model are considered here. We first explore the case that the cumulative latency distribution is of gamma type:

$$\nu([0, a]) = \int_0^a g_m(s; r) ds, \quad g_m(s, r) = \frac{r^m s^{m-1}}{(m-1)!} e^{-rs}, \quad s \geq 0. \quad (37)$$

The mean latency is  $\tau = m/r$  and the variance is  $\sigma^2 = m/r^2$  where  $m \in \mathbb{N}$  and  $r > 0$ . Furthermore, we assume that the burst size is independent of latency duration:

$$b(a) \equiv b \quad (38)$$

In this case, the spreading speed is determined by (25) where  $\Psi$  (see (22)) is given by

$$\Psi(s) = b \left( \frac{r}{r+s} \right)^m = b \left( \frac{\tau}{\tau + \sigma^2 s} \right)^{\tau^2/\sigma^2}.$$

$\log(\Psi(s)/b)$  is an increasing function of the latent period variance  $v = \sigma^2$  and a decreasing function of the mean latent period  $\tau$ , implying that the spreading speed  $c^*$  is increasing with  $\sigma^2$  and decreasing with  $\tau$ . Indeed,

$$\begin{aligned} \frac{\partial}{\partial v} \log(\Psi(s)/b) &= \frac{\tau^2}{v^2} \left( \log(1+x) - \frac{x}{1+x} \right) > 0 \\ \frac{\partial}{\partial \tau} \log(\Psi(s)/b) &= \frac{\tau}{v} \left( -\log(1+x) - \left( \log(1+x) - \frac{x}{1+x} \right) \right) < 0 \end{aligned}$$

where  $x = vs/\tau$ .

The basic phage reproduction number is given by

$$\mathcal{R}_0 = \frac{kB_0 b}{\alpha}. \quad (39)$$

Indeed, this expression for  $\mathcal{R}_0$  holds whenever  $b$  is constant, regardless of the probability measure  $\nu$ . Recall that nontrivial spreading solutions and traveling wave solutions exist only when  $\mathcal{R}_0 > 1$  and that  $\alpha \geq kB_0$  is required for biological consistency. These relations imply that we must have

$$kB_0 \leq \alpha < bkB_0$$

to observe phage spreading.

If (37) and (38) hold and if we let

$$I^j(t, x) = \frac{k}{r} \int_0^\infty g_j(t-s; r) B(s, x) V(s, x) ds, \quad 1 \leq j \leq m$$

then we may write (4) as a coupled system of ODEs, that effectively produce the latency delay, and a single PDE for viruses:

$$\begin{aligned} V_t &= d\Delta V - \alpha V + brI^m \\ B_t &= -kBV \\ I_t^1 &= kB V - rI^1 \\ I_t^j &= r(I^{j-1} - I^j), \quad 2 \leq j \leq m \end{aligned} \quad (40)$$

Here, we have assumed that the spreading initiated a very long time ago, so  $B$  and  $V$  are defined for  $t \leq 0$  and that  $i(t, a, x)$  is given by the first expression of (2) for all  $t$ . Therefore, the burst term in the  $V$  equation is given by

$$bk \int_0^\infty B(t-a, x)V(t-a, x)d\nu(a) = brI^m(t, x).$$

(40) results from the linear chain trick, see e.g. [17]. We note that the case  $m = 1$  gives an exponentially distributed latent period, yielding a system that is very similar to the one proposed by Yin and McCaskill [24], the only difference being the absence of the virus desorption reaction.

Another case of interest is when the latent period is assumed to be a fixed constant  $\tau$ , which results from the survivorship function  $\mathfrak{F}(a) = 1 - H(a - \tau)$ , where  $H(t)$  is the usual Heaviside function with unit jump at the origin. In this case, the equation for viruses becomes:

$$V_t = d\Delta V - \alpha V + bkB(t - \tau, x)V(t - \tau, x), \quad t > \tau \quad (41)$$

where  $b = b(\tau)$ .

In this case, the spreading speed is determined by (25) where  $\Psi$  (see (22)) is given by

$$\tilde{\Psi}(s) = be^{-s\tau}.$$

and  $\mathcal{R}_0$  by (39). It is easily seen that  $\tilde{\Psi}(s) < \Psi(s)$  for the same value of mean latency  $\tau$  and consequently (see (24)) the spreading speed  $c^*$  is lower for the fixed latency case than for the gamma-distributed latency.

**7. Estimates and approximations of the spreading speed.** Koch [10] argued that the speed of spread is proportional to  $\sqrt{d/\tau}$ . As far the diffusion constant is concerned, we rigorously showed that this estimate is correct. We consider the case of a fixed lysis time  $\tau$ , in other words, where  $V$  is given by (41), and show that the spreading speed is not proportional to  $1/\sqrt{\tau}$ . Koch made his argument in 1964 when it was not yet widely known that the solutions of reaction diffusion equations spread with finite speed even when there is no delay.

We can assume that  $d = 1$ . Then

$$G(c, \lambda) = \frac{\beta e^{-\lambda c \tau}}{\lambda c + \alpha - \lambda^2},$$

with

$$\beta = kB_0b = \mathcal{R}_0\alpha. \quad (42)$$

The spreading speed  $c^*$  is the solution of

$$\begin{aligned} \beta e^{-\lambda c \tau} &= \lambda c + \alpha - \lambda^2, \\ c\tau(\lambda c + \alpha - \lambda^2) &= 2\lambda - c, \end{aligned}$$

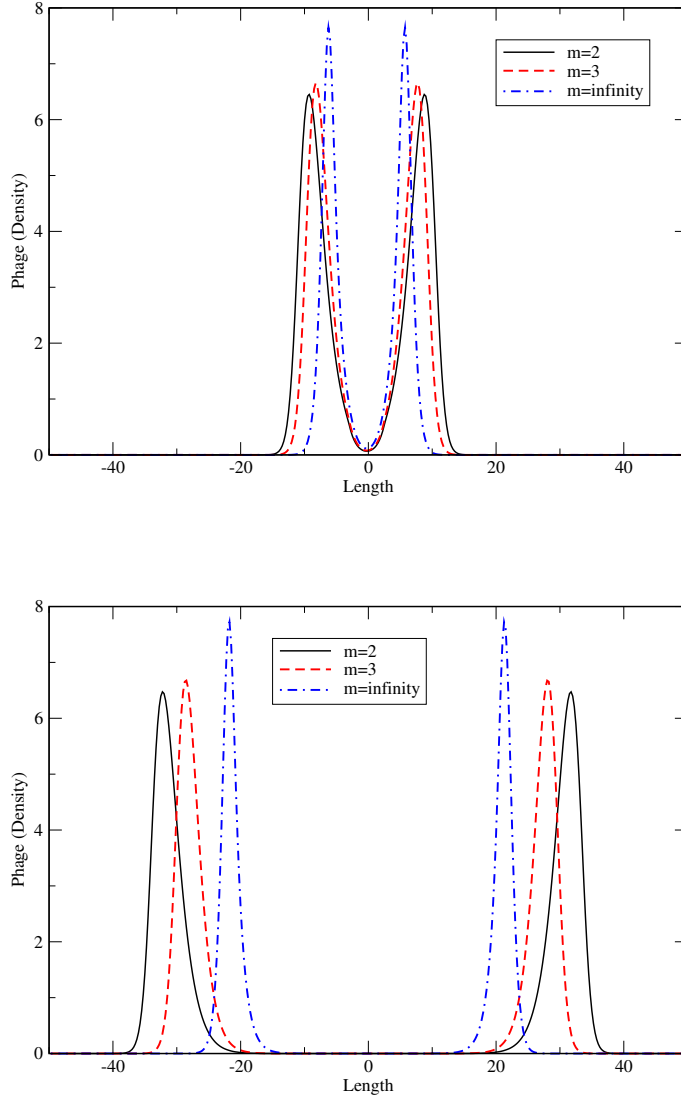


FIGURE 1. Plot showing phage density at time  $T = 5$  (top) and  $T = 15$  (bottom) for (40) and (41). Solid lines correspond to  $r = m = 2$ , dashed lines correspond to  $r = m = 3$ , and hashed lines to  $r = m = \infty$ , i.e., to (41). In all cases the mean latent period is 1.0 while its variance is 0.5, 0.33, and 0 respectively, confirming that wave speed increases with the variance. Other parameters are  $k = 1$ ,  $\alpha = 2$ ,  $b = 30$ . A centered finite difference scheme in space and an Adam-Bashforth scheme in time are used to approximate the solutions.

where  $\beta > \alpha$ . We multiply the second equation by  $\lambda$  and set  $\xi = c\lambda$ ,

$$\begin{aligned}\beta e^{-\xi\tau} &= \xi + \alpha - \lambda^2, \\ \xi\tau(\xi + \alpha - \lambda^2) &= 2\lambda^2 - \xi.\end{aligned}$$

We solve the second equation for  $\lambda^2$ ,

$$\lambda^2 = \xi \frac{\tau(\xi + \alpha) + 1}{2 + \xi\tau}. \quad (43)$$

We substitute the result into the first equation,

$$\beta e^{-\xi\tau} = \xi + \alpha - \xi \frac{\tau(\xi + \alpha) + 1}{2 + \xi\tau}.$$

We rearrange

$$\beta e^{-\xi\tau}(2 + \xi\tau) = (\xi + \alpha)(2 + \xi\tau) - \xi\tau(\xi + \alpha) - \xi.$$

We simplify,

$$0 = \xi + 2\alpha - \beta e^{-\xi\tau}(2 + \xi\tau) = F(\tau, \xi). \quad (44)$$

Once  $\xi$  has been found, we obtain  $c$  from (43) and  $\xi = c\lambda$ ,

$$c^2 = \frac{(2 + \xi\tau)\xi}{\tau(\xi + \alpha) + 1}. \quad (45)$$

There are two cases at least in which the solutions can be explicitly found,

$$\begin{aligned}\tau = 0: & \quad \xi = 2(\beta - \alpha), \quad c^2 = 4(\beta - \alpha), \\ \tau = 1/\alpha: & \quad c^2 = \xi = \alpha \ln(\beta/\alpha).\end{aligned} \quad (46)$$

$F$  is a strictly increasing function of both  $\tau$  and  $\xi$ . So there exists a unique solution  $\xi > 0$  which is a strictly decreasing function of  $\tau$ ,

$$\xi \leq 2(\beta - \alpha). \quad (47)$$

It follows from the implicit function theorem that  $\xi$  is a differentiable function of  $\tau$ .

Let  $\zeta = \tau\xi$ . Then

$$0 = \xi + 2\alpha - \beta e^{-\zeta}(2 + \zeta) := G(\zeta, \xi). \quad (48)$$

$G$  is a strictly increasing function of both  $\xi$  and  $\zeta$ . So  $\zeta$  is a strictly decreasing function of  $\xi$  and thus a strictly increasing function of  $\tau$ .

If  $\tau \rightarrow \infty$ ,  $\xi \rightarrow 0$  and  $\zeta = \xi\tau \nearrow \zeta_\infty$  where  $\zeta_\infty$  is the solution of

$$0 = \alpha - \beta e^{-\zeta_\infty} \left(1 + \frac{\zeta_\infty}{2}\right).$$

As a function of  $\xi$  and  $\tau$ ,  $c^2$  is a strictly increasing function of  $\xi$  and a strictly decreasing function of  $\tau$ . Since  $\xi$  is a strictly decreasing function of  $\tau$ ,  $c^2$ , considered as a function of  $\tau$ , is a strictly decreasing function of  $\tau$ . Further

$$(c\tau)^2 = \frac{(2 + \zeta)\zeta}{(\xi + \alpha) + (1/\tau)}$$

is a strictly increasing function of  $\zeta$  and  $\tau$  and a strictly decreasing function of  $\xi$  and thus a strictly increasing function of  $\tau$ ,

$$(c\tau)^2 \nearrow \frac{(2 + \zeta_\infty)\zeta_\infty}{\alpha}, \quad \tau \rightarrow \infty.$$

So, for large  $\tau$ , the spreading speed is approximately proportional to  $1/\tau$ . We perform a Taylor expansion of

$$\begin{aligned}\theta(\zeta) &= e^{-\zeta}(2 + \zeta), \\ \theta(0) &= 2, \quad \theta'(\zeta) = -e^{-\zeta}(\zeta + 1) \\ \theta'(0) &= -1, \quad \theta''(\zeta) = e^{-\zeta}\zeta.\end{aligned}$$

Thus

$$\theta(\zeta) = 2 - \zeta + \frac{1}{2}\zeta^2 e^{-\tilde{\zeta}} \tilde{\zeta}, \quad 0 < \tilde{\zeta} < \zeta.$$

Hence

$$2 - \zeta \leq \theta(\zeta) \leq 2 - \zeta + \frac{1}{2}\zeta^3, \quad \zeta \geq 0.$$

We obtain the inequalities,

$$\beta[2 - \xi\tau] \leq \xi + 2\alpha \leq \beta[2 - \xi\tau + (1/2)(\xi\tau)^3].$$

They can be transformed into

$$\frac{2(\beta - \alpha)}{1 + \beta\tau} \leq \xi \leq \frac{2(\beta - \alpha)}{1 + \beta\tau} + \frac{(\beta/2)(\xi\tau)^3}{1 + \beta\tau}. \quad (49)$$

Since  $\xi \leq 2(\beta - \alpha)$ ,

$$\frac{2(\beta - \alpha)}{1 + \beta\tau} \leq \xi \leq \frac{2(\beta - \alpha)[1 + 2\tau^3\beta(\beta - \alpha)^2]}{1 + \beta\tau}. \quad (50)$$

This means that the estimate from below is also a good approximation if  $\tau$  is small or  $\beta - \alpha$  is small. Since  $c^2$  is an increasing function of  $\xi$ , by (45),

$$c^2 \geq \frac{2(1 + \beta\tau) + 2(\beta - \alpha)\tau}{\tau(2(\beta - \alpha) + \alpha(1 + \beta\tau)) + 1 + \beta\tau} \frac{2(\beta - \alpha)}{1 + \beta\tau}.$$

We reorganize introducing  $\delta = \beta - \alpha$

$$c^2 \geq \frac{(1 + \beta\tau) + \delta\tau}{(1 + [\beta - \delta]\tau)(1 + \beta\tau) + 2\delta\tau} \frac{4(\beta - \alpha)}{1 + \beta\tau}.$$

We simplify

$$c^2 \geq 4 \frac{\beta - \alpha}{1 + \beta\tau} \frac{1 + \beta\tau + \delta\tau}{(1 + \beta\tau)^2 + \delta\tau - \delta\beta\tau^2} \geq 4 \frac{\beta - \alpha}{(1 + \beta\tau)^2}.$$

This is still a good approximation if  $\tau$  is small,

$$c \geq \frac{2\sqrt{\beta - \alpha}}{1 + \beta\tau}.$$

While the dependence of  $c$  on  $\tau$  is interesting because of Koch's conjecture,  $\beta$  is the parameter that is most amenable to experimental manipulation by changing the density of bacteria. As we already mentioned, our formulas are good approximations if  $\beta$  is not much larger than  $\alpha$ . Now we will explore how  $c$  depends on large  $\beta$ . Arguments as before show that  $\xi$  and  $c$  are strictly increasing functions of  $\beta$  as to be expected and that  $\xi \rightarrow \infty$  and  $c \rightarrow \infty$  as  $\beta \rightarrow \infty$ .

We rewrite (44) as

$$e^{\xi\tau} = \beta \frac{2 + \xi\tau}{\xi + 2\alpha} = \frac{\beta}{\alpha} \frac{1 + \tau(\xi/2)}{1 + \alpha(\xi/2)}. \quad (51)$$

We take logarithms,

$$\xi\tau = \ln(\beta/\alpha) + \ln(1 + \tau(\xi/2)) - \ln(1 + (1/\alpha)(\xi/2)). \quad (52)$$

By a Taylor expansion,

$$\xi\tau \leq 2\ln(\beta/\alpha).$$

We substitute this inequality into (52),

$$\xi\tau \leq \ln(\beta/\alpha) + \ln(1 + \ln(\beta/\alpha)).$$

We first consider the case  $\alpha\tau \geq 1$ . Then  $\xi\tau \geq \ln(\beta/\alpha)$ . We conclude that  $\frac{\xi\tau}{\ln(\beta/\alpha)} \rightarrow 1$  as  $\beta/\alpha \rightarrow \infty$ .

If  $1 \geq \alpha\tau$ , then  $\xi\tau \leq \ln(\beta/\alpha)$  and

$$\ln(\beta/\alpha) - \ln\left(1 + \frac{1}{2\alpha} \ln(\beta/\alpha)\right) \leq \xi\tau \leq \ln(\beta/\alpha).$$

Again this implies that  $\frac{\xi\tau}{\ln(\beta/\alpha)} \rightarrow 1$  as  $\beta/\alpha \rightarrow \infty$ . From (45),  $c^2/\xi \rightarrow 1$  as  $\xi \rightarrow \infty$ , so

$$\frac{c}{\sqrt{\ln(\beta/\alpha)}} \rightarrow \sqrt{\tau}, \quad \beta/\alpha \rightarrow \infty. \quad (53)$$

Recall that

$$\xi\tau \leq 2\ln(\beta/\alpha) = 2\ln\left(1 + \frac{\beta - \alpha}{\alpha}\right) \leq 2\frac{\beta - \alpha}{\alpha}.$$

We substitute this inequality into (49),

$$\frac{2(\beta - \alpha)}{1 + \beta\tau} \leq \xi \leq \frac{2(\beta - \alpha)}{1 + \beta\tau} + \frac{(\beta/2)\left(2\frac{\beta - \alpha}{\alpha}\right)^3}{1 + \beta\tau} = \frac{2(\beta - \alpha)}{1 + \beta\tau} \left(1 + \frac{2\beta(\beta - \alpha)^2}{\alpha^3}\right).$$

This shows that  $\xi \approx \frac{2(\beta - \alpha)}{1 + \beta\tau}$  is also a good approximation if  $\beta - \alpha > 0$  is small, uniformly for  $\tau \geq 0$ ,

$$\frac{\xi(1 + \beta\tau)}{2(\beta - \alpha)} \rightarrow 1, \quad \beta \searrow \alpha, \quad \text{uniformly for } \tau \geq 0. \quad (54)$$

Let  $\alpha\tau \geq 1$ . Then  $c^2$  is an increasing function of  $\xi\tau$  and

$$\frac{2\xi}{1 + \alpha\tau} \leq c^2 \leq \frac{2\xi}{1 + \alpha\tau} \frac{1 + \ln(\beta/\alpha)}{1 + \frac{2}{1 + \alpha\tau} \ln(\beta/\alpha)}.$$

Let  $\alpha\tau \leq 1$ . Then  $c^2$  is a decreasing function of  $\xi\tau$  and, since  $\xi \leq 2(\beta - \alpha)$ ,

$$\frac{2\xi}{1 + \alpha\tau} \geq c^2 \geq 2\xi \frac{1 + (\beta - \alpha)\tau}{1 + \alpha\tau + 2(\beta - \alpha)\tau} = 2\xi \frac{1 + (\beta - \alpha)\tau}{1 + \beta\tau + (\beta - \alpha)\tau} \geq \frac{2\xi}{1 + \beta\tau}.$$

We conclude

$$\frac{c^2}{2\xi}(1 + \alpha\tau) \rightarrow 1, \quad \beta \searrow \alpha, \quad \text{uniformly for } \tau \geq 0.$$

By (54),

$$\frac{c^2}{4(\beta - \alpha)}(1 + \alpha\tau)(1 + \beta\tau) \rightarrow 1, \quad \beta \searrow \alpha, \quad \text{uniformly for } \tau \geq 0.$$

So

$$c \frac{1 + \alpha\tau}{2\sqrt{\beta - \alpha}} \rightarrow 1, \quad \beta \searrow \alpha, \quad \text{uniformly for } \tau \geq 0.$$

## REFERENCES

- [1] E. Beretta and Y. Kuang, *Modeling and analysis of a marine bacteriophage infection with latency*, Nonlinear Analysis RWA, **2** (2001), 35–74.
- [2] C. Beaumont, J.-B. Burie, A. Ducrot and P. Zongo, *Propagation of Salmonella within an industrial hens house*, SIAM J. Appl. Math., **72** (2012), 1113–1148.
- [3] A. Campbell, *Conditions for existence of bacteriophages*, Evolution, **15** (1961), 153–165.
- [4] P. DeLeenheer and H. L. Smith, *Virus dynamics: A global analysis*, SIAM J. Appl. Math., **63** (2003), 1313–1327.
- [5] O. Diekmann, *Limiting behaviour in an epidemic model*, Nonlinear Analysis, TMA, **1** (1977), 459–470.
- [6] O. Diekmann and H. G. Kaper, *On the bounded solutions of a nonlinear convolution equation*, Nonlinear Anal.: Theory, Methods, Appl., **2** (1978), 721–737.
- [7] E. Ellis and M. Delbrück, *The growth of bacteriophage*, J. of Physiology, **22** (1939), 365–384.
- [8] J. Fort and V. Mendez, *Time-delayed spread of viruses in growing plaques*, Physical Review Letters, **89** (2002), 178101.
- [9] D. A. Jones, G. Röst, H. L. Smith and H. R. Thieme, *On spread of phage infection of bacteria in a petri dish*, SIAM Journal on Applied Mathematics, **72** (2012), 670–688.
- [10] A. L. Koch, *The growth of viral plaques during enlargement phase*, J. Theor. Biol., **6** (1964), 413–431.
- [11] Y. Lee and J. Yin, *Imaging the propagation of viruses*, Communication to the Editor, Biotechnology and Bioengineering, **52** (1996), 438–442.
- [12] B. Levin, F. Stewart and L. Chao, *Resource-limited growth, competition, and predation: A model, and experimental studies with bacteria and bacteriophage*, Amer. Naturalist, **111** (1977), 3–24.
- [13] M. A. Lewis, B. Li and H. F. Weinberger, *Spreading speed and linear determinacy for two-species competition models*, J. Math. Biol., **45** (2002), 219–233.
- [14] M. A. Nowak and R. M. May, “Virus Dynamics,” Oxford University Press, New York, 2000.
- [15] V. Ortega-Cejas, J. Fort, V. Mendez and D. Campos, *Approximate solution to the speed of spreading viruses*, Physical Review E, **69** (2004), 031909.
- [16] A. S. Perelson and P. W. Nelson, *Mathematical analysis of HIV-1 dynamics in vivo*, SIAM Rev., **41** (1999), 3–44.
- [17] H. L. Smith and H. R. Thieme, *Persistence of bacteria and phages in a chemostat*, J. of Math. Biol., **64** (2012), 951–979.
- [18] H. R. Thieme, *A model for the spatial spread of an epidemic*, J. Math. Biology, **4** (1977), 337–351.
- [19] H. R. Thieme, *Asymptotic estimates of the solutions of nonlinear integral equations and asymptotic speeds for the spread of populations*, J. Reine Angew. Math., **306** (1979), 94–121.
- [20] H. R. Thieme, *Density-dependent regulation of spatially distributed populations and their asymptotic speed of spread*, J. Math. Biology, **8** (1979), 173–187.
- [21] H. R. Thieme, “Mathematics in Population Biology,” Princeton University Press, Princeton, 2003.
- [22] H. R. Thieme and X.-Q. Zhao, *Asymptotic speeds of spread and traveling waves for integral equations and delayed reaction-diffusion models*, JDE, **195** (2003), 430–470.
- [23] H. F. Weinberger, M. A. Lewis and B. Li, *Analysis of linear determinacy for spread in cooperation models*, J. Math. Biol., **45** (2002), 183–218.
- [24] J. Yin and J. S. McCaskill, *Replication of viruses in a growing plaque: A reaction-diffusion model*, Biophysics J., **61** (1992), 1540–1549.
- [25] J. Yin and L. You, *Amplification and spread of viruses in a growing plaque*, J. Theor. Biol., **200** (1999), 365–373.

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