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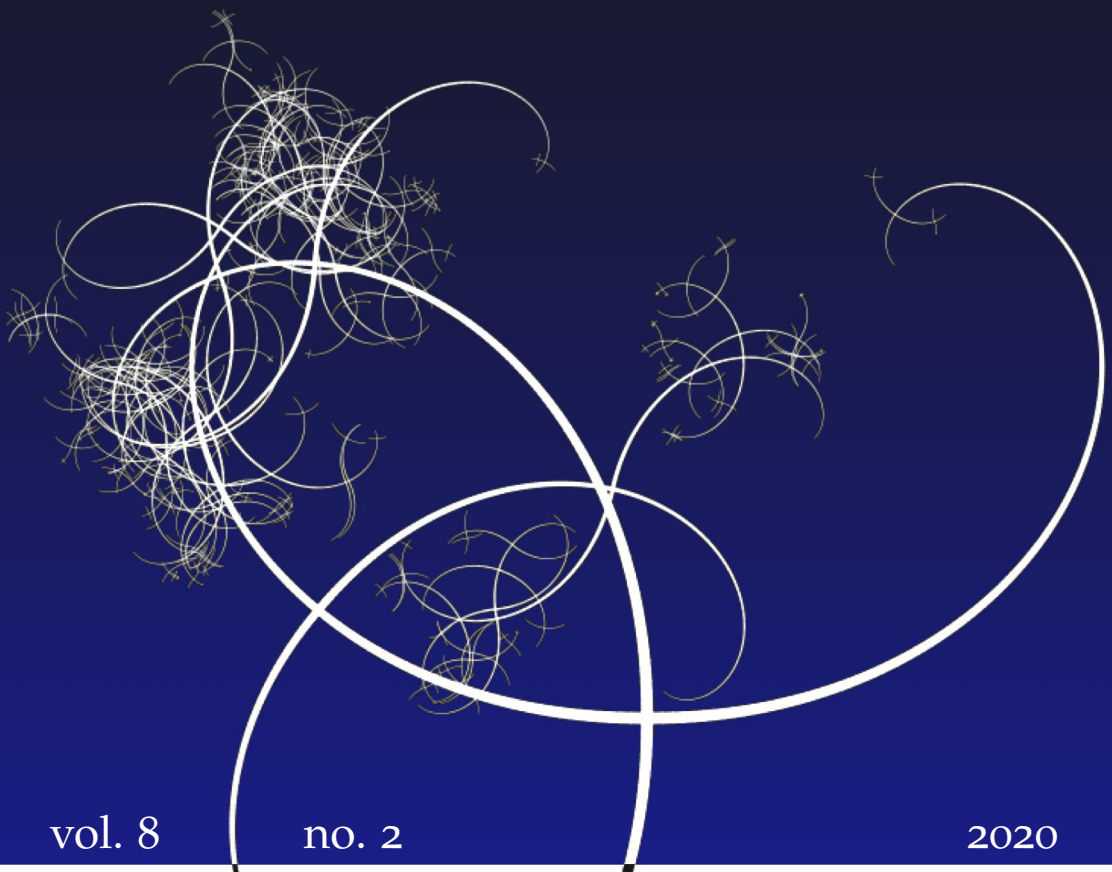

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GENOTYPE-DEPENDENT VIRUS DISTRIBUTION AND COMPETITION OF VIRUS STRAINS

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Virus density distribution as a function of genotype considered as a continuous variable and of time is studied with a nonlocal reaction-diffusion equation taking into account virus competition for the host cells and its elimination by the immune response and by the genotype-dependent mortality. The existence of virus strains, that is, of positive stable stationary solutions decaying at infinity, is determined by the admissible intervals in the genotype space where the genotype-dependent mortality is less than the virus reproduction rate, and by the immune response under some appropriate assumptions on the immune response function characterizing virus elimination by immune cells. The competition of virus strains is studied, first, without immune response and then with the immune response. In the absence of immune response, the strain dynamics is different in a short time scale where they converge to some intermediate slowly evolving solutions depending on the initial conditions, and in a long time scale where their distribution converges to a stationary solution. Immune response can essentially influence the strain dynamics either stabilizing them or eliminating one of the strains. An antiviral treatment can also influence the competition of virus strains, and it can lead to the emergence of resistant strains, which were absent before the treatment because of the competition with susceptible strains.

1. Introduction

A fundamental feature of many RNA virus infections of major public concern (e.g., human immunodeficiency virus type I (HIV) and hepatitis C virus (HCV)) is an error-prone replication [Domingo and Perales 2018]. The high genetic variability of HIV and HCV and selection of the most adapted mutants determine the ability of the virus population to escape the immune response and develop resistance to the antiviral therapy [Coffin and Swanstrom 2013; Gaudieri et al. 2009]. The variability of the viruses is considered to be one of the key factors in the pathogenesis of the respective infectious disease. Variation of the genetic structure of

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the viral population is the result of the interaction of the replication, mutation, recombination, immune-mediated elimination, and drug-dependent suppression of the virus replication. An important step towards a mechanistic understanding of the evolution of the heterogeneous virus populations is provided by the models which consider explicitly the infection of target cells, interaction with the immune system, and drug-dependent blockade of the virus replication.

To describe and analyze the dynamics of genetic heterogeneity of evolving virus populations, the concept of quasispecies provides a general framework to deal with an ensemble of genomes [Eigen 1971; Biebricher and Eigen 2006]. A more formal approach to studying the evolution of quasispecies is based on considering the mutation-selection processes acting on the virus strains according to their fitness values. The respective deterministic models are formulated using systems of ODEs. The standard form of the quasispecies model in mathematical virology is the set of ODE equations [Nowak and May 2000]

$$\frac{d\boldsymbol{v}}{dt} = \boldsymbol{W}\boldsymbol{v} - d(\boldsymbol{v})\boldsymbol{v}, \quad \boldsymbol{W} = \begin{pmatrix} a_1 Q_{11} & a_2 Q_{21} & \cdots & a_n Q_{n1} \\ a_1 Q_{12} & a_2 Q_{22} & \cdots & a_n Q_{n2} \\ \vdots & \vdots & \ddots & \vdots \\ a_1 Q_{1n} & a_2 Q_{2n} & \cdots & a_n Q_{nn} \end{pmatrix}, \; d(\boldsymbol{v}) = \frac{\sum_{i=1}^{n} a_i v_i}{\sum_{i=1}^{n} v_i}. \tag{1-1}$$

Here, the vector $\boldsymbol{v}$ characterizes the abundance of genomes composing the population, $\boldsymbol{v} = \{v_1, v_1, \ldots, v_n\}$, a_i stand for the replication rates of i-th genome (quasispecies), $i = 1, \ldots, n$, and $\boldsymbol{Q} = (Q_{ij})$ is the mutation matrix. The last term describes the competition of the genomes for survival. The model considers the balance of production and elimination of the quasispecies and as such bears no specific link to real processes underpinning the collective dynamics of the genomes. Another framework is provided by stochastic models taking the form of genetic algorithms [Bocharov et al. 2005; Vijay et al. 2008]. The distributed parameter approach with respect to the mutant frequency as a continuous variable was proposed in [Rouzine et al. 2001] using the forward Kolmogorov equation.

Some general regularities underlying the evolution of viral quasispecies (equivalently, the ensembles of virus strains) have been elucidated empirically. The viruses can escape immune control by generating mutations within the peptide epitopes, and the epitope inducing the strongest T cell response is subject to the strongest selective pressure [McMichael and Carrington 2019]. The dynamics of drug-resistant mutants depends on a number of virus replication parameters, such as the availability and the spectrum of target cells, the epistatic interactions between specific mutations, etc. [Martínez et al. 2011]. However, a deeper insight into the impact of virus population properties and its sensitivity to drugs and the immune responses requires the development of mathematical models with an explicit description of

the interplay between the above processes in producing the survival advantages of specific virus strains, characterized in general as the fitness values.

The fitness value can be estimated in vitro under certain special conditions [Martínez et al. 2011]. However, its quantification for real infections remains a challenge [Ganusov et al. 2011] as it results from a complex system of factors, such as virus production in target cells, host-dependent immune responses, and drug efficacy. We have recently developed a novel mathematical framework for predicting and quantifying the virus diversity evolution during infection of a host organism [Bessonov et al. 2020].

In this study we examine the properties of the formulated mathematical model to shed new light on the collective behavior of virus genome ensembles (strains) in relation to the parameters of mutation, replication, interaction with the immune system, and the susceptibility to the antiviral drugs. We consider the equation

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + au(1 - bI(u)) - uf(u) - \sigma(x)u, \tag{1-2}$$

describing the evolution of virus density depending on the genotype x considered as a continuous variable and on time t. The first term in the right-hand side of this equation characterizes virus mutation and the second term its reproduction; the next term specifies virus elimination by immune response, and the last term its death. We now describe each of these terms in more detail.

- Assuming there is a sequence of reversible mutations with consecutive genotypes x_i, we can write the equation for the density u_i of virus with genotype x_i:

$$\frac{du_i}{dt} = \mu(u_{i-1} - u_i) + \mu(u_{i+1} - u_i), \tag{1-3}$$

  where μ is the frequency of mutations. This equation represents a discretization of the diffusion equation with the diffusion coefficient proportional to μ. Virus mutation described by the diffusion operator was previously considered in [Kimura 1964; Sasaki 1994]. In a more general case, one should take into account a more complex mutation pattern (see, e.g., [Martínez et al. 2011]).

- The virus multiplication term is proportional to the virus density u and to the quantity of uninfected host cells $(1 - bI(u))$. Here 1 is a dimensionless total number of cells, and $bI(u)$ is the number of infected cells, which is proportional to the total virus quantity $I(u) = \int_{-\infty}^{\infty} u(x, t)\, dx$ (see Section 4 for more detail).

- Virus elimination by immune cells is proportional to the virus density and to the quantity of immune cells c. The latter is supposed to be a function of virus density. The function $f(u)$ is sufficiently smooth with $f(u) > 0$ for $u > 0$. It grows for sufficiently small u, since the immune response is stimulated by

antigens, and it can be down-regulated for sufficiently large u, since the high viral load infection can suppress immune response (via exhaustion mechanisms). This term can contain time delay taking into account clonal expansion of immune cells [Bocharov et al. 2018], but we do not consider it in this work.

- The last term in the right-hand side of (1-2) describes virus natural death and its elimination by some antiviral treatment. Let us note that the death rate can depend on virus genotype x.

We consider virus strain as density distribution concentrated around some genotype value. Mathematically speaking, it is a positive solution of (1-2) decaying at infinity. We will determine conditions of the existence of such solutions to delineate the rules characterizing the competition of different strains and their response to treatment. In particular, we will see how the elimination of some strains by treatment can lead to the emergence of the strains resistant to treatment. We will begin the analysis of the existence and competition of virus strains due to the genotype-dependent mortality in the absence of immune response (Section 2), and we will continue with the investigation of the influence of immune response (Section 3). We discuss the modeling approach and the results in Section 4. Some technical calculations and proofs are placed in Appendices A, B, and C in order to simplify the reading of the paper.

2. Localized solutions in the absence of immune response

We begin the analysis of (1-2) in the case without immune response, $f(u) \equiv 0$. We will present conditions on the death function $\sigma(x)$ providing the existence of localized positive solutions describing virus strains. After that, we will study the competition of two strains.

2A. *Existence of stationary solutions.*

Model problem. Consider the equation

$$Du'' + u(1 - I(u)) - \sigma(x)u = 0 \tag{2-1}$$

on the whole axis, where $I(u) = \int_{-\infty}^{\infty} u(x)\,dx$, $\sigma(x) = \sigma_0 > 1$ for $|x| \geq x_0$, and $\sigma(x) = 0$ for $|x| < x_0$, for x_0 some positive number. We look for a positive bounded solution of this equation. Clearly, it can exist only if $I(u) < 1$. Set

$$1 - I(u) = k^2. \tag{2-2}$$

Then (2-1) can be written as

$$Du'' + k^2 u = 0, \quad |x| < x_0, \qquad Du'' + k^2 u - \sigma_0 u = 0, \quad |x| \geq x_0. \tag{2-3}$$

Therefore,

$$u(x) = c_1 \cos(\mu x), \quad |x| < x_0, \qquad u(x) = c_2 e^{\pm \lambda x}, \quad |x| \geq x_0,$$

where c_1 and c_2 are some positive constants, $\mu = k/\sqrt{D}$, and $\lambda = \sqrt{\sigma_0 - k^2}/\sqrt{D}$ ($k^2 < \sigma_0$). From the continuity of the solution and of its first derivative at $x = \pm x_0$ we obtain the equalities

$$c_1 \cos(\mu x_0) = c_2 e^{-\lambda x_0}, \qquad c_1 \mu \sin(\mu x_0) = c_2 \lambda e^{-\lambda x_0}. \tag{2-4}$$

Dividing the second equation by the first, we get the equation with respect to k:

$$\sqrt{\sigma_0 - k^2} = k \tan(k x_0/\sqrt{D}). \tag{2-5}$$

We can now determine the integral $I(u)$:

$$I(u) = \int_{-\infty}^{\infty} u(x)\, dx = \frac{2c_1}{\mu} \sin(\mu x_0) + \frac{2c_2}{\lambda} e^{-\lambda x_0}.$$

Taking into account the first relation in (2-4), we have

$$I(u) = 2c_1 \left(\frac{1}{\mu} \sin(\mu x_0) + \frac{1}{\lambda} \cos(\mu x_0) \right).$$

The coefficient c_1 can be determined from (2-2):

$$c_1 = (1 - k^2)/(2h(k)), \quad h(k) = \frac{1}{\mu} \sin(\mu x_0) + \frac{1}{\lambda} \cos(\mu x_0),$$

and $c_2 = c_1 e^{\lambda x_0} \cos(\mu x_0)$.

Let us recall that we are looking for a solution $k < 1$ of (2-5). Such solution exists if $x_0/\sqrt{D}$ is greater than the critical value

$$\xi^* = \frac{1}{k} \arctan \sqrt{\frac{\sigma_0}{k^2} - 1}, \tag{2-6}$$

and it does not exist if $x_0/\sqrt{D} < \xi^*$. For x_0 large enough, there are multiple solutions satisfying this condition. We can now formulate the following result.

Theorem 2.1. *Let $\sigma(x) = \sigma_0 > 1$ for $|x| \geq x_0$, and $\sigma(x) = 0$ for $|x| < x_0$, where x_0 is some positive number. Then* (2-1) *has a positive solution decaying at infinity for $x_0/\sqrt{D} > \xi^*$, and such solution does not exist for $x_0/\sqrt{D} \leq \xi^*$. Here ξ^* is given by expression* (2-6).

Generalization of the existence result. The previous theorem is based on the explicit construction of a solution for a piecewise-constant function $\sigma(x)$. The existence result can be generalized for some class of functions using a more sophisticated mathematical method based on the topological degree and a priori estimates of solutions (Leray–Schauder method).

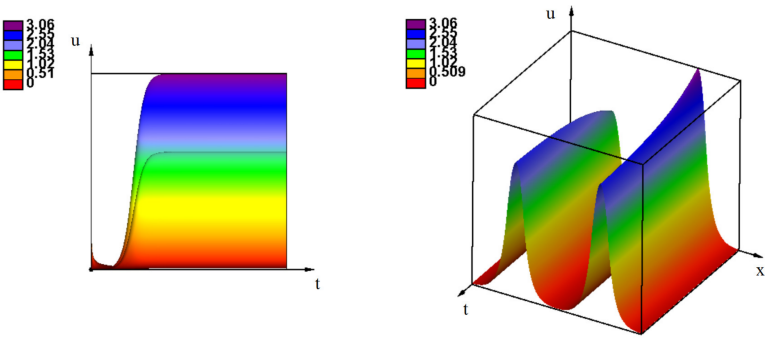

Figure 1. Solution $u(x,t)$ of (1-2) in numerical simulations. Left: projection of solution on the (t,u)-plane for $t=60$. Right: 3D solution for $t=10^5$. The values of parameters are $L=1$, $a=b=1$, $D=0.001$, $\sigma(x)=0$ for $0.2<x<0.3$ and $0.7<x<0.8$ and $=1$ otherwise, and initial condition $=0.1$ for $0.5<x<0.52$.

Theorem 2.2. *Suppose that $\sigma(x)$ is a sufficiently smooth bounded function such that $\sigma(x)=0$ for $|x|\le x_0$ and $\sigma(x)\ge\sigma_0\ge 1$ for $|x|\ge x_1$, where $x_1>x_0>\pi/2$. Then* (2-1) *has a positive solution decaying at infinity.*

The proof of this theorem is given in Appendix C.

2B. ***Two admissible intervals.*** We showed in the previous subsection that a localized positive solution of (2-1) exists for a sufficiently large admissible interval or for a small mutation rate (diffusion coefficient). This localized solution corresponds to a virus strain. In order to study the competition of two strains for the host cells, we will now consider the death rate function $\sigma(x)$ with two admissible intervals, $\sigma(x)=0$ for $x_1\le|x|\le x_2$ and $\sigma=\sigma_0>0$ otherwise. Here $x_2>x_1>0$.

The analytical solution of (1-2) with such function $\sigma(x)$ is quite complex, and it is presented in Appendix A. It is shown that existence and multiplicity of solutions can be formulated in terms of the parameter $h=(x_2-x_1)/\sqrt{D}$ characterizing the length of the admissible interval normalized by the diffusion coefficient. There exists a positive solution decaying at infinity if $h>h_c$ for some critical value h_c, and such solution does not exist if $h<h_c$. Moreover, it is shown that there are two branches of solutions; one of them is a symmetric (even) function, while another one is asymmetric. In order to study the stability of these solutions, we carry out numerical simulations of the initial boundary value problem for (1-2) on a bounded interval $0<x<L$ with periodic boundary conditions. We set $f(u)\equiv 0$, and $I(u)=\int_0^L u(x,t)\,dx$.

An example of numerical simulations is shown in Figures 1 and 2. Behavior of solutions is characterized by a fast convergence to an intermediate solution and

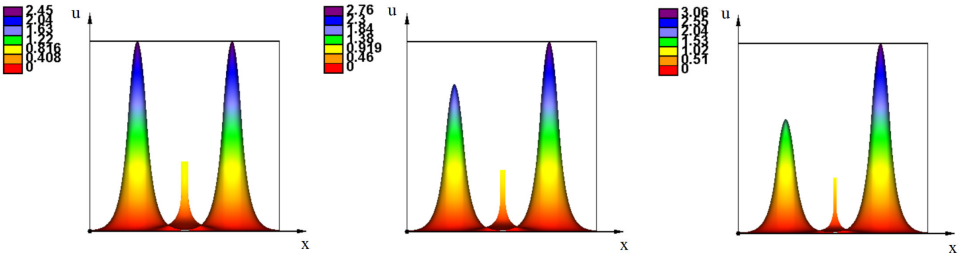

Figure 2. Solution $u(x,t)$ of (1-2) in numerical simulations. The intermediate stationary solution (projection on the (x,u)-plane) is shown for different initial conditions equal to 0.1 for $0.48 < x < 52$ (left), $0.49 < x < 0.52$ (middle), and $0.50 < x < 0.52$ (right). A small peak at the center of the interval shows the initial condition. The values of parameters are $L = 1$, $a = b = 1$, $D = 0.001$, and $\sigma(x) = 0$ for $0.2 < x < 0.3$ and $0.7 < x < 0.8$ and $= 1$ otherwise.

then by a slow convergence to a stationary solution (Figure 1). The intermediate solution resembles two pulses with the maxima located at the centers of the admissible intervals. Since the initial condition is not symmetric with respect to the center of the interval, this solution is not symmetric either, and the ratio between the pulses' maxima depends on the initial condition (Figure 2). The characteristic time T_1 of the convergence to this solution is on the order of 10 (dimensionless units). After reaching their intermediate values, in this time scale they remain constant. The intermediate solution converges to the stationary solution in a longer time scale determined by the value of the diffusion coefficient (Figure 1, right). For $D = 0.001$ considered in this example, it is of the order 10^5, that is, four orders of magnitude larger. The stationary solution resembles two pulses symmetric with respect to the center of the interval. Thus, in terms of dynamical systems, we have a fast manifold with convergence to the intermediate solution and a slow manifold with convergence to the stationary solution. Though the stationary solution is globally asymptotically stable, dynamics of solutions in the realistic time scale can be determined by the intermediate solution.

The convergence time exponentially grows with the decrease of D and becomes so large for $D < 0.001$ that the stationary solution may not be reached (Appendix A, Figure 9). In this case, the dynamics of the solution is determined by the intermediate solution, which depends on the initial condition and on the parameters.

Thus, we have an unusual and counterintuitive situation where instead of a unique (for given parameters) globally stable stationary solution, we should consider a continuous family of intermediate solutions. We will discuss below biological implications of this result.

3. The influence of immune response

3A. ***Virus reproduction and the effect of antiviral immune response.*** In order to study the influence of immune response on virus distribution in the space of genotypes, we begin with the case without natural genotype-dependent virus death, $\sigma(x) \equiv 0$. In this case, the equation for the virus density distribution is

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + au(1 - bI(u)) - uf(u). \tag{3-1}$$

The immune response function is increasing for u sufficiently small and decreasing for u sufficiently large. We begin with some model examples.

Constant immune response. Set $f(u) \equiv c$, where c is a positive constant. Integrating (3-1), we get the equation with respect to integral $I(u)(t)$ considered as a function of time:

$$\frac{dI}{dt} = aI(1 - c/a - bI). \tag{3-2}$$

If $c \geq a$, then $I(t) \to 0$ as $t \to \infty$. If $c < a$, then $I(t) \to (1 - c/a)/b$. In both cases, $\sup_x u(x) \to 0$ as $t \to \infty$. Let us discuss this convergence in the case where $c < a$. The stationary solution $u = 0$ of (3-1) is unstable in this case. Indeed, the corresponding spectral problem has a part of the spectrum in the right half-plane. However, we affirm that the solution of this equation converges to zero in the uniform norm. This result seems counterintuitive, and it should be proved.

Proposition 3.1. *Let $u_0(x)$ be a bounded integrable function. The solution of* (3-1) *on the whole axis with the initial condition $u(x, 0) = u_0(x)$ uniformly converges to* 0 *as $t \to \infty$.*

Proof. Without loss of generality we can set $a = b = 1$ and $c = 0$. It follows from (3-2) that $|1 - I(t)| \leq k_1 e^{-t}$, where k_1 is a positive constant. Therefore, solution $u(x, t)$ of (3-1) can be estimated from above by the solution $u_1(x, t)$ of the equation

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + k_1 e^{-t} u. \tag{3-3}$$

We will show that the solution of this equation with a bounded initial condition decaying at infinity uniformly converges to 0. If the initial condition $u(x, 0)$ does not depend on x and it equals some constant k_2, then its solution does not depend on x either, and it satisfies the equation

$$\frac{dv}{dt} = k_1 e^{-t} v, \quad v(0) = k_2. \tag{3-4}$$

We find $v(t) = k_2 e^{k_1} e^{-k_1 e^{-t}}$. Hence,

$$|v(t)| \leq k_2, \quad t \geq 0, \tag{3-5}$$

and a similar estimate holds for the solution $u_1(x, t)$ of (3-3).

Consider a solution $u_2(x,t)$ of (3-3) with a bounded even positive integrable initial condition decaying at infinity. Then the solution is also an even positive function with a maximum at $x=0$. It is bounded by virtue of estimate (3-5).

We will prove that $u_2(0,t)$ converges to 0 as $t\to\infty$. Suppose that this is not the case. Then there exists $\epsilon>0$ such that

$$u_2(0,t)\geq\epsilon \tag{3-6}$$

for all t sufficiently large. Indeed, if this is not true, then $u_2(0,t)$ converges to 0 along a sequence $t=t_n$. By virtue of the semigroup property of the solution and estimate (3-5), we conclude that $u_2(0,t)$ converges to 0 for all $t\to\infty$. This contradiction proves (3-6). Next, since the last term in the right-hand side of (3-3) converges to 0 as $t\to\infty$, then $u_2(x,t)\geq\epsilon/2$ for $|x|\leq N(t)$, where $N(t)\to\infty$ as $t\to\infty$. Hence, $J(t)=\int_{-\infty}^{\infty}u_2(x,t)\,dx\to\infty$ as $t\to\infty$.

Integrating (3-3) with respect to x from $-\infty$ to ∞, we obtain the equation for $J(t)$:

$$\frac{dJ}{dt}=k_1e^{-t}J.$$

As above, we verify that its solution remains bounded. This contradiction proves the convergence $u_2(0,t)\to 0$. Since the maximum of this solution is reached at $x=0$, then $u_2(x,t)$ uniformly converges to 0 as $t\to\infty$.

It remains to note that any positive bounded integrable initial condition for (3-3) can be estimated from above by an even function satisfying the conditions above. Therefore, the solution with this initial condition uniformly converges to 0. □

It follows from this proposition that the solution of (3-1) with a constant immune response uniformly converges to 0. If $c\geq a$, then $I(u)$ also vanishes for large time, while for $c<a$, it converges to a positive constant. This means that in the first case infection is completely eliminated, while in the second case, the total virus quantity remains constant. Furthermore, they do not form a localized solution in the space of genotypes corresponding to a virus strain but they diffuse in the genotype space covering a growing genotype range.

Increasing immune response. Clonal expansion of immune cells is stimulated by the antigen. Therefore, function $f(u)$ is increasing, at least for not very large values of u for which excess of the virus can lead to the exhaustion of immune response. If $b=0$, then (3-1) is a conventional reaction-diffusion equation in the monostable case, and its solutions are described by reaction-diffusion waves.

Proposition 3.2. *Suppose that $f(u)$ is a smooth growing function, $f(u)>0$ for $u>0$. Then* (3-1) *does not have a positive stationary solution with the zero limits at infinity.*

Proof. Suppose that (3-1) has a positive stationary solution $w(x)$ with the zero limits at infinity. Then it satisfies the problem

$$w'' + w(1 - I(w) - f(w)) = 0, \quad w(\pm\infty) = 0, \tag{3-7}$$

where we set, without loss of generality, $D = a = b = 1$. Then it has a maximum at some point $x = x_m$, $w_m = w(x_m)$. Let us verify that

$$I(w) + f(w_m) < 1. \tag{3-8}$$

Indeed, if $I(w) + f(w_m) > 1$, then we obtain a contradiction in signs in (3-7) at $x = x_m$. If $I(w) + f(w_m) = 1$, then by virtue of the uniqueness of solution, $w(x) \equiv w_m$, and the conditions at infinity cannot be satisfied.

Since $f(w)$ is an increasing function, it follows from (3-8) that the inequality $I(w)+f(w(x))<1$ holds for all $x \in \mathbb{R}$. Consider the equation $w''+w(k-f(w))=0$, where $k = 1-I(w) > 0$. Since $k-f(0) > 0$, then the equation $w''+w(k-f(0)) = 0$, linearized about $w = 0$, does not have positive solutions vanishing at infinity. This contradiction proves the proposition. □

This proposition affirms that (3-1) does not have a positive stationary solution. Similar to Proposition 3.1, we can expect that the solution of the Cauchy problem uniformly converges to zero. This statement is not yet proved, and it represents an open question for future analysis.

Decreasing immune response. Since virus can kill immune cells and downregulate immune response (e.g., HIV), we consider here a decreasing function $f(u)$. In the case of a bounded interval $0 < x < L$ and the integral $I(u) = \int_0^L u(x,t)\,dx$, (3-1) has a constant stationary solution. It can lose its stability, resulting in the emergence of pulses (Figure 3). The bifurcation of pulses can be studied by the conventional stability and bifurcation analysis. This analysis is not applicable in the case of the whole axis.

Thus, the case of decreasing immune response is principally different in comparison with a constant or an increasing immune response. Depending on parameters, there can exist localized positive solutions corresponding to a virus strain.

We consider a model example where the existence of solutions can be proved.

Proposition 3.3. *Let $f(u) = p-u$. Then there exist positive values p_1, p_2, $p_1 < p_2$, such that* (3-1) *has a positive stationary solution decaying at infinity for $p_1 < p < p_2$, and it does not have positive a solution for $0 < p < p_1$ and $p > p_2$.*

Proof. We look for a positive solution of problem (3-7). Set $k = 1 - I(w)$. Since $0 < I(w) < 1$, then $0 < k < 1$. Then problem (3-7) can be written as

$$w'' + w(k - f(w)) = 0, \quad w(\pm\infty) = 0. \tag{3-9}$$

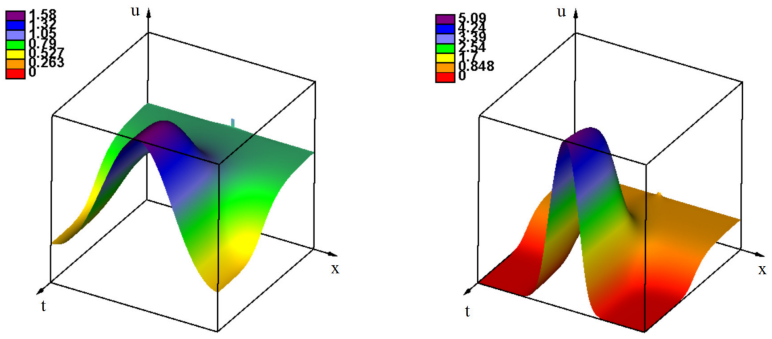

Figure 3. Convergence to the stationary solutions of (1-2) for $f(u) = k_2 e^{-k_3 u}$ and different values of the diffusion coefficient: $D = 0.0015$ (left) and $D = 0.0001$ (right). The values of other parameters are $L = 1$, $a = b = 1$, $k_2 = 0.2$, and $k_3 = 1$.

Existence of solution of this problem can be studied analytically. Suppose that such solution exists, and denote it by $w_k(x)$, where the subscript k shows its dependence on the parameter k. Then we obtain the following equation with respect to k:

$$1 - \int_{-\infty}^{\infty} w_k(x)\,dx = k. \tag{3-10}$$

Existence of its solution determines the existence of solution of problem (3-7). For $f(w) = b - w$, (3-9) becomes

$$w'' - pw + w^2 = 0,$$

where $p = b - k$. Set $w(x) = pv(\sqrt{p}x)$. Then $v(y)$ satisfies the equation

$$v'' - v + v^2 = 0.$$

It has a positive solution $v_0(y)$ such that $v_0(\pm\infty) = 0$. Hence, $w_k(x) = pv_0(\sqrt{p}x)$, and from (3-10) we obtain

$$I_0\sqrt{b-k} = 1 - k, \tag{3-11}$$

where $I_0 = \int_{-\infty}^{\infty} v_0(y)\,dy$. Assertion of the proposition follows from the analysis of this equation. □

The method of solutions presented here can be generalized for the functions $f(u) = b - u^n$, $n > 1$.

3B. ***Interaction of genotype-dependent virus mortality and immune response.*** We can now study the interaction of immune response with the genotype-dependent virus mortality. If the function $\sigma(x)$ has two admissible intervals, then we showed

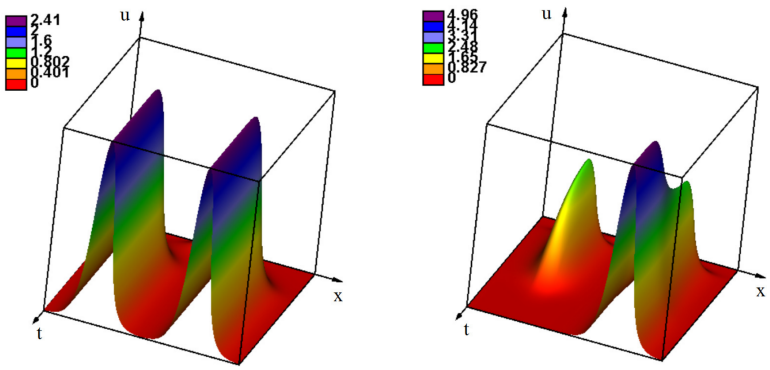

Figure 4. Numerical simulations of (1-2). In the case of symmetric initial condition, there is a bimodal virus density distribution with equal peaks (left). A small asymmetry in the initial condition leads to the disappearance of one peak and to the increase of the other one (right). The values of parameters are $L = 1$, $a = b = 1$, $D = 0.001$, $\sigma(x) = 0$ for $0.2 < x < 0.3$ and $0.7 < x < 0.8$ and $= 1$ otherwise, initial condition $= 0.1$ for $0.48 < x < 0.52$ (left) and $0.481 < x < 0.52$ (right), $f(u) = k_2 e^{-k_3 u}$, $k_2 = 0.2$, and $k_3 = 1$.

in Section 2B that two strains coexist. Their dynamics is described by intermediate solutions slowly convergent to the symmetric bimodal distribution. Immune response influences these dynamics, and this influence depends on the immune response function $f(u)$.

Increasing immune response. We begin the analysis of the influence of immune response on competing virus strains with the case of an increasing function $f(u)$. We consider for certainty a linear function, $f(u) = k_1 u$. In this case, even if the initial condition is not symmetric, the solution rapidly converges to a symmetric distribution with equal peaks in the admissible intervals. The intermediate solutions observed before are not detected here.

Decreasing immune response. In the case of a decreasing function, $f(u) = k_2 e^{-k_3 u}$, the bimodal solution is symmetric in the case of a symmetric initial condition. However, a small asymmetry of the initial condition leads to the disappearance of one strain and to the increase of another one (Figure 4). Thus, the symmetric solution exists but is unstable.

Bell-shaped immune response. Consider the immune response function $f(u) = k_1 u e^{-k_3 u}$ growing for small u and decaying for large u. In the case of two admissible intervals, the solution can converge to a unimodal or to a bimodal distribution depending on the values of parameters (Figure 5). If k_3 is sufficiently small, then the growing branch of this function determines the behavior of solutions, and there

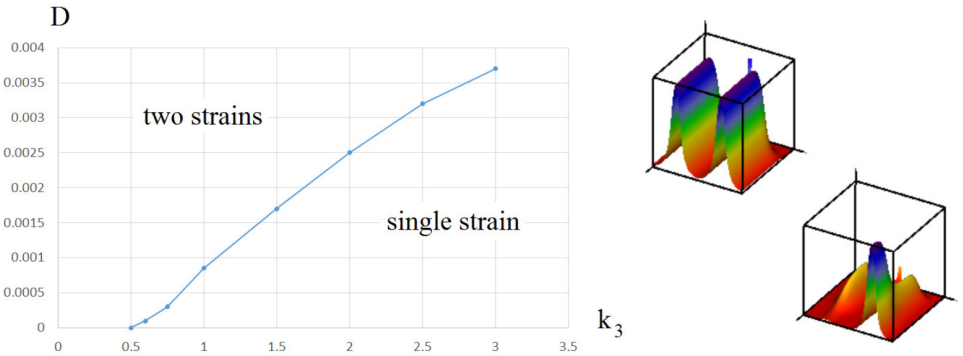

Figure 5. Numerical simulations of (1-2) in the case of bell-shaped function $f(u)$ and two admissible intervals of the function $\sigma(x)$. Depending on the values of parameters, there are two persistent strains, or one of them vanishes. The values of parameters are $L = 1$, $a = b = 1$, $\sigma(x) = 0$ for $0.2 < x < 0.3$ and $0.7 < x < 0.8$ and $= 1$ otherwise, initial condition $= 0.9$ for $0.481 < x < 0.52$, $f(u) = k_1 u e^{-k_3 u}$, and $k_1 = 1$. Two examples of the simulations at the right are carried out with $D = 0.001$, $k_3 = 1$, and $k_3 = 1.2$.

are two persistent strains. If k_3 is large enough, then the decaying branch becomes dominating, and only one strain survives.

3C. ***The influence of treatment.*** In the case of two admissible intervals of the genotype-dependent mortality function $\sigma(x)$, there are two persistent strains rapidly converging to intermediate asymptotics depending on initial condition (Section 2B). Immune response can either preserve both strains or eliminate one (Section 3B).

We will now analyze how the competition of virus strains is influenced by a genotype-dependent virus treatment. We suppose that the function σ depends on time,

$$\sigma(x,t) = \begin{cases} \sigma_0(x), & 0 \le t \le t_0, \\ \sigma_1(x), & t > t_0. \end{cases}$$

Here $\sigma_0(x)$ is the original mortality rate, t_0 is the moment of time when treatment is applied, and $\sigma_1(x)$ is the mortality rate for which the effect of treatment is taken into account. In particular, treatment can eliminate one of the admissible intervals and influence the corresponding strain.

Let us illustrate the influence of treatment on the dynamics of virus strains by a simple case without immune response, $f(u) \equiv 0$. Consider two admissible intervals, $I_1 = [0.2, 0.3]$ and $I_2 = [0.7, 0.8]$, where $\sigma_0(x) = 0$, and $\sigma_0(x) = 1$ outside of these two intervals. The emergence of virus strains depends on the initial condition. If it is localized at the center of the interval ($0.49 < x < 0.51$), then two equal strains

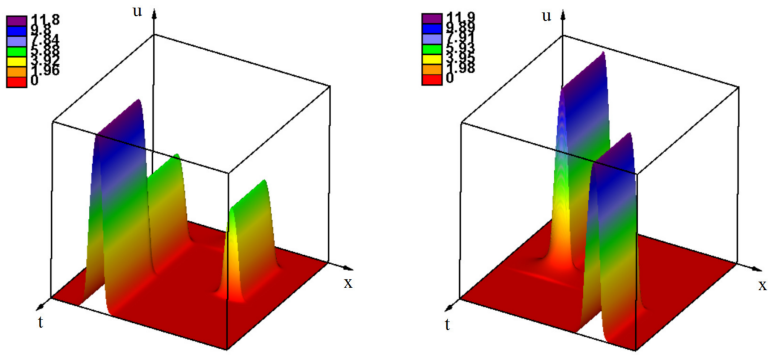

Figure 6. Numerical simulations of (1-2) without immune response and with a time-dependent mortality rate σ. In the case of two equal strains, treatment eliminates one of them and reinforces another one (left). In the case of a single strain, treatment eliminates it leading to the emergence of another strain (right). The values of parameters are $L = 1$, $a = b = 1$, $D = 0.0001$, $\sigma(x) = 0$ for $0.2 < x < 0.3$ and $0.7 < x < 0.8$ and $= 1$ otherwise, initial condition $= 0.1$ for $0.49 < x < 0.51$ (left) and $0.24 < x < 0.26$ (right), and $f(u) \equiv 0$.

emerge in the corresponding admissible intervals (Figure 6, left). At some moment of time $t = t_0$ we change the mortality rate to the function $\sigma_1(x)$ such that it equals 0 only in the first admissible interval, and it equals 1 in the second interval. Then the second strain rapidly disappears while the first strain grows. The total viral load (the integral of solution) does not change.

In the second case, the support of the initial condition is localized inside the first admissible interval, $0.24 \le x \le 0.26$. Only one strain emerges while another one is absent (cf. Section 2B). Applying treatment, we eliminate the first virus strain. After some time, the second strain appears (Figure 6, right). It could not appear before treatment because of the competition between the strains. Thus, an antiviral treatment can lead to the emergence of new strains. Moreover, the new strain is resistant to treatment since treatment acts on the first admissible interval but not on the second one.

4. Discussion

Virus mutation represents a big challenge for biomedical research and clinical medicine. There are hundreds of HIV mutants which can replace each other in the process of treatment. Resistant strains can emerge due to their natural evolution or due to antiviral treatment. On the other hand, virus evolution is an interesting

object of theoretical studies. It has some features in common with the evolution of biological species, but it is faster and explicit in the sense that the virus itself is a relatively simple object, and its environment is also reduced to the host organism. Immune response of the host organism is very complex, but in the first approximation its consideration can be reduced to the multiplication of immune cells as a reaction to the antigen and to the elimination of the antigen.

Model. There are two main approaches to model virus mutations, discrete and continuous. In the discrete approach, there is a finite number of strains interacting with each other due to mutations (fluxes) and, possibly, due to the competition for host cells [Nowak and May 2000]. The corresponding ODE models resemble the models of competition of species in population dynamics. The advantage of such models is that they can be biologically realistic since virus strains and mutation characteristics can be taken from biological data. Furthermore, such models are relatively simple and easy to study in the case of two or three strains. However, they become very cumbersome for a large number of strains (equations), and their detailed analysis is literally impossible.

In continuous models, virus density distribution is considered as a function of genotype interpreted as a continuous variable [Kimura 1964; Sasaki 1994]. Though it is more difficult in this approach to describe a complex graph of virus strain connections by mutations, it is more appropriate to the investigation of the dynamics of this distribution. In this work we further develop this approach taking into account virus competition for host cells, immune response, and genotype-dependent mortality either natural or due to the antiviral treatment. This model is represented by the nonlocal reaction-diffusion equation (1-2), where the nonlocal term determines the virus multiplication rate. Indeed, the rate of cell infection is proportional to the virus density u with the logistic limitation term $(1 - bI(u))$ depending on the total virus quantity. It is similar to carrying capacity in population dynamics, and it determines the limitation on the total infection supported by the organism. Hence, the concentration of infected cells C_i is described by the equation

$$\frac{dC_i}{dt} = ku(1 - bI(u)) - \gamma C_i,$$

where the last term on the right-hand side characterizes death of infected cells. In the quasistationary approximation where the rates of cell infection and death are sufficiently high, we get $C_i = k/\gamma u(1 - bI(u))$. Thus, the virus multiplication term, which is proportional to the concentration of infected cells C_i, can be written as $au(1 - I(u))$ (see (1-2)).

Let us note that there are two possible time delays in the model, one of them in the virus multiplication term and another one in the immune response term due to the clonal expansion of immune cells. Time delay in the immune response

is taken into account in the reaction-diffusion models with time delay [Bessonov et al. 2020; Bocharov et al. 2016; Trofimchuk and Volpert 2018]. In this work we consider either stationary solutions of the corresponding equations or their long-time dynamics. Moreover, the characteristic diffusion time related to mutations is much longer than the characteristic time of virus multiplication or cell proliferation. In this case, the influence of time delay can be neglected.

Virus strains. From the modeling point of view, a virus strain can be represented by a density distribution concentrated around some genotype x_0 and rapidly decaying as the genotype x goes away from x_0. A persistent virus strain corresponds to a positive stable stationary solution $u_0(x)$ with a maximum at some $x = x_0$. Existence of such solutions is not a priori known, and one of the objectives of our modeling study is to establish the conditions of the existence and stability of such solutions.

In our previous work [Bessonov et al. 2020], we showed that there are two mechanisms leading to the existence of stable stationary solutions of (1-2). One of them is determined by the admissible intervals where the virus mortality rate is low. Another one is related to the immune response. It is important to note here that the immune response function should have a decreasing branch. Otherwise, virus strains considered as positive stationary solutions of (1-2) decaying at infinity do not exist. For the existence of strains, admissible intervals should be sufficiently large and the virus mutation rate (diffusion coefficient) sufficiently small.

Competition of strains. The main goal of this work is to study the competition of virus strains emerging in two different admissible intervals. In the case without immune response, the behavior of strains should be considered in two time scales, fast and slow. In the fast time scale, they rapidly converge to some intermediate stationary solutions. The characteristic convergence time is on the order of 10 dimensionless time units. In the time scale of 10^2–10^3 units, they do not practically change. The relative abundance of the two strains depends on the initial viral load (initial condition). Thus, there is a continuous family of intermediate stationary solutions determined by the initial condition.

In a slow time scale on the order of 10^5 units, both strains become equal to each other. It should be noted that the characteristic fast and slow scales strongly depend on the diffusion coefficient. The values presented in our study are obtained for $D = 10^{-3}$. The order of magnitude of the slow time scale rapidly grows with the decrease of the diffusion coefficient, and for $D = 10^{-4}$ the limitation on the computational time does not allow us to reach it.

From the biomedical point of view, the existence of a family of intermediate solutions can bear important implications. In a short time scale, one needs to treat the strains determined by the initial viral load and not by their asymptotics for large time.

We have shown that the mode of immune response strongly influences the behavior of solutions. A growing response function $f(u)$ eliminates the long scale dynamics, and the passage to the equal strains becomes fast. A decreasing response function eliminates one of the two competing strains. Finally, a bell-shaped function can have both effects depending on which of its two branches is dominating.

Limitations and perspectives. Equation (1-2) is derived under the assumption of consecutive mutations (see (1-3)). It can be considered as a small selection approximation of a more general model [Saakian et al. 2008] with a symmetric fitness function. The model considered in this work does not take into account complex intracellular regulation of virus reproduction and of immune response, the participation of different cells in the immune response, and some other aspects of virus-host interaction. On the other hand, this simplification allows us to reveal some general qualitative properties of virus evolution which might be impossible to predict in a more detailed model.

Overall, the presented modeling approach opens up interesting perspectives and allows various developments including time delay, other nonlocal terms, two-dimensional problems, and so on.

Appendix A: Stationary solution for two admissible intervals

Consider the equation

$$Du'' + u(1 - I(u)) - \sigma(x)u = 0 \tag{A-1}$$

on the whole axis, where $\sigma(x) = 0$ for $x_1 \le |x| \le x_2$ and $\sigma(x) = \sigma_0$ for $|x| < x_1$ and $|x| > x_2$. Here σ_0, x_1, and x_2 are some positive numbers, $x_1 < x_2$. We will search for a nonzero bounded solution of this equation with zero limits at infinity.

Set

$$1 - I(u) = k^2. \tag{A-2}$$

If $I(u) \ge 1$, then $u = 0$ is the only bounded solution of (A-1). Hence, $0 < I(u) < 1$, and $k^2 < 1$. Then (A-1) can be written as

$$Du'' + (k^2 - \sigma_0)u = 0, \quad |x| < x_1, \ |x| > x_2, \tag{A-3}$$

$$Du'' + k^2 u = 0, \quad x_1 \le |x| \le x_2. \tag{A-4}$$

Assuming that $k^2 < \sigma_0$, we will look for its solution in the form

$$u(x) = \begin{cases} c_1 e^{\lambda x}, & x < -x_2, \\ c_2 \cos(\mu x) + c_3 \sin(\mu x), & -x_2 \le x \le -x_1, \\ c_4 e^{\lambda x} + c_5 e^{-\lambda x}, & -x_1 < x < x_1, \\ c_6 \cos(\mu x) + c_7 \sin(\mu x), & x_1 \le x \le x_2, \\ c_8 e^{-\lambda x}, & x > x_2, \end{cases}$$

where

$$\lambda = \sqrt{\sigma_0 - k^2}/\sqrt{D}, \quad \mu = k/\sqrt{D}.$$

From the continuity of the solution and of its first derivative,

$$u(\pm x_i - 0) = u(\pm x_i + 0), \quad u'(\pm x_i - 0) = u'(\pm x_i + 0), \quad i = 1, 2,$$

we get the equations

$$c_1 e^{-\lambda x_2} = c_2 \cos(\mu x_2) - c_3 \sin(\mu x_2), \tag{A-5}$$

$$c_1 \lambda e^{-\lambda x_2} = c_2 \mu \sin(\mu x_2) + c_3 \mu \cos(\mu x_2), \tag{A-6}$$

$$c_4 e^{-\lambda x_1} + c_5 e^{\lambda x_1} = c_2 \cos(\mu x_1) - c_3 \sin(\mu x_1), \tag{A-7}$$

$$c_4 \lambda e^{-\lambda x_1} - c_5 \lambda e^{\lambda x_1} = c_2 \mu \sin(\mu x_1) + c_3 \mu \cos(\mu x_1), \tag{A-8}$$

$$c_4 e^{\lambda x_1} + c_5 e^{-\lambda x_1} = c_6 \cos(\mu x_1) + c_7 \sin(\mu x_1), \tag{A-9}$$

$$c_4 \lambda e^{\lambda x_1} - c_5 \lambda e^{-\lambda x_1} = -c_6 \mu \sin(\mu x_1) + c_7 \mu \cos(\mu x_1), \tag{A-10}$$

$$c_8 e^{-\lambda x_2} = c_6 \cos(\mu x_2) + c_7 \sin(\mu x_2), \tag{A-11}$$

$$-c_8 \lambda e^{-\lambda x_2} = -c_6 \mu \sin(\mu x_2) + c_7 \mu \cos(\mu x_2). \tag{A-12}$$

Since we are looking for a nonzero solution, then the determinant of this system should be equal zero. This condition gives an equation with respect to k. The additional condition (A-2) will allow us to determine the coefficients c_i and the solution. From (A-5) and (A-6), we get

$$c_2 = f_2(\lambda, \mu) c_1, \qquad c_3 = f_3(\lambda, \mu) c_1, \tag{A-13}$$

where

$$f_2(\lambda, \mu) = e^{-\lambda x_2}(\mu \cos(\mu x_2) + \lambda \sin(\mu x_2))/\mu,$$
$$f_3(\lambda, \mu) = e^{-\lambda x_2}(-\mu \sin(\mu x_2) + \lambda \cos(\mu x_2))/\mu.$$

From (A-7) and (A-8),

$$c_4 = f_4(\lambda, \mu) c_1, \qquad c_5 = f_5(\lambda, \mu) c_1, \tag{A-14}$$

where

$$\begin{aligned} f_4(\lambda,\mu) &= ((\lambda\cos(\mu x_1) + \mu\sin(\mu x_1))\, f_2 + (-\lambda\sin(\mu x_1) + \mu\cos(\mu x_1))\, f_3) e^{\lambda x_1}/(2\lambda) \\ &= (2\lambda\mu\cos(\mu(x_2 - x_1)) + (\lambda^2 - \mu^2)\sin(\mu(x_2 - x_1))) e^{\lambda(x_1 - x_2)}/(2\lambda\mu), \\ f_5(\lambda,\mu) &= ((\lambda\cos(\mu x_1) - \mu\sin(\mu x_1))\, f_2 - (\lambda\sin(\mu x_1) + \mu\cos(\mu x_1))\, f_3) e^{-\lambda x_1}/(2\lambda) \\ &= (\lambda^2 + \mu^2)\sin(\mu(x_2 - x_1)) e^{-\lambda(x_1 + x_2)}/(2\lambda\mu). \end{aligned}$$

From (A-9) and (A-10), we get

$$c_6 = f_6(\lambda, \mu) c_1, \qquad c_7 = f_7(\lambda, \mu) c_1, \tag{A-15}$$

where

$$f_6(\lambda,\mu) = ((f_4e^{\lambda x_1} + f_5e^{-\lambda x_1})\mu\cos(\mu x_1) - (f_4e^{\lambda x_1} - f_5e^{-\lambda x_1})\lambda\sin(\mu x_1))/\mu$$
$$= f_4(\mu\cos(\mu x_1) - \lambda\sin(\mu x_1))e^{\lambda x_1}/\mu + f_5(\mu\cos(\mu x_1) + \lambda\sin(\mu x_1))e^{-\lambda x_1}/\mu,$$
$$f_7(\lambda,\mu) = ((f_4e^{\lambda x_1} + f_5e^{-\lambda x_1})\mu\sin(\mu x_1) + (f_4e^{\lambda x_1} - f_5e^{-\lambda x_1})\lambda\cos(\mu x_1))/\mu$$
$$= f_4(\mu\sin(\mu x_1) + \lambda\cos(\mu x_1))e^{\lambda x_1}/\mu + f_5(\mu\sin(\mu x_1) - \lambda\cos(\mu x_1))e^{-\lambda x_1}/\mu.$$

From (A-11) and (A-12),

$$c_6\lambda\cos(\mu x_2) + c_7\lambda\sin(\mu x_2) = c_6\mu\sin(\mu x_2) - c_7\mu\cos(\mu x_2).$$

Taking into account (A-15), we obtain

$$f_4(2\lambda\mu\cos(\mu(x_2 - x_1)) + (\lambda^2 - \mu^2)\sin(\mu(x_2 - x_1)))e^{\lambda x_1}$$
$$= f_5(\lambda^2 + \mu^2)\sin(\mu(x_2 - x_1))e^{-\lambda x_1}.$$

Substituting the expressions for f_4, f_5, we obtain $f_4^2 = f_5^2$, or

$$2\lambda\mu\cos(\mu(x_2-x_1))+(\lambda^2-\mu^2)\sin(\mu(x_2-x_1)) = \pm(\lambda^2+\mu^2)\sin(\mu(x_2-x_1))e^{-2\lambda x_1}.$$

Hence,

$$\tan(\mu(x_2 - x_1)) = \frac{2\lambda\mu}{\mu^2 - \lambda^2 \pm (\mu^2 + \lambda^2)e^{-2\lambda x_1}}. \tag{A-16}$$

This equality can be considered an equation with respect to k:

$$\tan(k(x_2 - x_1)/\sqrt{D}) = \frac{2k\sqrt{\sigma_0 - k^2}}{2k^2 - \sigma_0 \pm \sigma_0 e^{-2\sqrt{\sigma_0 - k^2}x_1/\sqrt{D}}}. \tag{A-17}$$

Let us note that the sign $+$ in this equation corresponds to the symmetric solution and $-$ to an asymmetric solution (see Figure 7). For $x_1 = 0$ we obtain the same equation as for the single admissible interval.

In order to describe the behavior of solutions of this equation under the variation of parameters, let us denote $h = (x_2 - x_1)/\sqrt{D}$. We will consider h as an independent parameter and will vary it for the other parameters σ_0 and $x_1/\sqrt{D}$ fixed. If h is small enough, then (A-17) does not have solutions with $|k| < 1$. If h is greater than some critical value h_c^1, then there is a solution $|k| < 1$ of the equation with sign $+$. In the interval $k_c^1 < k < k_c^2$ for some other critical value k_c^2, there is only one solution. The second solution, corresponding to the equation with $-$ appears for $k > k_c^2$ (Figure 8). The branch of solutions of the equation with $-$ disappears for some k_c^3 because the right-hand side of this equation becomes infinite. On the other hand, another branch of tangent in the left-hand side of this equation provides a solution with a negative k. Next, the first branch of solutions for the equation with $+$ disappears for some $k_c^4 > k_c^3$, and it also reappears for $k < 0$.

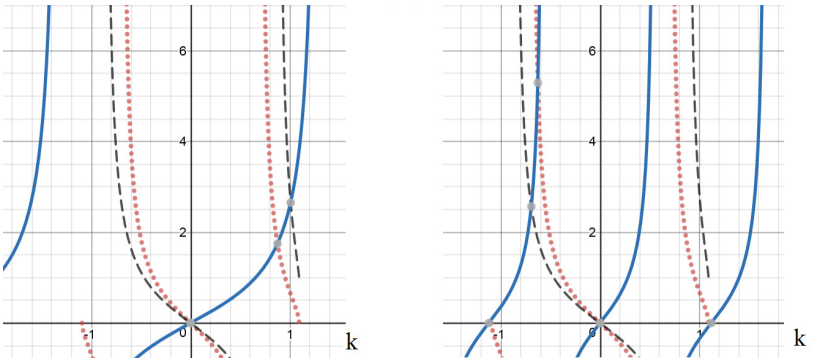

Figure 7. Graphical solution of (A-17) for the values of parameters $\sigma = 1.2$, $x_1/\sqrt{D} = 1$, $(x_2 - x_1)/\sqrt{D} = 1.2$ (left), and $= 2.8$ (right). The function on the left-hand side of this equation is shown by a solid line, and the right-hand side with $+$ is shown by a dotted line and with $-$ by a dashed line.

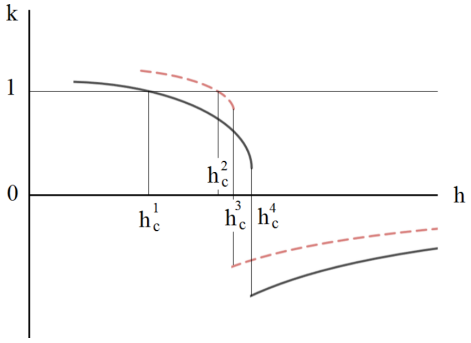

Figure 8. Schematic representation of the bifurcation diagram. The solid line corresponds to the solution of (A-17) with $+$ and the dashed line to the solution of the equation with sign $-$.

Thus, this equation can have zero, one, or two solutions depending on h. Further increase of h brings other branches of tangent and the number of solutions grows. However, we are interested only in positive and stable solutions. We expect that the branch of solutions of the equation with $+$ is stable for small h, and with $-$ for large h. There can exist an interval of bistability for $h_c^3 < h < h_c^4$.

We can now find the integral $I(u)$. In the symmetric case,

$$I(u) = 2\int_{-\infty}^{0} u(x)\,dx$$
$$= 2\left[\frac{c_1}{\lambda}e^{-\lambda x_2} + \frac{1}{\mu}(c_2\sin(\mu x) - c_3\cos(\mu x))_{-x_2}^{x_1} + \frac{c_4}{\lambda}(e^{\lambda x} - e^{-\lambda x})_{-x_1}^{0}\right].$$

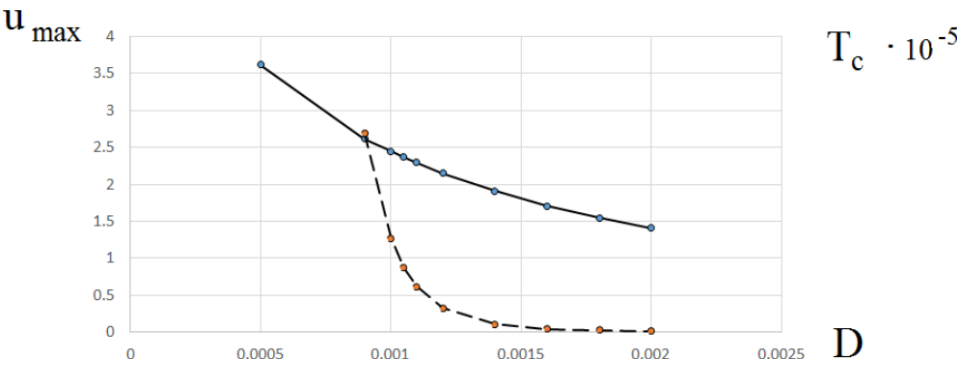

Figure 9. The maximal value of the stationary solution (solid line) and characteristic convergence time to the stationary solution (dashed line). The values of parameters are $L = 1$, $a = b = 1$, $D = 0.001$, $\sigma(x) = 0$ for $0.2 < x < 0.3$ and $0.7 < x < 0.8$ and $= 1$ otherwise, and initial condition $= 0.1$ for $0.49 < x < 0.52$.

From expressions (A-13), (A-14), and (A-15) and equality (A-2), we find c_1. Therefore, we can determine the coefficients c_2, c_3, c_4 and the solution $u(x)$. It can be done similarly in the nonsymmetric case.

Figure 9 shows the dependence of the stationary solution on the diffusion coefficient and of the convergence time to the stationary solution. We determine the convergence time T_c as the time when the difference $|u_m^1 - u_m^2|$ of the two maxima u_m^1 and u_m^2 of the pulses becomes less than 0.01. The convergence time rapidly increases as the diffusion coefficient decreases, and the simulation time becomes too large for $D < 0.001$.

Appendix B: Numerical implementation

In numerical simulations we consider the equation

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + au(1 - bI(u)) - uf(u) - \sigma(x)u$$

on a bounded interval $0 < x < L$ with two different realizations:

- Periodic boundary conditions, and the integral is given by the formula

$$I(u) = \frac{1}{2N}\int_{x-N}^{x+N} u(x,t)\,dx.$$

  If the limits of the integral go beyond the interval $[0, L]$, then the function $u(x,t)$ is continued by periodicity.

- Neumann boundary conditions, and the integral is given by the formula

$$I(u) = \int_0^L u(x,t)\,dx.$$

The numerical results presented in the work have been obtained with the first method. We have verified that the second method gives similar results.

Appendix C: Proof of Theorem 2.2

Consider the equation

$$u'' + u(1 - I(u)) - \sigma(x)u = 0 \tag{C-1}$$

on the whole axis, where $I(u) = \int_{-\infty}^{\infty} u(x)\,dx$ and $\sigma(x)$ is a bounded nonnegative sufficiently smooth function. We look for positive solutions of this equations with zero limits at infinity. We will apply here the topological degree method. We begin with a priori estimates of solutions.

Lemma C.1. *Let $u(x)$ be a positive solution of* (C-1), $u(\pm\infty) = 0$. *Then $I(u) < 1$.*

The proof of the lemma follows directly from the maximum principle. Indeed, if $I(u) \geq 1$, then $u(x)$ is a solution of the equation $u'' + q(x)u = 0$ with $q(x) \leq 0$ and $q(x) \not\equiv 0$. Therefore, $u(x)$ cannot have positive maximum or negative minimum. Hence, $u(x) \equiv 0$.

Lemma C.2. *Suppose that $\sigma(x) = \sigma_0 > 1$ for $|x| \geq x_1$ with some positive σ_0 and x_1. Then $u(x_1) < \sqrt{\sigma}_0/2$.*

Proof. For $x \geq x_1$, (C-1) gives $u'' - au = 0$, where $a = \sigma_0 - (1 - I(u)) < \sigma_0$, $a > 0$. Then

$$u(x) = u(x_1)e^{-\sqrt{a}(x-x_1)}, \qquad \int_{x_1}^{\infty} u(x)\,dx = \frac{u(x_1)}{\sqrt{a}} > \frac{u(x_1)}{\sqrt{\sigma}_0}.$$

Hence,

$$1 > I(u) > 2\int_{x_1}^{\infty} u(x)\,dx > \frac{2u(x_1)}{\sqrt{\sigma}_0}.$$

This inequality proves the lemma. □

Lemma C.3. *Suppose that $\sigma(x)$ is a continuous function and $\sup_x \sigma(x) \leq M$. Then a positive solution $u(x)$ admits an estimate which depends only on M.*

Proof. The solution $u(x)$ of (C-1) satisfies the boundary problem

$$v'' + b(x)v = 0, \quad v(\pm x_1) = u(\pm x_1),$$

on the interval $-x_1 \leq x \leq x_1$. Here $b(x) = 1 - I(u) - \sigma(x)$ is a bounded continuous function, $|b(x)| \leq M + 1 \equiv m$. According to the previous lemma, the boundary

values of the solution are bounded. Therefore, it is sufficient to estimate a maximum of the solution inside the interval. Suppose that the function $v(x)$ has a global maximum at some point $x_0 \in [-x_1, x_1]$. Then

$$|v'(x)| = \left| \int_{x_0}^{x} v''(y)\, dy \right| \le m v(x_0) |x - x_0|.$$

Hence,

$$v(x) = v(x_0) + \int_{x_0}^{x} v'(y)\, dx \ge v(x_0) - \tfrac{1}{2} m v(x_0)(x - x_0)^2 = v(x_0) g(x),$$

where $g(x) = \frac{1}{2} - m(x - x_0)^2$. Denote by Ω the interval in $[-x_1, x_1]$ where this function is positive. Then $\int_\Omega g(x)\, dx \ge \kappa > 0$, where the constant depends only on M and possibly on x_1. Hence, $1 > I(v) > \kappa v(x_0)$. This estimate proves the lemma. □

We will use the topological degree theory to prove the existence of solutions [Volpert 2014]. Lemma C.3 above provides a priori estimates of solutions. Consider the operator

$$A_\theta(u) = u'' + u(1 - I(u)) - \sigma_\theta(x) u,$$

acting from the Hölder space $C^{2+\alpha}(\mathbb{R})$ into the space $C^\alpha(\mathbb{R})$. Here $0 < \alpha < 1$ and $\theta \in [0, 1]$ is a parameter. We will suppose for simplicity that $\sigma_\theta(x)$ is an infinitely differentiable function with respect to x and θ. Other conditions will be specified later.

Denote by L_θ the operator obtained by linearization of the operator $A_\theta(u)$ about $u = 0$:

$$L_\theta v = v'' + v - \sigma_\theta(x) v.$$

Lemma C.4. *Suppose that the principal eigenvalue of the operator L_θ is positive for $\theta_0 \le \theta \le \theta_1$ and for some θ_0, θ_1. Then there exists $\epsilon > 0$ such that $u_m = \sup_x u(x) \ge \epsilon$ for any positive solution of the equation $A_\theta(u) = 0$, $\theta_0 \le \theta \le \theta_1$.*

Proof. Suppose that the assertion of the lemma does not hold and there is a sequence of solutions $u_k(x)$ for $\theta = \theta_k$ such that $u_{m_k} \to 0$. Without loss of generality we can assume that $\theta_k \to \theta_*$ for some $\theta_* \in [\theta_0, \theta_1]$. Then

$$0 = A_{\theta_k}(u_k) = A_{\theta_k}(0) + L_{\theta_k} u_k + o(\|u_k\|) = L_{\theta_k} u_k + o(\|u_k\|).$$

Set $v_k = u_k / \|u_k\|$. Then $L_{\theta_k} v_k = o(1)$. Since L_{θ_k} is proper with respect to v and θ, the sequence v_k is compact and we can choose a convergent subsequence $v_k \to v_0$. Hence, $L_{\theta_*} v_0 = 0$. Since the functions $u_k(x)$ are positive, then $v_0(x) > 0$ for all x. Therefore, the operator L_{θ_*} has a zero eigenvalue with a positive eigenfunction. However, the only positive eigenfunction corresponds to the principal eigenvalue. We obtain a contradiction with the assumption that the principal eigenvalue of the operator L_{θ^*} is positive. □

Theorem C.5. *Suppose $\sigma(x) = \sigma_0 > 1$ for $|x| \geq x_1$ with some positive σ_0 and x_1, and the principal eigenvalue of the problem*

$$u'' + u - \sigma(x)u = \lambda u \tag{C-2}$$

is positive. Then (C-1) *has a positive solution converging to* 0 *at infinity.*

Proof. Set $\sigma_\theta(x) = (1-\theta)\sigma(x) + \theta\sigma_0$. Since $\sigma_0 > 1$, then the operator L_1 has the spectrum in the left half-plane. Let us note that the essential spectrum $S_e(L_\theta)$ of the operator L_θ does not depend on θ, and $\operatorname{Re} S_e(L_\theta) \leq -\delta < 0$ for some positive δ. Denote the principal eigenvalue of this operator, that is, the eigenvalue with the maximal real part, by $\lambda_0(\theta)$. According to the assumption of the theorem $\lambda_0(0) > 0$. It is a monotonically decreasing function of $\theta \in [0, 1]$, and there exists such $\theta_0 \in [0, 1]$ that

$$\lambda_0(\theta_0) = 0, \quad \lambda_0(\theta) > 0 \text{ for } 0 < \theta \leq \theta_0, \quad \lambda_0(\theta) < 0 \text{ for } \theta_0 < \theta \leq \theta_1.$$

Here θ_1 is some value in the interval $(\theta_0, 1]$. Since the eigenvalue can approach the essential spectrum, we cannot guarantee its existence for all $\theta \in [0, 1]$.

Let us consider the equation $A_\theta(u) = 0$ in a small vicinity of the bifurcation point $\theta = \theta_0$. For this value of parameter, the trivial solution $u = 0$ loses its stability, leading to the appearance of another solution $u_\theta(x)$. This solution is positive since the principal eigenfunction $v_0(x)$ is positive [Volpert and Volpert 2000]. Furthermore, the index of this solution, that is, the value of the degree with respect to a small ball containing this solution, equals 1. Indeed, from the homotopy invariance of the degree, it follows that

$$\operatorname{ind}(0) + \operatorname{ind}(u_\theta) + \operatorname{ind}(\tilde{u}_\theta) = 1$$

for all $\theta > \theta_0$ and sufficiently close to θ_0. Here $\tilde{u}_\theta(x)$ is a negative solution bifurcating from the trivial solution and approaching $-v_0(x)$. Since $\operatorname{ind}(0) = -1$ because it equals $(-1)^\nu$, where $\nu = 1$ is the number of positive eigenvalues of the linearized operator, then $\operatorname{ind}(u_\theta) = \operatorname{ind}(\tilde{u}_\theta) = 1$.

It follows from Lemma C.3 that $\|u\|_{C^{2+\alpha}(\mathbb{R})} < M_0$ for some positive constant M_0 and for any positive solution u of the equation $A_\theta(u) = 0$. Next, from Lemma C.4 we conclude that $\|u\|_{C^{2+\alpha}(\mathbb{R})} > \delta(\theta)$ for some positive $\delta(\theta)$, $\theta < \theta_0$. Consider the domain

$$\Omega = \{u \in C^{2+\alpha}(\mathbb{R}) \mid u(x) > 0,\ x \in \mathbb{R},\ \delta_0 < \|u\|_{C^{2+\alpha}(\mathbb{R})} < M_0\}$$

for some $\delta_0 > 0$ sufficiently small. Choose $\theta_2 < \theta_0$ such that $\delta(\theta) > \delta_0$ for $0 \leq \theta \leq \theta_2$. Since $A_\theta(u) \neq 0$ for $u \in \partial\Omega$, $0 \leq \theta \leq \theta_2$, then the value of the degree $\gamma(A_\theta, \Omega)$ does not depend on $\theta \in [0, \theta_2]$. Hence, $\gamma(A_0, \Omega) = \gamma(A_{\theta_2}, \Omega) = \operatorname{ind}(u_{\theta_2}) = 1$, and equation $A_0(u) = 0$ has a solution in Ω. □

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