International Journal of Applied Mathematics

Volume 36 No. 5 2023, 715-733
ISSN: 1311-1728 (printed version); ISSN: 1314-8060 (on-line version)
doi: http://dx.doi.org/10.12732/ijam.v36i5.10

STABILITY ANALYSIS OF A VIRAL IMMUNE RESPONSE MODEL INVOLVING TWO TIME DELAYS

Fatima Boudchich[1 §], Jaafar El Karkri[1],
Rajae Aboulaich[1], Vitaly Volpert[2]

[1] Laboratory LERMA, Mohammadia School of Engineers
Mohammed V University in Rabat, Avenue Ibn Sina
B.P 765, Agdal Rabat 10090, MOROCCO

[2] Institut Camille Jordan, UMR 5208 CNRS
University Lyon 1, 69622 Villeurbanne, FRANCE
and
Peoples Friendship University of Russia
(RUDN University), 6 Miklukho-Maklaya St.
Moscow, 117198, RUSSIAN Federation

Abstract: We study the qualitative behaviour of the homogeneous in space solution of a two delays differential equation arising from an immune response mathematical model. We use the monotone dynamical systems framework. First, existence and smoothness of solutions are investigated. Then, sufficient conditions of the free-infection and the endemic equilibriums asymptotic stability are derived for different types of the function representing the efficiency of immune response-mediated virus elimination. Then, we use clinical data to calibrate the differential equation and illustrate the analytical results by numerical simulation with the obtained parameters values.

AMS Subject Classification: 34K20, 37N25
Key Words: immune response mathematical modeling, delay differential equations, monotone dynamical systems, exponential ordering, global stability, asymptotic stability

Received: June 25, 2023

[§]Correspondence author

1. Introduction

The dynamics of viral infection is a question of public health and medicine which attracts researchers interest particularly epidemiologists and applied mathematicians. It depends on several factors including the nature of the infection, its severity and mainly the associated response of the immune system. Thus several works have been devoted to this issu. They are based on different methodologies, notabley, ordinary differential equations, partial differential equations, stochatic equations, hybrid modelling or novel methodologies for complex problems solving. They often describe the interaction betwen the hole population of virus and different immune system's cells populations. See for instance [20, 28, 4, 30].

In this work we are interested in the following reaction diffusion partial differential equation:

$$\begin{cases} \dfrac{\partial v}{\partial t} = D_1.\dfrac{\partial^2 v}{\partial x^2} + K.v.\left(1-v\right) - \sigma.v.C\ , \\ \dfrac{\partial C}{\partial t} = D_2.\dfrac{\partial^2 C}{\partial x^2} + \left(C_0 + \Phi\left(v_\tau\right).C\right).\left(1-C\right) - \psi\left(v_\omega\right).C\ , \end{cases} \tag{1}$$

introduced by Bocharov et all in [2] as a model of viral infection spreading in tissues with delayed immune response (See Figure 1 page 4 [2]). Where v is the local virus concentration and C is Lymphocites cells concentration. The variable x describes the spatial position of the immune cell and the virus in the tissue while t is the temporal variable. We use the notations $v_\omega\left(x,t\right) = v\left(x,t-\omega\right)$ and $v_\tau\left(x,t\right) = v\left(x,t-\tau\right)$, for all $(x,t) \in \left(\mathbb{R}^+\right)^2$. The terms $D_1.\frac{\partial^2 v}{\partial x^2}$ and $D_2.\frac{\partial^2 C}{\partial x^2}$ represent the spatial diffusion of viruses and immune cells. D_1 and D_2 are the viruses and immune cells diffusion coefficients respectively. The positive number K is the virus replication rate assumed to be constant. Virus reproduction is described by the logistic term $K.v.(1-v)$, and its elimination by the immune cells is given by the term $\sigma.v.C$. The term $\left(C_0 + \Phi\left(v_\tau\right).C\right).\left(1-C\right)$ illustrates the rate of appearance of immune cells in the peripheral organs after migration from the bone marrow and thymus and proliferating there. The delay τ corresponds to the delay in the immunological reaction due to the duration of proliferation. The term $\psi\left(v_\omega\right).C$ represents the death of the immune cells and μ is the time needed for programming of activated CTLs to apoptosis. The strength of the antiviral immune response given by the terms $\Phi\left(v_\tau\right).C$ and $\psi\left(v_\omega\right).C$, depends on virus concentration at time $t-\tau$ and $t-\omega$. The time delay τ can be of the order of several days. It is determined by the duration of proliferation and maturation of immune cells and ω is the time

needed for immune cells apoptosis. For more details we refer to [2, 3]. The modelling of such dynamics can include a restricted class of dynamical systems, enjoying a comparison principle with respect to a closed order relation on the state space, called monotone, order-preserving or increasing sysytems. To study the qualitative behaviour of solutions of such systems, many approaches and theories can be applied but the more appropriate one is monotone dynamical systems stability theory introduced by Muller [26] and Kamke [16]. Then widely used by variours authors like Hirsh, Matano or H.L Smith (for more details we refer to [12, 23, 34, 35]). El Karkri and Niri [7, 8] employed this aproach to inestigate stability of endemic equilibrium of an epidemiological model.

In the present paper, we genralize the work presented in [6] where authors considered the same model but with a single time delay and they establish sufficient conditions of asymptotic and global stability for the equilibria. We shall prove that under suitable conditions on model's parameters the equilibrium are asymptotically stable. We show that under suitable conditions we get the asymptotique stability of the infection-free equilibrium ($v^* = 0$). We also give different conditions involving the strength of the antiviral immune response terms and the time delays τ and μ, to get asymptotic stability of the infection equilibrium ($v^* \neq 0$). This shows how the asymptotic behaviour of our model is closely affected by the time delays and antiviral immune response efficiency.

The contents of this paper are arranged as follows. In Section 2, the model is presented and reduced to get the main functional differential equation. Then some preliminary results concerning existence, regularity of solutions and basic elements of monotone dynamical systems stability theory are recalled. Then in Section 3 asymptotic stability criterion are inverstigated. In Section 4 in order to compare analytical and numerical stability conditions we apply the theoretical result to clinical data of Ebola and Covid-SARS cases. The paper ends with a short conclusion.

2. The model and the delay differential equation

In this section, we recall main properties, hypothesis and preliminaries of the dynamical system describing the present immunological model and given by The equation (1).

In the following, we assume that v and C are temporal functions. Conse-

quently, The equation (1) becomes

$$\begin{cases} \dfrac{\partial v}{\partial t} = K.v\left(t\right).\left(1-v\left(t\right)\right) - \sigma.v\left(t\right).C\left(t\right), \\ \dfrac{\partial C}{\partial t} = \left(C_0 + \Phi\left(v\left(t-\tau\right)\right).C\left(t\right)\right).\left(1-C\left(t\right)\right) - \psi\left(v\left(t-\omega\right)\right).C\left(t\right). \end{cases} \tag{2}$$

According to [2], we can assume that $\psi\left(v\right) = R.\psi_0\left(v\right)$ and $\phi\left(v\right) = R.\phi_0\left(v\right)$ with R large closed to $+\infty$. After dividing the second equation in (2) by R, we get

$$\tfrac{1}{R}.\tfrac{\partial C}{\partial t} = \left(\tfrac{C_0}{R} + \Phi_0\left(v_\tau\right).C\right).\left(1-C\right) - \psi_0\left(v_\omega\right).C\ .$$

For $R \longrightarrow +\infty$, we have $0 = 0 + \Phi_0\left(v_\tau\right).C.\left(1-C\right) - \psi_0\left(v_\omega\right).C$.

Thus $\Phi_0\left(v_\tau\right).\left(1-C\right) - \psi_0\left(v_\omega\right) = 0$, i.e. $C = 1 - \frac{\psi_0(v_\omega)}{\Phi_0(v_\tau)} = g\left(v_\omega, v_\tau\right)$.

The second equation in (2) is, then, reduced to

$$\frac{dv}{dt}\left(t\right) = K.v\left(t\right).\left(1-v\left(t\right)\right) - \sigma.v\left(t\right).g\left(v\left(t-\tau\right), v\left(t-\omega\right)\right), \tag{3}$$

with $g\left(s,l\right) = 1 - \frac{\psi_0(l)}{\Phi_0(s)} = 1 - \frac{R.\psi_0(l)}{R.\Phi_0(s)} = 1 - \frac{\psi(l)}{\Phi(s)}$.

The differential equation (3) can be written as

$$\frac{dv}{dt}\left(t\right) = H\left(v_t\right), \tag{4}$$

with

$$H\left(\varphi\right) = K.\varphi\left(0\right).\left(1-\varphi\left(0\right)\right) - \sigma.\varphi\left(0\right).g\left(\varphi\left(-\tau\right), \varphi\left(-\omega\right)\right),$$

for all $\varphi \in C^0\left(\left[-\max\left(\tau,\omega\right), 0\right], \mathbb{R}\right)$.

In all this work, the function g is assumed to be of class C^1 on a subset $\left(]a,b[\right)^2$ of $\mathbb{R}_+^2$ such that $[0,1] \subset]a,b[$, with $g\left(x,y\right) > 0$ for all $(x,y) \in]a,b[^2$. We denote $M = \max\left(\tau,\omega\right)$ for the rest of the paper.

Theorem 1. *(Existence, continuity and smoothness of solutions) For all $\varphi \in C([-M,0],[0,1])$, the delay differential equation(3) has a unique solution $v(\varphi,.) : t \longmapsto u(\varphi,t)$ defined on $[-M,+\infty[$. Furthermore, $v(\varphi,.)$ is continuous on $[-M,+\infty[$ and of class C^1 on $[0,+\infty[$.*

Proof. Since g is C^1 on $\left(]a,b[\right)^2$, the functional

$$H :\ \psi \mapsto H\left(\psi\right) = K.\psi\left(0\right).\left(1-\psi\left(0\right)\right) - \sigma.\psi\left(0\right).g\left(\psi\left(-\tau\right), \psi\left(-\omega\right)\right), \tag{5}$$

is C^1 on the open subset $C\left([-M,0],(]a,b[)^2\right)$ of C. Then H is continuous and Lipschitzian on all compact subsets of $C\left([-M,0],(]a,b[)^2\right)$. According to the existence and smoothness theorem in (Hale (1993), the delay differential equation (3) has a unique continuous solution $v(\psi,.)=v_\psi(.)$ on $[-M,+\infty[$. By the same theorem, we have $v(\psi,.)$ is C^1 on $[0+\infty[$. □

Theorem 2. *Under the hypothesis of Theorem 1, we have $v_\varphi(t)\in[0,1]$ for all $t\in[0,+\infty[$, that is $C([-M,0],[0,1])$ is positively invariant for the semi-flow generated by the delay differential equation (3) (see [32] for the definition and the properties of positively invariant subsets).*

Proof. Assume that $\varphi\in C([-M,0],[0,1])$. Let us prove that $v_\varphi(t)\in[0,1]$ for all $t\in[0,+\infty[$.

Assume that $\{t\geq 0: v_\varphi(t)>1\}\neq\emptyset$. Put $t_0=\inf\{t\geq 0: v_\varphi(t)>1\}$ and $v=v_\varphi$. We have $t_0\geq 0$, $v(t_0)=1$ and $v'(t_0)=Kv(t_0)(1-v(t_0))-\sigma v(t_0)g(v(t_0-\tau),v(t_0-\omega))$. Thus,

$$\begin{aligned} v'(t_0) &= Kv(t_0)(1-v(t_0))-\sigma v(t_0)g(v(t_0-\tau),v(t_0-\omega)) \\ &= K(1-1)-\sigma g(v(t_0-\tau),v(t_0-\omega)) \\ &= -\sigma g(v(t_0-\tau),v(t_0-\omega)))<0. \end{aligned}$$

The inequality $v'(t_0)<0$ is in contradiction with the minimality of t_0. Consequently, $\{t\geq 0: v_\varphi(t)>1\}=\emptyset$, and then $v_\varphi(t)\leq 1$ for any $t\geq 0$.

Now assume that $\{t\geq 0/v_\varphi(t)<0\}\neq\emptyset$. Put $t_1=\inf\{t>0/v_\varphi(t)<0\}$ and $v=v_\varphi$. We have $v(t_1)=0$ with $t_1\geq 0$ and for a certain $t_2>t_1$ $v(t_2)>0$. Put $\alpha=sup\{t\in[t_1,t_2]\ /\ v(t)=0\}$. Thus, $\alpha<t_2$, $v(\alpha)=0$ and $v(t)>0$ for all $t\in]\alpha,t_2]$. Then, we have $\frac{v'(t)}{v(t)}=K(1-v(t)-\sigma g(v(t-\tau),v(t-\omega)))$ for all $t\in]\alpha,t_2]$.

Thus, $v(t)>0$ and $\dfrac{d\ln(v(t))}{dt}=K(1-v(t))-\sigma g(v(t-\tau),v(t-\omega))$, for all $t\in]\alpha,t_2]$.

Then,

$$\begin{aligned} \lim_{t\to\alpha,\,t>\alpha}\frac{d\ln(v(t))}{dt} &= K(1-v(\alpha))-\sigma g(v(\alpha-\tau),v(\alpha-\omega)) \\ &= K-\sigma g(v(\alpha-\tau),v(\alpha-\omega)). \end{aligned}$$

On the other hand, $\lim\limits_{\substack{t\to\alpha\\ t>\alpha}} v(t)=v(\alpha)=0$.

Thus, $\lim\limits_{\substack{t\to\alpha\\ t>\alpha}} \ln\left(v\left(t\right)\right) = -\infty$. It is in contradiction with the fact that

$$\lim_{\substack{t\to\alpha\\ t>\alpha}} \frac{d\,ln\left(v(t)\right)}{dt}\left(t=\alpha\right) = K - \sigma g(v\left(\alpha-\tau\right), v\left(\alpha-\omega\right)) \in \mathbb{R}.$$

This means that the assumption $\{t \geq 0 / v_\varphi(t) < 0\} \neq \emptyset$ fails. Consequently, $\{t \geq 0 / v_\varphi(t) < 0\} = \emptyset$ which means that $v_\varphi(t) \geq 0$ for all $t \in [-M, +\infty[$.

We conclude that $v_\varphi(t) \in [0,1]$ for all $t \in [0, +\infty[$.

In other words, $v_\varphi(t) \in [0,1]$ for all $\varphi \in C([-M,0],[0,1])$ and all $t \in [0,+\infty[$. □

Equilibrium points

For all $x \in [0,1]$, put $\hat{x}\left(\theta\right) = x$ for all $\theta \in [-M,0]$. We have $\hat{x} \in C\left([-M,0],[0,1]\right)$. The steady state equation is $H(v) = 0$ which has the solutions $v_0 = 0$, and all $v^* \in]0,1]$ satisfying $\sigma f(v^*) = K(1-v^*)$ with $f\left(x\right) = g\left(x,x\right)$ for all $x \in [0,1]$.

The number of nontrivial solutions of the steady state's equation depends on the nature of the C^1 nonnegative function f. In Section 3 we aim to provide sufficient conditions on the dynamical system's parameters under which the asymptotic stability holds.

3. The asymptotic stability of equilibriums

In this section, we supply sufficient conditions for asymptotic stability of the equilibriums in the sense of the monotone dynamical systems theory. First we recall the following notions.

Definition 3. A continuous linear functional $h : C \longrightarrow \mathbb{R}$ is said to verify the (L_μ) assumption if, for some $\mu > 0$, we have

$h(\omega) + \mu.\omega(0) \geq 0$ for all $\omega \in C$ and $\omega \geq_\mu 0$.

Let $x \in \mathbb{R}$, we denote by $\hat{x} \in C$ the constant function defined by $\hat{x}(\theta) = x$ for all $\theta \in [-r,0]$. Consider the function $\tilde{h}$ defined on $\{x \in \mathbb{R} / \hat{x} \in C\}$ by

$$\tilde{h}(x) \quad = \quad h(\hat{x}). \tag{6}$$

Theorem 4. *([29, 32]) Consider the following delay differential equation:*

$$\begin{cases} x'(t) = h(x_t) \quad \text{for } t \geq 0, \\ x(t) = \phi(t) \quad \text{for } -\tau \leq t \leq 0. \end{cases} \tag{7}$$

Let $\tilde{h}$ be defined by (6). Suppose that h is continuously differentiable in a neighbourhood of an equilibirum x^* of (7) and $dh(x^*)$ verifies (L_μ) for some $\mu > 0$, then

(i) if $\tilde{h}'(x^*) < 0$ then x^* is asymptotically stable.

(ii) if $\tilde{h}'(x^*) > 0$ then x^* is unstable.

In what follows and for all $x \in [0,1]$, we denote $f(x) = g(\hat{x}, \hat{x})$. It is clearly seen that f is C^1 in $[0,1]$.

3.1. The asymptotic stability of the zero equilibrium

Theorem 5. *If $f(0) > \dfrac{K}{\sigma}$, then the equilibrium 0 is asymptotically stable. If $f(0) < \dfrac{K}{\sigma}$, then the equilibrium 0 is unstable.*

Proof. For all $\varphi \in C([-M,0],[0,1])$ and all $\psi \in C$, we have

$$\begin{aligned} dH(\varphi)(\psi) &= K[(1 - 2\varphi(0)\psi(0)] - \sigma g(\varphi(-\tau), \varphi(-\omega)))\psi(0) \\ &\quad -\sigma\varphi(0)\frac{\partial g}{\partial x}(\varphi(-\tau), \varphi(-\omega))\psi(-\tau) - \sigma\varphi(0)\frac{\partial g}{\partial y}(\varphi(-\tau), \varphi(-\omega))\psi(-\omega). \end{aligned}$$

Then

$$dH(0)(\psi) = (K - \sigma.f(0)).\psi(0) \quad \text{for all } \psi \in C.$$

Thus, for $\mu > K + \sigma\|g\|_\infty$ and all $\psi >_\mu 0$ we have $dH(0)(\psi) + \mu\psi(0) > 0$. Hence, (L_μ) holds for $dH(0)$.

With notations above, we have

$$\tilde{H}(x) = K.x.(1-x) - \sigma.x.f(x) \quad \text{for all} \quad x \in [0,1].$$

Then, $\tilde{H}'(x) = K.(1-2x) - \sigma.f(x) - \sigma.x.f'(x)$ for all $x \in [0,1]$.

Particularly, $\tilde{H}'(0) = K - \sigma f(0))$. It follows that if $f(0) > \dfrac{K}{\sigma}$, then $\tilde{H}'(0) < 0$. In other words and by Theorem4, [29], 0 is asymptotically stable. Otherwise, if $f(0) < \dfrac{K}{\sigma}$, then $\tilde{H}'(0) > 0$, and then 0 is unstable. The proof is completed. □

3.2. Asymptotic stability of the equilibrium v^* if $f'(v^*) < 0$

Let v^* be a nonzero equilibrium of the delay differential equation (3). In this section we assume that $f'(v^*) < 0$. For all $\psi \in C$, we have

$$\begin{cases} dH(v^*)(\psi) = K[(1-2.v^*) - \sigma.g(v^*,v^*)].\psi(0) \\ \qquad\qquad -\sigma.v^*.\dfrac{\partial g}{\partial x}(v^*,v^*).\psi(-\tau) - \sigma.v^*.\dfrac{\partial g}{\partial y}(v^*,v^*).\psi(-\omega), \\ \tilde{H}'(v^*) = K(1-2.v^*) - \sigma f(v^*) - \sigma v^*.f'(v^*). \end{cases}$$

However, $K(1-v^*) - \sigma.g(v^*,v^*) = K(1-v^*) - \sigma f(v^*) = 0$, as v^* is an equilibrium. Thus,

$$\begin{cases} \tilde{H}'(v^*) = -Kv^* - \sigma v^*.f'(v^*) = -v^*(K + \sigma f'(v^*)), \\ dH\,(v^*)\,(\psi) = -Kv^*.\psi\,(0) - \sigma.v^*.\dfrac{\partial g}{\partial x}(v^*,v^*).\psi(-\tau) - \sigma.v^*.\dfrac{\partial g}{\partial y}(v^*,v^*).\psi(-\omega). \end{cases}$$

Theorem 6. *Let v^* be a non zero equilibrium of the delay differential equation (3) such that $\dfrac{\partial g}{\partial x}(v^*,v^*) < 0$, $\dfrac{\partial g}{\partial y}(v^*,v^*) < 0$ and $f'(v^*) < 0$.*

- *If $-\dfrac{K}{\sigma} < f'(v^*) < 0$, then the equilibrium v^* is asymptotically stable.*
- *If $f'(v^*) < -\dfrac{K}{\sigma}$, then v^* is unstable.*

Proof. Let $\mu > 0$ and $\psi > 0$. We have

$$\begin{cases} \psi \geq 0 \ \text{ and } \ \psi \neq 0, \\ s \mapsto \psi(s)e^{\mu s} \ \text{ is increasing.} \end{cases}$$

Obviously, $\psi(0) > 0$ and $\psi\,(-\tau) \geq 0$. Since $f'(v^*) < 0$, we have

$$\begin{aligned} dH(v^*)(\psi) + \mu.\psi(0) &= [\mu - Kv^*]\psi(0) - [\sigma.v^*.\frac{\partial g}{\partial x}(v^*,v^*).\psi(-\tau) \\ &+ \sigma.v^*.\frac{\partial g}{\partial y}(v^*,v^*).\psi(-\omega)] \\ &\geq (\mu - Kv^*)\psi(0). \end{aligned}$$

Then, for $\mu > Kv^*$, we have $dH(v^*)(\psi) + \mu.\psi(0) > 0$. Hence, the property (L_μ) holds for $dH(v^*)$. We can clearly see that

$$\tilde{H}'(v^*) < 0 \Leftrightarrow K + \sigma f'(v^*)) > 0 \Leftrightarrow f'(v^*) > -\frac{K}{\sigma}.$$

Moreover, $\tilde{H}'(v^*) > 0 \Leftrightarrow f'(v^*) < -\dfrac{K}{\sigma}$. The theorem is then proved. □

3.3. Asymptotic stability of the equilibrium v^* if $f'(v^*) > 0$.

Let v^* be an equilibrium of the delay differential equation(3) such that $v^* > 0$. In this section we assume that $f'(v^*) > 0$. Consider the following assumption:

$$v^*(\frac{\partial g}{\partial x}(v^*, v^*)\tau - \frac{\partial g}{\partial y}(v^*, v^*)\omega) > \frac{1}{\sigma}. \qquad (H^1)$$

Theorem 7. *Let v^* be a non zero equilibrium of the delay differential equation (3) such that $\dfrac{\partial g}{\partial x}(v^*, v^*) > 0$, $\dfrac{\partial g}{\partial y}(v^*, v^*) > 0$ and $f'(v^*) > 0$. If the condition (H^1) is satisfied, then v^* is asymptotically stable.*

Proof. We have

$$dH(v^*)(\psi) = -Kv^*.\psi(0) - \sigma v^*.\frac{\partial g}{\partial x}(v^*, v^*).\psi(-\tau) - \sigma v^*.\frac{\partial g}{\partial y}(v^*, v^*).\psi(-\omega), \forall \psi \in C.$$

Let us set

$$\begin{cases} \lambda = -Kv^*, \\ \eta_x = -\sigma v^* \frac{\partial g}{\partial x}(v^*, v^*), \\ \eta_y = -\sigma v^* \frac{\partial g}{\partial y}(v^*, v^*), \\ \eta_x^- = \min(\eta_x, 0), \\ \eta_y^- = \min(\eta_y, 0). \end{cases}$$

Then, $dH(v^*)(\psi) = \lambda\psi(0) + \eta\psi(-\tau) + \eta\psi(-\omega)$ for all $\psi \in C$.

For all $\mu \geq 0$, for all $\psi \geq_\mu 0$ we have

$$\begin{aligned} dH(v^*)(\psi) + \mu\psi(0) &= (\lambda + \mu)\psi(0) + \eta_x\psi(-\tau) + \eta_y\psi(-\omega) \\ &\geq h(\mu)\psi(0), \end{aligned}$$

where

$$h(\mu) = \lambda + \mu + \eta_x^- e^{\mu\tau} + \eta_y^- e^{\mu\omega} \quad \text{for all } \mu \geq 0.$$

$dH(v^*)$ satisfies (L_μ) if and only if there exists $\mu \geq 0$ such that $h(\mu) \geq 0$.

First, remark that $h(\mu) = \lambda + \mu + \eta_x^- e^{\mu\tau} + \eta_y^- e^{\mu\omega} \geq \lambda + \mu + (\eta_x^- + \eta_y^-)e^{\mu M}$.

Then, if $\lambda + \eta_x^- + \eta_y^- > 0$ we have $h(0) > 0$. which is not the case here because both λ and η are nonpositive. Else h increases from $h(0) = \lambda + \eta_x^- + \eta_y^-$ and reaches its maximum at μ^* such that $h'(\mu^*) = 0$.

We have $h'(\mu^*) = 1 + \eta_x^- \tau e^{\mu^*\tau} + \eta_y^- \omega e^{\mu^*\omega} = 0$.

Then μ^* satisfies $\mu^*\tau = \ln(\frac{-1-\eta_y^- \omega e^{\mu^*\omega}}{\eta_x^- \tau})$, and $\mu* > 0$. Then, $\frac{-1-\eta_y^- \omega e^{\mu^*\omega}}{\eta_x^- \tau} > 1$. Calculating, we obtain the following estimation

$$1 + \eta_x^- \tau \leq \eta_y^- \omega,$$

consequentely if (H^1) holds, then $dH(v^*)$ verifies (L_μ). Since $f'(v^*) > 0$, we have

$$\tilde{H}'(v^*) = -v^*(K + \sigma f'(v^*)) < 0.$$

Then, Theorem 4 applies and the equilibrium v^* is asymptotically stable. □

4. Numerical simulations and application to clinical cases of certain infectious diseases

To illustrate the theoretical results above, we calibrate the delay differential equation (3) using given real clinical data in order to obtain optimized parameters under R software using the library "deSolve". Then, we use MATLAB solver "dde23" to obtain simulations for different initial values. Recalling that

$$g\,(x, y) = 1 - \frac{\psi\,(y)}{\Phi\,(x)},$$

we consider two particular cases of Φ and ψ. Namely, when both functions are linear and the case where ψ is linear and Φ is nonlinear. The choice of typical forms of g is motivated by the previous studies in basic papers on this model, where authors used to distingish two principal cases of the immune efficiency function; a monotone one, and a bell-shaped form one (see [1, 2]).

4.1. First typical form of g: linear ψ and linear Φ

Consider the following form of g

$$g\,(x, y) = 1 - \frac{ay + b}{cx + d}, \tag{8}$$

where $c > 0$ and $d > 0$. The equilibriums are $v_0 = 0$ and $v^* \in \{v_1^*, v_2^*\}$ which are roots of the polynomial $p(r) = c\frac{K}{\sigma}r^2 + \Big(\frac{K}{\sigma}(d-c) + c - a\Big)r + \Big(d(1-\frac{K}{\sigma}) - b\Big)$. (i.e. satisfying the equation $\sigma f(v^*) = \sigma g(v^*, v^*) = K(1 - v^*)$).

Stability for v_0: We have $f(0) = g(0, 0) = 1 - \frac{b}{d}$. One can see that, if $\frac{b}{d} < 1 - \frac{K}{\sigma}$,

then the equilibrium v_0 is stable, and if $\frac{b}{d} > 1 - \frac{K}{\sigma}$, then v_0 is unstable.
Stability for v^*:

$$\begin{cases} \frac{\partial g}{\partial x}(v^*, v^*) = \frac{c(av^* + b)}{(cv^* + d)^2}, \\ \frac{\partial g}{\partial y}(v^*, v^*) = \frac{-a}{cv^* + d}, \\ f'(v^*) = \frac{bc - ad}{(cv^* + d)^2}. \end{cases}$$

First in the case where $bc - ad < 0$, the equilibrium v^* is asymptotically stable; provided that $\frac{bc - ad}{(cv^* + d)^2} > \frac{-K}{\sigma}$, and it is unstable if $\frac{bc - ad}{(cv^* + d)^2} < \frac{-K}{\sigma}$.

While in the case where $bc - ad > 0$ the condition (H_1) of asymptotic stability can be reformulated as: $v^*(\frac{c(av^* + b)}{cv^* + d}\tau + a\omega) > \frac{cv^* + d}{\sigma}$.

4.1.1. Numerical application

For $\tau = 1$, $\omega = 2$ and for $K = 0.5$, $\sigma = 0.25$ we take the following values for parameters $a = 0.4$, $b = 0.1$, $c = 0.3$ and $d = 0.4$, we obtain two roots of p; $v_1^* = -1$ and $v_2^* = 0.8333$. As a biological value we consider just the second equilibrium v_2^*. Calculations gave $g'(v_2^*) < 0$. Then the asymptotic stability of v_2^* is ensured (since we have $\frac{bc - ad}{(cv_2^* + d)^2} = -0.307 > -2 = \frac{-K}{\sigma}$) . Moreover one can observe in Figure 1 that for different initial values$\varphi_1(t) = 1$, $\varphi_2(t) = 0.9$, $\varphi_3(t) = 0.1 \exp 2t + 0.25$,
$\varphi_4(t) = 0.5(1.02 - 0.7 \exp 2t)$ and $\varphi_5(t) = 0.11(0.5 \exp t + 0.2)$, we the four respectively corresponding solutions u_1, u_2, u_3, u_4, and u_5 converge monotonically to the endemic equilibrium $v_2^* \simeq 0.83333$.

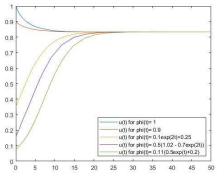

Figure 1: Numerical simulations for different initial values under conditions of stability of the endemic equilibrium corresponding $\tau = 1$ and $\omega = 2$.

4.1.2. Application to SARS-CoV-2 infection clinical case

Time t (days)	8	9	10	11	12	13	14	15
Viral load v(t)	0.158	1.412	1.585	0.1	0.016	0.001	0.0004	0.0001

Table 1: Normalised (divide by 10^6) number of copies per 10^3 cells during 8 days from the day of virus detection (day 8).

We use the clinical case measures in Table 1 of SARS-CoV-2 for patient 2 from [19] (Figure 2). The delay τ represents the duration of cell proliferation and differentiation to effector cells. It is equal to the incubation period of SARS-CoV-2. According to recent works [25, 31], this period varies between 5 and 9 days, we take the mean value $\tau = 7$ days for the immune cells activation delay and $\omega = 9$ days for the cells apoptosis delay.

The calibration of the equation with the clinical data (see Table 1) for the case of linear ψ, linear Φ as in(8) and for $K = \sigma = 0.5$, gives the following parameters $a \simeq 1.36183279$, $b \simeq -0.13305134$, $c \simeq 0.19769703$ and $d \simeq 0.01210387$. For $\tau = 7$ and $\omega = 9$ and for the four different initial values$\varphi_1(t) = 0.1$, $\varphi_2(t) = 0.3$, $\varphi_3(t) = 0.25 \exp t + 0.2$, and $\varphi_4(t) = 0.5(1 - 0.25 * \exp 2t)$, we observe that the four respectively corresponding solutions u_1, u_2, u_3, and u_4 converge monotonically to the endemic equilibrium $v^*{}_{cov} \simeq 0.013$ as shown in Figure 2.

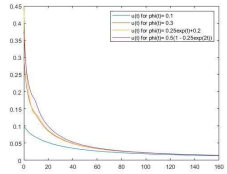

Figure 2: Numerical simulations corresponding to a COVID-19 case with $\tau = 7$ days and $\omega = 9$ days.

4.2. Second typical form of g: linear ψ, nonlinear Φ

For $\psi(x) = x + d$ and $\Phi(y) = (y + d)(1 - a\exp(-\frac{(y-b)^2}{2c^2}))$ we get

$$g\,(x, y) = 1 - \frac{y+d}{x+d}\big[1 - a\exp(-\frac{(y-b)^2}{2c^2})\big]. \tag{9}$$

We denote $f(x) := g\,(x, x) = a\exp(-\frac{(x-b)^2}{2c^2})$. Remark that $f(.)$ is good-shaped.

Stability for v_0: We have $f(0) = g(0, 0) = a\exp(-\dfrac{b^2}{2c^2})$.

One can see that, if $a\exp(-\frac{b^2}{2c^2}) > \frac{K}{\sigma}$, then the equilibrium$v_0$ is stable. And if $a\exp(-\frac{(b)^2}{2c^2}) < \frac{K}{\sigma}$, then v_0 is unstable.

Stability for v^*:

$$\begin{cases} \dfrac{\partial g}{\partial x}(v^*, v^*) = \dfrac{1}{v^*+d}(1 - a\exp(-\dfrac{(v^*-b)^2}{2c^2})), \\ \dfrac{\partial g}{\partial y}(v^*, v^*) = \dfrac{-1}{v^*+d}[1 - (1 - \dfrac{v^*-b}{c^2})a\exp(-\dfrac{(v^*-b)^2}{2c^2})], \\ f'(v^*) = -\dfrac{a}{c^2}(v^*-b)\exp(-\dfrac{(v^*-b)^2}{2c^2}). \end{cases}$$

First, in the case where $v^* < b$, the equilibrium v^* is asymptotically stable; provided that $\dfrac{a}{c^2}(v^*-b)\exp(-\dfrac{(v^*-b)^2}{2c^2}) < \dfrac{K}{\sigma}$.

And it is unstable if $\dfrac{a}{c^2}(v^*-b)\exp(-\dfrac{(v^*-b)^2}{2c^2}) > \dfrac{K}{\sigma}$.

While in the case where $v^* - b > 0$, the condition $H1$ of asymptotic stability can be reformulated as:

$$v^*[(1 - (1 - \frac{v^*-b}{c^2})a\exp(-\frac{(v^*-b)^2}{2c^2}))\tau + (1 - a\exp(-\frac{(v^*-b)^2}{2c^2}))\omega] > \frac{v^*+d}{\sigma}.$$

4.2.1. Application to a second SARS-CoV-2 infection case

For the present example, data is taken from [9], and represents p-values of viral copies measurements from nasopharyngeal swabs tests, for 67 confirmed COVID-19 patients between mild and severe cases. We still consider the time incubation of the virus or the immune cell's activation delay as $\tau = 7$ days and the cell's apoptosis delay as $\omega = 9$ days.

The calibration of the equation with the clinical data of a COVID-19 virus infected patient (see Table 2) for the second form of g (9) and for $K = 0.5$, $\sigma =$

Time t (Days)	1	3	5	7	9	11	13	15	17	19	21
Viral load v(t)	1	25.12	19.95	2.51	0.631	0.158	0.1	0.063	0.051	0.039	0.035

Table 2: The normalised (divide by 10^6) number of copies per 100 cells during 21 days post-infection (See [9]).

0.25 and a fixed $d = 1$, gives the following parameters $a \simeq 2.242$, $b \simeq 0.059$ and $c \simeq 0.0013$. For $\tau = 7$ and $\omega = 9$ and for the four different initial values $\varphi_1(t) = 0.1,\ \varphi_2(t) = 0.3,\ \varphi_3(t) = 0.4 \exp t + 0.2,$ and $\varphi_4(t) = 0.5(1 - 0.25 * \exp 2t)$, we observe that the four respectively corresponding solutions $u_1,\ u_2,\ u_3$, and u_4 converge monotonically to the endemic equilibrium $v^*{}_{cov} \simeq 0.248$ as shown in Figure 3.

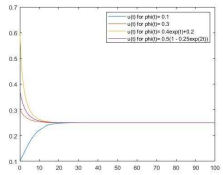

Figure 3: Numerical simulations corresponding to a COVID-19 case with $\tau = 7$ days and $\omega = 9$ days.

4.2.2. Application to Ebola Virus Deseas infection case

Time t (Days post-infection)	5	6	7	8	9	10
Viral load v(t)	0.061	0.141	0.205	0.3	0.165	0.06
Time t (Days post-infection)	11	12	13	14	15	16
Viral load v(t)	0.04	0.003	0.0034	0.0002	0.00017	0.00002

Table 3: The normalised (divide by 10^2) number of copies per 10^6 cells during 16 days from the day of Ebola virus detection (day 5 post-infection) (See [24]).

In this example we calibrate the model (for the nonlinear specific form of g as in (9)) to clinical measurement of viral load in blood taken from a patient who survived to Ebola virus disease. Data is collected from [24]. The viral

load mesurement is performed; per 2×10^6 cells; directly from a sample tube containing patient blood. Table 3 presents the viral load given by normalised (divide by 10^2) number of copies (virions) per 10^6 cells, from the day of Ebola virus detection (day 5 post-infection) and over 16 post-infection days. We consider the time incubation of the virus is $\tau = 5$ days and the cell's apoptosis delay is $\omega = 10$ days.

The calibration of the equation with the clinical data of an Ebola virus disease infected patient (see Table 3) for the second form of g (9) and for $K = 0.5$, $\sigma = 0.25$ and a fixed $d = 1$, gives the following parameters $a \simeq 5.2585$, $b \simeq 0.0557$ and $c \simeq 0.0014$. For $\tau = 5$ and $\omega = 10$ and for the four different initial values $\varphi_1(t) = 0.1$, $\varphi_2(t) = 0.15$, $\varphi_3(t) = 0.25 \exp t + 0.2$, and $\varphi_4(t) = 0.5(1-0.25*\exp 2t)$, we observe that the four respectively corresponding solutions u_1, u_2, u_3, and u_4 converge monotonically to the endemic equilibrium $v^*{}_{cov} \simeq 0.25$ as shown in Figure 4.

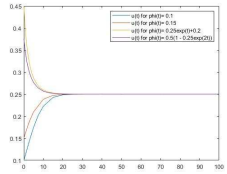

Figure 4: Numerical simulations corresponding to an Ebola virus disease case with $\tau = 5$ days and $\omega = 10$ days.

5. Conclusion

In this work we establish asymptotic stability results for a DDE describing viral infection against delayed immune response. The model involves two delays, one is related to the clonal expansion of immune cells and other one to their death. We investigate under suitable conditions including the immune efficiency function g and the delays τ and ω, the asymptotic stability or the unstability of the infection-free equilibrium. Particulary if $g(0,0) > \frac{K}{\sigma}$ for a sufficiently smooth g the infection-free equilibrium 0 is asymptotically stable that means if the immune system is activated and surpasses the viral load then we obtain the extinction of virus by the immune cells. Furthermore we show that stability of pandemic equilibrium ($v^* \neq 0$) is closely related to the form of g as well as the value of the delays τ and ω but independently of the initial value φ. Then we

examine the obtained stability conditions for typical cases of g and we apply the theoretical results to real clinical data of SARS-CoV-2 and Ebola virus diseases. The numerical simulations show that different solutions converge to the stationary one monotonically (i.e. the nearest the solution starts from the equilibrium value the fastest it tends to it). As it can be observed from the simulations, we can have global convergence of the solutions to a particular steady state. Therefore, a study of global stability of solutions for this model can be the subject of further investigations.

Acknowledgements

The authors are thankful to the editor and anonymous reviewers for the careful reading of the manuscript and fruitful comments, which have improved the manuscript. The contribution of the first, the second and the third author was supported by the project "PHC Magrheb 22MAG22" while the fourth author was supported by RUDN University Startegic Academic Leadership Program, Russian Federation.

References

[1] N. Bessonov, G. Bocharov, T.M. Touaoula, S. Trofimchuk and V. Volpert, Delay reaction-diffusion equation for infection dynamics, *Discrete and Continuous Dynamical Systems, Ser. B*, **24**, No 5 (2019), 2073-2091.

[2] G. Bocharov, A. Meyerhans, N. Bossonov, S. Trofimchuk and V. Volpert, Modelling the dynamics of virus infection and immune response in space and time, *International Journal of Parallel, Emergent and Distributed Systems* (2017), 1-15.

[3] G. Bocharov, Modelling the dynamics of LCMV infection in mice: conventional and exhaustive CTL responses. *J. Theor. Biol.*, **192** (1998), 283-308.

[4] A. Bouchnita, G. Bocharov, A. Meyerhans and V. Volpert, Hybrid approach to model the spatial regulation of T cell responses, *BMC Immunology*, **18** (Suppl. 1), No 29 (2017), 11-22.

[5] F. Boudchich, J.E. Karkri and R. Aboulaich, Stability analysis of a delay differential equation describing the antiviral immune response, *International Journal of Dynamical Systems and Differential Equations*, **13**, No 1 (2023), 76-89.

[6] J. El Karkri, F. Boudchich, V. Volpert and R. Aboulaich, Stability analysis of a delayed immune response model to viral infection, *Differential Equations and Dynamical Systems* (2022), 1–21.

[7] J. El Karkri and K. Niri, Stability analysis of a delayed SIS epidemiological model. *Int. J.Dynamical Systems and Differential Equations*, **6**, No 2 (2016), 173-185.

[8] J. El Karkri and K. Niri, Global asymptotic stability of an SIS epidemic model with variable population size and a delay, *Int. J. Dynamical Systems and Differential Equations*, **7**, No 4 (2017), 289-300.

[9] Z. Habli, S. Saleh, H. Zaraket and ML. Khraiche, COVID-19 in-vitro diagnostics: State-of-the-Art and challenges for Rapid, Scalable, and High-Accuracy Screening. *Front. Bioeng. Biotechnol.*, **8** (2021), 605702; doi: 10.3389/fbioe.2020.605702.

[10] J.K. Hale and S.M. Verduyn Lunel, *Introduction to Functional Differential Equations*, Springer Verlag, Berlin (1993).

[11] M. Hirsch, Systems of differential equations which are competitive or cooperative 1: Limit sets. *SIAM Journal on Applied Mathematics*, **13** (1982), 167-179.

[12] M. Hirsch, Systems of differential equations which are competitive or cooperative 1: limit sets, *SIAM J. Appl. Math.*, **13** (1982), 167-179.

[13] M. Hirsch, Systems of differential equations which are competitive or cooperative II: convergence almost everywhere, *SIAM J. Math. Anal.*, **16** (1985), 423-439.

[14] M. Hirsch, Stability and convergence in strongly monotone dynamical systems, *Journal fur die Reine und Angewandte Mathematik*, **383** (1988), 1-53.

[15] A.L. Jenner, R.A. Aogo, S. Alfonso, V. Crowe, X. Deng, A.P. Smith, et al., COVID-19 virtual patient cohort suggests immune mechanisms driving disease outcomes, *PLoS Pathog*, **17**, No 7 (2021), e1009753; doi:10.1371/journal. ppat.1009753.

[16] E. Kamke, Zur Theorie der Systeme gewöhnlicher Differentialgleichungen, II (German), *Acta Mathematica*, **58**, No 1 (1932), 57-85.

[17] M. Krasnoselskii, *Positive Solutions of Operator Equations*, Noordhoff, Groningen (1964).

[18] M. Krasnoselskii, *The Operator of Translation Along Trajectories of Differential Equations*, Transl. Math. Monographs, Providence, **19** (1968).

[19] F.X. Lescure, L. Bouadma, D. Nguyen, M. Parisey, P.H. Wicky, S. Behillil, Y. Yazdanpanah, et al., Clinical and virological data of the first cases of COVID-19 in Europe: A case series, *The Lancet Infectious Diseases*, **20**, No 6 (2020), 697-706.

[20] G. Marchuk, *Mathematical Modelling of Immune Response in Infectious Diseases*, Kluwer Academic Publishers (1997).

[21] R.H. Martin and H.L. Smith, Abstract functional differential equations and reaction-diffusion syastems, *Trans. of the Amer. Math. Soc.*, **21**, No 1 (1990).

[22] R.H. Martin and H.L. Smith, Reaction-diffusion systems with time delays: Monotonicity, invariance and convergence, *Journal fur die Reine und Angewandte Mathematik*, **413** (1991), 1-35.

[23] H. Matano, Existence of nontrivial unstable sets for equilibriums of strongly order preserving systems, *J. of the Fac. Sci., the Univ.of Tokyo*, **30** (1984), 645-673.

[24] A.K. McElroy, R.S. Akondy, D.R. Mcllwain, H. Chen, Z. Bjornson-Hooper, N. Mukherjee,..., and C.F. Spiropoulou, Immunologic timeline of Ebola virus disease and recovery in humans, *JCI Insight*, **5**, No 10 (2020).

[25] C. Melenotte, et al., Immune responses during COVID-19 infection, *Oncoimmunology*, **9**, No 1 (2020), 1807836.

[26] M. Muller, Uber das Fundamental theorem in der Theorie der gewohnlichen Differentialgleichungen (German), *Mathematische Zeitschrift*, **26**, No 1 (1927), 619-645.

[27] L. Musey, et al., Cytotoxic T cell responses, viral load and disease progression in early HIV-type 1 infection, *N. Engl. J. Med*, **337**, (1997), 1267-1274.

[28] M.A. Nowak and C.R.M. Bangham, Population dynamics of immune response to persitent viruses. *Seinece, New Ser.*, **272** (1996), 74-79.

[29] M. Pituk, Convergence to equilibria in scalar nonquasimonotone functional differential equations, *J. Differential Equations*, **193** (2003), 95-130.

[30] S.A. Prokopiou, L. Barbarroux, S. Bernard, J. Mafille, Y. Leverrier, C. Arpin, J. Marvel, O. Gandrillon and F. Crauste, Multiscale modeling of the early CD8+ T T-Cell immune response in lymph nodes: An integrative study, *Computation*, **2** (2014), 159-181.

[31] M. Sadria, A.T. Layton, Modeling within-Host SARS-CoV-2 infection dynamics and potential treatments, *Viruses*, **13** (2021) 1141; doi:10.3390/v13061141.

[32] H.L. Smith, *Monotone Dynamical Systems: An Introduction to the Theory of Competitive and Cooperative Systems*, Mathematical Surveys and Monographs, **41**, Amer. Math. Soc. Providence (1995).

[33] H.L. Smith and H. Thieme, Convergence for strongly ordered preserving semiflows, *SIAM J. Math. Anal.*, **22** (1991), 1081-1101.

[34] H.L. Smith and H. Thieme, Quasi Convergence for strongly ordered preserving semiflows, *SIAM J. Math. Anal.*, **21** (1990), 673-692.

[35] H.L. Smith and H. Thieme, Monotone semiflows in scalar non-quasi-monotone functional differential equations, *J. Math. Anal. Appl*, **150** (1990), 289-306.

[36] H.L. Smith and H. Thieme, Strongly order preserving semiflows generated by functional differential equations, *J. Diff. Eqns.*, **93** (1991), 332-363.

[37] S. Trofimchuk and V. Volpert, Traveling waves for a bistable Reaction-diffusionequation with delay, *SIAM J. Math. Anal.*, **50**, No 1 (2018), 1175-1199.

[38] Y. Wang, X.Q. Zhao, The convergence of a class of reaction-diffusion systems, *J. London Math. Soc.*, **64**, No 2 (2001), 395-408.

[39] T.S. Yi and L.H. Huang, Convergence and stability for essentially strongly order-preserving semiflows, *J. of Differential Equations*, **221** (2006), 36-57.

[40] T.S. Yi and X. Zou, New generic quasi-convergence principles with applications, *J. of Math. Anal. and Appl.*, **353** (2009), 178-185.