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Claude-Michel Brauner, Danaelle Jolly, Luca Lorenzi, Rodolphe Thiébaud. HETEROGENEOUS VIRAL ENVIRONMENT IN A HIV SPATIAL MODEL. 2009. hal-00383320

HAL Id: hal-00383320

<https://hal.science/hal-00383320>

Preprint submitted on 13 May 2009

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HETEROGENEOUS VIRAL ENVIRONMENT IN A HIV SPATIAL MODEL

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ABSTRACT. We consider the basic model of virus dynamics in the modeling of Human Immunodeficiency Virus (HIV), in a $2D$ heterogenous environment. It consists of two ODEs for the non-infected and infected CD_4^+ T -lymphocytes, T and I , and a parabolic PDE for the virus V . We define a new parameter λ_0 as an eigenvalue of some Sturm-Liouville problem, which takes the heterogenous reproductive ratio into account. For $\lambda_0 < 0$ the trivial non-infected solution is the only equilibrium. When $\lambda_0 > 0$, the former becomes unstable whereas there is only one positive infected equilibrium. Considering the model as a dynamical system, we prove the existence of a universal attractor. Finally, in the case of an alternating structure of viral sources, we define a homogenized limiting environment. The latter justifies the classical approach via ODE systems.

1. Introduction. The acute infection by the Human Immunodeficiency Virus (in short HIV) is characterized by a huge depletion of the CD_4^+ T -lymphocytes (CD_4) and a peak of the virus load [7]. After few weeks, these two components reach a steady state which characterizes the asymptomatic phase of the infection. Before the availability of highly active antiretroviral therapy, this later phase lasted after 10 years in median with an accelerated decrease of CD_4 and an increase of virus load. A substantial number of nonlinear ODE systems have been suggested by Perelson et al. (see [21, 22]) to model the complex dynamics of HIV-host interaction. For instance, such models have been used to estimate the infected cell half-life and the viral clearance during antiretroviral therapy [11, 20, 29], or to understand the dynamics during acute infection [23].

2000 *Mathematics Subject Classification.* Primary: 35K55; Secondary: 35B35, 92C50.

Work partially supported by the research project ANR-BBSRC SysBio: Applied statistical and mathematical modelling of peripheral T-Lymphocyte homeostasis.

The common basic model of viral dynamics [2] includes three variables: T , the non-infected CD_4 , I , the infected CD_4 , and V , the free virus:

$$T_t = \alpha - \gamma VT - \mu_T T, \quad (1.1a)$$

$$I_t = \gamma VT - \mu_I I, \quad (1.1b)$$

$$V_t = N\mu_I I - \mu_V V. \quad (1.1c)$$

This model, describing the interaction between the replicating virus of HIV and host cells, is based on some simple hypotheses. Non-infected target cells are produced by the thymus at a constant rate α and die at a rate μ_T . By contact with the free virus particles (virions) they become infected at a rate proportional to their abundance, γVT (see Fig. 1). These infected cells die at a rate μ_I and produce free viruses during their life-time at a rate N . Free particles are removed at a rate called the clearance μ_V . All these parameters are generally positive constants. This simple model study has led to interesting results (see [18, 28]) and suggested a treatment strategy (see [2]).

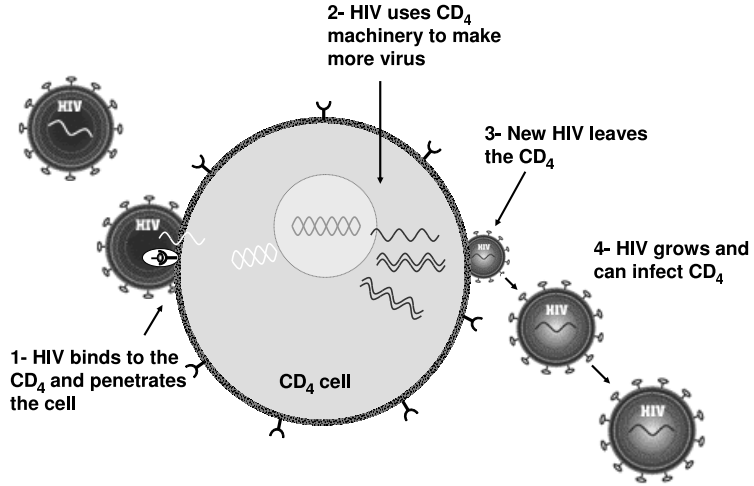


FIGURE 1. The HIV life cycle

It is easily seen that the system has two equilibria:

- (i) the *non-infected* steady state

$$T_u = \frac{\alpha}{\mu_T}, \quad I_u = 0, \quad V_u = 0,$$

which corresponds to a non-negative equilibrium in case of no infection;

- (ii) the *infected* steady state

$$T_i = \frac{\mu_V}{\gamma N}, \quad I_i = \frac{\alpha\gamma N - \mu_T\mu_V}{\gamma N}, \quad V_i = \frac{\alpha\gamma N - \mu_T\mu_V}{\gamma\mu_V}, \quad (1.2)$$

also called *seropositivity* steady state, corresponding to a positive equilibrium in case of infection.

Some authors (see e.g., [2, 18]) have considered the basic reproductive ratio R_0 :

$$R_0 = \frac{\gamma\alpha N}{\mu_T\mu_V}, \quad (1.3)$$

a dimensionless parameter defined by epidemiologists as *the average number of infected cells that derive from any one infected cell in the beginning of the infection* [18, p. 16]. Stability properties of the two steady states are usually studied around this quantity: if $R_0 < 1$ the non-infected steady state is stable, if $R_0 > 1$ the infected steady state has a biological meaning and it is stable, while at $R_0 = 1$ both steady states coincide. So, $R_0 = 1$ is a bifurcation point (see Fig. 2). Further

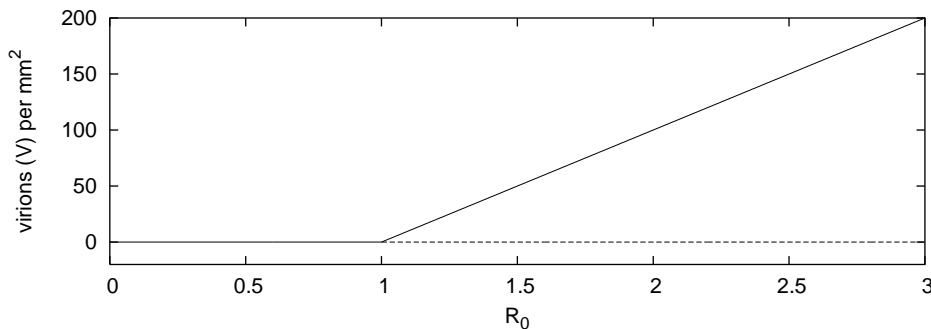


FIGURE 2. Typical bifurcation diagram, with R_0 varying between 0 and 3, as a function of α . The solid line represents the stable branch of V , the dashed line the unstable one. The other parameters have the values: $\gamma = 0.001$, $N = 1000$, $\mu_T = 0.1$, $\mu_I = 0.5$, $\mu_V = 10$.

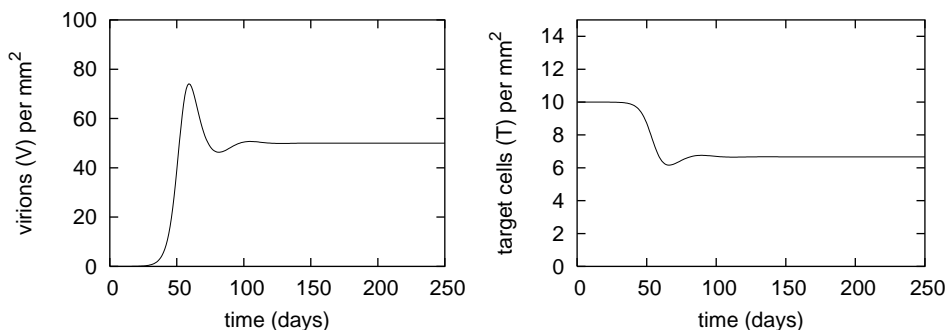


FIGURE 3. Profiles of virus (left) and target cells (right) in the case of infection. Here $R_0 = 1.5$ and the other parameters have the same values as in Fig. 2.

models have been used involving other populations present in the immune system (see [17, 18, 4]). However, these models assume that the populations T , I , V are homogeneous over the space for all time, which is a common, but not a very realistic, assumption. Actually, the interaction between the virus and the immune system (either as a target with CD_4 or as an agent for controlling infection) is localized according to the type of tissues [3] and also in a given tissue (e.g. lymph nodes). To examine the effects of both diffusion and spatial heterogeneity, Funk et al. [8] introduced a discrete model based on (1.1a)-(1.1c). These authors adopted a two-dimensional square grid with 21×21 sites and assumed that the virus can move

to the eight nearest neighboring sites. They pointed out that the presence of a spatial structure enhances population stability with respect to non-spatial models. However, our analysis does not confirm this observation (see Section 4 below).

Recently, Wang et al. [26] generalized Funk et al.'s model. They assumed that the hepatocytes can not move under normal conditions and neglected their mobility, while viruses can move freely and their motion follows a Fickian diffusion. They proposed the following system of two ODEs coupled with a parabolic PDE for the virus:

$$T_t = \alpha - \gamma VT - \mu_T T, \quad (1.4a)$$

$$I_t = \gamma VT - \mu_I I, \quad (1.4b)$$

$$V_t = N\mu_I I - \mu_V V + d_V \Delta V, \quad (1.4c)$$

where d_V is the diffusion coefficient. They assumed that the domain is the whole real line and proved the existence of traveling waves. Wang et al. [27] introduced a delay to take into account the time between infection of a target cell and the emission of viral particles [6]. They considered (1.4a)-(1.4c) in a one-dimensional interval with Neumann boundary conditions.

In the spirit of the above works, we intend to study System (1.4a)-(1.4c) in a two-dimensional spatial domain $(0, \ell) \times (0, \ell)$ with periodic boundary conditions. There are two main situations:

- (i) the environment is *homogeneous* and, hence, all the parameters in (1.4a)-(1.4c) are constant. Therefore, the system with diffusion has the same equilibria as System (1.1a)-(1.1c);
- (ii) the environment is *heterogeneous*, therefore certain parameters become positive functions of the space variable. Then, the virus is spatially structured.

For simplicity, we assume throughout the paper that only the rate α varies while the other parameters are fixed positive constants. In fact, it is biologically plausible to assume that the arrival of new CD_4 may vary according to local areas. More precisely, α is piecewise continuous and periodic in each variable with period ℓ . Then it is convenient to define the *heterogeneous reproductive ratio*:

$$R_0(x) = \frac{\gamma N \alpha(x)}{\mu_T \mu_V}, \quad x \in (0, \ell) \times (0, \ell). \quad (1.5)$$

The sites where $R_0(x) < 1$ are called *sinks* while the sites where $R_0(x) > 1$ are called *sources* [8].

The paper is organized as follows. In Section 2 we are interested in the stationary problem associated with (1.4a)-(1.4c) and its non-negative equilibria. The virus equilibrium verifies the elliptic semilinear equation

$$d_V \Delta V - \mu_V V = -\mu_T \mu_V R_0(x) \frac{V}{\gamma V + \mu_T}, \quad (1.6)$$

with periodic boundary conditions. A first issue is to define a parameter which will play the role of the bifurcation parameter R_0 in the case the latter is constant. A candidate for this role is the largest eigenvalue λ_0 of the operator:

$$d_V \Delta + \mu_V (R_0 - 1) Id, \quad (1.7)$$

which is the linearization around $V \equiv 0$ of (1.6). For the reader's convenience, we recall some basic facts about two-dimensional Sturm-Liouville eigenvalue problems with periodic boundary conditions such as (1.7) and give some proofs in Appendix A.

It is clear that, whenever R_0 is a constant, $\lambda_0 = \mu_V(R_0 - 1)$. Therefore, we distinguish two cases, depending upon the sign of λ_0 :

- (i) $\lambda_0 \leq 0$: the trivial non-infected solution $V_u \equiv 0$ is the only solution of (1.6);
- (ii) $\lambda_0 > 0$: (1.6) has exactly two non-negative solutions, namely the trivial non-infected solution $V_u \equiv 0$ and the positive infected solution V_i .

Section 3 is devoted to the study of the evolution problem (1.4a)-(1.4c). In the case $\lambda_0 < 0$, we prove that the trivial non-infected solution (T_i, I_i, V_i) is asymptotically stable. Then, we turn our attention to the biologically relevant case $\lambda_0 > 0$. First, we prove the non-infected solution becomes unstable. Second, we consider (1.4a)-(1.4c) as a dynamical system and prove the existence of an universal (or maximal) attractor. Since the system is only partly dissipative, we use a result of Marion [16]. The following Section 4 is devoted to some special cases where the positive infected solution V_i is stable. Particular attention is paid to the case when R_0 is a constant: in this case discrete Fourier transform can be applied.

We point out that our proof can be extended to further models in HIV literature. It is not difficult to take a logistic term into account in the T equation [22], although the steady equation (1.6) will be more involved. Adding such a term, Hopf bifurcations have been observed numerically in ODE systems (see [20]). Therefore, proving the stability of the infected solution may be, in general, challenging.

In the last section (Section 5), we consider the case when a heterogeneous environment is formed of sinks and sources alternating very rapidly, with a heterogeneous reproductive ratio $R_0(\frac{x}{\varepsilon})$. We determine the homogenized limiting medium as $\varepsilon \rightarrow 0$. It is fully characterized by a constant reproductive ratio, the mean value of R_0 . Therefore, the classical approach of HIV dynamics via ODEs in a homogenous environment can be *a posteriori* justified in this respect.

Notation. Throughout this paper, for any $\ell > 0$, we denote by L^2 the usual space of functions $f : (0, \ell)^2 \rightarrow \mathbb{R}$ such that f^2 is integrable. The square $(0, \ell)^2$ will be simply denoted by Ω_ℓ . By H^k we denote the Sobolev space of order k , i.e., the subset of L^2 of all the functions whose distributional derivatives up to k -th order are in L^2 . Both L^2 and H^2 are endowed with their Euclidean norm. Finally, by H_{\sharp}^k we denote the closure in H^k of the space C_{\sharp}^m of all m -th continuously differentiable functions $f : \mathbb{R}^2 \rightarrow \mathbb{R}$ which are periodic with period ℓ in each variable. The space H_{\sharp}^k is endowed with the norm of H^k . Finally, we denote by Id the identity operator.

2. A semilinear equation for the virus steady states: existence and uniqueness of the equilibria. We start from the system for the virus dynamics:

$$T_t = \alpha - \gamma VT - \mu_T T, \quad (2.1a)$$

$$I_t = \gamma VT - \mu_I I, \quad (2.1b)$$

$$V_t = N\mu_I I - \mu_V V + d_V \Delta V, \quad (2.1c)$$

set in Ω_ℓ . Periodic boundary conditions for T, I and V are prescribed.

We are interested in the existence of steady state solutions to the equations (2.1a)-(2.1c) which belong to the space $L^2 \times L^2 \times H_{\sharp}^2$. Clearly, any steady state solution to Problem (2.1a)-(2.1c) is a solution to the following stationary system:

$$\alpha - \gamma VT - \mu_T T = 0, \quad (2.2a)$$

$$\gamma VT - \mu_I I = 0, \quad (2.2b)$$

$$N\mu_I I - \mu_V V + d_V \Delta V = 0. \quad (2.2c)$$

From a biological point of view, only non-negative solutions to (2.2a)-(2.2c) have a meaning. Hence, we limit ourselves to proving the existence of this kind of steady state solutions.

System (2.2a)-(2.2c) can be reduced to a single scalar equation for the unknown V . Actually, it is not difficult to infer from (2.2a), (2.2b) that

$$T = \frac{\alpha}{\gamma V + \mu_T}, \quad I = \frac{\gamma \alpha V}{\mu_I(\gamma V + \mu_T)}.$$

Hence, the function V turns out to solve the equation

$$d_V \Delta V - \mu_V V = -\frac{\gamma \alpha N V}{\gamma V + \mu_T} = -\mu_T \mu_V R_0 \frac{V}{\gamma V + \mu_T}, \quad (2.3)$$

associated with periodic boundary conditions.

2.1. Existence and uniqueness of non-negative equilibria. In this subsection we will provide a thorough study of the equation (2.3). As it has been already stressed, we are interested in non-negative solutions only.

Clearly, equation (2.3) always admits the trivial non-infected solution $V \equiv 0$ and, hence, Problem (2.1a)-(2.1c) admits

$$T_u(x) = \frac{\alpha(x)}{\mu_T}, \quad I_u(x) = 0, \quad V_u(x) = 0, \quad x \in \Omega_\ell, \quad (2.4)$$

as a (trivial) steady state solution. We will call the triplet (T_u, I_u, V_u) the non-infected solution.

We are interested in studying the uniqueness of the non-infected solution in the class of all the non-negative steady state solutions to Problem (2.1a)-(2.1c). Of course, in the case when uniqueness does not hold (a situation which can actually occur, look for instance at the case when $R_0 > 1$ and α is constant, discussed in the introduction) we want to characterize all biological relevant steady state solutions to Problem (2.1a)-(2.1c).

For this purpose, we need to recall the following results about Sturm-Liouville eigenvalue problems in dimension two with periodic boundary conditions.

Theorem 2.1. *Let d and μ be, respectively, a positive constant and a bounded measurable function. Further, let $\mathcal{A} : H_{\sharp}^2 \rightarrow L^2$ be the operator defined by $\mathcal{A}u = d\Delta u - \mu u$ for any $u \in H_{\sharp}^2$. Then, the spectrum of \mathcal{A} consists of eigenvalues only. Moreover, its maximum eigenvalue λ_{\max} is given by the following formula:*

$$\lambda_{\max} = - \inf_{\psi \in H_{\sharp}^1, \psi \neq 0} \left\{ \frac{d \int_{\Omega_\ell} |\nabla \psi|^2 dx + \int_{\Omega_\ell} \mu \psi^2 dx}{\int_{\Omega_\ell} \psi^2 dx} \right\}. \quad (2.5)$$

Finally, the eigenspace corresponding to the eigenvalue λ_{\max} is one dimensional and contains functions which do not change sign in $\overline{\Omega_\ell}$.

This is a rather classical result. Nevertheless, for the reader's convenience, we give a proof in Appendix A.

In view of Theorem 2.1, we can define the constant λ_0 to be the maximum eigenvalue of the operator $\varphi \mapsto d_V \Delta \varphi + \mu_V (R_0 - 1) \varphi$, which is the linearization around $V \equiv 0$ of operator $V \mapsto d_V \Delta V - \mu_V V + \mu_T \mu_V R_0 \frac{V}{\gamma V + \mu_T}$. According to (2.5),

$$-\lambda_0 = \inf_{\psi \in H_{\sharp}^1, \psi \neq 0} \left\{ \frac{d_V \int_{\Omega_\ell} (\psi_x)^2 dx + \mu_V \int_{\Omega_\ell} (1 - R_0) \psi^2 dx}{\int_{\Omega_\ell} \psi^2 dx} \right\}. \quad (2.6)$$

As we are going to show, the uniqueness of the non-infected steady state solution is related to the value of λ_0 .

Lemma 2.2. *If $\lambda_0 \leq 0$, then the non-infected solution (T_u, I_u, V_u) (see (2.4)) is the only non-negative solution of (2.1a)-(2.1c).*

Proof. We argue by contradiction. Let us suppose that Problem (2.2a)-(2.2c) admits another solution (T^*, I^*, V^*) different from (T_u, I_u, V_u) . Then, the function $V^* \in H_{\sharp}^2$ does not identically vanish in Ω_ℓ and it solves the equation (2.3). Multiplying both the sides of this equation by V^* and integrating by parts in Ω_ℓ , we get:

$$d_V \int_{\Omega_\ell} |\nabla V^*|^2 dx + \mu_V \int_{\Omega_\ell} \left(1 - \frac{\mu_T R_0}{\gamma V^* + \mu_T} \right) (V^*)^2 dx = 0,$$

or, equivalently,

$$\begin{aligned} d_V \int_{\Omega_\ell} |\nabla V^*|^2 dx + \mu_V \int_{\Omega_\ell} (1 - R_0) (V^*)^2 dx \\ + \mu_V \int_{\Omega_\ell} R_0 \left(1 - \frac{\mu_T}{\gamma V^* + \mu_T} \right) (V^*)^2 dx = 0. \end{aligned}$$

Since V^* does not identically vanish in Ω_ℓ , the last integral term is positive, implying that

$$d_V \int_{\Omega_\ell} |\nabla V^*|^2 dx + \mu_V \int_{\Omega_\ell} (1 - R_0) (V^*)^2 dx < 0.$$

Hence, the infimum in (2.5) is negative which contradicts our assumption $-\lambda_0 \geq 0$. \square

Remark 2.3. From formula (2.6) it is immediate to check that, when the maximum of R_0 in Ω_ℓ is less than or equal to 1, the constant λ_0 is non-positive. Hence, in this situation the non-infected solution is the only relevant steady state solution to Problem (2.1a)-(2.1c) in complete agreement with the case when R_0 is constant (see the Introduction).

The result in Lemma 2.2 is very sharp as the following theorem shows.

Theorem 2.4. *Suppose that $\lambda_0 > 0$. Then, there exists a steady state solution (T_i, I_i, V_i) to Problem (2.1a)-(2.1c) whose components are all positive in $\overline{\Omega_\ell}$, with*

$$T_i = \frac{\alpha}{\gamma V_i + \mu_T}, \quad I_i = \frac{\gamma \alpha V_i}{\mu_I (\gamma V_i + \mu_T)}. \quad (2.7)$$

Moreover, (T_u, I_u, V_u) and (T_i, I_i, V_i) are the only steady state solutions whose components are non-negative in Ω_ℓ .

Proof. It is clear, that we can limit ourselves to dealing with the equation (2.3). Being rather long, we split the proof into two steps.

Step 1: (existence). To prove the existence of a positive solution to the equation (2.3) in H_{\sharp}^2 , we use the classical method of upper and lower solutions. To simplify the notation, we denote by \mathcal{R} the sup-norm of the function R_0 . We look for an upper solution \bar{v}_0 of (2.3) as a constant $C > 0$. It is immediate to check that the best choice of \bar{v}_0 is

$$\bar{v}_0(x) \equiv \frac{\mu_T (\mathcal{R} - 1)}{\gamma}, \quad x \in \overline{\Omega_\ell}.$$

Note that, by Remark 2.3, \mathcal{R} is strictly greater than 1.

To determine a lower solution, in the spirit of [14, Chapt. 13, Sec. 3], we take as a candidate to be a lower solution the function $\underline{v}_0 = c\varphi_0$ with $c > 0$ to be fixed. Here, φ_0 is the unique (positive) solution to the equation $d_V \Delta \varphi_0 + \mu_V (R_0 - 1)\varphi_0 = \lambda_0 \varphi_0$ which satisfies $\sup_{x \in \Omega_\ell} \varphi_0(x) = 1$.

If we plug $c\varphi_0$ in (2.3), we get

$$\begin{aligned} & d_V \Delta(c\varphi_0) - \mu_V c\varphi_0 + \mu_T \mu_V R_0 \frac{c\varphi_0}{\gamma c\varphi_0 + \mu_T} \\ &= \lambda_0 c\varphi_0 + \mu_T \mu_V R_0 \frac{c\varphi_0}{\gamma c\varphi_0 + \mu_T} - \mu_V R_0 c\varphi_0 \\ &= c\varphi_0 \left(\lambda_0 - \gamma \mu_V R_0 \frac{c\varphi_0}{\gamma c\varphi_0 + \mu_T} \right) \\ &\geq c\varphi_0 \left(\lambda_0 - \frac{\gamma c \mu_V \mathcal{R}}{\mu_T} \right). \end{aligned}$$

Since $\lambda_0 > 0$ is fixed, the last side of the previous chain of inequalities is non-negative as soon as $\lambda_0 \mu_T - \gamma c \mu_V \mathcal{R} \geq 0$. Hence, if we fix

$$c = \min \left\{ \frac{\lambda_0}{\gamma \mu_V \mathcal{R}}, \frac{\mu_T (\mathcal{R} - 1)}{\gamma} \right\},$$

the function $\underline{v}_0 = c\varphi_0$ turns out to be a positive lower solution to the equation (2.3) and it satisfies $\underline{v}_0 \leq \bar{v}_0$ in Ω_ℓ .

Hence, the classical method of upper and lower solutions provides us with a positive solution to the equation (2.3). It is enough to define the sequence (\bar{v}_n) by recurrence in following way: for any fixed $n \in \mathbb{N}$, \bar{v}_n is the unique solution in H_{\sharp}^2 of the equation

$$d_V \Delta \bar{v}_n - \mu_V \bar{v}_n + \mu_T \mu_V R_0 \frac{\bar{v}_{n-1}}{\gamma \bar{v}_{n-1} + \mu_T} = 0.$$

Since the function $t \mapsto h(t) := \frac{t}{\gamma t + \mu_T}$ is increasing in $[0, +\infty)$, the maximum principle (see Proposition B.1) shows that the sequence (\bar{v}_n) is pointwise non-increasing. Moreover, $\underline{v}_0 \leq \bar{v}_n \leq \bar{v}_0$ for any $n \in \mathbb{N}$. Hence, the sequence (\bar{v}_n) is bounded. Moreover, by very general results for the heat equation, there exist positive constants C_1 and C_2 , independent of n , such that

$$\|\bar{v}_n\|_{H_{\sharp}^2} \leq C_1 \|R_0 h(\bar{v}_{n-1})\|_{L^2} \leq C_2 \|\bar{v}_{n-1}\|_{L^2},$$

for any $n \in \mathbb{N}$. Thus, the sequence (\bar{v}_n) is bounded in H_{\sharp}^2 as well. Since it converges pointwise in $\bar{\Omega}_\ell$, we can now infer that \bar{v}_n converges strongly in H_{\sharp}^1 and weakly in H_{\sharp}^2 to a function $v \in H_{\sharp}^2$ which, of course, turns out to be a solution to the equation (2.3). For further details on the method of lower and upper solutions, we refer the reader, e.g., to the monograph [19].

Step 2: (uniqueness). To prove the uniqueness of the nontrivial non-negative solution to the equation (2.3), we adapt to our situation a method due to H.B. Keller [13].

Let us suppose that u is another nontrivial non-negative solution to (2.3). Then, the function $w := v - u$ belongs to H_{\sharp}^2 and solves the equation

$$d_V \Delta w - \mu_V w + \mu_T^2 \mu_V R_0 q(u, v) w = 0, \quad (2.8)$$

where

$$q(x, y) = \frac{1}{(\gamma x + \mu_T)(\gamma y + \mu_T)}, \quad x, y \geq 0.$$

Let us denote by $\lambda_{\max}(u, v)$ and $\lambda_{\max}(u, 0)$, the maximum eigenvalues in L^2 of the operators

$$d_V \Delta + \mu_T^2 \mu_V R_0 q(u, v) Id$$

and

$$d_V \Delta + \mu_T^2 \mu_V R_0 q(u, 0) Id,$$

respectively. By Theorem 2.1, they are given by the formula

$$\lambda_{\max}(u, jv) = - \inf_{\psi \in H_0^1, \psi \neq 0} \left\{ \frac{d_V \int_{\Omega_\ell} |\nabla \psi|^2 dx - \mu_T^2 \mu_V \int_{\Omega_\ell} R_0 q(u, jv) \psi^2 dx}{\int_{\Omega_\ell} \psi^2 dx} \right\},$$

for $j = 0, 1$. Since v is non-negative and it does not identically vanish, $q(u, v) \leq q(u, 0)$ and there exists an open subset of Ω_ℓ where $q(u, v) < q(u, 0)$. Hence, $\lambda_{\max}(u, v) < \lambda_{\max}(u, 0)$. Clearly, since w satisfies (2.8) and it does not identically vanish in $\overline{\Omega_\ell}$, then $\mu_V \leq \lambda_{\max}(u, v) < \lambda_{\max}(u, 0)$.

Let us now rewrite the equation satisfied by u in the following way:

$$d_V \Delta u - \lambda_{\max}(u, 0) u + \mu_T^2 \mu_V R_0 q(u, 0) u = (\mu_V - \lambda_{\max}(u, 0)) u := \varphi.$$

Fredholm alternative implies that φ should be orthogonal to ζ , where by ζ we have denoted the function which spans the eigenspace associated with the eigenvalue $\lambda_{\max}(u, 0)$. As it has been already remarked (see Theorem 2.1), the function ζ does not change sign in $\overline{\Omega_\ell}$. Similarly, since $\mu_V < \lambda_{\max}(u, 0)$, φ is non-positive and it does not identically vanish since u does not. Hence, the function φ cannot be orthogonal to ζ and this leads us to a contradiction. The proof is now complete. \square

2.2. Numerical illustration (steady state). In accordance with Funk et al. [8], the domain Ω_ℓ is a discrete square grid with $n \times n$ sites of equal dimension $\ell/n \times \ell/n$. We assume in this numerical part that all parameters vary randomly from site to site in such a way that $0.1 \leq R_0(x) \leq 5.0$. We deal with two cases:

- (i) In the first case, see Fig. 5 (left), the distribution of R_0 is as in Fig. 4a. The sources represent only 26% of the sites. We compute $\lambda_0 = -1.70$. Solving numerically the equation (2.3), we find the non-infected solution $V_u \equiv 0$. We also represent T_u according to Formula (2.4).

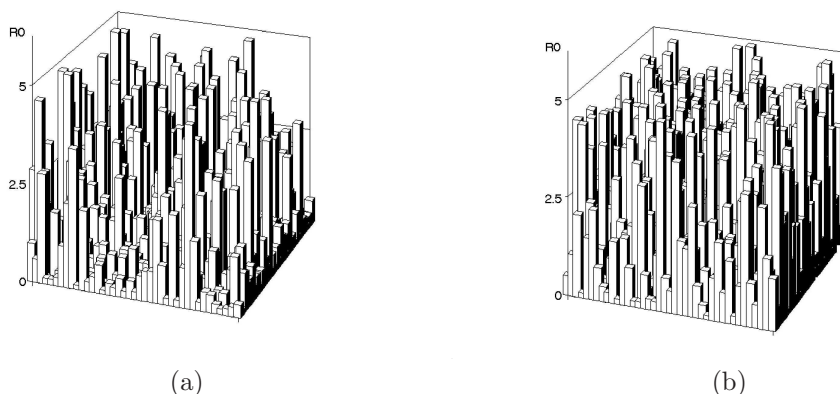


FIGURE 4. Two distributions of R_0 on a 40×40 grid. (a): 26% of the sites are sources; (b): 50% of the sites are sources.

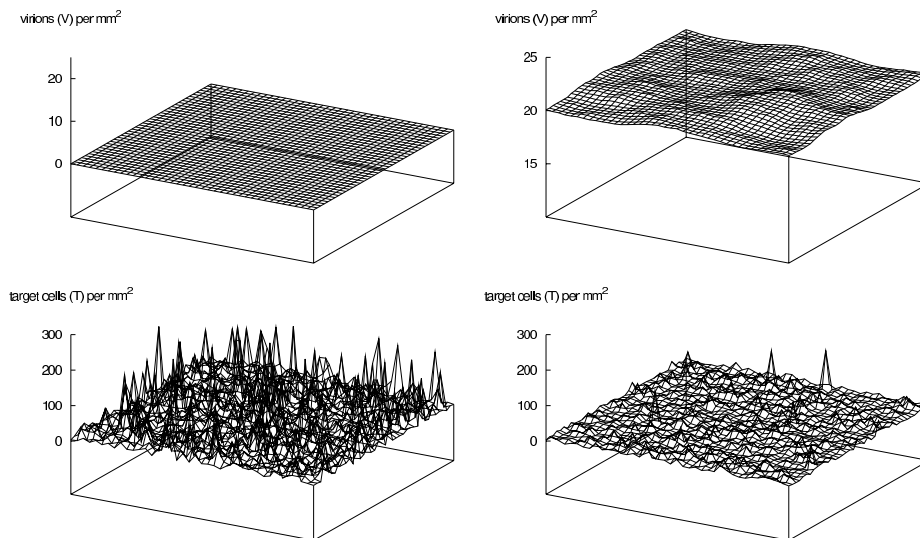


FIGURE 5. Densities of virus V (top) and target cells T (bottom). Left: R_0 as in Fig. 4a, $\lambda_0 < 0$ (no infection). Right: R_0 as in Fig. 4b, $\lambda_0 > 0$ (infection). Here $d_V = 1$, $\ell = 1$, $N = 40$.

- (ii) In the second case, see Fig. 5 (right), the distribution of R_0 is as in Fig. 4b. Now the sources represent half of the sites. The eigenvalue $\lambda_0 = 4.30$ is positive. Numerically, we observe the positive infected solution V_i of (2.3). Note that V_i is smoothly structured in space although R_0 is not. We also represent T_i according to Formula (2.7).

3. Study of the dynamical system. We recall the evolution problem for the virus dynamics:

$$T_t = \alpha - \gamma VT - \mu_T T, \quad (3.1a)$$

$$I_t = \gamma VT - \mu_I I, \quad (3.1b)$$

$$V_t = N\mu_I I - \mu_V V + d_V \Delta V, \quad (3.1c)$$

set in Ω_ℓ with periodic boundary conditions. We consider (3.1a)-(3.1c) as a dynamical system $\mathcal{S}(t)$, which has two equilibria: the non-infected trivial solution (T_u, I_u, V_u) and the infected, positive solution (T_i, I_i, V_i) , the latter for $\lambda_0 > 0$ only. At first, we prove that the non-infected solution is stable for $\lambda_0 < 0$ and unstable for $\lambda_0 > 0$. By stable we mean *asymptotically* stable. For $\lambda_0 > 0$ the instability of (T_u, I_u, V_u) does not usually imply the stability of (T_i, I_i, V_i) . Our aim is to prove the existence of a universal (or maximal) attractor which attracts all the orbits (see e.g., [25]). Since System (3.1a)-(3.1c) is only partly dissipative, we will use a result of Marion [16]. Some special cases where the stability of the infected solution is granted will be discussed afterwards.

Let us introduce the following notations: \mathcal{D} is the domain in \mathbb{R}^3 defined by:

$$\mathcal{D} = \{(x, y, z) \in \mathbb{R}^3 : 0 \leq x + y \leq M_1, 0 \leq z \leq M_2\},$$

where M_1, M_2 are positive constants which will be fixed throughout the proof of the next theorem. We also set for $\mathbf{u} := (u_1, u_2, u_3)$:

$$\mathbf{H} = \{\mathbf{u} \in (L^2)^3 : \mathbf{u}(x) \in \mathcal{D} \text{ for a.e. } x \in \Omega_\ell\}, \quad \mathbf{V} = L^2 \times L^2 \times H_{\sharp}^1.$$

Our main result is the following theorem.

Theorem 3.1. *The following properties are met:*

- (i) if $\lambda_0 < 0$, the trivial non-infected solution to Problem (3.1a)-(3.1c) is stable;
- (ii) if $\lambda_0 > 0$, the trivial non-infected solution to Problem (3.1a)-(3.1c) is unstable;
- (iii) if $\lambda_0 > 0$ and $\alpha \in W^{1,\infty}(\Omega_\ell)$, the dynamical system $\mathcal{S}(t)$ associated with (3.1a)-(3.1c) possesses a universal attractor that is connected in \mathbf{H} .

3.1. Proof of (i). We begin the proof observing that the linearization (around (T_u, I_u, V_u)) of Problem (3.1a)-(3.1c) is associated with the linear operator \mathcal{L}_u defined by

$$\mathcal{L}_u = \begin{pmatrix} -\mu_T Id & 0 & -\frac{\gamma\alpha}{\mu_T} Id \\ 0 & -\mu_I Id & \frac{\gamma\alpha}{\mu_T} Id \\ 0 & N\mu_I Id & d_V \Delta - \mu_V Id \end{pmatrix}.$$

Its realization L_u in $(L^2)^3$ with domain $D(L_u) = L^2 \times L^2 \times H_{\sharp}^2$ generates an analytic strongly continuous semigroup. Indeed, L_u is a bounded perturbation of the diagonal operator

$$\begin{pmatrix} -\mu_T Id & 0 & 0 \\ 0 & -\mu_I Id & 0 \\ 0 & 0 & d_V \Delta - \mu_V Id \end{pmatrix},$$

defined in $L^2 \times L^2 \times H_{\sharp}^2$, which is clearly sectorial since all its entries are. Hence, we can apply [15, Prop. 2.4.1(i)] and conclude that L_u is sectorial. Since H_{\sharp}^2 is dense in L^2 , the associated analytic semigroup is strongly continuous.

Let us prove that all the elements of the spectrum of L_u have negative real part. In view of the linearized stability principle (see e.g., [10, Chapt. 5, Cor. 5.1.6]) this will imply that the trivial non-infected solution to Problem (3.1a)-(3.1c) is stable.

To study the spectrum of the operator L_u , we fix $\mathbf{f} = (f_1, f_2, f_3) \in (L^2)^3$ and consider the resolvent system

$$(\lambda + \mu_T)\varphi_1 + \frac{\alpha\gamma}{\mu_T}\varphi_3 = f_1, \tag{3.2a}$$

$$(\lambda + \mu_I)\varphi_2 - \frac{\alpha\gamma}{\mu_T}\varphi_3 = f_2, \tag{3.2b}$$

$$(\lambda + \mu_V)\varphi_3 - d_V \Delta \varphi_3 - N\mu_I \varphi_2 = f_3, \tag{3.2c}$$

where we look for a triplet of functions $\varphi_1, \varphi_2 \in L^2$ and $\varphi_3 \in H_{\sharp}^2$. Suppose that λ differs from both $-\mu_I$ and $-\mu_T$ (which belong to the essential spectrum). Then, we can use equations (3.2a) and (3.2b) to make φ_1 and φ_2 explicit in terms of φ_3 . In particular, replacing the expression of φ_2 in terms of φ_3 into (3.2c) and

using the very definition of the function R_0 (see (1.5)), we can transform Problem (3.2a)-(3.2c) into the equivalent equation for φ_3 only:

$$(\lambda + \mu_V)\varphi_3 - d_V \Delta \varphi_3 - \frac{\mu_I \mu_V}{\lambda + \mu_I} R_0 \varphi_3 = \frac{N \mu_I}{\lambda + \mu_I} f_2 + f_3. \quad (3.3)$$

Adding and subtracting $-\mu_V R_0$ from the left-hand side of (3.3), we can rewrite the equation (3.3) into the equivalent form:

$$(\lambda + \mu_V)\varphi_3 - d_V \Delta \varphi_3 - \mu_V R_0 \varphi_3 + \mu_V R_0 \frac{\lambda}{\lambda + \mu_I} \varphi_3 = \frac{N \mu_I}{\lambda + \mu_I} f_2 + f_3. \quad (3.4)$$

Note that, for any $\lambda \in \mathbb{C}$, the operator A_λ defined by the left-hand side of (3.4) has compact resolvent. Hence, its spectrum consists of eigenvalues only. We are going to prove that, for $\lambda \in \mathbb{C}$ with non-negative real part, 0 is not an eigenvalue of A_λ . For this purpose, we observe that $-\lambda_0$ can be equivalently characterized as the infimum of the ratio

$$\frac{d_V \int_{\Omega_\ell} |\nabla \psi|^2 dx + \mu_V \int_{\Omega_\ell} (1 - R_0) |\psi|^2 dx}{\int_{\Omega_\ell} |\psi|^2 dx}$$

when ψ runs in the set of all the complex-valued functions $\psi = \psi_1 + i\psi_2$, with $\psi_1, \psi_2 \in H_{\sharp}^1$. This shows, in particular, that

$$-\lambda_0 \int_{\Omega_\ell} |\psi|^2 dx \leq d_V \int_{\Omega_\ell} |\nabla \psi|^2 dx + \mu_V \int_{\Omega_\ell} (1 - R_0) |\psi|^2 dx, \quad (3.5)$$

for any function ψ as above.

Let now φ_3 be a complex-valued solution to (3.4). Multiplying both the sides of such an equation by the conjugate of φ_3 and integrating by parts, we easily see that

$$\begin{aligned} (\lambda + \mu_V) \int_{\Omega_\ell} |\varphi_3|^2 dx + d_V \int_{\Omega_\ell} |\nabla \varphi_3|^2 dx - \mu_V \int_{\Omega_\ell} R_0 |\varphi_3|^2 dx \\ + \frac{\mu_V \lambda}{\lambda + \mu_I} \int_{\Omega_\ell} R_0 |\varphi_3|^2 dx = 0. \end{aligned} \quad (3.6)$$

Taking the real part of both the sides of (3.6) and using (3.5), we obtain

$$(\operatorname{Re} \lambda + \mu_V) \int_{\Omega_\ell} |\varphi_3|^2 dx - \lambda_0 \int_{\Omega_\ell} |\varphi_3|^2 dx + \mu_V \frac{|\lambda|^2 + \mu_I \operatorname{Re} \lambda}{|\lambda + \mu_I|^2} \int_{\Omega_\ell} |\varphi_3|^2 dx \leq 0.$$

Since, by assumptions, $\lambda_0 < 0$ and R_0 is a positive-valued function, the only solution to the previous inequality, when $\operatorname{Re} \lambda \geq 0$, is the trivial function $\varphi_3 \equiv 0$. Hence, for these values of λ , 0 is not an eigenvalue of the operator A_λ , i.e., any λ with non-negative real part belongs to the resolvent set of the operator L_u .

3.2. Proof of (ii). Again in view of the linearized stability principle, to prove the instability of non-infected solution (T_u, I_u, V_u) we can limit ourselves to showing that L_u admits a positive eigenvalue. Hence, we are led to the study of Problem (3.2a)-(3.2c) with $f_1 \equiv f_2 \equiv f_3 \equiv 0$. Since the parameters μ_T , μ_I and μ_V are all positive and we are looking for positive eigenvalues λ , we can limit ourselves, as in the proof of (i), to studying the equation

$$d_V \Delta \varphi_3 + \mu_V \left(\frac{\mu_I R_0}{\lambda + \mu_I} - 1 \right) \varphi_3 = \lambda \varphi_3.$$

For any $s \geq 0$, let us consider the operator $d_V \Delta + \mu_V \left(\frac{\mu_I R_0}{s + \mu_I} - 1 \right) Id$ defined in H_{\sharp}^2 . By Theorem 2.1 its spectrum consists of eigenvalues only, and the largest one is given by the following formula:

$$-\lambda(s) = \inf_{\psi \in H_{\sharp}^1, \psi \neq 0} \left\{ \frac{d_V \int_{\Omega_{\ell}} |\nabla \psi|^2 dx + \mu_V \int_{\Omega_{\ell}} \left(1 - \frac{\mu_I R_0}{s + \mu_I} \right) \psi^2 dx}{\int_{\Omega_{\ell}} \psi^2 dx} \right\}.$$

As it is immediately seen, $\lambda(0) = \lambda_0$. Moreover, since the function $s \mapsto \frac{\mu_I R_0}{s + \mu_I}$ is continuous, decreasing in $[0, +\infty)$ and it tends to 0 as $s \rightarrow +\infty$, the function $s \mapsto \lambda(s)$ is continuous, decreasing and tends to

$$\lambda(+\infty) = - \inf_{\psi \in H_{\sharp}^1, \psi \neq 0} \left\{ \frac{d_V \int_{\Omega_{\ell}} |\nabla \psi|^2 dx + \mu_V \int_{\Omega_{\ell}} \psi^2 dx}{\int_{\Omega_{\ell}} \psi^2 dx} \right\},$$

as $s \rightarrow +\infty$, i.e., it converges to the largest eigenvalue of the operator $d_V \Delta - \mu_V Id$, which clearly is $-\mu_V$. Now, since $s \mapsto \lambda(s)$ is a decreasing continuous function mapping $[0, +\infty)$ into $[-\mu_V, \mu_V^{-1} \lambda_0]$, it is immediate to check that the fixed point equation $s = \lambda(s)$ has a positive solution. Of course, this fixed point is the positive eigenvalue of the operator L_u we were looking for. This accomplishes the proof.

3.3. Proof of (iii). Let us show that [16, Thm. 5.1] applies. In this respect the assumption $\alpha \in W^{1,\infty}(\Omega_{\ell})$ is enough. To avoid conflict with notations, throughout the proof, T denotes time as usual, whereas the triplet (T, I, V) is denoted by (u_1, u_2, u_3) . We split the proof into several steps.

Step 1. Here, we prove that, for any $\mathbf{u}_0 := (u_{0,1}, u_{0,2}, u_{0,3}) \in (L^2)^3$, the Cauchy problem

$$\begin{cases} D_t u_1(t, \cdot) = -\mu_T u_1(t, \cdot) - \gamma u_1(t, \cdot) u_3(t, \cdot) + \alpha(\cdot), & t > 0, \\ D_t u_2(t, \cdot) = -\mu_I u_2(t, \cdot) + \gamma u_1(t, \cdot) |u_3(t, \cdot)|, & t > 0, \\ D_t u_3(t, \cdot) = \Delta u_3(t, \cdot) - \mu_V u_3(t, \cdot) + N \mu_I u_2(t, \cdot), & t > 0, \\ u_i(0, \cdot) = u_{0,i}, \quad i = 1, 2, 3, \end{cases} \quad (3.7)$$

Problem (3.7) admits a unique classical solution defined in some time domain $(0, T_*)$. Here, by classical solution, we mean a vector valued function \mathbf{u} such that $u_1, u_2 \in C^1((0, T_*); L^2) \cap C([0, T_*]; L^2)$ and $u_3 \in C([0, T_*]; L^2) \cap C^1((0, T_*); L^2) \cap C((0, T_*); H_{\sharp}^2)$.

Problem (3.7) is semilinear with a nonlinear term which is a continuous function from $L^2 \times L^2 \times D_{\Delta_2}(\beta, 2)$ into $L^2 \times L^2 \times L^2$ for any $\beta \in (1/2, 1)$. Here, $D_{\Delta_2}(\beta, 2)$ is the interpolation space of order $(\beta, 2)$ between L^2 and the domain of the realization Δ_2 of the Laplacian with periodic boundary conditions in L^2 (i.e., $D(\Delta_2) = H_{\sharp}^2$). Hence, $D_{\Delta_2}(\beta, 2) = (L^2, H_{\sharp}^2)_{\beta, 2}$ and this latter space coincides with $H_{\sharp}^{2\beta}$, which continuously embeds into the space C_{\sharp} of all continuous and periodic (with period ℓ in each variable) functions (see e.g., [9, Thm. 1.4.4.1]).

To prove the existence of a classical solution to Problem (3.7), let us fix $\beta \in (1/2, 1)$ and introduce, for any $T > 0$, the space $C_{\beta}(T)$ consisting of all functions $v : (0, T) \rightarrow D_{\Delta_2}(\beta, \infty)$ such that $\|v\|_{C_{\beta}(T)} := \sup_{t \in (0, T]} \|t^{\beta} v(t, \cdot)\|_{D_{\Delta_2}(\beta, \infty)} < +\infty$. Clearly, $C_{\beta}(T)$ is a Banach space when endowed with the above norm. Moreover, $D_{\Delta_2}(\beta, \infty)$ is continuously embedded into $D_{\Delta_2}(\beta - \varepsilon, 2)$ for any $\varepsilon \in (0, \beta)$. We now fix ε small enough such that $\theta = \beta - \varepsilon > 1/2$. From the above results, it is

immediate to infer that $C_\beta(T)$ is embedded into the set of all continuous functions $f : (0, T] \times \overline{\Omega}_\ell \rightarrow \mathbb{R}$ and there exists a positive constant C_1 , independent of T , such that

$$\sup_{t \in (0, T]} t^\theta \|f(t, \cdot)\|_\infty \leq C_1 \|f\|_{C_\beta(T)}. \quad (3.8)$$

Let us solve the Cauchy problem for u_1 , taking u_3 as a parameter. The (unique) solution to such a problem in $C^1((0, T]; L^2) \cap C([0, T]; L^2)$ is the function u_1 defined by

$$\begin{aligned} u_1(t, \cdot) = & \exp\left(-\mu_T t - \gamma \int_0^t u_3(s, \cdot) ds\right) u_{0,1} \\ & + \alpha(\cdot) \int_0^t \exp\left(-\mu_T(t-s) - \gamma \int_s^t u_3(r, \cdot) dr\right) ds, \end{aligned} \quad (3.9)$$

for any $t \in (0, T]$. If $u_{0,1}$ is bounded and continuous in Ω_ℓ this result is straightforward. In the general case, we approximate $u_{0,1} \in L^2$ by a sequence of smooth functions $u_{0,1}^{(n)}$. It is immediate to check that the function $u_1^{(n)}$ defined by (3.9), with $u_{0,1}^{(n)}$ instead of $u_{0,1}$, converges to the function u_1 in (3.9) in $C([0, T]; L^2)$, by dominated convergence. Similarly, $D_t u_1^{(n)}$ converges to $D_t u_1$ in $C([\varepsilon, T - \varepsilon]; L^2)$ for any $\varepsilon > 0$. It follows that the function u_1 in (3.9) is a solution to the Cauchy problem for u_1 also in the case when $u_{0,1}$ is in L^2 .

Let us now denote by Λ_1 the operator defined in $C_\beta(T)$ by the right-hand side of (3.9). A very easy computation shows that Λ_1 maps $C_\beta(T)$ into $C^{1-\theta}([0, T]; L^2)$. Moreover,

$$\|\Lambda_1(v)\|_{C([0, T]; L^2)} \leq \exp\left(\frac{C_1}{1-\theta} \gamma T^{1-\theta} \|v\|_{C_\beta(T)}\right) (\|u_{0,1}\|_{L^2} + T\|\alpha\|_{L^2}), \quad (3.10a)$$

$$\begin{aligned} & \|\Lambda_1(v) - \Lambda_1(w)\|_{C([0, T]; L^2)} \\ & \leq \exp\left(\frac{C_1}{1-\theta} \gamma T^{1-\theta} \max(\|v\|_{C_\alpha(T)}, \|w\|_{C_\beta(T)})\right) \\ & \quad \times \left(1 + \frac{C_1}{(1-\theta)(2-\theta)} \gamma T^{2-\theta} \|\beta\|_{L^2}\right) \|w - v\|_{C_\beta(T)}. \end{aligned} \quad (3.10b)$$

We now consider the equation for u_2 . Replacing $u_1 = \Lambda_1(u_3)$ in the right-hand side of this equation and using the same argument as above, we easily see that the (unique) solution in $C([0, T]; L^2) \cap C^1((0, T]; L^2)$ is the function u_2 defined by

$$u_2(t, \cdot) = e^{-t\mu_I} u_{0,2} + \gamma \int_0^t e^{-\mu_I(t-s)} |u_3(s, \cdot)| (\Lambda_1(u_3))(s, \cdot) ds, \quad t \in [0, T]. \quad (3.11)$$

Let us denote by Λ_2 the operator defined in $C_\beta(T)$ by the right-hand side of (3.11). Taking (3.8), (3.10a) and (3.10b) into account, one can easily show that

$$\begin{aligned} \|\Lambda_2(v)\|_{C([0, T]; L^2)} & \leq \|u_{0,2}\|_{L^2} + \frac{C_1}{1-\theta} \gamma T^{1-\theta} \|v\|_{C_\beta(T)} (\|u_{0,1}\|_{L^2} + T\|\alpha\|_{L^2}) \\ & \quad \times \exp\left(\frac{C_1}{1-\theta} \gamma T^{1-\theta} \|v\|_{C_\beta(T)}\right), \end{aligned} \quad (3.12a)$$

$$\|\Lambda_2(v)\|_{C^{1-\theta}([0, T]; L^2)} \leq \left(\frac{1}{\mu_I} T^\theta + 1\right) \|u_{0,2}\|_{L^2}$$

$$\begin{aligned}
& + \frac{C_1}{1-\theta} \gamma (1 + T^{1-\theta}) \|v\|_{C_\beta(T)} \exp\left(\frac{C_1}{1-\theta} \gamma T^{1-\theta} \|v\|_{C_\beta(T)}\right) \\
& \quad \times (\|u_{0,1}\|_{L^2} + T\|\alpha\|_{L^2}), \tag{3.12b}
\end{aligned}$$

$$\begin{aligned}
& \|\Lambda_2(w) - \Lambda_2(v)\|_{C([0,T];L^2)} \\
& \leq \frac{C_1}{1-\theta} \gamma T^{1-\theta} \exp\left(\frac{C_1}{1-\theta} \gamma T^{1-\theta} \max(\|v\|_{C_\beta(T)}, \|w\|_{C_\beta(T)})\right) \|w - v\|_{C_\beta(T)} \\
& \quad \times \left\{ \|u_{0,1}\|_{L^2} + T\|\theta\|_{L^2} + \|v\|_{C_\beta(T)} \left(1 + \frac{C_1}{(1-\theta)(2-\theta)} \gamma T^{2-\theta} \|\beta\|_{L^2}\right) \right\}, \tag{3.12c}
\end{aligned}$$

for any $v, w \in C_\beta(T)$. Let us now observe that (u_1, u_2, u_3) is a classical solution to Problem (3.7) if and only if u_3 is a fixed point of the operator Γ , formally defined by

$$(\Gamma(v))(t, \cdot) = e^{-t\mu_V} e^{t\Delta_2} u_{0,3} + \int_0^t e^{-\mu_V(t-s)} e^{(t-s)\Delta_2} (\Lambda_2(v))(s, \cdot) ds, \quad t \in (0, T).$$

We are going to prove that the operator Γ is a contraction in $\mathcal{B}_\beta(T) = \{u \in C_\beta(T) : \|u\|_{C_\beta(T)} \leq M\}$ provided that T and M are properly chosen. As a first step, let us prove that Γ maps $\mathcal{B}_\beta(T)$ into itself if T, M are suitably chosen. For this purpose, we set

$$K := \sup_{t>0} \|t^\beta e^{t\Delta_2}\|_{D_{\Delta_2}(\beta, \infty)}.$$

Taking (3.12a) into account, we can estimate

$$\begin{aligned}
\|\Gamma(v)\|_{C_\beta(T)} & \leq K \left\{ \|u_{0,3}\|_{L^2} + \frac{T}{1-\beta} \|u_{0,2}\|_{L^2} \right. \\
& \quad \left. + \frac{C_1 M}{(1-\beta)(1-\theta)} \gamma T^{2-\theta} \exp\left(\frac{C_1}{1-\theta} \gamma T^{1-\theta} M\right) (\|u_{0,1}\|_{C_\beta(T)} + T\|\alpha\|_{L^2}) \right\},
\end{aligned}$$

for any $v \in \mathcal{B}_\beta(T)$. Hence, if we fix $M > K\|u_{0,3}\|_{L^2}$, we can then choose T small enough such that $\|\Gamma(v)\|_{C_\beta(T)} \leq M$ for any $v \in \mathcal{B}_\beta(T)$. Moreover, taking (3.12c) into account, we can estimate

$$\begin{aligned}
\|\Gamma(w) - \Gamma(v)\|_{C_\beta(T)} & \leq \frac{K}{1-\beta} T \|\Lambda_2(w) - \Lambda_2(v)\|_{C([0,T];L^2)} \\
& \leq \frac{KC_1}{(1-\beta)(1-\theta)} \gamma T^{2-\theta} \exp\left(\frac{C_1}{1-\theta} \gamma T^{1-\theta} M\right) \|w - v\|_{C_\beta(T)} \\
& \quad \times \left\{ \|u_{0,1}\|_{L^2} + T\|\alpha\|_{L^2} + M \left(1 + \frac{C_1}{(1-\theta)(2-\theta)} \gamma T^{2-\theta} \|\alpha\|_{L^2}\right) \right\},
\end{aligned}$$

for any $v, w \in \mathcal{B}_\beta(T)$. This estimate shows that Γ is a $1/2$ -contraction provided that T is sufficiently small. We can thus apply the Banach fixed point theorem and conclude that there exist $T > 0$ and a unique function $u_3 \in \mathcal{B}_\beta(T)$ solving the equation $\Gamma(u_3) = u_3$.

The function u_3 actually belongs to $C([0, T]; L^2) \cap C^1((0, T]; L^2) \cap C((0, T]; H_\beta^2)$. Indeed, by (3.12b), the function $\Lambda_2(u_3)$ is in $C^{1-\beta}([0, T]; L^2)$. Therefore, [15, Thm. 4.3.1(i)] guarantees that the function $\Gamma(u_3)$ has the claimed regularity properties. Moreover, $D_t u_3 = \Delta u_3 - \mu_V u_3 + \Lambda_2(u_3)$ in $(0, T]$. As a byproduct, the triplet (u_1, u_2, u_3) is a classical solution to Problem (3.7).

By a classical argument we can extend the solution (u_1, u_2, u_3) to a maximal solution defined in some time domain $[0, T_*)$. This vector valued function (still denoted by (u_1, u_2, u_3)) enjoys the following properties: $u_1, u_2 \in C([0, T_*); L^2) \cap C^1((0, T_*); L^2)$, $u_3 \in C([0, T_*); L^2) \cap C^1((0, T_*); L^2) \cap C((0, T_*); H_{\sharp}^2)$.

Step 2. Here, we prove that if $\mathbf{u}_0 \geq 0$ (where the inequality is meant component-wise) then the maximal defined solution \mathbf{u} to Problem (3.7) is non-negative as well in $(0, T_*)$. Clearly, using formulae (3.9) and (3.11) it is immediate to check that u_1 and u_2 are both non-negative whenever $u_{0,1}$ is.

Let us now consider the problem for u_3 , which we rewrite here:

$$\begin{cases} D_t u_3(t, \cdot) = \Delta u_3(t, \cdot) - \mu_V u_3(t, \cdot) + N \mu_I u_2(t, \cdot), & t \in (0, T_*), \\ u_3(0, \cdot) = u_{0,3}. \end{cases} \quad (3.13)$$

The heat semigroup is positive in C_{\sharp} by the maximum principle. Since the heat semigroup in C_{\sharp} is the restriction to C_{\sharp} of the heat semigroup $\{e^{t\Delta_2}\}$ in L^2 , by density it follows that $\{e^{t\Delta_2}\}$ is non-negative as well. This is enough for our aims. Indeed, the function u_3 is given by the variation of constants formula

$$u_3(t, \cdot) = e^{t(\Delta_2 - \mu_V)} u_{0,3} + N \mu_I \int_0^t e^{(t-s)(\Delta_2 - \mu_V)} u_2(s, \cdot) ds, \quad t \in (0, T_*), \quad (3.14)$$

$u_{0,3}$ and u_2 being non-negative, the function u_3 is non-negative as well.

We have so proved that any solution to Problem (3.7), corresponding to an initial datum in the first octant, is confined to the first octant for any $t \in (0, T_*)$. In such a case we can forget the absolute value in (3.7).

Step 3. Here, we prove that any solution \mathbf{u} to Problem (3.7), corresponding to an initial datum $\mathbf{u}_0 \in \mathcal{D}$, exists for any positive time and it stays bounded. Here,

$$\begin{aligned} \mathcal{D} &= \{(x, y, z) \in \mathbb{R}^3 : 0 \leq x + y \leq M_1, 0 \leq z \leq M_2\}, \\ M_1 &= \frac{\|\alpha\|_{\infty}}{\min\{\mu_T, \mu_I\}}, \quad M_2 = \frac{M_1 N \mu_I}{\mu_V} \|\alpha\|_{\infty}. \end{aligned} \quad (3.15)$$

For this purpose, it is convenient to introduce the so-called Svab-Zeldovich variable $v = u_1 + u_2$. As it is immediately seen, the function v satisfies the Cauchy problem

$$\begin{cases} D_t v(t, \cdot) = \alpha - \mu_T u_1 - \mu_I u_2, & t \in (0, T_*), \\ v(0, \cdot) = u_{0,1} + u_{0,2}. \end{cases}$$

Since u_1 and u_2 are both positive, then

$$D_t v(t, \cdot) \leq \alpha - \min\{\mu_T, \mu_I\} v(t, \cdot) := \alpha - \mu v(t, \cdot) \leq \|\alpha\|_{\infty} - \mu v(t, \cdot), \quad t \in (0, T_*). \quad (3.16)$$

Multiplying both the sides of (3.16) by a non-negative function $\varphi \in L^2$ and integrating over Ω_{ℓ} , one obtains that the function $w(t) = \int_{\Omega_{\ell}} v(t, x) \varphi(x) dx$ is in $C^1([0, T_*))$ and solves the differential inequality

$$D_t w(t) \leq \|\alpha\|_{\infty} \|\varphi\|_{L^1(\Omega_{\ell})} - \mu w(t), \quad t \in (0, T_*).$$

Hence,

$$w(t) \leq e^{-\mu t} \left(\int_{\Omega_{\ell}} v(0, x) \varphi(x) dx + \frac{1}{\mu} (e^{\mu t} - 1) \|\alpha\|_{\infty} \int_{\Omega_{\ell}} \varphi(x) dx \right), \quad t \in (0, T_*),$$

or, equivalently,

$$\int_{\Omega_{\ell}} \left(v(t, x) - e^{-\mu t} v(0, x) - \frac{1}{\mu} (1 - e^{-\mu t}) \|\alpha\|_{\infty} \right) \varphi(x) dx \leq 0, \quad t \in (0, T_*).$$

From this integral inequality, we can infer that

$$v(t, x) \leq e^{-\mu t} v(0, x) + \frac{1}{\mu} (1 - e^{-\mu t}) \|\alpha\|_\infty \leq \frac{1}{\mu} \|\alpha\|_\infty = M_1, \quad (3.17)$$

for any $t \in [0, T_*)$ and almost any $x \in \Omega_\ell$.

Since $v = u_1 + u_2$ and u_1 and u_2 are both non-negative, it follows that u_1 and u_2 can be estimated by the right-hand side of (3.17).

Finally, let us consider the function u_3 . From (3.14) and the above results, we can infer that

$$D_t u_3(t, \cdot) \leq \Delta u_3(t, \cdot) - \mu_V u_3(t, \cdot) + M_1 N \mu_I, \quad t \in (0, T_*).$$

Note that the function $\bar{u}_3 \equiv M_2$, with M_2 being given by (3.15), satisfies the previous inequality. Hence, if $u_{0,3} \leq M_2$, then, the solution to Problem (3.13) is bounded from above by M_2 . With the previous choices of M_1 and M_2 , we see that the solution to Problem (3.7) which corresponds to $\mathbf{u}_0 \in \mathcal{D}$, stays in \mathcal{D} for any $t \in (0, T_*)$. By virtue of [15, Prop. 7.1.8], \mathbf{u} can be extended to all the positive times.

Step 4. Here, we show that, for any $\mathbf{u}_0 \in \mathcal{D}$, the solution \mathbf{u} that we have determined in the previous steps is, in fact, the unique weak solution to Problem (3.7) which belongs to $L^2((0, T); L^2) \times L^2((0, T); L^2) \times L^2((0, T); H_{\sharp}^1)$ for any $T > 0$. Even if the following arguments are standard, for the reader's convenience we go into details.

As a first step, we observe that, since u_1 , u_2 and u_3 are bounded, the weak derivatives $D_t u_1$ and $D_t u_2$ are in $L^\infty((0, +\infty) \times \Omega_\ell) = L^\infty((0, \infty); L^\infty(\Omega_\ell))$. Hence, u_1 and u_2 are locally Lipschitz continuous in $[0, +\infty)$ with values in $L^\infty(\Omega_\ell)$.

Let us now consider the Cauchy problem for u_3 (i.e., problem (3.13)). Since u_2 is Lipschitz continuous in $[0, T]$ with values in L^2 , for any $T > 0$, by [15, Thm. 4.3.1(i)], such a Cauchy problem admits a solution which is in $C([0, T]; L^2) \cap C^1((0, T); L^2) \cap C((0, T); H_{\sharp}^2)$. By the weak maximum principle, the Cauchy problem (3.13) admits a unique weak solution. Hence, $u_3 \in C([0, T]; L^2) \cap C^1((0, T); L^2) \cap C((0, T); H_{\sharp}^2)$. Now, we turn back to the equations for u_1 and u_2 and conclude that $D_t u_1$ and $D_t u_2$ are in $C([0, T]; L^2)$ for any $T > 0$, this implying that u_1 and u_2 are in $C^1([0, T]; L^2)$. Hence, any weak solution to Problem (3.7) with data in \mathcal{D} is such that $u_1, u_2 \in C^1([0, T_*]; L^2)$ and $u_3 \in C([0, T_*]; L^2) \cap C^1((0, T_*); L^2) \cap C((0, T_*); H_{\sharp}^2)$. Since we have proved uniqueness of the solution in this class of functions, uniqueness of the weak solution follows as well.

Since for non-negative solutions the Cauchy problem (3.7) coincides with problem (3.1a)-(3.1c), we have, thus, established the following:

Proposition 3.2. *For every $\mathbf{u}_0 \in \mathbf{H}$, the Cauchy problem (3.7) possesses a unique solution for all time, $\mathbf{u}(t) \in \mathbf{H}$ for all t , $\mathbf{u} \in L^2(0, T; \mathbf{V})$ for all $T > 0$. The mapping $\mathcal{S}(t) := \mathbf{u}_0 \mapsto \mathbf{u}(t)$ is continuous in \mathbf{H} . Furthermore, if $\mathbf{u}_0 \in \mathbf{V}$, then $u_3 \in L^2(0, T; H_{\sharp}^2)$.*

Step 3. We are now in a position to apply [16, Thm. 5.1]. The set

$$\mathcal{D} = \{(x, y, z) \in \mathbb{R}^3 : 0 \leq x + y \leq M_1, 0 \leq z \leq M_2\},$$

is a positively convex, compact region of \mathbb{R}^3 . To meet all the hypotheses of [16, Thm. 5.1], it remains to consider the non-dissipative part of (3.7), i.e. the equations for

u_1 and u_2 which we rewrite in the compact form:

$$D_t \begin{pmatrix} u_1 \\ u_2 \end{pmatrix} + \begin{pmatrix} \mu_T + \gamma u_3 & 0 \\ -\gamma u_3 & \mu_I \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \end{pmatrix} + \begin{pmatrix} \alpha \\ 0 \end{pmatrix} := G(\cdot, u_3) \begin{pmatrix} u_1 \\ u_2 \end{pmatrix} + g(\cdot).$$

Obviously the matrix $G(\cdot, u_3)$ has positive eigenvalues whenever $u_3 \geq 0$, which are bounded from below by positive constants. Hence,

$$\langle G(\cdot, u_3)\xi, \xi \rangle \geq \mu_T \|\xi\|^2,$$

for any $\xi \in \mathbb{R}^2$. Thus, condition (4.6) in [16] is satisfied. The proof of Theorem 3.1 is completed.

4. A gamut of some special cases.

4.1. Numerical illustration (evolution). We continue the discussion of Subsection 2.2 in the framework of the evolution problem (3.1a)-(3.1c). In the first case ($\lambda_0 < 0$), only the non-infected steady state $V_u \equiv 0$ exists. We solve (3.1a)-(3.1c) under particular initial conditions: we start the infection at the center of the grid with an inoculum of one viral unit, assuming that T and I are at their uninfected steady state. One observes that the virus vanishes very rapidly and the target cells return to their initial level (see Fig. 6 left) in accordance with the stability of the uninfected equilibrium V_u . In the second case ($\lambda_0 > 0$), two equilibria exist, V_u and V_i . Starting with the same initial conditions, the virus population grows while the population of target cells decreases. Both of them achieve an equilibrium corresponding to the positive infected solution (see Fig. 6 right).

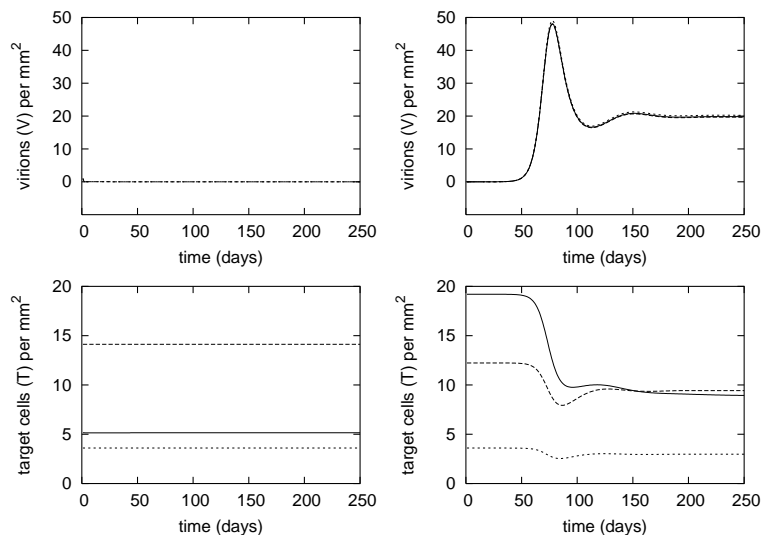


FIGURE 6. Dynamics of free virus (top) and target cells (bottom) on a 40×40 grid. Left: R_0 as in Fig. 4a, $\lambda_0 < 0$ (no infection); right: R_0 as in Fig. 4b, $\lambda_0 > 0$ (infection). The solid, the long and the short dashed lines depict respectively the dynamics at (10,10), at the site of viral inoculum (20,20) and at a border site (1,1). Here $d_V = 1$, $\ell = 1$.

We are now going to review some particular cases where the stability of the infected solution is granted.

4.2. Homogeneous environment with diffusion. We consider the case when α is a constant such that R_0 (see (1.3)) is a constant, as well, greater than 1, together with $d_V > 0$ as in [8].

The linearization around (T_i, I_i, V_i) (see (1.2)) of Problem (3.1a)-(3.1c) is associated with the linear operator

$$\mathcal{L}_i = \begin{pmatrix} -\mu_T R_0 Id & 0 & -\frac{\mu_V}{N} Id \\ \mu_T (R_0 - 1) Id & -\mu_I Id & \frac{\mu_V}{N} Id \\ 0 & N\mu_I Id & d_V \Delta - \mu_V Id \end{pmatrix}.$$

The same arguments as in the proof of Theorem 3.1(i) show that the realization L_i of the operator \mathcal{L}_i in $(L^2)^3$ with domain $D(L_i) = L^2 \times L^2 \times H_{\sharp}^2$ generates an analytic strongly continuous semigroup. We are going to determine its spectrum. For this purpose we use the discrete Fourier transform.

We consider the realization Δ_2 of the operator Δ with domain H_{\sharp}^2 . Its real eigenvalues can be labeled as a non-increasing sequence $(-\lambda_k)$, $k = 0, 1, \dots$. Only $\lambda_0 = 0$ is simple, the other eigenvalues being negative such that $-\lambda_k \rightarrow -\infty$ as $k \rightarrow +\infty$.

We claim that the spectrum of the operator L_i is given by

$$\sigma(L_i) = \{-\mu_I, -\mu_T R_0\} \cup \bigcup_{k \in \mathbb{N} \cup \{0\}} \sigma_k, \quad (4.1)$$

where σ_k is the spectrum of the matrix

$$M_k = \begin{pmatrix} -\mu_T R_0 & 0 & -\frac{\mu_V}{N} \\ \mu_T (R_0 - 1) & -\mu_I & \frac{\mu_V}{N} \\ 0 & N\mu_I & -\lambda_k d_V - \mu_V \end{pmatrix}.$$

To check the claim, let us observe that, if a function $\mathbf{v} = (v_1, v_2, v_3)$ in $L^2 \times L^2 \times H^2$ solves the resolvent equation $\lambda \mathbf{u} - L_i \mathbf{u} = \mathbf{f}$, for some $\lambda \in \mathbb{C}$ and $\mathbf{f} = (f_1, f_2, f_3)$ in $(L^2)^3$, then its Fourier coefficients $(v_{1,k}, v_{2,k}, v_{3,k})$ ($k = 0, 1, \dots$) solve the infinitely many equations

$$\begin{pmatrix} \lambda + \mu_T R_0 & 0 & \frac{\mu_V}{N} \\ -\mu_T (R_0 - 1) & \lambda + \mu_I & -\frac{\mu_V}{N} \\ 0 & -N\mu_I & \lambda + \lambda_k d_V + \mu_V \end{pmatrix} \begin{pmatrix} v_{1,k} \\ v_{2,k} \\ v_{3,k} \end{pmatrix} = \begin{pmatrix} f_{1,k} \\ f_{2,k} \\ f_{3,k} \end{pmatrix}, \quad k = 0, 1, \dots,$$

where $f_{i,k}$ denotes the k -th Fourier coefficient of the function f_i ($i = 1, 2, 3$). Clearly, any eigenvalue of M_k ($k = 0, 1, \dots$) is an eigenvalue of L_i . Therefore,

$$\sigma(L_i) \supset \bigcup_{k \in \mathbb{N} \cup \{0\}} \sigma_k.$$

On the other hand, if $\lambda \notin \sigma_k$ for any $k = 0, 1, \dots$, then all the coefficients $(v_{1,k}, v_{2,k}, v_{3,k})$ are uniquely determined through the formulae

$$\begin{aligned} v_{1,k} &= \frac{1}{\mathcal{P}_k(\lambda)} \left\{ [(\lambda + \mu_I)(\lambda + \lambda_k d_V + \mu_V) - \mu_I \mu_V] f_{1,k} - \mu_I \mu_V f_{2,k} \right. \\ &\quad \left. - \frac{\mu_V}{N} (\lambda + \mu_I) f_{3,k} \right\}, \\ v_{2,k} &= \frac{1}{\mathcal{P}_k(\lambda)} \left\{ \mu_T (R_0 - 1) (\lambda + \lambda_k d_V + \mu_V) f_{1,k} + (\lambda + \mu_T R_0) (\lambda + \lambda_k d_V + \mu_V) f_{2,k} \right. \\ &\quad \left. + \frac{\mu_V}{N} (\mu_T + \lambda) f_{3,k} \right\}, \\ v_{3,k} &= \frac{1}{\mathcal{P}_k(\lambda)} \left\{ N \mu_I \mu_T (R_0 - 1) f_{1,k} + N \mu_I (\lambda + \mu_T R_0) f_{2,k} \right. \\ &\quad \left. + (\lambda + \mu_T R_0) (\lambda + \mu_I) f_{3,k} \right\}, \end{aligned}$$

where

$$\mathcal{P}_k(\lambda) = \lambda^3 + b_k \lambda^2 + c_k \lambda + d_k = 0, \quad k = 0, 1, \dots$$

and

$$\begin{aligned} b_k &= \mu_T R_0 + \mu_I + \mu_V + d_V \lambda_k, \\ c_k &= \mu_T R_0 (\mu_I + \mu_V) + d_V \lambda_k (\mu_T R_0 + \mu_I), \\ d_k &= \mu_I \mu_V \mu_T (R_0 - 1) + d_V \lambda_k \mu_I \mu_T R_0. \end{aligned}$$

Note that, if λ differs from both $-\mu_I$ and $-\mu_T R_0$, then

$$\mathcal{P}_k(\lambda) \sim d_V \left\{ \lambda^2 + \lambda (\mu_T R_0 + \mu_I) + \mu_I \mu_T R_0 \right\} \lambda_k, \quad \text{as } k \rightarrow +\infty.$$

Hence, for any $\lambda \notin \{-\mu_I, -\mu_T R_0\} \cup \bigcup_{k \in \mathbb{N} \cup \{0\}} \sigma_k$, it holds that

$$\begin{aligned} v_{1,k} &\sim \frac{\lambda + \mu_I}{\lambda^2 + \lambda (\mu_T R_0 + \mu_I) + \mu_I \mu_T R_0} f_{1,k}, \\ v_{2,k} &\sim \frac{\mu_T (R_0 - 1) f_{1,k} + (\lambda + \mu_T R_0) f_{2,k}}{\lambda^2 + \lambda (\mu_T R_0 + \mu_I) + \mu_I \mu_T R_0}, \\ v_{3,k} &\sim \frac{N \mu_I \mu_T (R_0 - 1) f_{1,k} + N \mu_I (\lambda + \mu_T R_0) f_{2,k} + (\lambda + \mu_T R_0) (\lambda + \mu_I) f_{3,k}}{d_V \left\{ \lambda^2 + \lambda (\mu_T R_0 + \mu_I) + \mu_I \mu_T R_0 \right\}} \frac{1}{\lambda_k}, \end{aligned}$$

as $k \rightarrow +\infty$. It follows that the sequences $\{v_{1,k}\}$, $\{v_{2,k}\}$ and $\{\lambda_k v_{3,k}\}$ are in ℓ^2 . This shows that the series whose Fourier coefficients are $v_{1,k}$, $v_{2,k}$ and $v_{3,k}$, respectively, converge in L^2 (the first two ones) and in H_{\sharp}^2 (the latter one). The inclusion

$$\sigma(L_i) \subset \{-\mu_I, -\mu_T R_0\} \cup \bigcup_{k \in \mathbb{N} \cup \{0\}} \sigma_k$$

follows. We now observe that a straightforward computation shows that $\lambda = -\mu_T R_0$ is in the essential spectrum of L_i . Also $\lambda = -\mu_I$ belongs to the essential spectrum of L_i and, in the case when $\mu_I = \mu_T$, it belongs also to the point spectrum. The set equality (4.1) is proved.

Clearly σ_k has three eigenvalues (counted with their multiplicity), either all real, or one real and two complex conjugates. Routh-Hurwitz criterion enables us to determine whether the elements of σ_k have negative real parts. The latter holds if and only if b_k , d_k and $b_k c_k - d_k$ are positive, which is clearly true whenever $R_0 > 1$.

Remark 4.1. As it is easily seen σ_0 is the spectrum of the operator

$$\begin{pmatrix} -\mu_T R_0 Id & 0 & -\frac{\mu_V}{N} Id \\ \mu_T (R_0 - 1) Id & -\mu_I Id & \frac{\mu_V}{N} Id \\ 0 & N\mu_I Id & -\mu_V Id \end{pmatrix},$$

which is associated with the linearization at (T_i, I_i, V_i) of Problem (1.1a)-(1.1c). Since, as we have already remarked, the spectrum of L_i is the union of the sets σ_k ($k \in \mathbb{N} \cup \{0\}$) and the points $-\mu_I, -\mu_T R_0$, the scenario is one of the following:

- (a) the diffusion does not improve the stability of the solution (T_i, I_i, V_i) . Therefore, the stability issue is identical to that of the ODE system ($d_V = 0$);
- (b) the diffusion worsen the stability of the solution (T_i, I_i, V_i) .

Therefore, we are unable to confirm Funk et al. [8], who pointed out that the presence of a spatial structure enhances population stability with respect to non-spatial models. Only some smoothing effect can be credited to the diffusion.

4.3. Death rates $\mu_I \leq \mu_T, \lambda_0 > 0$. This case leads to a mathematically interesting framework although it has little biological relevance, since $\mu_I > \mu_T$ in the literature (e.g., $\mu_T = 0.01, \mu_I = 0.39$ in [5]). For the latter reason we will not elaborate the case extensively.

Using the Svab-Zeldovich variable $v = u_1 + u_2$ we can transform Problem (3.1a)-(3.1c) into the following equivalent one for the unknowns u_1, v and u_3 :

$$\begin{cases} D_t u_1(t, \cdot) = -\mu_T u_1(t, \cdot) - \gamma u_1(t, \cdot) u_3(t, \cdot) + \alpha(\cdot), & t > 0, \\ D_t v(t, \cdot) = \alpha - \mu_I v(t, \cdot) - (\mu_T - \mu_I) u_1(t, \cdot), & t > 0, \\ D_t u_3(t, \cdot) = \Delta u_3(t, \cdot) - \mu_V u_3(t, \cdot) + N\mu_I v(t, \cdot) - N\mu_I u_1(t, \cdot), & t > 0, \\ u_i(0, \cdot) = u_{0,i}, \quad i = 1, 3, \\ v(0, \cdot) = u_{0,1} + u_{0,2}. \end{cases} \quad (4.2)$$

It is not difficult to see that the mapping $u_3 \mapsto u_1$ is non-increasing, so is the mapping $u_1 \mapsto v$ thanks to the hypothesis $\mu_T - \mu_I > 0$. Hence, the mapping $u_3 \mapsto v$ is non-decreasing. Finally, the mapping $u_3 \mapsto u_2 = v - u_1$ is non-decreasing. Based on these observations, following [19] it is possible to construct two sets of monotone sequences which converge to the solution of (4.2). These sequences start respectively from upper and lower solutions defined as in Section 2, to stay away from the trivial solution. It is well-known that a solution of an evolution problem constructed via such a monotone sequence scheme, with suitable initial conditions between upper and lower solutions, achieves a stable equilibrium (see [19]). Therefore, the infected solution is asymptotically stable. Numerical computations in the phase plan (see Fig. 7) illustrate the difference in the virus dynamics when $\mu_I < \mu_T$ (monotonicity) and $\mu_I > \mu_T$ (spirals).

4.4. Quasi-steady problem. In this part we assume that T and I are at their equilibrium. In such a case, (3.1a)-(3.1c) reads

$$\begin{aligned} 0 &= \alpha - \gamma VT - \mu_T T, \\ 0 &= \gamma VT - \mu_I I, \\ V_t &= N\mu_I I - \mu_V V + d_V \Delta V, \end{aligned}$$

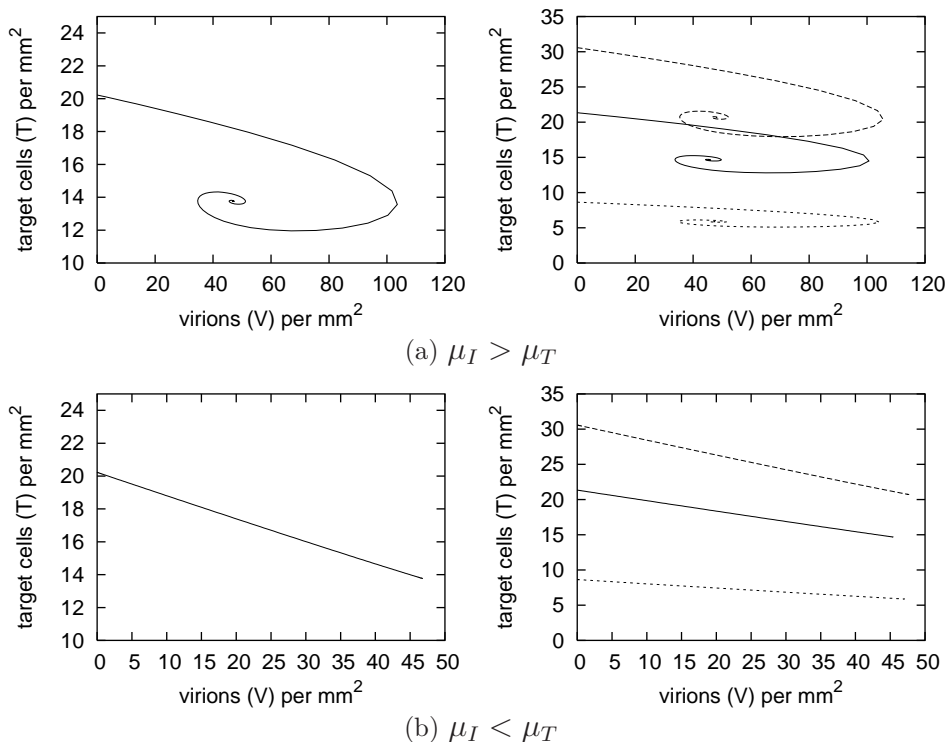


FIGURE 7. Virus vs. target cells in the phase plane, in the case of infection. Left: mean values. Right: the solid, the long and the short dashed lines depict, respectively, the values at (10,10), at the site of viral inoculum (20,20), and at a border site (1,1). The parameters have the following values: $\gamma = 0.001$, $N = 1000$, $\mu_T = 0.1$, $\mu_V = 10$, $d_V = 1$, $\ell = 1$; α varies between 0.1 and 5.0; $\mu_I = 1$ in (a), $\mu_I = 0.01$ in (b).

which is equivalent to the scalar parabolic equation for V only, with periodic boundary conditions:

$$V_i = d_V \Delta V - \mu_V V + \mu_T \mu_V R_0 \frac{V}{\gamma V + \mu_T}. \quad (4.3)$$

The latter is the natural evolution problem associated with (2.3). It is clear that (4.3) has the same non-positive equilibria, namely $V_u = 0$ and $V_i > 0$, in the case when $\lambda_0 > 0$. The stability of V_i can be proved according to [10, Sec. 5.3] by constructing a Lyapunov function.

5. Homogenization. This section is concerned with the case wherein the environment is heterogeneous and is formed of rapidly alternating sinks and sources. For a fixed integer k , we imagine that Ω_ℓ is divided into a network of k^2 periodic squares Ω_ε , where $\varepsilon = \ell/k$. The heterogeneous reproductive ratio R_0 will depend upon ε , see Fig. 8b. The idea of homogenization is to let $\varepsilon \rightarrow 0$ and find the equivalent homogenized medium. Therefore, such a heterogeneous environment can be replaced by its homogenized limit for easier computations and analysis.

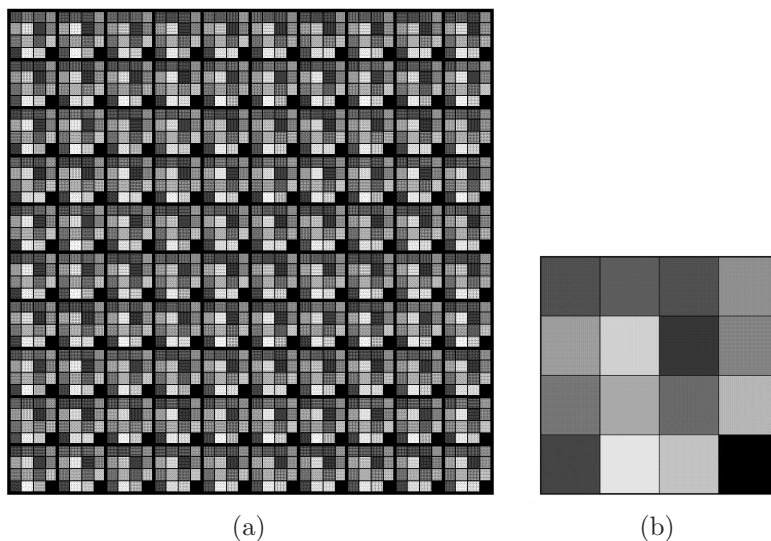


FIGURE 8. Periodic structure with $\ell = 1$ (a): Ω_1 is divided in a network of 40×40 sites. The sites are pieced together in 4×4 periodic squares Ω_ε with $\varepsilon = 0.1$. (b): zoom of Ω_ε which contains 16 sites. The darkness represents the scale of R_0 on each site (the darker the square, the larger is R_0).

More precisely, we introduce a normalized periodic function R_0 as a function of the variable $y = (y_1, y_2)$, of period $(1, 1)$, and we define:

$$R_0^\varepsilon(x_1, x_2) = R_0\left(\frac{x_1}{\varepsilon}, \frac{x_2}{\varepsilon}\right).$$

Remark 5.1. $x = (x_1, x_2)$ is the macroscopic variable while $y = (y_1, y_2)$ is the microscopic one.

We consider the problem:

$$d_V \Delta V^\varepsilon - \mu_V V^\varepsilon = -\mu_T \mu_V R_0^\varepsilon \frac{V^\varepsilon}{\gamma V^\varepsilon + \mu_T}, \quad (5.1)$$

on Ω_ℓ with periodic boundary conditions as above. The idea is to find the limiting homogenized equation as $\varepsilon \rightarrow 0$. We start with the following lemma:

Lemma 5.2. Let $R_0 : \mathbb{R}^2 \rightarrow \mathbb{R}$ be a periodic (with period 1 in each variable), piecewise continuous function. For $x \in \mathbb{R}^2$ and $\varepsilon > 0$, set $R_0^\varepsilon(x) = R_0(\frac{x}{\varepsilon})$. Then, the following properties are met.

- (i) R_0^ε tends to $\mathcal{M}_y(R_0)$ as $\varepsilon \rightarrow 0$, weakly in $L^p_{\text{loc}}(\mathbb{R}^2)$ for any $p \geq 1$;
- (ii) For any $\varepsilon > 0$, set

$$-\lambda_0^\varepsilon = \inf_{\psi \in H^1_\#, \psi \neq 0} \left\{ \frac{d_V \int_{\Omega_\ell} |\nabla \psi|^2 dx + \mu_V \int_{\Omega_\ell} (1 - R_0^\varepsilon) \psi^2 dx}{\int_{\Omega_\ell} \psi^2 dx} \right\}. \quad (5.2)$$

Then, $\lambda_0^\varepsilon \rightarrow \mu_V (\mathcal{M}_y(R_0) - 1)$ as $\varepsilon \rightarrow 0$.

Proof. Property (i) follows straightforwardly from e.g., [12, p. 5]. Thanks to (i), one can take the limit as $\varepsilon \rightarrow 0$ in the right-hand side of (5.2) and show that λ_0^ε tends to the largest eigenvalue of

$$d_V \Delta - \mu_V(1 - \mathcal{M}_y(R_0))Id,$$

on Ω_ℓ with periodic boundary conditions. Let us prove this claim. As a first step, we observe that there exist two constants C_1 and C_2 such that $C_1 \leq \lambda_0^\varepsilon \leq C_2$, since the function R_0^ε is bounded.

Next, λ_0^ε is the largest eigenvalue of the Sturm-Liouville eigenvalue problem

$$d_V \Delta \psi - \mu_V(1 - R_0^\varepsilon)\psi = \lambda \psi,$$

with periodic boundary conditions we documented in Theorem 2.1, associated with the eigenfunction ψ^ε . We may assume that $\int_{\Omega_\ell} (\psi^\varepsilon)^2 dx = 1$. As we pointed it out in Theorem 2.1, ψ^ε does not change sign.

It is clear that ψ^ε is bounded in $H_\#^2$. Then, there exists an infinitesimal sequence $\{\varepsilon_n\}$ such that $\lambda_0^{\varepsilon_n} \rightarrow \lambda_0^0$, $\psi^{\varepsilon_n} \rightarrow \psi^0$ weakly in $H_\#^2$, strongly in $H_\#^{2-\eta}$ and (hence) uniformly in $\overline{\Omega}_\ell$. Note that $\int_{\Omega_\ell} (\psi^0)^2 dx = 1$ and ψ^0 does not change sign.

Since

$$d_V \Delta \psi^{\varepsilon_n} - \mu_V(1 - R_0^{\varepsilon_n})\psi^{\varepsilon_n} = \lambda^{\varepsilon_n} \psi^{\varepsilon_n},$$

it is not difficult to pass to the limit in the above equation as $n \rightarrow +\infty$ in the distributional sense and see that

$$d_V \Delta \psi^0 - \mu_V(1 - \mathcal{M}_y(R_0))\psi^0 = \lambda_0^0 \psi^0, \quad (5.3)$$

with periodic boundary conditions. Therefore, λ_0^0 is an eigenvalue of the operator $d_V \Delta - \mu_V(1 - R_0^\varepsilon)Id$, associated with the eigenfunction ψ^0 . Since ψ^0 does not change sign, λ_0^0 is the largest eigenvalue of (5.3). Obviously, ψ^0 is a constant, hence λ_0^0 is explicit. Finally, checking that all the sequence λ_0^ε converges to λ_0^0 , as $\varepsilon \rightarrow 0$, is an easy task. \square

Next, we prove the following result.

Theorem 5.3. *Assume that $\mathcal{M}_y(R_0) > 1$. Then, there exists ε_0 such that, for any $\varepsilon \in (0, \varepsilon_0]$, the equation (5.1) has a positive solution $V^\varepsilon \in H_\#^2$. As $\varepsilon \rightarrow 0$, V^ε tends to*

$$V^0 = \frac{\mu_T}{\gamma}(\mathcal{M}_y(R_0) - 1),$$

in $H_\#^1$ and uniformly in $\overline{\Omega}_\ell$.

Proof. As a first step, we observe that, since $\mathcal{M}_y(R_0) > 1$, from Lemma 5.2(ii) it follows that there exist $\delta, \varepsilon_0 > 0$ such that $\lambda_0^\varepsilon > \delta$ for $\varepsilon \in (0, \varepsilon_0]$, and (5.1) has a unique positive solution V^ε . Clearly, ΔV^ε is bounded in $L^\infty(\Omega_\ell)$ and this implies that V^ε is bounded in $H_\#^2$. Arguing as in the proof of Lemma 5.2, one can extract an infinitesimal sequence $\{\varepsilon_n\}$ such that V^{ε_n} converges strongly in $H^{2-\eta}$ to a limit $V^0 \in H_\#^2$, which verifies the equation

$$d_V \Delta V^0 - \mu_V V^0 = -\mu_T \mu_V \mathcal{M}_y(R_0) \frac{V^0}{\gamma V^0 + \mu_T}. \quad (5.4)$$

Because of the periodic boundary conditions, Equation (5.4) has only constant solutions. Therefore,

$$-\mu_V V^0 = -\mu_T \mu_V \mathcal{M}_y(R_0) \frac{V^0}{\gamma V^0 + \mu_T},$$

and it only remains to prove that V^0 is not the trivial solution. With obvious notations, we recall (see the proof of Theorem 2.4) that $V^\varepsilon \geq \underline{v}_0^\varepsilon = c^\varepsilon \varphi_0^\varepsilon$ where φ_0^ε is the positive eigenfunction associated with the largest eigenvalue λ_0^ε and

$$c^\varepsilon = \min \left\{ \frac{\lambda_0^\varepsilon}{\gamma \mu_V \mathcal{R}}, \frac{\mu_T (\mathcal{R} - 1)}{\gamma} \right\} \geq \min \left\{ \frac{\delta}{\gamma \mu_V \mathcal{R}}, \frac{\mu_T (\mathcal{R} - 1)}{\gamma} \right\}.$$

Since $\max \varphi_0^\varepsilon = 1$, it is clear that V^ε remains bounded away from 0 whenever $\varepsilon \leq \varepsilon_0$.

Finally, checking that V^ε itself converges to V^0 as $\varepsilon \rightarrow 0$ is immediate. This concludes the proof. \square

5.1. Numerical illustration (homogenization). We consider a model where R_0 is as in Fig. 8, taking its values on the elementary 4×4 grid (b) as in Tab. 1.

j	$R_0(1, j)$	$R_0(2, j)$	$R_0(3, j)$	$R_0(4, j)$
1	1.60	1.41	1.55	0.819
2	0.800	0.165	2.59	0.872
3	1.20	0.489	1.37	0.453
4	2.09	4.25E-4	0.270	2.80

TABLE 1. Values of $R_0(i, j)$, $i, j = 1, \dots, 4$, on Ω_ε as in Fig. 8b, to be viewed as a 4×4 matrix.

It is easy to compute the mean value $\mathcal{M}_y(R_0) = 1.16$ and the homogenized viral density $V^0 = 16.1$. Fig. 9 shows how the virus V^ε at $\varepsilon = 0.1$ (left) oscillates slightly around its homogenized limit V^0 (right).

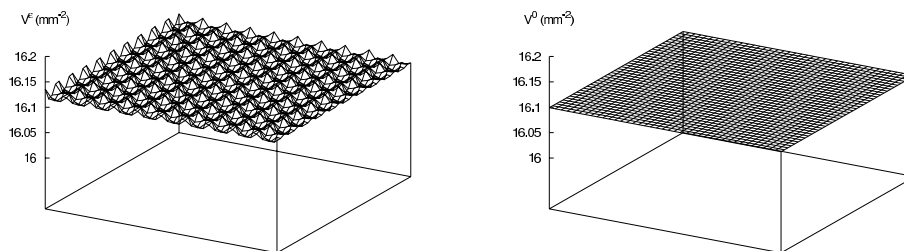


FIGURE 9. V^ε (left) vs. V^0 (right). The grid and parameters are as in Fig. 8 and Tab. 1; $\varepsilon = 0.1$, $d_V = 1$, $\ell = 1$.

Appendix A. Proof of Theorem 2.1.

Proof. It is well known that the realization Δ_2 of the Laplacian in L^2 , with domain H_{\sharp}^2 , is a sectorial operator. Since \mathcal{A} , is a bounded perturbation of the Laplacian, \mathcal{A} is sectorial as well, and, hence, its spectrum is not empty. Let us fix $\lambda_0 \in \rho(\mathcal{A}) \cap (\mu_\infty, +\infty)$ such that $[\lambda_0, +\infty)$ is in the resolvent set of T . Here, by μ_∞ we denote the sup-norm of the function μ . The operator $\mathcal{A}_0 := \mathcal{A} - \lambda_0 I$ turns out to be invertible and its resolvent set contains $[0, +\infty)$. Since the operator T_0^{-1} is continuous from L^2 into H_{\sharp}^2 , it is continuous, in particular, from H_{\sharp}^1 into itself, when this latter space is endowed with the inner product

$$\begin{aligned} \langle v, w \rangle &= d \int_{\Omega_\ell} (D_{x_1} v D_{x_1} w + D_{x_2} v D_{x_2} w) dx + \int_{\Omega_\ell} (\mu + \lambda_0) v w dx \\ &:= d \int_{\Omega_\ell} \nabla v \cdot \nabla w dx + \int_{\Omega_\ell} (\mu + \lambda_0) v w dx, \end{aligned}$$

which is equivalent to the Euclidean inner product of H^1 . Since H_{\sharp}^2 is compactly embedded into H_{\sharp}^1 (see e.g., [1, Thm. 3.7]), the operator \mathcal{A}_0^{-1} is compact from H_{\sharp}^1 into itself. Moreover, \mathcal{A}_0^{-1} is self-adjoint in H_{\sharp}^1 . Indeed,

$$\begin{aligned} \langle \mathcal{A}_0^{-1} u, v \rangle &= d \int_{\Omega_\ell} \nabla \mathcal{A}_0^{-1} u \cdot \nabla v dx + \int_{\Omega_\ell} (\mu + \lambda_0) \mathcal{A}_0^{-1} u v dx \\ &= -d \int_{\Omega_\ell} \Delta \mathcal{A}_0^{-1} u v dx + \int_{\Omega_\ell} (\mu + \lambda_0) \mathcal{A}_0^{-1} u v dx \\ &= - \int_{\Omega_\ell} u v dx, \end{aligned} \tag{A.1}$$

for any $u, v \in L^2$. Now, from the general theory of self-adjoint compact operators, it follows that the spectrum of \mathcal{A}_0^{-1} consists of a sequence of real eigenvalues which converges to 0. As a byproduct, the spectrum of \mathcal{A}_0 consists of a sequence of eigenvalues diverging to $-\infty$. More precisely, $\sigma(\mathcal{A}_0) \subset (-\infty, 0)$ and $\lambda \in \sigma(\mathcal{A}_0)$ if and only if λ^{-1} is in $\sigma(\mathcal{A}_0^{-1})$. In particular, the maximum eigenvalue of \mathcal{A}_0 is the inverse of the minimum eigenvalue of \mathcal{A}_0^{-1} . Since \mathcal{A}_0^{-1} is a compact operator, its minimum eigenvalue is defined by

$$\lambda_{\min}(\mathcal{A}_0^{-1}) = \inf_{\psi \in H_{\sharp}^1, \psi \neq 0} \left\{ \frac{\langle \mathcal{A}_0^{-1} \psi, \psi \rangle}{\langle \psi, \psi \rangle} \right\}.$$

Taking (A.1) into account, we can estimate

$$\begin{aligned} \lambda_{\min}(\mathcal{A}_0^{-1}) &= \inf_{\psi \in H_{\sharp}^1, \psi \neq 0} \left\{ \frac{- \int_{\Omega_\ell} \psi^2 dx}{d_V \int_{\Omega_\ell} |\nabla_x \psi|^2 dx + \int_{\Omega_\ell} (\mu + \lambda_0) \psi^2 dx} \right\} \\ &= - \sup_{\psi \in H_{\sharp}^1, \psi \neq 0} \left\{ \frac{\int_{\Omega_\ell} \psi^2 dx}{d_V \int_{\Omega_\ell} |\nabla_x \psi|^2 dx + \int_{\Omega_\ell} (\mu + \lambda_0) \psi^2 dx} \right\} \\ &= - \left(\inf_{\psi \in H_{\sharp}^1, \psi \neq 0} \left\{ \frac{d \int_{\Omega_\ell} |\nabla_x \psi|^2 dx + \int_{\Omega_\ell} \mu \psi^2 dx}{\int_{\Omega_\ell} \psi^2 dx} \right\} + \lambda_0 \right)^{-1}. \end{aligned}$$

Formula (2.5) follows at once, observing that $\lambda_{\max}(\mathcal{A}) = \lambda_0 + \lambda_{\max}(\mathcal{A}_0)$.

The last assertion of the theorem follows from the Krein-Rutman Theorem applied to the restriction of \mathcal{A}_0 to the space $C_{\sharp}(\mathbb{R}^2)$ (of all functions $f : \mathbb{R}^2 \rightarrow \mathbb{R}$ which are continuous with period ℓ in each variable), via the maximum principle

(see e.g., [24]). Indeed, since H_{\sharp}^2 is continuously embedded into $C_{\sharp}(\mathbb{R}^2)$, the restriction $(\mathcal{A}_0^{-1})|_{C_{\sharp}(\mathbb{R}^2)}$ of the operator \mathcal{A}_0^{-1} to $C_{\sharp}(\mathbb{R}^2)$ is compact from $C_{\sharp}(\mathbb{R}^2)$ into itself. Moreover, it is clear that \mathcal{A}_0^{-1} and $(\mathcal{A}_0^{-1})|_{C_{\sharp}(\mathbb{R}^2)}$ have the same eigenvalues. Let now f be a non-negative (non trivial) function in $C_{\sharp}(\mathbb{R}^2)$. Then, the function $\mathcal{A}_0^{-1}f$ is in H_{\sharp}^2 . Hence, in particular, it belongs to $H^2((-\ell, 2\ell) \times (-\ell, 2\ell))$ and solves the equation $(\mu + \lambda_0)u - d\Delta u = f$. By the classical maximum principle, u is non-negative in $(-\ell, 2\ell) \times (-\ell, 2\ell)$. Actually u is everywhere positive. Indeed if $u(x_0) = 0$ at some point $x_0 \in (-\ell, 2\ell) \times (-\ell, 2\ell)$, then, still by the maximum principle, it would follow that $u \equiv 0$ in $[-\ell, 2\ell] \times [-\ell, 2\ell]$, which clearly cannot be the case. \square

Appendix B. A maximum principle.

Proposition B.1. *Let \mathcal{L} be a second order operator with constant coefficients. Let $u \in H_{\sharp}^2$ satisfy the inequality $\mathcal{L}u \leq 0$. Then, $u \geq 0$. Similarly, if u belongs to $C^1((0, T); C(\overline{\Omega_{\ell}})) \cap C([0, T]; H_{\sharp}^2)$, is such that $\mathcal{L}u \in C([0, T] \times \Omega_{\ell})$, and it satisfies the differential inequalities $D_t u - \mathcal{L}u \geq 0$ and $u \leq 0$ in $[0, T] \times \partial\Omega_{\ell}$, then, $u \leq 0$ in $[0, T] \times \Omega_{\ell}$.*

Proof. For the reader's convenience, we sketch the proof of the second statement, the first one being a particular case of the second one. Since H_{\sharp}^2 continuously embeds in the set of all continuous functions which are periodic, with period ℓ with respect to all the variables, then u can be extended by periodicity with a function (still denoted by u) which is continuous in $[0, T] \times \mathbb{R}^N$ and is therein continuously differentiable with respect to the time variable.

Suppose by contradiction that u is not everywhere non-positive in $[0, T] \times \mathbb{R}^N$. Then, u has a negative minimum at some point $(t_0, x_0) \in (0, T_0] \times (-\ell, 2\ell)^2$. Then, clearly, $D_t u(t_0, x_0) \leq 0$. Moreover, since $\mathcal{L}u$ is a continuous function, $\mathcal{L}u(t_0, x_0) \geq 0$. The classical maximum principle yields the assertion. \square

Acknowledgment. One of the authors (L.L.) greatly acknowledges the Institute of Mathematics of the University of Bordeaux I for the warm hospitality during his visit as an invited professor (2008-2009).

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