

## A REACTION-DIFFUSION SYSTEM WITH TIME-DELAY MODELING VIRUS PLAQUE FORMATION

HAL L. SMITH AND HORST R. THIEME

**1 Introduction** Based on the work of [16], we introduce a model of virus spread on its bacterial host. The model couples a delayed diffusion equation for viruses (phages) with a differential-delay equation for infected bacteria and an ordinary differential equation for susceptible bacteria, but can be reduced to a single delayed partial differential equation. After infection of susceptible bacteria, viruses incubate in infected bacterial cells for a fixed length of time before the cells burst and the released viruses spread by diffusion. This creates a stage structure for viruses with an immobile and a mobile stage, which links our model to stage structured dispersal models as they have been considered by Herb Freedman and coauthors [6, 7, 15].

In a previous article [8], it was shown that virus infection spreads at a constant speed and that traveling wave solutions representing a wave of viral infection. Consequently, it was natural to consider the model on an infinite spatial domain, the entire two-dimensional plane. In this paper, we analyze the model in its natural setting of a bounded domain which in the applications is the surface of a Petri dish, a disk.

**2 Model and main result** We assume that host bacteria in agar do not grow or diffuse. The virus latent period is assumed to have duration exactly  $\tau$  units of time: a host cell infected at time  $t$  lyses at time  $t + \tau$ . We assume that on average  $\beta > 0$  virus are released when an infected host cell lyses;  $\beta$  is called the “burst size” or “yield.” Viruses diffuse and adsorb to host bacteria creating infected cells. Virus

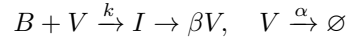
---

The work of the first author was supported by NSF Grant DMS-0918440. The work of the second author was supported by NSF Grant DMS-0715451.

Keywords: Virus plaque, virus spread, incubation delay.

Copyright ©Applied Mathematics Institute, University of Alberta.

density is denoted by  $V$ , bacteria density is denoted by  $B$ , and infected bacteria density is denoted by  $I$ . Our model is essentially captured by the schematic reactions:



where a cell remains in the infected  $I$ -compartment exactly  $\tau$  units of time. Here,  $\alpha \geq 0$  denotes virus decay rate and  $k$  denotes virus adsorption rate.

It is assumed 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 virus can only be produced by the lysing of the initial cohort  $I^0$  of infected cells:

$$\begin{aligned} (2.1) \quad V_t &= d\Delta V - kVB + \beta I^0(\tau - t, x) - \alpha V, \\ B_t &= -kBV, \quad x \in \Omega, \quad 0 \leq t \leq \tau, \\ I_t &= kBV - I^0(\tau - t, x). \end{aligned}$$

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

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

$$\begin{aligned} (2.2) \quad V_t &= d\Delta V - kVB + \beta kB(t - \tau, x)V(t - \tau, x) - \alpha V, \\ B_t &= -kBV, \quad x \in \Omega, \quad t > \tau, \\ I_t &= kBV - kB(t - \tau, x)V(t - \tau, x). \end{aligned}$$

Here,  $k$  is the adsorption constant and  $d$  is the effective diffusion constant for phage. Note that virus adsorption to already infected cells is neglected.  $\Omega$  denotes the domain, typically in applications, a disk in the plane  $\mathbb{R}^2$ . 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.

$V$  must satisfy Neumann boundary conditions

$$(2.3) \quad \frac{\partial V}{\partial n}(x) = 0, \quad x \in \partial\Omega,$$

where  $n = n(x)$ ,  $x \in \partial\Omega$ , denotes the outward pointing normal vector field.

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

$$(2.4) \quad \begin{aligned} I(t, x) &= \int_0^t kB(\nu, x)V(\nu, x) d\nu + \int_0^{\tau-t} I^0(s, x) ds \\ &= B(0, x) - B(t, x) + \int_0^{\tau-t} I^0(s, x) ds, \quad 0 < t \leq \tau, \\ I(t, x) &= \int_{t-\tau}^t kB(\nu, x)V(\nu, x) d\nu \\ &= B(t - \tau, x) - B(t, x), \quad t > \tau. \end{aligned}$$

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

$$(2.5) \quad B(0, x) = B_0(x), \quad V(0, x) = V_0(x).$$

Solutions of our system exist, are unique, and nonnegative, globally in time.

**Theorem 2.1.** *Let  $B_0$  and  $V_0$  be nonnegative and continuous on  $\bar{\Omega}$ . Assume that  $I^0$  is continuous on  $[0, \tau] \times \bar{\Omega}$  and is continuously differentiable with respect to  $t$  and twice continuously differentiable in  $x$  in  $[0, \tau] \times \Omega$ . Then there exists a unique nonnegative solution  $(V, B)$  satisfying (2.1) on  $(0, \tau] \times \Omega$ , (2.2) on  $(\tau, \infty) \times \Omega$ , and (2.3) and (2.5).  $(V, B)$  is bounded on  $[0, T] \times \bar{\Omega}$  for each  $T > 0$ .*

Theorem 2.1 is proved by the method of steps. See Theorem 2.1 of [8]. Our main result follows. We consider separately the case with virus decay ( $\alpha > 0$ ) and without virus decay ( $\alpha = 0$ ). It is convenient to introduce

$$(2.6) \quad \hat{V}_0(\tau, x) = V_0(x) + \beta \int_0^\tau I^0(s, x) ds,$$

the sum of the viruses that are initially present and of the cumulative amount of viruses that have been released by the initial cohort of infected bacterial cells.

**Theorem 2.2.** *Let the assumptions of Theorem 2.1 be satisfied and let  $(V, B)$  be the corresponding solution of (2.1)–(2.2). Assume that  $\beta > 1$  and  $\widehat{V}_0(\tau, \cdot)$  is not equal to zero almost everywhere.*

*If  $\alpha = 0$  and*

$$\inf_{x \in \Omega} \left( \widehat{V}_0(\tau, x) + B_0(x) \right) > 0,$$

*then*

$$B(t, x) \searrow 0, \quad V(t, x) \rightarrow V_\infty, \quad t \rightarrow \infty, \quad \text{uniformly in } x \in \overline{\Omega},$$

*where*

$$(2.7) \quad V_\infty = \frac{1}{|\Omega|} \left( \int_{\Omega} \widehat{V}_0(\tau, x) \, dx + (\beta - 1) \int_{\Omega} B_0(x) \, dx \right)$$

*and  $|\Omega|$  is Lebesgue measure of  $\Omega$ .*

*If  $\alpha > 0$ , then*

$$B(t, x) \searrow B_0(x)e^{-ku_\infty(x)}, \quad V(t, x) \rightarrow 0, \quad t \rightarrow \infty, \quad \text{uniformly in } x \in \overline{\Omega},$$

*where  $u = u_\infty(x)$  is the unique nonnegative solution of the boundary value problem*

$$(2.8) \quad 0 = d\Delta u + \widehat{V}_0(\tau, x) + B_0(x)(\beta - 1)(1 - e^{-ku}) - \alpha u$$

*satisfying Neumann boundary condition (2.3); in fact,  $u_\infty(x) > 0$ ,  $x \in \Omega$ .*

In case  $\alpha = 0$ , the model ignores virus decay, and the only loss of virus is due to adsorption to bacteria. Ultimately, all bacteria are lysed and converted into virus. The factor  $\beta - 1$  in front of the integral of  $B_0(x)$  reflects that one virus is lost due to adsorption to each uninfected bacteria while  $\beta$  progeny virus are released when the infected cell lyses; the larger factor  $\beta$  in the last term reflects that these bacteria were infected by virus before  $t = 0$ .

In case  $\alpha > 0$ , the virus will ultimately vanish, leaving behind a quantity of uninfected bacteria.

**3 Reduction to a single diffusion equation** We proceed as in Diekmann [3, 4] and Thieme [13] for epidemic models in the late 1970s to reduce the system (2.1)–(2.2) to a single scalar equation (see also [5, Ch. 8.5], [12], and [14, Ch. 20]). Define

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

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

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

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

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

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

Now, integrate from  $\tau$  to  $t \geq \tau$  and from 0 to  $t \leq \tau$ , respectively,

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

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

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

with

$$(3.4) \quad \mu(x) = B_0(x)k, \quad \nu(x) = \beta\mu(x),$$

and

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

and

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

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

$$(3.7) \quad f(0) = 0, \quad f'(0) = 1.$$

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

**Lemma 3.1.** *Let  $M = \|\widehat{V}_0\|_\infty + \beta\|B_0\|_\infty$ . If  $\alpha = 0$ , then  $u(t, x) \leq Mt$ ,  $t \geq 0$ ,  $x \in \Omega$ ; if  $\alpha > 0$ , then  $u(t, x) \leq \frac{M}{\alpha}(1 - e^{-\alpha t})$ ,  $t \geq 0$ ,  $x \in \Omega$ .*

*Proof.* By Theorem 2.1,  $u \geq 0$  is a classical solution of (3.3) for  $t > 0$ . It satisfies  $u_t \leq d\Delta u + M - \alpha u$  and  $u(0, x) = 0$ . The result follows by a standard comparison principle argument.  $\square$

Notice that  $\widehat{V}_0$  defined in (3.5) is a constant function of  $t \geq \tau$  and that  $\widehat{V}_0(\tau, x)$  is given by (2.6).

**Theorem 3.2.** *Let  $\beta \geq 1$  and  $\widehat{V}_0(\tau, \cdot)$  not equal to zero almost everywhere on  $\Omega$ .*

*If  $\alpha = 0$ , then  $u(t, x) \rightarrow \infty$  as  $t \rightarrow \infty$  uniformly in  $x \in \bar{\Omega}$  and  $B(t, x) \rightarrow 0$  as  $t \rightarrow \infty$ , uniformly in  $x \in \bar{\Omega}$ .*

*If  $\alpha > 0$ , then  $u(t, x) \rightarrow u_\infty(x)$  as  $t \rightarrow \infty$  uniformly in  $x \in \bar{\Omega}$  and  $B(t, x) \rightarrow \exp(-ku_\infty(x))$  as  $t \rightarrow \infty$ , uniformly in  $x \in \bar{\Omega}$ , where  $u_\infty$  is the unique positive solution of (2.8) and (2.3).*

*Proof.* Assume that  $\alpha = 0$ . Choose  $c \geq \mu(x)$  for all  $x \in \Omega$  and

$$(3.8) \quad g_c(x, u) = cu - \mu(x)f(u).$$

Then  $g_c(x, u)$  is increasing in  $u \geq 0$ . Let now  $\Gamma(t, x, y)$ ,  $t > 0$ ,  $x \in \bar{\Omega}$ ,  $y \in \Omega$ , be the Green's function associated with the differential operator  $\partial_t - d\Delta_x$  and Neumann boundary conditions [9, VI.2.2]. By (3.3),

$$(3.9) \quad u(t, x) = v_c(t, x) + \int_0^t \int_{\Omega} e^{-cs} \Gamma(s, x, y) g_c(u(t-s, y)) dy ds + \int_0^t \int_{\Omega} e^{-cs} \Gamma(s, x, y) \nu(y) f(u(t-s-\tau, y)) dy ds$$

with

$$(3.10) \quad v_c(x, t) = \int_0^t \int_{\Omega} e^{-cs} \Gamma(s, x, y) \widehat{V}_0(t-s, y) dy ds.$$

Recall/notice that  $u(t, x)$  and  $v_c(t, x)$  are increasing functions of  $t \geq 0$  and so have limits  $u(\infty, x)$  and  $v_0(\infty, x)$  in  $[0, \infty]$ . By Beppo Levi's theorem of monotone convergence,

$$u(\infty, x) = v_0(\infty, x) + \int_0^{\infty} \int_{\Omega} e^{-cs} \Gamma(s, x, y) ds g_c(u(\infty, y)) ds dy + \int_0^{\infty} \int_{\Omega} e^{-cs} \Gamma(s, x, y) \nu(y) f(u(\infty, y)) ds dy$$

with

$$v_0(\infty, x) = \int_0^{\infty} \left( \int_{\Omega} e^{-cs} \Gamma(s, x, y) ds \right) \widehat{V}_0(\tau, y) dy, \quad \widehat{V}_0(\tau, y) = V_0(y) + \beta \int_0^{\tau} I^0(s, y) ds.$$

See (3.5). By (3.8) and  $\nu(x) = \beta\mu(x)$ ,

$$u(\infty, x) = v_0(\infty, x) + \int_0^{\infty} \int_{\Omega} e^{-cs} \Gamma(s, x, y) cu(\infty, y) ds dy + \int_0^{\infty} \int_{\Omega} e^{-cs} \Gamma(s, x, y) (\beta - 1) \mu(y) f(u(\infty, y)) ds dy.$$

Assume that  $\widehat{V}_0(\tau, \cdot)$  is not 0 almost everywhere on  $\Omega$ . Suppose that  $u(\infty, x) < \infty$  for some  $x \in \Omega$ . Then  $\underline{u} = \inf_{\bar{\Omega}} u(\infty, \cdot) \in [0, \infty)$ ,  $\underline{v}_0 =$

$\inf_{\bar{\Omega}} v_0(\infty, \cdot) \in (0, \infty)$  and

$$\begin{aligned} \underline{u} &\geq \underline{v}_0 + \int_0^\infty \int_{\Omega} e^{-cs} \Gamma(s, x, y) c \underline{u} \, ds \, dy \\ &\quad + \int_0^\infty \int_{\Omega} e^{-cs} \Gamma(s, x, y) (\beta - 1) \mu(y) f(\underline{u}) \, ds \, dy. \end{aligned}$$

Since  $\int_{\Omega} \Gamma(s, x, y) \, dy = 1$ , if  $\beta \geq 1$

$$\underline{u} \geq \underline{v}_0 + \underline{u} > \underline{u}.$$

This contradiction implies  $u(t, x) \rightarrow \infty$  as  $t \rightarrow \infty$ ,  $x \in \bar{\Omega}$ . So  $e^{-ku(t,x)} \searrow 0$  as  $t \rightarrow \infty$ ,  $x \in \bar{\Omega}$ . By Dini's lemma, this convergence is uniform for  $x \in \bar{\Omega}$ . In turn,  $u(t, x) \rightarrow \infty$  as  $t \rightarrow \infty$ , uniformly in  $x \in \bar{\Omega}$ .

Assume that  $\alpha > 0$ . Now,  $u$  is increasing and bounded above by Lemma 3.1. The forward orbit is then pre-compact in  $C(\bar{\Omega})$  and, therefore, converges uniformly to equilibrium. The only equilibrium is the unique positive solution of (2.8) and (2.3). Existence and uniqueness of  $u_\infty$  follows on writing the differential equation (2.8) as a fixed point problem. Let  $u_0 = (-d\Delta + \alpha I)^{-1} \widehat{V}_0$  and set  $u_\infty = u_0 + w$ . Then  $w \in C(\bar{\Omega})_+$  satisfies

$$w = (\beta - 1)k(-d\Delta + \alpha I)^{-1}[B_0 f(u_0 + w)]$$

Using that  $f$  is increasing, bounded and concave,  $\beta > 1$ , and that  $(-d\Delta + \alpha I)^{-1}$  is compact on  $C(\bar{\Omega})$ , the result follows from Theorem 24.2 in [1]. Indeed, the fixed point  $w$  is the limit  $w_n \nearrow w$ , where  $w_0 = 0$  and  $w_{n+1} = (\beta - 1)k(-d\Delta + \alpha I)^{-1}[B_0 f(u_0 + w_n)]$ .  $\square$

**Proposition 3.3.** *Assume that  $\alpha = 0$ ,  $\beta > 1$  and  $\inf_{\Omega}(\widehat{V}_0(\tau, \cdot) + B_0(\cdot)) > 0$ . Then there exists  $t_0 > 0$  and  $\epsilon > 0$ ,  $\kappa > 0$  such that*

$$(3.11) \quad u(t, x) \geq \epsilon(t - t_0) \text{ and } B(t, x) \leq B_0(x)e^{-\kappa(t-t_0)}, \quad t > t_0, \quad x \in \Omega.$$

*Proof.* Notice that  $f(u(t, x)) \rightarrow 1$  as  $t \rightarrow \infty$ , uniformly in  $x \in \Omega$  by the previous Theorem. Hence there exists some  $t_0 > \tau$  and  $\delta > 0$  such that

$$(3.12) \quad u_t \geq d\Delta u + \widehat{V}_0(\tau, x) + \delta B_0(x), \quad t \geq t_0.$$

By assumption there exists some  $\epsilon > 0$  such that

$$(3.13) \quad u_t \geq d\Delta u + \epsilon, \quad t \geq t_0.$$

A comparison argument shows that  $u(t, x) \geq \epsilon(t - t_0)$ .  $\square$



**Lemma 3.4.** *Let the hypotheses of Proposition 3.3 hold. Then there exists  $C > 0$ , depending on initial conditions  $B_0$  and  $V_0$ , such that  $V(t, x) \leq C$ ,  $t \geq 0$ ,  $x \in \Omega$ .*

*Proof.* Let  $b_n = \sup_{x \in \Omega} B(n\tau, x)$  and  $v_n = \sup\{V(s, x) : (n - 1)\tau \leq s \leq n\tau, x \in \Omega\}$ . Then, for  $n \geq 1$ , we have

$$V_t \leq d\Delta V + \beta k b_{n-1} v_n, \quad n\tau \leq t \leq (n + 1)\tau, \quad x \in \Omega.$$

By the comparison principle, it follows that

$$V(t, x) \leq v_n + \beta k b_{n-1} v_n (t - n\tau), \quad n\tau \leq t \leq (n + 1)\tau, \quad x \in \Omega.$$

Hence,  $v_{n+1} \leq (1 + \beta k b_{n-1} \tau) v_n$ ,  $n \geq 1$ , and therefore,

$$v_n \leq v_1 \prod_{j=0}^{n-2} (1 + \beta k b_j \tau).$$

In view of (3.11), there exists  $b^*$  such that  $b_j \leq b^* e^{-j\kappa\tau}$ , so

$$v_n \leq v_1 \prod_{j=0}^{n-2} (1 + \beta k \tau b^* e^{-j\kappa\tau}).$$

It follows that  $V$  is bounded if we show that the series  $\sum_j \ln(1 + \beta k \tau b^* e^{-j\kappa\tau})$  converges. But this follows from the ratio test because

$$\lim_{j \rightarrow \infty} \frac{\ln(1 + \beta k \tau b_0 e^{-(j+1)\kappa\tau})}{\ln(1 + \beta k \tau b^* e^{-j\kappa\tau})} = e^{-\kappa\tau} < 1.$$

□

**4 Proof of main result** Let

$$v(t) = \int_{\Omega} V(t, x) dx, \quad b(t) = \int_{\Omega} B(t, x) dx.$$

Integrating the equation for  $V$  for the initial latent period, (2.1), over  $\Omega$ , replacing the term  $kBV$  by  $-B_t$ , and using the boundary conditions and the divergence theorem, we find that

$$v'(t) - b'(t) = -\alpha v(t) + \beta \int_{\Omega} I^0(\tau - t, x) dx \equiv \beta i^0(\tau - t);$$

the equation may be integrated yielding

$$v(\tau) - b(\tau) = -\alpha \int_0^\tau v(s) ds + v(0) - b(0) + \beta \int_0^\tau i^0(\tau - s) ds.$$

A similar integration of the equation for  $V$  following the first latent period, (2.2), results in

$$(v(t) - b(t) + \beta b(t - \tau))' = -\alpha v.$$

Integrating and using the formula above results in

$$\begin{aligned} v(t) - b(t) + \beta b(t - \tau) &= v(\tau) - b(\tau) + \beta b(0) + \alpha \int_\tau^t v(s) ds \\ &= -\alpha \int_0^t v(s) ds + v(0) + (\beta - 1)b(0) \\ &\quad + \beta \int_0^\tau i^0(\tau - s) ds, \quad t > \tau. \end{aligned}$$

Integrating over  $\Omega$  the equation for  $B$  results in  $b'(t) \leq 0$  so  $b(t) \searrow b(\infty)$  as  $t \rightarrow \infty$ . This implies that the limit  $v(t) \rightarrow v(\infty)$  exists and

$$(4.1) \quad v(\infty) + \alpha \int_0^\infty v(s) ds = v(0) + (\beta - 1)(b(0) - b(\infty)) + \beta \int_0^\tau i^0(s) ds.$$

If  $\alpha = 0$ ,  $\beta \geq 1$  and  $\widehat{V}_0(\tau, \cdot)$  not equal to zero, then  $b(\infty) = 0$  by Theorem 3.2 and therefore

$$(4.2) \quad v(t) \rightarrow v(\infty) = v(0) + (\beta - 1)b(0) + \beta \int_0^\tau \int_\Omega I^0(r, x) dx dr.$$

If  $\alpha > 0$  and  $\beta \geq 1$ , then  $b(\infty) = \int_\Omega B_0(x) e^{-ku_\infty(x)} dx \geq 0$  by Theorem 3.2 and by (4.1) we have  $v(\infty) = 0$  and

$$\begin{aligned} \alpha \int_0^\infty \int_\Omega V(t, x) dx dt &= v(0) + (\beta - 1)(b(0) - b(\infty)) \\ &\quad + \beta \int_0^\tau \int_\Omega I^0(r, x) dx dr. \end{aligned}$$

**Theorem 4.1.** *Suppose  $\alpha = 0$ . Let  $\widehat{V}_0(t, x)$  be not identically zero in  $\Omega$  and  $\beta \geq 1$ . If  $(V, B)$  is the corresponding solution of (2.1)–(2.2), then*

$$B(t, x) \searrow 0, \quad V(t, x) \rightarrow V_\infty, \quad t \rightarrow \infty, \quad \text{uniformly in } x \in \overline{\Omega},$$

where  $V_\infty$  is given by (2.7).

*Proof.* We first show  $V(t, \cdot) \in L^2(\Omega)$ ,  $t > 0$  and  $V(t, \cdot) \rightharpoonup V_\infty$  (weak convergence in  $L^2(\Omega)$ ). Write  $V(t, \cdot) = V(t) = \sum_{j=0}^\infty u_j(t)\phi_j$ , where  $\{\phi_j\}$  are the normalized eigenfunctions of the Laplacian w.r.t. Neumann boundary conditions and  $\{\lambda_j\}$  are the eigenvalues:  $\lambda_{j+1} \leq \lambda_j \leq \dots < \lambda_0 = 0$ . By taking inner product of the equation for  $V$  with  $\phi_j$ , we get the equations for  $u_j(t)$ :

$$u'_j(t) = \lambda_j u_j(t) + f_j(t), \quad j \geq 0,$$

where  $f_j(t)$  will be identified below. We have already solved the equation for  $u_0$ , called  $v$  above, so we consider the case  $j \geq 1$ . Our goal is to show that

$$(4.3) \quad u_j(t) \rightarrow 0, \quad t \rightarrow \infty, \quad j \geq 1.$$

Solving the differential equation for  $u_j$  results in

$$u_j(t) = e^{\lambda_j t} u_j(0) + \int_0^t e^{\lambda_j(t-s)} f_j(s) ds.$$

The integral term converges to zero if  $\int_0^\infty |f_j(s)| ds < \infty$ , so this condition is sufficient for (4.3) since  $\lambda_j < 0$ .

$f_j(t) = \langle \phi_j, -kBV(t) + \beta kBV(t - \tau) \rangle$ , where  $\langle \cdot, \cdot \rangle$  denotes the inner product in  $L^2(\Omega)$ . We estimate as follows:

$$\begin{aligned} \int_0^\infty |\langle \phi_j, kBV(t) \rangle| dt &\leq - \int_\Omega |\phi_j(x)| \left( \int_0^\infty B_t dt \right) dx \\ &= \int_\Omega |\phi_j| B_0(x) dx \leq \|B_0\|_2, \end{aligned}$$

where  $\|B_0\|_2$  denotes the norm of  $B_0$  in  $L^2(\Omega)$ . Obviously, a similar estimate can be made of the delayed term, the only difference being the factor  $\beta$ . Thus,  $f_j$  is integrable, and this completes our sketch of the proof of (4.3).

Weak convergence  $V(t, \cdot) \rightharpoonup V_\infty$  follows from  $u_j(t) \rightarrow 0$ ,  $t \rightarrow \infty$ ,  $j \geq 1$  provided  $V(t)$  is bounded in  $L^2(\Omega)$  for large  $t$ . See Theorem 3.5.3 in [2]. But Lemma 3.4 implies global  $L^2(\Omega)$ -boundedness of  $V$ .

We claim that the trajectory  $\{V(t, \cdot) : t \geq 0\}$  is precompact in  $C(\overline{\Omega})$  because, by Lemma 3.4, it is bounded in  $C(\overline{\Omega})$ . See, e.g., Theorem 2.5-5 [11] or Theorem 7.2 of Chapter V in [10], which provide a uniform bound on the gradient of  $V$ . Thus, if  $t_n \rightarrow \infty$ , then  $\{V(t_n, \cdot)\}_n$  has a uniformly convergent subsequence, i.e., there is a subsequence  $\{V(t_{n_j})\}_j$  with  $V(t_{n_j}) \rightarrow \phi$  in  $C(\overline{\Omega})$ . But then  $V(t_{n_j}) \rightarrow \phi$  weakly in  $L^2(\Omega)$  and hence  $\phi = V_\infty$  by uniqueness of the weak limit. Since every convergent subsequence of  $\{V(t_n, \cdot)\}_n$  converges to  $V_\infty$ , it follows that  $V(t_n, \cdot) \rightarrow V_\infty$  in  $C(\overline{\Omega})$ . Consequently,  $V(t, \cdot) \rightarrow V_\infty$  as  $t \rightarrow \infty$ .  $\square$

**Theorem 4.2.** *If  $\alpha > 0$ ,  $V(t, x) \rightarrow 0$  as  $t \rightarrow \infty$ , uniformly for  $x \in \Omega$ .*

*Proof.* For  $t \geq 2\tau$ ,  $V$  satisfies the inequality

$$\begin{aligned} V(t, x) &\leq c \int_\tau^t \int_\Omega \Gamma(t-s, x, y) e^{-\alpha(t-s)} V(s-\tau, y) dy ds \\ &\quad + c \int_0^\tau \int_\Omega \Gamma(t-s, x, y) e^{-\alpha(t-s)} \Gamma^0(\tau-s, y) ds dy \\ &\quad + \int_\Omega \Gamma(t, x, y) e^{-\alpha t} V_0(y) dy. \end{aligned}$$

Here,  $c > 0$ , among other things, incorporates  $\sup_{x \in \Omega} B_0(x)$ . We will use smoothness and boundedness properties of the Green's function  $\Gamma$  described in Chapter VI, Theorem 3.1 of [9].

Let  $\epsilon \in (0, \tau]$ . By the Chapman-Kolmogorov equation, for  $t \geq \epsilon$ ,

$$\Gamma(t, x, y) = \int_\Omega \Gamma(\epsilon, x, z) \Gamma(t-\epsilon, z, y) dz \leq \gamma_\epsilon \int_\Omega \Gamma(t-\epsilon, z, y) dz = \gamma_\epsilon$$

with

$$\gamma_\epsilon = \sup_{x, y \in \Omega} \Gamma(\epsilon, x, y).$$

For  $t \geq 2\tau$ ,

$$\begin{aligned} V(t, x) &\leq c \int_{t-\epsilon}^t \int_{\Omega} \Gamma(t-s, x, y) e^{-\alpha(t-s)} V(s-\tau, y) dy ds \\ &\quad + c \int_{\tau}^{t-\epsilon} \int_{\Omega} \Gamma(t-s, x, y) e^{-\alpha(t-s)} V(s-\tau, y) dy ds \\ &\quad + c e^{-\alpha(t-\tau)} \gamma_{\tau} \int_0^{\tau} \int_{\Omega} e^{-\alpha r} I^0(r, y) dr dy \\ &\quad + \gamma_{\tau} e^{-\alpha t} \int_{\Omega} V_0(y) dy. \end{aligned}$$

Since  $V$  is bounded on every interval  $[\tau, \sigma]$  with  $\sigma > 0$ ,

$$\begin{aligned} V(t, x) &\leq c\epsilon \sup_{t-\epsilon \leq s \leq t} \sup_{y \in \Omega} V(s-\tau, y) \\ &\quad + c\gamma_{\epsilon} \int_{\tau}^{t-\epsilon} e^{-\alpha(t-s)} \int_{\Omega} V(s-\tau, y) dy ds \\ &\quad + e^{-\alpha(t-\tau)} M_V, \quad t \geq 2\tau, \end{aligned}$$

with some constant  $M_V > 0$ . After a substitution,

$$\begin{aligned} (4.4) \quad \sup_{x \in \Omega} V(t, x) &\leq c\epsilon \sup_{t-2\tau \leq r \leq t-\tau} \sup_{y \in \Omega} V(r, y) \\ &\quad + c\gamma_{\epsilon} \int_{\tau}^t e^{-\alpha(r-\tau)} \left( \int_{\Omega} V(t-r, y) dy \right) dr \\ &\quad + e^{-\alpha(t-\tau)} M_V. \end{aligned}$$

We fix  $\epsilon \in (0, 1/(2c))$ . Since  $\int_{\Omega} V(t, y) dy$  is a bounded function of  $t \geq 0$ , there exists  $\widetilde{M}_V > 0$  such that

$$\sup_{x \in \Omega} V(t, x) \leq c\epsilon \sup_{t-2\tau \leq r \leq t-\tau} \sup_{y \in \Omega} V(r, y) + \widetilde{M}_V, \quad t \geq 2\tau.$$

Let  $\sigma > 2\tau$ . Then

$$\begin{aligned} \sup_{2\tau \leq t \leq \sigma} \sup_{x \in \Omega} V(t, x) &\leq c\epsilon \sup_{0 \leq s \leq \sigma} \sup_{y \in \Omega} V(t, y) + \widetilde{M}_V \\ &\leq c\epsilon \left( \sup_{2\tau \leq r \leq \sigma} \sup_{y \in \Omega} V(r, y) + \sup_{0 \leq r \leq 2\tau} \sup_{y \in \Omega} V(r, y) \right) + \widetilde{M}_V. \end{aligned}$$

Then, as  $c\epsilon \leq 1/2$ ,

$$\sup_{2\tau \leq t \leq \sigma} \sup_{x \in \Omega} V(t, x) \leq \sup_{0 \leq r \leq 2\tau} \sup_{y \in \Omega} V(r, y) + 2\widetilde{M}_V.$$

This holds for all  $\sigma > 2\tau$ . This implies that  $V$  is bounded on  $[\tau, \infty)$ .

Now, by (4.4),

$$\begin{aligned} \sup_{x \in \Omega} V(t, x) &\leq \frac{1}{2} \sup_{r \geq t-2\tau} \sup_{x \in \Omega} V(r, x) \\ &\quad + c\gamma_\epsilon \int_\tau^t e^{-\alpha(r-\tau)} \left( \int_\Omega V(t-r, y) dy \right) dr \\ &\quad + ce^{-\alpha(t-\tau)} M_V, \quad t \geq 2\tau. \end{aligned}$$

We take the limit superior as  $t \rightarrow \infty$ . By a version of Fatou's lemma,

$$\begin{aligned} \limsup_{t \rightarrow \infty} \sup_{x \in \Omega} V(t, x) &\leq \frac{1}{2} \limsup_{t \rightarrow \infty} \sup_{x \in \Omega} V(r, x) \\ &\quad + \frac{c\gamma_\epsilon}{\alpha} \limsup_{t \rightarrow \infty} \int_\Omega V(t, y) dy + 0. \end{aligned}$$

Since  $\int_\Omega V(t, y) dy \rightarrow 0$  as  $t \rightarrow \infty$ , this implies that

$$\limsup_{t \rightarrow \infty} \sup_{x \in \Omega} V(t, x) = 0,$$

i.e.,  $V(t, x) \rightarrow 0$  as  $t \rightarrow \infty$ , uniformly for  $x \in \Omega$ .  $\square$

**Acknowledgement** The authors thank an anonymous referee for helpful comments.

## REFERENCES

1. H. Amann, *Fixed point equations and nonlinear eigenvalue problems in ordered Banach spaces*, SIAM Rev. **18** (1976), 620–709.
2. L. Debnath and P. Mikusinski, *Introduction to Hilbert Spaces with Applications*, 2nd ed., Academic Press, San Diego, 1999.
3. O. Diekmann, *Limiting behaviour in an epidemic model*, Nonlinear Anal. TMA **1** (1977), 459–470.

4. O. Diekmann, *Thresholds and travelling waves for the geographical spread of infection*, J. Math. Biol. **6** (1978), 109–130.
5. O. Diekmann and J. A. P. Heesterbeek, *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation*, Wiley, Chichester, 2000.
6. H. I. Freedman and Q.-L. Peng, *Global stability in a diffusive stage-structured population system with two time delays*, Canad. Appl. Math. Quart. **5** (1997), 397–422.
7. H. I. Freedman and J.-H. Wu, *Persistence and global asymptotic stability of single species dispersal models with stage structure*, Quart. Appl. Math. **49** (1991), 351–371.
8. D. A. Jones, G. Röst, H. L. Smith and H. R. Thieme, *Spread of phage infection of bacteria in a petri dish*, SIAM J. Appl. Math. **72** (2012), 670–688, <http://dx.doi.org/10.1137/110848360>.
9. M. G. Garroni and J. L. Menaldi, *Green Functions for Second Order Parabolic Integro-Differential Problems*, Longman Scientific & Technical, Essex, 1992.
10. O. Ladyženskaja, V. Solonnikov and N. Uralčeva, *Linear and Quasilinear Equations of Parabolic Type*, vol 23, Transl. of Math. Mono., AMS, Providence, R.I., 1968.
11. A. W. Leung, *Systems of Nonlinear Partial Differential Equations*, Kluwer Acad. Pub., Norwell, MA., 1989.
12. L. Rass and J. Radcliffe, *Spatial Deterministic Epidemics*, AMS, Providence, 2003.
13. H. R. Thieme, *A model for the spatial spread of an epidemic*, J. Math. Biol. **4** (1977), 337–351.
14. H. R. Thieme, *Mathematics in Population Biology*, Princeton University Press, Princeton, 2003.
15. J.-H. Wu and H. I. Freedman, *Global stability in a population model with dispersal and stage structure*, in: Differential Equations Models in Biology, Epidemiology and Ecology (Claremont, CA, 1990), S. Busenberg, M. Martelli (eds.), 257–267, Lecture Notes in Biomath. 92, Springer, Berlin, 1991.
16. J. Yin and J. S. McCaskill, *Replication of viruses in a growing plaque: a reaction-diffusion model*, Biophysics J. **61** (1992), 1540–1549.

SCHOOL OF MATHEMATICAL AND STATISTICAL SCIENCES,  
ARIZONA STATE UNIVERSITY, TEMPE, AZ 85287, USA.

*E-mail address:* halsmith@asu.edu

*E-mail address:* thieme@math.asu.edu

