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VIRAL INFECTION MODEL WITH DIFFUSION AND STATE-DEPENDENT DELAY: A CASE OF LOGISTIC GROWTH

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Abstract. We propose a virus dynamics model with reaction-diffusion and logistic growth terms, intracellular state-dependent delay and a general non-linear infection rate functional response. Classical solutions with Lipschitz in-time initial functions are investigated. This type of solutions is adequate to the discontinuous change of parameters due to, for example, drug administration. The Lyapunov functions approach is used to analyse stability of interior infection equilibria which describe the cases of a chronic disease.

Key words. Reaction-diffusion, evolution equations, Lyapunov stability, state-dependent delay, virus infection model.

AMS subject classifications. 93C23, 34K20,35K57, 97M60

1. Introduction. Our goal is to discuss a wide class of mathematical models of viral diseases. Many viruses (as Ebola virus, Zika virus, HIV, HBV, HCV and others) continue to be a major global public health issues, according to World Health Organization. Particularly, from The Global hepatitis report (WHO, April 2017) [25] we know that "a large number of people - about 325 million worldwide in 2015 - are carriers of hepatitis B or C virus infections, which can remain asymptomatic for decades." and "Viral hepatitis caused 1.34 million deaths in 2015, a number comparable to deaths caused by tuberculosis and higher than those caused by HIV. However, the number of deaths due to viral hepatitis is increasing over time, while mortality caused by tuberculosis and HIV is declining."

In such a situation any steps toward understanding the dynamics of viral diseases are important.

There are variety of models described by systems of ordinary differential equations and/or partial differential equations with or without delays which describe dynamics of different viral infections. Delays could be bounded or unbounded, concentrated or distributed, constant, time-dependent or state-dependent.

The classical models [12, 14] contain ordinary differential equations (without delay) for three variables: susceptible host cells T, infected host cells T^* and free virus particles V. The intracellular delay is an important property of the biological problem, so we start with the delay problem

$$\begin{cases} \dot{T}(t) = \lambda - dT(t) - f(T(t), V(t)), \\ \dot{T}^*(t) = e^{-\omega h} f(T(t-h), V(t-h)) - \delta T^*(t), \\ \dot{V}(t) = N\delta T^*(t) - cV(t). \end{cases} \tag{1.1}$$

In system (1.1), susceptible cells T are produced at a rate λ, die at rate dT, and become infected at rate $f(T, V)$. Properties and examples of incidence function f are discussed below. Infected cells T^* die at rate δT^*, free virions V are produced by infected cells at rate $N\delta T^*$ and are removed at rate $cV(t)$. In (1.1) h denotes the delay

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between the time a virus particle contacts a target cell and the time the cell becomes actively infected (start producing new *free* virions). It is clear that the constancy of the delay is just an extra assumption which essentially simplifies the study, but has no biological background.

To the best of our knowledge, viral infection models with state-dependent delay (SDD) have been considered for the first time in [20] (see also [21]). It is well known that differential equations with discrete state-dependent delay are always non-linear by its nature (see the review [5] for more details and discussion).

As usual in the study of delay systems with (maximal) delay $h > 0$ [4, 8], for a function $v(t), t \in [a-h, b] \subset \mathbf{R}, b > a$, we denote the history segment $v_t = v_t(\theta) \equiv v(t+\theta), \theta \in [-h, 0], t \in [a, b]$.

Consider a connected bounded domain $\Omega \subset \mathbf{R^n}$ with a smooth boundary $\partial\Omega$. Let $T(t,x), T^*(t,x), V(t,x)$ represent the densities of uninfected cells, infected cells and free virions at position $x \subset \Omega$ at time t.

In [22] the following system with SDD η is investigated

$$\begin{cases} \dot{T}(t,x) = \lambda - dT(t,x) - f(T(t,x), V(t,x)) + d^1 \Delta T(t,x), \\ \dot{T}^*(t,x) = e^{-\omega h} f(T(t-\eta(u_t),x), V(t-\eta(u_t),x)) - \delta T^*(t,x) + d^2 \Delta T^*(t,x), \\ \dot{V}(t,x) = N\delta T^*(t,x) - cV(t,x) + d^3 \Delta V(t,x). \end{cases} \tag{1.2}$$

Here the dot over a function denotes the partial time derivative i.g, $\dot{T}(t,x) = \frac{\partial T(t,x)}{\partial t}$, all the constants $\lambda, d, \delta, N, c, \omega$ are positive while $d^i, i = 1, 2, 3$ (diffusion coefficients) are non negative. In (1.2) (and in (1.3) below), a solution denoted by $u(t) = u(t,\cdot) = (T(t,\cdot), T^*(t,\cdot), V(t,\cdot))$, see the argument of the state-dependent delay η in the second equation. The precise definition of a solution is given below (Def. 2.1).

We consider a general functional response $f(T,V)$ satisfying natural assumptions presented below. In earlier models (with constant or without delay) the study was started in case of bilinear $f(T,V) = \text{const} \cdot TV$ and then extended to more general classes of non-linearities. For more details and discussion see [1, 3, 7, 11, 22].

We mention that the term $e^{-\omega h}$ in front of f (see the second equation (1.2)), in fact, states that only *a part* of the cell population survived during the virus incubation period. Clearly, it should be less than 1. It is an assumption which is not too precise in *nonlinear systems*. It could be regarded as a coefficient (strictly smaller than 1) and could be easily incorporated into the definition of the function f. We keep this coefficient in the form of $e^{-\omega h}$ for the only reason to simplify for the reader the comparison of computations with the constant delay case.

In this note we are interested in the following PDEs system with state-dependent delay η

$$\begin{cases} \dot{T}(t,x) = rT(t,x)\left(1 - \frac{T(t,x)}{T_K}\right) - dT(t,x) - f(T(t,x), V(t,x)) + d^1 \Delta T(t,x), \\ \dot{T}^*(t,x) = e^{-\omega h} f(T(t-\eta(u_t),x), V(t-\eta(u_t),x)) - \delta T^*(t,x) + d^2 \Delta T^*(t,x), \\ \dot{V}(t,x) = N\delta T^*(t,x) - cV(t,x) + d^3 \Delta V(t,x). \end{cases} \tag{1.3}$$

Let us discuss the principal difference in the first equations of (1.2) and (1.3). In system (1.2), uninfected target cells T are produced by the body at a constant rate λ which is relevant, for example, in case of HIV. In contrast, the first term in the first equation of (1.3) is the classical logistic growth term (Pierre Verhulst term) for the population of uninfected cells T. The constant T_K is the so-called carrying capacity for the population T, which has the clear biological meaning. System (1.3) is more

relevant in case of chronic infections with viruses such as, for example, hepatitis B (HBV) and hepatitis C (HCV). Here $T(t,x)$ and $T^*(t,x)$ represent uninfected and infected liver cells (hepatocytes). The carrying capacity could be also considered for the sum of uninfected and infected cells (c.f. [6]), but we decide to use it for uninfected hepatocytes (liver cells) only for the following biological reason. It is well-known that the development of HBV, HCV infections is usually connected with development of fibrosis. The last indicates that the regeneration of healthy hepatocytes is not quick enough to fill all the available (free) space in liver. This available space appears as a result of natural death of both uninfected and infected hepatocytes as well as killing of infected cells by immune system. The above suggests that the presence of infected cells does not make essential restriction on the regeneration of healthy hepatocytes T.

Boundary conditions are of Neumann type for the corresponding unknown if $d^i \neq 0$ i.e. $\frac{\partial T(t,x)}{\partial n}|_{\partial\Omega} = 0$ if $d^1 \neq 0$ and similarly for $T^*(t,x)$ and $V(t,x)$. Here $\frac{\partial}{\partial n}$ is the outward normal derivative on $\partial\Omega$. In case $d^i = 0$, no boundary conditions are needed for the corresponding unknown(s). For more discussion see [22].

Our main goals are to present the existence and uniqueness results for the model (1.3) in the sense of classical solutions, and to study the local asymptotic stability of non-trivial disease equilibria. We apply the Lyapunov approach [9] to the state-dependent delay PDE model (1.3) and allow, but not require, diffusion terms in each state equation. For the Lyapunov approach in context of viral infection models (with constant delay or nondelay cases) see e.g. works by A.Korobeinikov, C.McCluskey [7, 11] and references therein. Our main interest is in discussion of the state-dependent delay.

2. Main results. We use the basic functional framework described in [10] and applied to the system (1.2) in [22].

Define the following linear operator $-\mathcal{A}^0 = diag\,(d^1\Delta, d^2\Delta, d^3\Delta)$ in $C(\overline{\Omega}; \mathbf{R^3})$ with $D(\mathcal{A}^0) \equiv D(d^1\Delta) \times D(d^2\Delta) \times D(d^3\Delta)$. Here, for $d^i \neq 0$ we set $D(d^i\Delta) \equiv \{v \in C^2(\overline{\Omega}) : \frac{\partial v(x)}{\partial n}|_{\partial\Omega} = 0\}$ and $D(d^j\Delta) \equiv C(\overline{\Omega})$ for $d^j = 0$. We omit the space coordinate x, for short, for unknown $u(t) = (T(t), T^*(t), V(t)) \in X \equiv [C(\overline{\Omega})]^3 \equiv C(\overline{\Omega}; \mathbf{R^3})$. It is well-known that the closure $-\mathcal{A}$ (in X) of the operator $-\mathcal{A}^0$ generates a C_0-semigroup $e^{-\mathcal{A}t}$ on X which is analytic and nonexpansive [10, p.5]. We denote the space of continuous functions by $C \equiv C([-h,0]; X)$ equipped with the sup-norm $||\psi||_C \equiv \max_{\theta\in[-h,0]} ||\psi(\theta)||_X$.

We write, the system (1.3) in the following abstract form

$$\frac{d}{dt}u(t) + \mathcal{A}u(t) = F(u_t), \qquad t > 0. \tag{2.1}$$

The non-linear continuous mapping $F : C \to X$ is defined by

$$F(\varphi)(x) = \begin{pmatrix} r\,\varphi^1(0,x)\left(1 - \frac{\varphi^1(0,x)}{T_K}\right) - d\varphi^1(0,x) - f(\varphi^1(0,x), \varphi^3(0,x)) \\ e^{-\omega h} f(\varphi^1(-\eta(\varphi),x), \varphi^3(-\eta(\varphi),x)) - \delta\varphi^2(0,x) \\ N\delta\varphi^2(0,x) - c\varphi^3(0,x) \end{pmatrix}. \tag{2.2}$$

Here $\varphi = (\varphi^1, \varphi^2, \varphi^3) \in C$. Mapping F is *not* Lipschitz on the space C which is typical for a mapping which includes discrete state-dependent delays (see review [5] for ODE case and works [15, 16, 17, 2] for PDEs).

We need initial conditions $u(\theta,x) = \varphi(\theta,x) = (T(\theta,x), T^*(\theta,x), V(\theta,x)), \theta \in [-h,0]$ for the delay problem (2.1) (c.f. (1.3)):

$$\varphi \in Lip([-h,0];X) \equiv \left\{ \psi \in C : \sup_{s\neq t} \frac{||\psi(s)-\psi(t)||_X}{|s-t|} < \infty \right\}, \quad \varphi(0) \in D(\mathcal{A}). \tag{2.3}$$

In our study we use the standard (c.f. [13, Def. 2.3, p.106] and [13, Def. 2.1, p.105])

DEFINITION 2.1. *A function $u \in C([-h,T];X)$ is called a* `mild solution` *on $[-h,T)$ of the initial value problem (2.1), (2.3) if it satisfies (2.3) and $u(t) = e^{-\mathcal{A}t}\varphi(0) + \int_0^t e^{-\mathcal{A}(t-s)}F(u_s)\,ds, \quad t \in [0,T)$.*

A function $u \in C([-h,T);X) \bigcap C^1((0,T);X)$ is called a `classical solution` *on $[-h,T)$ of the initial value problem (2.1), (2.3) if it satisfies (2.3), $u(t) \in D(A)$ for $0 < t < T$ and (2.1) is satisfied on $(0,T)$.*

Assume the non-linear function $f : \mathbf{R^2} \to \mathbf{R}$ is Lipschitz continuous and satisfies

$$(\mathbf{Hf_1}) \quad \text{there exists } \mu > 0 \text{ such that } |f(T,V)| \le \mu|T| \text{ for all } T, V \in \mathbf{R}. \tag{2.4}$$

We have the following result

THEOREM 2.2. *Let nonlinear function f be Lipschitz and satisfy $(\mathbf{Hf_1})$ (see (2.4)), state-dependent delay $\eta : C \to [0,h]$ is locally Lipschitz. Then the initial value problem (2.1), (2.3) has a unique classical solution which is global in time i.e. defined for all $t \ge 0$.*

Proof of Theorem 2.2 follows the line of the proof of [22, Proposition 1].

Define the set (c.f. (2.3)), which is different from the one Ω_{Lip} in [22]:

$$\Omega_{Lip}^{log} \equiv \big\{ \varphi = (\varphi^1, \varphi^2, \varphi^3) \in Lip([-h,0];X)) \subset C,\ \varphi(0) \in D(\mathcal{A}) :$$

$$0 \le \varphi^1(\theta) \le \left(1 - \frac{d}{r}\right) T_K, 0 \le \varphi^2(\theta) \le \frac{\mu}{\delta}\left(1 - \frac{d}{r}\right) T_K e^{-\omega h},$$

$$0 \le \varphi^3(\theta) \le \frac{N\mu}{c}\left(1 - \frac{d}{r}\right) T_K e^{-\omega h}, \quad \theta \in [-h,0] \Big\}, \tag{2.5}$$

where μ is defined in $(\mathbf{Hf_1})$ and all the inequalities hold pointwise w.r.t. $x \in \overline{\Omega}$.

We need further assumptions (which include $(\mathbf{Hf_1})$) on Lipschitz function f :

$$(\mathbf{Hf_1}+) \begin{cases} f(T,0) = f(0,V) = 0, \quad \text{and} \quad f(T,V) > 0 \text{ for all } T > 0, V > 0; \\ f \text{ is strictly increasing in both coordinates for all } T > 0, V > 0; \\ \text{there exists } \mu > 0 \text{ such that } |f(T,V)| \le \mu|T| \text{ for all } T, V \in \mathbf{R}. \end{cases} \tag{2.6}$$

We have the following result

THEOREM 2.3. *Let non-linear Lipschitz function f satisfy $(\mathbf{Hf_1}+)$ (see (2.6)), state-dependent delay $\eta : C \to [0,h]$ is locally Lipschitz. Then Ω_{Lip}^{log} is invariant i.e. for any $\varphi \in \Omega_{Lip}^{log}$ the unique solution to problem (2.1), (2.3) satisfies $u_t \in \Omega_{Lip}^{log}$ for all $t \ge 0$.*

Proof of Theorem 2.3. The existence and uniqueness of solution is proven in theorem 2.2. The proof of the invariance part follows the invariance result of [10] with the use of the *almost Lipschitz property* of nonlinearity F. The estimates (for the subtangential condition) are the same as for the constant delay case, see e.g. [11, Theorem 2.2]. We do not repeat it here. It is important to notice that the solutions are classic for all $t \ge 0$ (but not for $t \ge h$ as could be in the case of merely continuous initial functions $\varphi \in C$). For more details see, e.g. [22]. The proof of Theorem 2.3 is complete.

2.1. Stationary solutions. Let us discuss stationary solutions of (1.3). By such solutions we mean time independent $\widehat{u}$ which, in general, may depend on $x \in \overline{\Omega}$. Consider the system (1.3) with $u(t) = u(t - \eta(u_t)) = \widehat{u}$ and denote the coordinates (a possible triple of coordinates) of a stationary solution by $(\widehat{T}, \widehat{T^*}, \widehat{V}) = \widehat{u} \equiv \widehat{\varphi}(\theta)$, $\theta \in [-h, 0]$. Since stationary solutions of (1.3) do not depend on the type of delay (state-dependent or constant) we have

$$\begin{cases} 0 = r\widehat{T}\left(1 - \frac{\widehat{T}}{T_K}\right) - d\widehat{T} - f(\widehat{T}, \widehat{V}), \qquad 0 = e^{-\omega h} f(\widehat{T}, \widehat{V}) - \delta\widehat{T^*}, \\ 0 = N\delta\widehat{T^*} - c\widehat{V}. \end{cases} \tag{2.7}$$

Equations hold pointwise w.r.t. $x \in \overline{\Omega}$.

It is easy to see that the trivial stationary solution $(\left(1 - \frac{d}{r}\right) T_K, 0, 0)$ always exists. We are interested in nontrivial disease stationary solutions of (1.3). We have from the first and second equations of (2.7) $\widehat{T^*} = \frac{r}{\delta} e^{-\omega h} \cdot \widehat{T}\left(1 - \frac{\widehat{T}}{T_K}\right) - \frac{d}{\delta} e^{-\omega h}\widehat{T}$ and from the third equation $\widehat{V} = \frac{N\delta}{c}\widehat{T^*}$. It gives the condition on the coordinate $\widehat{T}$ which should belong to $(0, \left(1 - \frac{d}{r}\right) T_K]$. Denote (c.f. [11, 20])

$$h_f^{log}(s) \equiv f\left(s\,, \frac{Nr}{c} e^{-\omega h} \cdot s\left(1 - \frac{s}{T_K}\right) - \frac{Nd}{c} e^{-\omega h} \cdot s\right)$$

$$-r \cdot s\left(1 - \frac{s}{T_K}\right) + d \cdot s. \tag{2.8}$$

Assume f satisfies

($\mathbf{Hf_2^{log}}$) $h_f^{log}(s) = 0$ has at least one and at most a finite number of roots on $(0, \left(1 - \frac{d}{r}\right) T_K]$.

We denote an arbitrary root of $h_f^{log}(s) = 0$ by $\widehat{T}$ and define the corresponding $\widehat{T^*} \equiv \frac{r}{\delta} e^{-\omega h} \cdot \widehat{T}\left(1 - \frac{\widehat{T}}{T_K}\right) - \frac{d}{\delta} e^{-\omega h}\widehat{T}$ and $\widehat{V} \equiv \frac{N\delta}{c}\widehat{T^*} = \frac{Nr}{c} e^{-\omega h} \cdot \widehat{T}\left(1 - \frac{\widehat{T}}{T_K}\right) - \frac{Nd}{c} e^{-\omega h}\widehat{T}$. The point $(\widehat{T}, \widehat{T^*}, \widehat{V})$ satisfies (2.7), so it is a a disease stationary solution of (1.3). We notice that in [22] the corresponding equation was written for coordinate $\widehat{T^*}$, while (2.8) is designed for $s = \widehat{T}$.

Remark (c.f. [22]). *We notice that the finiteness of roots (which are obviously isolated) does not allow the existence of equilibria which depend on spatial coordinate $x \in \Omega$. We remind that Ω is a connected set, so a function $v \in C(\overline{\Omega})$ may take either one or continuum values. Assumption* ($\mathbf{Hf_2^{log}}$) *implies $\widehat{T^*}(x) \equiv \widehat{T^*} \in \mathbf{R}$, so $(\widehat{T}, \widehat{T^*}, \widehat{V})$ is independent of $x \in \overline{\Omega}$.*

Remark. *It is important to mention that usually in study of stability properties of stationary solutions (for viral dynamics problems) one uses conditions on the so-called reproduction numbers. These conditions are used to separate the case of a unique stationary solution. Then the global stability of the equilibrium is investigated. In our study, taking into account the state-dependence of the delay, we discuss the local stability. As a consequence, it allows the co-existence of multiple equilibria. We believe this framework provides a way to model more complicated situations with rich dynamics (in contrast to a globally stable equilibrium). The conditions on the reproduction numbers do not appear explicitly here, but could be seen as particular sufficient conditions for* ($\mathbf{Hf_2^{log}}$).

2.2. Stability of disease stationary solutions. In this section we use the following *local* assumptions on f in a small neighborhood of a disease equilibrium (given by $(\mathbf{Hf_2^{log}})$).

$$(\mathbf{Hf_3}) \qquad \left(\frac{V}{\widehat{V}} - \frac{f(T,V)}{f(T,\widehat{V})}\right)\cdot\left(\frac{f(T,V)}{f(T,\widehat{V})} - 1\right) > 0. \tag{2.9}$$

One can check that the DeAngelis-Beddington functional response [1, 3] of the form $f(T,V) = \frac{kTV}{1+k_1T+k_2V}$, with $k, k_1 \geq 0, k_2 > 0$ satisfies $(\mathbf{Hf_3})$ globally. We also mention that the DeAngelis-Beddington functional response includes as a special case ($k_1 = 0$) the *saturated incidence* rate $f(T,V) = \frac{kTV}{1+k_2V}$.

We will also use the assumption

$(\mathbf{Hf_4})$ Function f is differentiable in a neighborhood of $(\widehat{T}, \widehat{V})$.

The main result is the following

THEOREM 2.4. *Let the nonlinear Lipschitz function f satisfy $(\mathbf{Hf_1}+), (\mathbf{Hf_2^{log}}), (\mathbf{Hf_3}), (\mathbf{Hf_4})$ (see (2.6), (2.9)), a root $\widehat{T}$ of $h_f^{log}(s) = 0$ (see (2.8) and $(\mathbf{Hf_2^{log}})$) satisfy $\widehat{T} > \frac{1}{2}(1 - \frac{d}{r})T_K$. Let state-dependent delay $\eta : C \to [0,h]$ be locally Lipschitz in C and continuously differentiable in a neighbourhood of equilibrium $\widehat{\varphi} \equiv (\widehat{T}, \widehat{T^*}, \widehat{V})$. Then the stationary solution $\widehat{\varphi}$ is locally asymptotically stable.*

In the proof we use the following Lyapunov functional with *state-dependent delay* along a solution of (1.3)

$$U^{\mathrm{sdd}}(t) \equiv \int_\Omega \left\{ \left(T(t,x) - \widehat{T} - \int_{\widehat{T}}^{T(t,x)} \frac{f(\widehat{T},\widehat{V})}{f(\theta,\widehat{V})}\, d\theta \right) e^{-\omega h} + \widehat{T^*}\cdot v\left(\frac{T^*(t,x)}{\widehat{T^*}}\right) \right.$$

$$\left. + \frac{\widehat{V}}{N}\cdot v\left(\frac{V(t,x)}{\widehat{V}}\right) + \delta\widehat{T^*}\int_{t-\eta(u_t)}^{t} v\left(\frac{f(T(\theta,x),V(\theta,x))}{f(\widehat{T},\widehat{V})}\right) d\theta \right\} dx. \tag{2.10}$$

In (2.10) the Volterra function $v(s) = s - 1 - \ln s : (0,+\infty) \to \mathbf{R}_+$ (c.f. [7, 11]) is used. The form of the functional is standard except the low limit of the last integral in (2.10) which is state-dependent. This state-dependence was first considered in [20] (see also [21]). For PDE (1.2) with constant delay case and $d^1 = d^2 = 0$, see e.g. [11] and for PDE with state-dependent delay (1.2) see [22]. We do not repeat here detailed calculations of the time derivative of $U^{\mathrm{sdd}}(t)$ along a solution of (1.3). They are similar to the ones of [22] and differ in the parts where the connection between coordinates of the stationary solution $\widehat{\varphi} = (\widehat{T}, \widehat{T^*}, \widehat{V})$ is used. The logistic growth term also makes difference to the study presented in [20, 22].

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