

Global stability properties for a delayed virus dynamics model with humoral immunity response and absorption effect

B. G. Sampath Aruna Pradeep
Department of Mathematics,
University of Ruhuna,
Matara, Sri Lanka.
Email: sampath@maths.ruh.ac.lk

Hazrat Ali
Department of Electrical Engineering,
COMSATS Institute of Information Technology,
Abbottabad, Pakistan.
Email: hazratali@ciit.net.pk

Abstract—A model for virus infection with absorption effect and humoral immunity response consisting of system of delay differential equations has been investigated. By direct calculations, the basic number of reproduction and humoral immune-activated reproduction numbers which are also known as threshold values have been obtained. The equilibria of the proposed model, the infection free equilibrium, humoral immune-inactivated equilibrium and humoral immune-activated equilibrium which are completely based on the basic number of reproduction, and humoral immune-activated reproduction number have been found by directly solving the system. Results obtained for Lyapunov functionals and using LaSalle's invariance principle with sufficient conditions, are: (i) the infection free equilibrium satisfied the global asymptotic stability criteria if the basic reproduction number is below unity or equal to unity. (ii) the humoral immune-inactivated equilibrium is globally asymptotically stable, provided that the humoral immune-activated reproduction number is below unit or equal to unity and the basic reproduction number exceeds unity, and (iii) the humoral immune-activated equilibrium satisfies the global asymptotic stability criteria for the case when humoral immune-activated reproduction number exceeds unity.

I. INTRODUCTION

Recently, many mathematicians have investigated dynamic properties of some dangerous viruses. Such studies include the hepatitis B and C viruses (HBV and HCV), the dengue virus and

the HIV. These analysis and results give more information to drug designers to produce effective medicines or vaccines. In 1996, Nowak and Bangham [1] proposed a model which was based on ordinary differential equations to investigate the viral dynamics in vivo. Based on the model, various kinds of models emerged (see, for examples, [3], [2]) by taking the state variables $x(t)$, $y(t)$ and $v(t)$ respectively representing the concentrations of the free virus particles, infected and uninfected cells in the body at time t . Further, authors of the articles [4], [6] and [5] have used the saturation response function, the Beddington-DeAngelis functional response and the non-separable form nonlinear incidence rate function, respectively. Zhang et al. [8] have considered a model with both terms cell-to-cell transmission as well as cell-to-virus infection, and have also studies the cure rate. Guo and Ma [7] have included apoptosis effect in to a delay differential equation system expecting the model to be biologically more sensible.

It is well known that when some viruses enter into the body, the immune system is activated and respond against them. As a result, the immune response which has two main lymphocytes B and T, (are also known as humoral and cellular immunity) helps to clean the infected cells and the viruses. According to [9], for malarial infections, the humoral immunity response tends to be more effective as compared to the cellular immunity response. Authors in [10], [11], [12], [13], have reported virus dynamics models with humoral immunity response

with cellular immunity response [15] or with both [14]. It can be seen that in most of the studies, virus dynamics models have been considered ignoring the absorption effect or considering reduction of the pathogens in the blood volume due to absorption into the uninfected cells. Recently, Pradeep and Ma [18], [19] and Xu [20] have studied delayed virus dynamics models with absorption effect with nonlinear functional response. The authors have obtained rigorous global dynamical properties by defining suitable Lyapunov functions and using LaSall's invariance principle ignoring the effect of the immunity system. Motivated by the above studies, we consider adopting the delayed system:

$$\begin{cases} \dot{x}(t) = \lambda - ax(t) - \beta x(t)v(t), \\ \dot{y}(t) = \beta e^{-m\tau} x(t-\tau)v(t-\tau) - by(t), \\ \dot{v}(t) = \gamma y(t) - cv(t) - pu(t)v(t) - \beta x(t)v(t), \\ \dot{u}(t) = \delta u(t)v(t) - du(t), \end{cases} \quad (\text{I.1})$$

where $u(t)$ represents concentration of the B cells at time t and rest of state variables have the same meaning as mentioned above. Uninfected cells are recruited at rate λ . δ is the proliferate at rate contacting B cells with virus and β is the infection rate. p is the B cells neutralization rate and γ is the rate of free virus production given the infected cells. Let m be the constant death rate of the infected cells having the ability to produce viruses. Therefore, the term $e^{-m\tau}$ gives the surviving probability. τ is the time period taken by a virus to enter into uninfected cell and infects the cell and produces virus from it. The parameters defined in model (I.1) are positive, while $\tau \geq 0$.

Next, we investigate existence, non-negativity and ultimate boundedness of the solutions of model (I.1).

Let $D = D([- \tau, 0], \mathbb{R}_+^4)$ be the Banach space. The initial condition for model (I.1) can be written for $\theta \in [- \tau, 0]$,

$$\begin{aligned} x(\theta) &= \phi_1(\theta), & y(\theta) &= \phi_2(\theta), \\ v(\theta) &= \phi_3(\theta), & u(\theta) &= \phi_4(\theta) \end{aligned} \quad (\text{I.2})$$

where $\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in D$.

Theorem I.1. *Under the initial condition (I.2), the solution $(x(t), y(t), v(t), u(t))$ of model (I.1) is existent, non-negative and unique, and bounded on $[0, +\infty)$.*

Proof: The existence and uniqueness of the solution can be easily proven by using the theorems in [17]. Let us show that the boundedness and non-negativeness of the solution $(x(t), y(t), v(t), u(t))$ on $[0, b)$. Considering the model (I.1) (first equation) for $t \in [0, \tau] \cap [0, b)$, we have that

$$\begin{aligned} \dot{x}(t) &= \lambda - ax(t) - \beta x(t)v(t), \\ &\geq -(a + \beta v(t))x(t). \end{aligned}$$

Hence,

$$x(t) \geq \phi_1(0)e^{-\int_0^t (a + \beta v(s)) ds}.$$

Similarly, from model (I.1) (second equation) for $t \in [0, \tau] \cap [0, b)$, we have that

$$\begin{aligned} \dot{y}(t) &= \beta e^{-m\tau} \phi_1(t-\tau)\phi_3(t-\tau) - by(t) \\ &\geq -by(t). \end{aligned}$$

Hence,

$$y(t) \geq \phi_2(0)e^{-bt}.$$

Using similar argument, one can show that $v(t) \geq \phi_3(0)e^{-\int_0^t (c + pu(s) + \beta x(s)) ds}$ and $u(t) \geq \phi_4(0)e^{\int_0^t (\delta v(s) - d) ds}$. Hence, model (I.1) has positive solutions on $[0, b)$. Now, let us show the ultimate boundedness of the solution. Based on the first equation, one has that

$$\dot{x}(t) \leq \lambda - ax(t).$$

Hence, it has that $\limsup_{t \rightarrow +\infty} x(t) \leq \lambda/a$.

Define the following function:

$$Z(t) = x(t) + y(t + \tau).$$

From the first two equations of model (I.1), it has that

$$\dot{Z}(t) \leq \lambda - \min(a, b)Z(t).$$

Hence, it has that $\limsup_{t \rightarrow +\infty} Z(t) \leq \lambda / \min(a, b)$. From the third equation, one has that

$$\dot{v}(t) \leq \frac{\lambda \gamma}{\min(a, b)} - cv(t).$$

Hence, it has that $\limsup_{t \rightarrow +\infty} v(t) \leq \frac{\lambda \gamma}{c \min(a, b)}$.

Define the following function:

$$H(t) = \delta v(t) + pu(t).$$

From the last two equations of model (I.1), it has that

$$\dot{H}(t) \leq \delta\gamma \frac{\lambda}{c \min(a,b)} - \min(c,d)H(t).$$

Hence, it has that $\limsup_{t \rightarrow +\infty} H(t) \leq \delta\gamma\lambda / (c \min(a,b) \cdot \min(c,d))$. Therefore, it has from solutions for functional differential equations (based on the continuation theorem), that the solution $(x(t), y(t), v(t), \text{ and } u(t))$ is existent, non-negative and unique, and bounded on $[0, +\infty)$. ■

Model (I.1) always gives an infection free equilibrium, $E_0(x_0 = \lambda/a, 0, 0, 0)$. The basic reproduction number for model (I.1) can be found as

$$R_0 = \frac{\beta\lambda\gamma e^{-m\tau}}{b(\beta\lambda + ac)}.$$

Then, there exists an infected with humoral immunity inactivated equilibrium $E_1(x_1, y_1, v_1, 0)$, such that;

$$v_1 = \frac{(\beta\lambda + ac)(R_0 - 1)}{c\beta}, \quad x_1 = \frac{cb}{\beta(\gamma e^{-m\tau} - b)},$$

$$y_1 = \frac{\beta e^{-m\tau} x_1 v_1}{b}.$$

The humoral immune-activated reproduction number of model (I.1) can be found as

$$R_1 = \frac{\delta\beta\lambda\gamma e^{-m\tau}}{b[(\beta\lambda + ac)\delta + c\beta d]}.$$

There exists an infected with humoral immunity activated equilibrium $E_2(x_2, y_2, v_2, u_2)$ where

$$v_2 = \frac{d}{\delta}, \quad y_2 = \frac{\beta e^{-m\tau} x_2 d}{b\delta},$$

$$x_2 = \frac{\lambda\delta}{\beta d + a\delta}, \quad u_2 = \frac{(\beta\lambda + ac)\delta + c\beta d}{p(\beta d + a\delta)} (R_1 - 1).$$

Next, let us investigate the stability properties of the equilibria. In this study, we have not given the local stability properties because the global stability properties are stronger than the local stability properties. In [16], the author has given a method to find appropriate Lyapunov function which can be helpful for investigation of the global properties of a basic virus dynamic model. In this study, we extend those results by using similar type of Lyapunov functions.

Theorem I.2. *If $R_0 \leq 1$, the infection free equilibrium, E_0 satisfies the global asymptotic stability criteria.*

Proof: Case I: Let us first take $\gamma e^{-m\tau} - b > 0$. Define,

$$M_{10} = V_{10} + \frac{\gamma}{\gamma e^{-m\tau} - b} y + \frac{b}{\gamma e^{-m\tau} - b} v$$

$$+ \frac{p\gamma}{\delta(\gamma e^{-m\tau} - b)} u + \frac{\beta\gamma e^{-m\tau}}{\gamma e^{-m\tau} - b} U_{10}.$$

where

$$V_{10} = x - x_0 - x_0 \ln \frac{x}{x_0}.$$

$$\dot{V}_{10} = \left(1 - \frac{x_0}{x}\right) (\lambda - ax(t) - \beta x(t)v(t)),$$

$$= ax_0 \left(2 - \frac{x_0}{x} - \frac{x}{x_0}\right) - \beta x_0 v_0 \left(\frac{xv}{x_0 v_0} - \frac{v}{v_0}\right),$$

and

$$U_{10} = \int_{-\tau}^0 x(t+s)v(t+s)ds,$$

$$\dot{U}_{10} = x(t)v(t) - x(t-\tau)v(t-\tau).$$

By taking the derivative of $M_{10}(t)$, we have that

$$\dot{M}_{10} = \dot{V}_{10} + \frac{\gamma}{\gamma e^{-m\tau} - b} \dot{y} + \frac{b}{\gamma e^{-m\tau} - b} \dot{v}$$

$$+ \frac{p\gamma}{\delta(\gamma e^{-m\tau} - b)} \dot{u} + \frac{\beta\gamma e^{-m\tau}}{\gamma e^{-m\tau} - b} \dot{U}_{10}$$

$$= ax_0 \left(2 - \frac{x_0}{x} - \frac{x}{x_0}\right) - \frac{dp\gamma}{\delta(\gamma e^{-m\tau} - b)} u$$

$$+ \frac{(\beta\lambda + ac)b}{a(\gamma e^{-m\tau} - b)} (R_0 - 1).$$

The derivative is taken along the positive solutions of model (I.1).

The term $2 - x_0/x - x/x_0$ is always negative when $x \neq x_0$ while equal to zero when $x = x_0$.

If $R_0 \leq 1$, one can see that $\dot{M}_{10} \leq 0$, for $t > 0$. It implies that E_0 is stable. Further, $\dot{M}_{10} = 0$ if $(x, y, v, u) = E_0$. That is, E_0 satisfies the global asymptotic stability criteria (by LaSalle's invariance principle)[17].

Case II: Again, let us take $\gamma e^{-m\tau} - b \leq 0$.

Define

$$M_{11} = y + \frac{b}{\gamma} v + \frac{pb}{\delta\gamma} u$$

$$+ \beta e^{-m\tau} \int_{-\tau}^0 x(t+\theta)v(t+\theta)d\theta.$$

By taking the derivative of $M_{11}(t)$ along the positive solutions of model (I.1), we have that

$$\begin{aligned} \dot{M}_{11} &= [\beta e^{-m\tau} x(t-\tau)v(t-\tau) - by] \\ &\quad + \frac{b}{\gamma}[\gamma y - cv - puv - \beta xv] \\ &\quad + \frac{pb}{\delta\gamma}[\delta uv - du] \\ &\quad + \beta e^{-m\tau} [xv - x(t-\tau)v(t-\tau)], \\ &= \frac{\beta}{\gamma}(\gamma e^{-m\tau} - b)xv - \frac{bc}{\gamma}v - \frac{pbd}{\delta\gamma}u. \end{aligned}$$

If $\gamma e^{-m\tau} \leq b$, one can see that $\dot{M}_{11} \leq 0$, for $t > 0$, and E_0 is stable. Further, $\dot{M}_{11} = 0$ if $(x, y, v, u) = E_0$. That is, E_0 satisfies the global asymptotic stability criteria [17]. ■

Note: Consider the function $G(t) = 1 - f(t) - \ln f(t)$, where $f(t) > 0$, for all $t > 0$. Then, function $G(t)$ has the properties, (i) $G(t)$ is always negative and (ii) $G(t) = 0$ if and only if $f(t) = 0$.

Remark: We use the notations x_τ instead of $x(t-\tau)$ and v_τ instead of $v(t-\tau)$ for reducing excess use of brackets.

Theorem I.3. *If $R_1 \leq 1 < R_0$ and $a(\gamma e^{-m\tau} - b) \geq b\beta v_1$ hold, the infected with humoral immunity inactivated equilibrium E_1 satisfied the global asymptotic stability criteria.*

Proof: Define,

$$\begin{aligned} M_{20} &= x - x_1 - x_1 \ln \frac{x}{x_1} \\ &\quad + \frac{m_2\gamma}{b} \left(y - y_1 - y_1 \ln \frac{y}{y_1} \right) \\ &\quad + m_2 \left(v - v_1 - v_1 \ln \frac{v}{v_1} \right) \\ &\quad + \frac{m_2 p}{\delta} u + \frac{m_2 \gamma \beta e^{-m\tau}}{b} U_{20}, \end{aligned}$$

where

$$U_{20} = \int_{t-\tau}^t [x(\theta)v(\theta) - x_1 v_1 - x_1 v_1 \ln x(\theta)v(\theta)] d\theta,$$

and $m_2 = b/(\gamma e^{-m\tau} - b)$.

By taking the derivative of $M_{20}(t)$ (The derivative is taken along the positive solutions of model

(I.1)), we have that

$$\begin{aligned} \dot{M}_{20} &= \left(1 - \frac{x_1}{x}\right) (\lambda - ax - \beta xv) \\ &\quad + \frac{m_2\gamma}{b} \left(1 - \frac{y_1}{y}\right) (\beta e^{-m\tau} x_\tau v_\tau - by) \\ &\quad + m_2 \left(1 - \frac{v_1}{v}\right) (\gamma y - cv - puv - \beta xv) \\ &\quad + \frac{m_2 p}{\delta} (\delta uv - du) \\ &\quad + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left[xv - x_\tau v_\tau + x_1 v_1 \ln \frac{x_\tau v_\tau}{xv} \right]. \end{aligned}$$

By substituting the values at the relevant equilibrium point, $\lambda = ax_1 + \beta x_1 v_1$, $cm_2 = \beta x_1$ and $by_1 = \beta e^{-m\tau} x_1 v_1$, one has that

$$\begin{aligned} \dot{M}_{20} &= ax_1 \left(2 - \frac{x_1}{x} - \frac{x}{x_1}\right) \\ &\quad + \beta x_1 v_1 \left(2 - \frac{x_1}{x} + m_2 \frac{x}{x_1}\right) \\ &\quad + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(1 - \frac{x_\tau v_\tau y_1}{x_1 v_1 y} + \ln \frac{x_\tau v_\tau y_1}{x_1 v_1 y}\right) \\ &\quad + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(1 - \frac{v_1 y}{v y_1} + \ln \frac{v_1 y}{v y_1}\right) \\ &\quad + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(1 - \frac{x_1}{x} + \ln \frac{x_1}{x}\right) \\ &\quad + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(\frac{x_1}{x} - 2\right) + m_2 p \left(v_1 - \frac{d}{\delta}\right) u, \\ &= x_1 \left(a - \frac{b\beta v_1}{\gamma e^{-m\tau} - b}\right) \left(2 - \frac{x_1}{x} - \frac{x}{x_1}\right) \\ &\quad + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(1 - \frac{x_\tau v_\tau y_1}{x_1 v_1 y} + \ln \frac{x_\tau v_\tau y_1}{x_1 v_1 y}\right) \\ &\quad + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(1 - \frac{v_1 y}{v y_1} + \ln \frac{v_1 y}{v y_1}\right) \\ &\quad + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(1 - \frac{x_1}{x} + \ln \frac{x_1}{x}\right) \\ &\quad + \frac{m_2 p [\delta(\beta\lambda + ac) + cd\beta]}{c\beta\delta} (R_1 - 1) u. \end{aligned}$$

If $R_1 \leq 1 < R_0$ and $a(\gamma e^{-m\tau} - b) \geq b\beta v_1$, one can see that $\dot{M}_{20} \leq 0$, for $t > 0$. It implies that the infected with humoral immunity inactivated equilibrium E_1 is stable. Further, $\dot{M}_{20} = 0$ if $(x, y, v, u) = E_1$. That is, the infected with humoral immunity

inactivated equilibrium E_1 globally asymptotically stable [17]. ■

Theorem I.4. *If $1 < R_1$ and $a(\gamma e^{-m\tau} - b) \geq \beta v_2 b$ hold, the infected with humoral immunity activated equilibrium E_2 is globally asymptotically stable.*

Proof: Defining the function for M_{30} ,

$$\begin{aligned} M_{30} = & x - x_2 - x_2 \ln \frac{x}{x_2} \\ & + \frac{m_2 \gamma}{b} \left(y - y_2 - y_2 \ln \frac{y}{y_2} \right) \\ & + m_2 \left(v - v_2 - v_2 \ln \frac{v}{v_2} \right) \\ & + \frac{m_2 p}{\delta} \left(u - u_2 - u_2 \ln \frac{u}{u_2} \right) \\ & + \frac{m_2 \gamma \beta e^{-m\tau}}{b} U_{30}, \end{aligned}$$

where

$$U_{30} = \int_{t-\tau}^t [x(\theta)v(\theta) - x_2 v_2 - x_2 v_2 \ln x(\theta)v(\theta)] d\theta.$$

By taking the derivative of $M_{30}(t)$ (along the positive solutions of model (I.1)), we have that

$$\begin{aligned} \dot{M}_{30} = & \left(1 - \frac{x_2}{x}\right) (\lambda - ax - \beta xv) \\ & + \frac{m_2 \gamma}{b} \left(1 - \frac{y_2}{y}\right) (\beta e^{-m\tau} x_\tau v_\tau - by) \\ & + m_2 \left(1 - \frac{v_2}{v}\right) (\gamma y - cv - puv - \beta xv) \\ & + \frac{m_2 p}{\delta} \left(1 - \frac{u_2}{u}\right) (\delta uv - du) \\ & + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left[xv - x_\tau v_\tau + x_2 v_2 \ln \frac{x_\tau v_\tau}{xv} \right]. \end{aligned}$$

At the infected with humoral immunity activated equilibrium E_2 from model (I.1), it has that $\lambda = ax_2 + \beta x_2 v_2$, $c = \gamma \beta x_2 e^{-m\tau} / b - pu_2 - \beta x_2$, $by_2 = \beta e^{-m\tau} x_2 v_2$. By substituting these values into above equation, it has that

$$\begin{aligned} \dot{M}_{30} = & ax_2 \left(2 - \frac{x_2}{x} - \frac{x}{x_2}\right) \\ & + \beta x_2 v_2 \left(1 - \frac{x_2}{x} + m_2 \frac{x}{x_2} + \frac{m_2 \gamma e^{-m\tau}}{b} + \frac{v}{v_2} \right. \\ & \left. - m_2 + m_2 \frac{v}{v_2} - \frac{m_2 \gamma e^{-m\tau}}{b} \frac{v}{v_2}\right) \\ & + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(1 - \frac{x_\tau v_\tau y_2}{x_2 v_2 y} + \ln \frac{x_\tau v_\tau y_2}{x_2 v_2 y}\right) \\ & + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(1 - \frac{v_2 y}{v y_2} + \ln \frac{v_2 y}{v y_2}\right) \\ & + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(1 - \frac{x_2}{x} + \ln \frac{x_2}{x}\right) \\ & + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(\frac{x_2}{x} - 2\right), \\ = & x_2 \left(a - \frac{\beta v_2 b}{\gamma e^{-m\tau} - b}\right) \left(2 - \frac{x_2}{x} - \frac{x}{x_2}\right) \\ & + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(1 - \frac{x_\tau v_\tau y_2}{x_2 v_2 y} + \ln \frac{x_\tau v_\tau y_2}{x_2 v_2 y}\right) \\ & + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(1 - \frac{v_2 y}{v y_2} + \ln \frac{v_2 y}{v y_2}\right) \\ & + \frac{m_2 \gamma \beta e^{-m\tau}}{b} \left(1 - \frac{x_2}{x} + \ln \frac{x_2}{x}\right). \end{aligned}$$

If $1 < R_1$ and $a(\gamma e^{-m\tau} - b) \geq \beta v_2 b$, one can see that $\dot{M}_{30} \leq 0$, for $t > 0$. It implies that the infected with humoral immunity activated equilibrium E_2 is stable. Further, $\dot{M}_{30} = 0$ if $(x, y, v, u) = E_2$. That is, the infected with humoral immunity activated equilibrium E_2 globally asymptotically stable [17]. ■

II. CONCLUSION

In this study, we proposed and investigated the stability behavior of a delayed virus dynamic model with absorption effect and humoral immunity response. It can be concluded that the global dynamics properties are completely based on the two threshold parameters R_0 and R_1 . From the results given in Theorem 1.2, if the basic reproduction number, which depends on negative exponential on the inter-cellular time delay is below unity or approaches unity, then the infection free equilibrium satisfied the global asymptotic stability criteria. The viruses are cleaned from the body and

the individual is not infected with virus disease. If the time delays can be increased by some drug therapies, it is possible to control the disease. According to the results given in Theorem 1.3, if the number of humoral immunity response reproduction is below unity or approaches unity and the basic reproduction number is greater than one, the infected with humoral immunity inactivated equilibrium satisfied the global asymptotic stability criteria. R_1 is also depended on negative exponential on the inter-cellular time, which means that it is impossible to clear out the viruses from the body even if the inter-cellular time is increased. It is conjectured that the infected with humoral immunity inactivated equilibrium and the infected with humoral immunity activated equilibrium should be globally asymptotically stable without any additional condition. However, we have technical problem to prove the global stability properties without these additional conditions. We leave it as an open problem to for future study. Further, the system has not occurred Hopf bifurcations although time delay is involved, by changing the stability behavior at the equilibria.

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