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Analysis of virus infection dynamics with delayed immune response

Fatima Boudchich^{1*}, Jaafar El Karkri¹ and Rajae Aboulaich¹

Abstract

In this work, we study the qualitative behaviour of a virus infection dynamics model with delayed immune response described by a scalar delay differential equation. Using monotone dynamical systems theory, we give sufficient conditions of local and global stability of given equilibriums. The obtained results are applied to a class of special forms of the immune system efficiency function. Then, we use clinical data to calibrate the differential equation and illustrate the analytical results by numerical simulation with the obtained parameters values.

Keywords: Modeling of immune response. Delay differential equations. Monotone dynamical systems. Exponential ordering. Global stability

1 Introduction

Several works have been devoted to the modelling of immune response, particularly, to viral infection. Most of them are based on Ordinary Differential Equations (ODEs) and describe the interaction between the host population of virus and different immune systems cells populations. Some works take into account the complexity of the immune responses. They use hybrid models (which represent a combination of different kinds of models). Many ones include time delays. In this work we study the stability of stationary solutions of the following delay differential equation describing a virus infection dynamics

$$\begin{cases} u'(t) = u(t)(1 - u(t) - f(u(t - \tau))) & \text{for } t \geq 0, \\ u(t) = \phi(t) & \text{for } -\tau \leq t \leq 0. \end{cases} \quad (1)$$

which is considered in . Where, u is the virus density distribution. Virus reproduction is described by the logistic term $u(1 - u)$ and its elimination by the immune cells is given by the term $uf(u_\tau)$, where $u_\tau(x, t) = u(x, t - \tau)$, and the function $f(u)$ specifies the efficiency of immune response-mediated virus elimination. The strength of the antiviral immune response given by the value of $f(\cdot)$ depends on virus concentration at time $t - \tau$ due to the duration of proliferation and maturation of immune cells.

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The Equation studied in this work was considered by Bocharov and collaborators [1] they studied the corresponding delay reaction-diffusion differential equation of the form which describes viral infection spreading in tissues and studied its dynamics and stability with numerical simulations in 1D and 2D cases. They identified various new regimes in the dynamics of delay reaction-diffusion equation. Such study is Biologically interesting, in fact, it suggests a richness of spatiotemporal patterns of infection dynamics in organs and tissues. Our purpose is to establish a non classical stability result using the monotone approach. The equilibriums of the equation are given by $v_0 = 0$, and all $v^* \in]0, 1]$ satisfying $f(v^*) = 1 - v^*$. The existence and the number of nontrivial equilibriums v^* depend on the form of the function f and so is their asymptotic behaviour. Therefore, We shall prove that for certain values of the model's parameters (notably the delay τ and the expression of f) the equilibrium are asymptotically stable. Then we distinguish two particular regimes of the function f (see Figure.1) namely a nondecreasing function and a changing monotonicity one, and under particular condition we get the global stability of the positive equilibrium. Numerical simulations illustrate theoretical results of global stability. Real clinical data of a COVID-19 patient will be used to calibrate models parameters for two particular forms of $f(u)$ and also for the case where f is only Lipschitz and not necessarily differentiable. Numerical simulations shall be exploited to forecast the immunological behaviour against the infection.

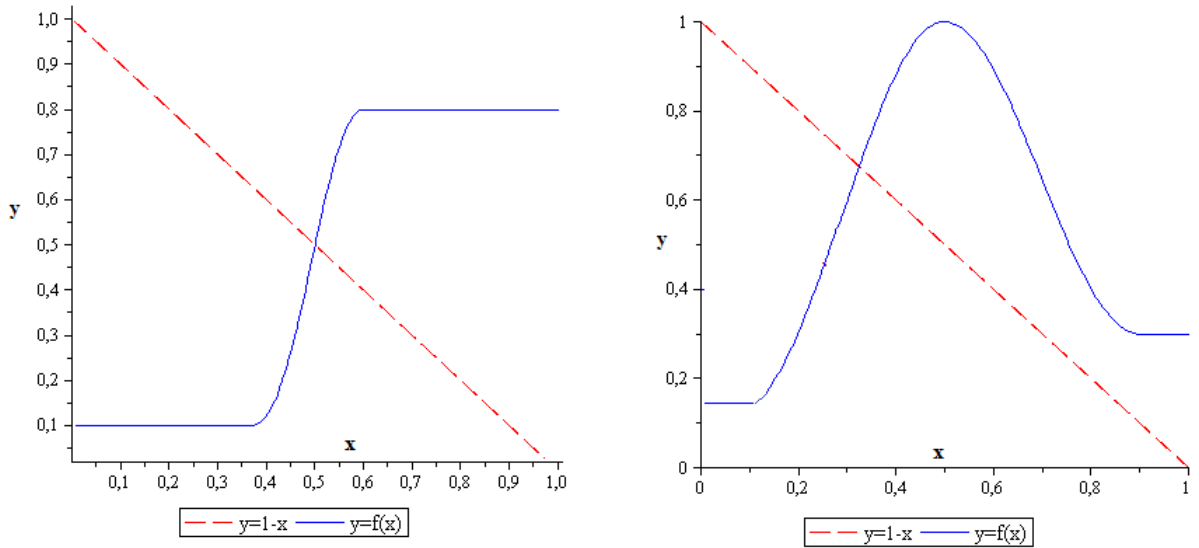


Figure 1: The two particular forms of the function f as it was considered in [1]

2 Preliminary and theoretical results

The delay differential equation (1) can be written in the form

$$\begin{cases} u'(t) = F(u_t) & \text{for } t \geq 0, \\ u(t) = \phi(t) & \text{for } -\tau \leq t \leq 0. \end{cases} \quad (2)$$

Where u_t is defined for all $(t, \theta) \in [0, +\infty[\times [-\tau, 0]$, by $u_t(\theta) = u(t + \theta)$ and F is defined by:

$$\begin{aligned} F : C([-\tau, 0], \mathbb{R}) &\longrightarrow \mathbb{R} \\ \varphi &\longmapsto F(\varphi) = \varphi(0)(1 - \varphi(0) - f(\varphi(-\tau))). \end{aligned}$$

We make the following hypotheses about the parameters of the system.

(H_0) the function f is of class C^1 on an interval $]a, b[$ such that $[0, 1] \subset]a, b[$, with $f(x) > 0$ for all $x \in [a, b]$.

Theorem 1 [5] (*Existence, continuity and smoothness of solutions*) For all $\varphi \in C([-\tau, 0], [0, 1])$, the delay differential equation (2) has a unique solution $u(\varphi, \cdot) : t \mapsto u(\varphi, t)$ defined on $[-\tau, +\infty[$. Furthermore, $u(\varphi, \cdot)$ is continuous on $[-\tau, +\infty[$ and of class C^1 on $[0, +\infty[$ and $u(\varphi, t) = u_\varphi(t) \in [0, 1]$ for all $t \geq 0$.

Theorem 2 [5] Under hypothesis of Theorem 1, we have $u_\varphi(t) \in [0, 1]$ for all $t \in [0, +\infty[$, that is $C([-\tau, 0], [0, 1])$ is positively invariant for the semi-flow generated by the delay differential equation (2) (see [10] for the definition and the properties of positively invariant subsets).

3 Stability analysis

Equilibrium points: The steady state equation is $F(u) = 0$ which has the solutions $v_0 = 0$, and all $v^* \in]0, 1]$ satisfying $f(v^*) = 1 - v^*$. The existence and the number of nontrivial equilibriums v^* depend on the form of the function f . In the next section we provide an asymptotic stability analysis of all equilibriums without any additional restriction on the form or on the smoothness of the C^1 nonnegative function f . Contrariwise, for global convergence and global asymptotic stability analysis supplementary hypothesis on f will be indispensable.

Theorem 3 The asymptotic stability of the free-infection equilibrium 0 [5]
If $f(0) > 1$, then the equilibrium 0 is asymptotically stable.
If $f(0) < 1$, then the equilibrium 0 is unstable.

Consider a nonzero equilibrium v^* of (2), and denote (H^1) the hypothesis

$$f'(v^*) > 0 \quad \text{and} \quad \ln\left(\frac{1}{\tau v^* f'(v^*)}\right) > 1 + \tau v^*. \quad (H^1)$$

Theorem 4 The asymptotic stability of the nonzero equilibrium v^* [5]
Let v^* be a non zero equilibrium of the delay differential equation (2).

- If $-1 < f'(v^*) < 0$, then the equilibrium v^* is asymptotically stable.
- If (H^1) holds, then the equilibrium v^* is asymptotically stable.
- If $f'(v^*) < -1$, then the equilibrium v^* is unstable.

Assume that the function f is non decreasing, (Figure 1, left) and sufficiently small, such that $f_1 = f(0) < 1$. Consider the following assumption

$$\ln\left(\frac{1}{\tau \cdot \|f'\|_\infty}\right) > \tau(\|f\|_\infty + 1) + 1. \quad (HG)$$

Theorem 5 The global stability of the nonzero equilibrium v^* for the first form of f [5]
If (HG) holds, then the positive equilibrium v^* is globally asymptotically stable on $C([-\tau, 0],]0, 1])$.

Time(D)	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
V load	5.011	0.199	0.01	0.0063	1.0056	0.008	0.0056	0.003	0.005	0.01	0.016	0.02	0.039	0.0015	0.0001	0.0001	0.0001

Figure 2: Viral load (concentration of infected cells u per 10^6 cells) during 17 days from the day of virus detection (day 8)

Let take f as in the right side of figure 1, and put $\|f'\|_{\infty}^+ = \max\{f'(x) : x \in [0, 1], f'(x) \geq 0\}$. Denote by (HG^+) the assumption

$$\ln\left(\frac{1}{\tau \cdot \|f'\|_{\infty}^+}\right) > \tau(\|f\|_{\infty} + 1) + 1.$$

Theorem 6 *The global stability of the nonzero equilibrium v^* for the second form of f [5] If (HG^+) holds, then the positive equilibrium v^* is globally asymptotically stable on $C([-\tau, 0], [0, 1])$.*

4 Application to SARS-CoV-2 (COVID-19) dynamics

In order to illustrate our results, we consider a case of SARS-CoV-2 and we shall obtain the corresponding equation to perform numerical simulations.

The considered data in the table of Figure 2 represents measures of the viral load in nasopharyngeal swab normalised using cell quantification, during several days, for a real patient (see details in [6]). The data are taken from the work of Lescure et al [6] (corresponding to graphic C for patient 3, in Figure 2, pp.702).

The method we employ consists to calibrate our equation with the clinical data in order to obtain optimized parameters, this was performed in R software using the library "deSolve". Then, simulations for different initial condition values are established using MATLAB solver "dde23". The delay (which means in the model net duration of cell proliferation and differentiation to effector cells) here represents the average duration of incubation of SARS-CoV-2. In several recent works related to study of SARS-CoV-2 dynamics this period can varies between 5 and 9 days or equals to 7 days (For detailed informations one can see for instance [7, 9]). Then for numerical simulations we will take the delay $\tau = 7$.

4.1 First typical form of f : linear function

Consider $f(u) = k_1 u + k_2$, with $k_1 > 0$ and $0 < k_2 < 1$. The unique non zero equilibrium is $v^* = \frac{1 - k_2}{1 + k_1}$. We have $\|f'\|_{\infty} = k_1$ and $\|f\|_{\infty} = k_1 + k_2$. Condition (HG) in this case becomes

$$\ln\left(\frac{1}{\tau \cdot \|f'\|_{\infty}}\right) > \tau(\|f\|_{\infty} + 1) + 1 \iff \ln\left(\frac{1}{\tau \cdot k_1}\right) > \tau(k_1 + k_2 + 1) + 1.$$

After calibrating the model for the form $f(u) = k_1 u + k_2$, with $k_1 > 0$ and $0 < k_2 < 1$ to the Covid-19 data we obtained the following parameters : $k_1 \simeq 0.28$ and $k_2 \simeq 0.989$. The assumption of asymptotic stability (H1) is satisfied for those parameters with $\tau = 7$. Four different cases of initial values are considered, $\varphi_1 = 0.01$, $\varphi_2(t) = 0.1 \exp t + 0.02$, $\varphi_3 = 0.1 \exp t + 0.05$, and $\varphi_4 = 0.1 \exp t + 0.1$. We observe that, the four solutions u_1 , u_2 , u_3 , and u_4 corresponding

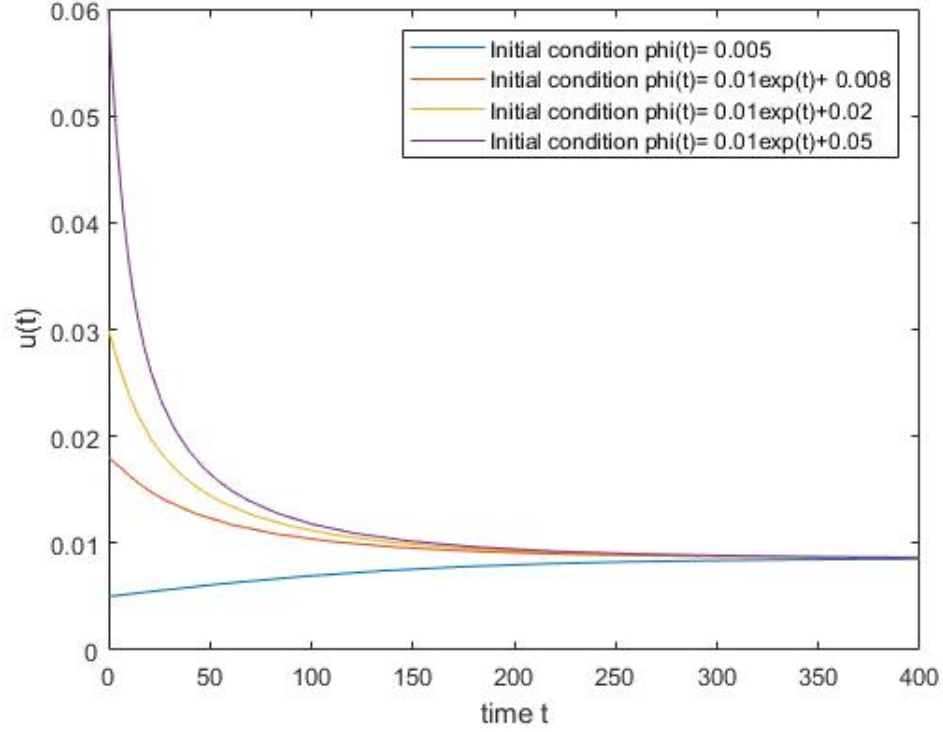


Figure 3: Numerical simulations corresponding to a covid-19 case for $f(u) = 0.28u + 0.98$ in 400 days

respectively to the initial values $\varphi_1, \varphi_2, \varphi_3,$ and $\varphi_4,$ converge monotonically to the non-zero equilibrium (or endemic equilibrium) which is $v^*_{cov} \simeq 0.00859$ (i.e the best the solution u_i is near to v^*_{cov} the fastest it tends to) as shown in Figure 3 and one can observe the monotonicity of convergence.

4.2 Second typical form of $f : f(x) = (ax + b) \cdot e^{-cx}$

Consider $f(x) = (ax + b) \cdot e^{-cx}$ with $a > 0, b > 0$ and $0 < \frac{1}{c} - \frac{b}{a} < 1$. We have $\|f'\|_{\infty}^+ = f'(0) = a - cb > 0$ and $\|f\|_{\infty} = f(x_0) = f\left(\frac{1}{c} - \frac{b}{a}\right) = \frac{a}{c} e^{\left(\frac{bc-a}{a}\right)}$. The condition (HG^+) can be reformulated explicitly as

$$(HG^+) \ln\left(\frac{1}{\tau \cdot (a - cb)}\right) > \tau \left(\frac{a}{c} e^{\left(\frac{bc-a}{a}\right)} + 1\right) + 1.$$

Calibrating to the COVID-19 data we obtain the parameters $a \simeq 0.157, b \simeq 0.988$ and $c \simeq 0.173$. Numerical simulation is performed for four different initial conditions and global stability occurs for the equilibrium $v^* \simeq 0.009$. See Figure.4

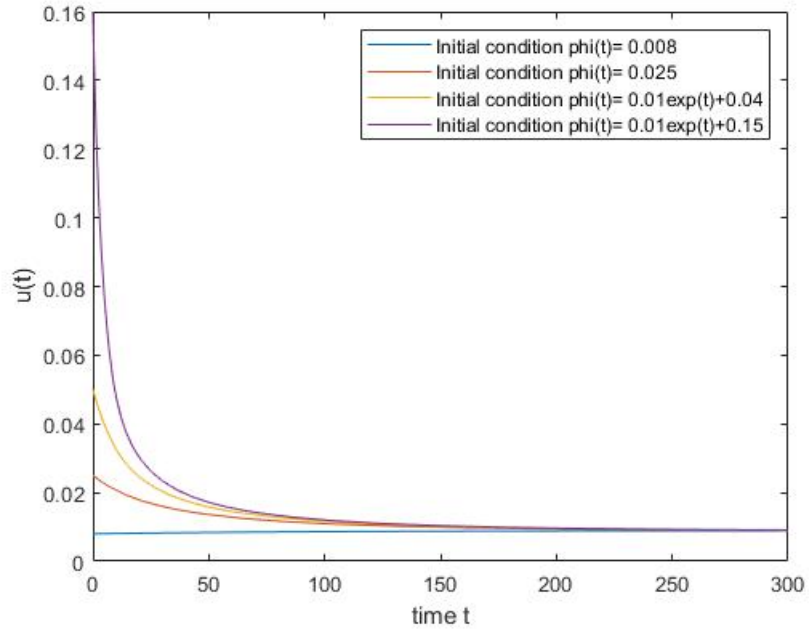


Figure 4: Numerical simulations corresponding to a covid-19 case. $f(u) = (0.16u + 0.988) \cdot e^{-0.173u}$ in 300 days

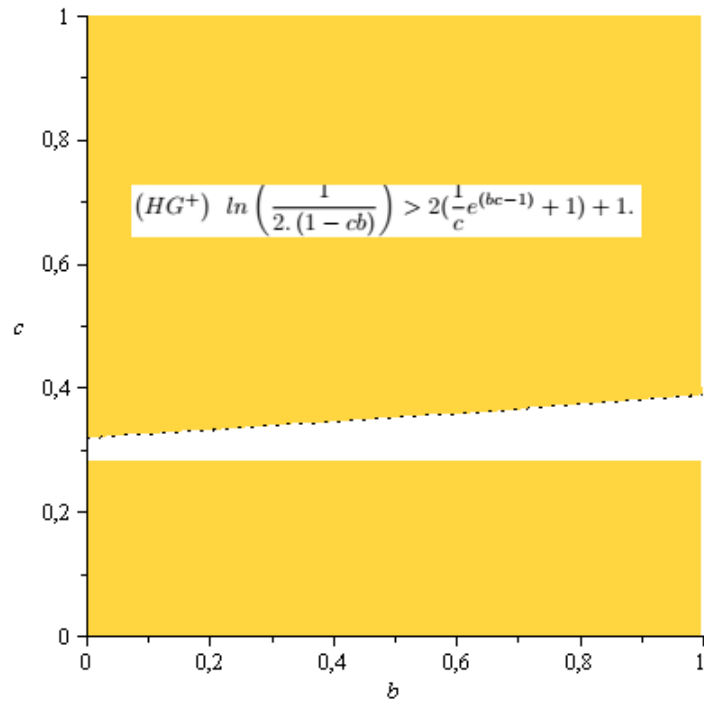


Figure 5: Global stability region for infected equilibrium v^* corresponding the condition (HG+) for $\tau = 2$ and $a = 1$

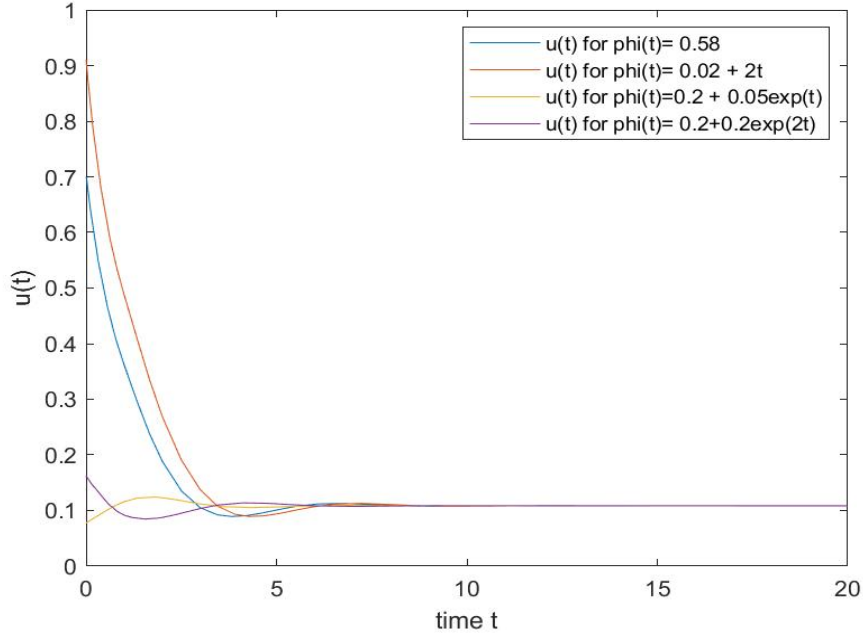


Figure 6: Numerical simulations corresponding to a covid-19 calibrated example case for the nonlinear piecewise function f

4.3 Case of f not necessarily differentiable

We calibrate the model to the clinical data for the nonlinear piecewise function of the form

$$f(u) = \begin{cases} au + b; & u \in [0, \tilde{u}] \\ \frac{u}{u^2 + c}; & u \in]\tilde{u}, 1] \end{cases}$$

Then we obtain the parameters a , b and c such that:

$$f(u) = \begin{cases} 0.98u + 0.41; & u \in [0, 0.01] \\ \frac{u}{u^2 + 0.11}; & u \in]0.01, 1] \end{cases}$$

For this case we apply a stability result established by M. Pituk [8]. According to [Theorem 3.1 [8]] all solutions converge to the equilibrium, which is globally stable. For numerical simulations, we take four different cases of initial values and we observe that, the four solutions corresponding respectively to those initial values, converge monotonically to the endemic equilibrium which is $v^* \simeq 0.11$. See Figure.6.

5 Conclusion

In this paper, we have studied a viral infection model with delayed immune response. Stability of the infection-free equilibrium v_0 and infected equilibrium v^* have been given using the monotonous dynamical theory. As the reader can see in the simulations, the convergence is monotone and the partial order relation in the initial values is conserved. Moreover, the proofs

in [5] show that the results are fundamentally based on the monotonicity framework presented in [8]. The theoretical and numerical results show that the dynamic behavior is closely related to the immune system efficiency given by f as well as the time delays. Once we have acceptable values of those two parameters we get the asymptotic and global stability independently of the initial condition and the solutions converge to the stable equilibrium under the obtained conditions.

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