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Generalized Viral Infection Model with Caputo Fractional Derivative, Cure Rate and Humoral Immunity

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Abstract. Infectious diseases pose a significant threat to global health, and mathematical modeling can be highly useful for understanding their transmission dynamics. Fractional differential equations have emerged as a powerful tool for modeling complex systems with memory and long-term interactions. In this paper, we provide a mathematical model of generalized viral infection with cure rate via FDEs. The basic reproduction number will be obtained and positivity and uniformly boundedness of solutions will be controlled. Three equilibrium points: infection-free equilibrium, immune-free equilibrium and chronic equilibrium, will also be calculated. It will be shown that the infection-free equilibrium is globally asymptotically stable if the reproduction number is less than one and if it is more than one, within certain conditions on humoral immune response reproduction rate, then the immune-free and the chronic equilibria are globally asymptotically stable. Finally, numerical simulations will be presented to establish the analytical calculations.

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1 Introduction

After the recent COVID-19 pandemic, the importance of studying infectious diseases and epidemics have been more and more noticed. Over the years, the human race has been repeatedly harmed by various pathogens. A wide range of new and historical infectious diseases in five time periods have been proposed in [27]. Mathematical modeling of infectious diseases is a powerful tool for understanding the nature of the pathogen, its mechanism of action and predicting its behavior. In fact, with the help of different types of differential equations, by adding different therapeutic and biological parameters, we can study and model many cases of infectious diseases such as the effect of medicine, the immune system, etc.

Fractional differential equations (FDEs) have been widely used in mathematical modeling of infectious diseases for their ability to model complex phenomena. FDEs are differential equations that involve fractional derivatives, which can capture non-local and memory effects in the dynamics of infectious diseases. These equations are particularly useful in modeling the spread of infectious diseases with long-range interactions, such as the spread of epidemics in populations with heterogeneous mixing patterns. In infectious disease modeling, FDEs have been used to describe the dynamics of disease transmission, incorporating factors such as spatial heterogeneity, population structure, and non-Markovian behavior (Markovian behavior is memoryless. It means future events only depend on the current situation and past events have no effect on it. On the other hand, in non-Markovian behavior, in addition to the current situation, past events also affect future events).

The application of diverse fractional equations to model physical and biological phenomena has grown considerably in recent years. Substantial research efforts have been devoted to key areas, including integro-differential equations [2, 4, 6, 19, 28], fractional differential inclusion systems [8], the KdV equation [1], vehicular traffic flow [10] and epidemiological models [22].

Numerical methods, such as the fractional order Euler method and the fractional order Runge-Kutta method have been employed to solve FDEs in infectious disease modeling. These methods allow for the efficient and accurate solution of FDEs, enabling researchers to better understand the dynamics of infectious diseases and to make more informed decisions regarding disease control and prevention strategies. Overall, FDEs have proven to be a valuable tool in the mathematical modeling of infectious diseases, providing a more comprehensive understanding of disease dynamics and aiding in the development of effective strategies for disease control and prevention.

Various infectious diseases such as COVID-19 [3, 15, 21, 23], HBV [5], HCV [25] , HIV [13, 17, 18, 26], and other kind of problems like Cancer [7, 14],

Diabetes [9] and heart attacks [24] have been investigated by mathematical modeling with FDEs. In [22], the authors collected all the recent studies based on the fractional models of different types of diseases with various fractional operators such as Caputo, Caputo Fabrizio, ABC, and constant proportional with Caputo, etc.

Applying a suitable Lyapunov function, Karaman in [16] investigated the global stability of a fractional-order Hepatitis B virus infection model. The authors of [29] extended a Caputo fractional order SICA model of HIV. They proved the local and uniform asymptotic stability of the disease-free equilibrium and uniform asymptotic stability of endemic equilibrium. Then, they established a numerical simulation to illustrate the theoretical results.

In this paper, we provide a general viral infection model by applying the Caputo fractional derivative as

$$\begin{aligned} D^{\beta}x(t) &= \lambda - dx - vf(x,v) - yg(x,y) + \alpha y, \\ D^{\beta}y(t) &= vf(x,v) + yg(x,y) - ay - \alpha y, \\ D^{\beta}v(t) &= ky - uv - qvw, \\ D^{\beta}w(t) &= gvw - hw. \end{aligned} \tag{1}$$

Here, x, y, v and w indicate the number of target cells or uninfected cells, infected cells, the virus and B lymphocytes cells (antibody response), respectively. In (1), $\beta \in (0,1)$ and functions $f(x,v)$ and $g(x,y)$ describe virus to cell and cell to cell transmission, respectively. Furthermore, the incidence functions $f(x,v)$ and $g(x,y)$ are assumed to be in $\mathbf{C}^1(\mathbb{R}^2_+)$ and satisfy the following properties:

$$\begin{aligned} &(\mathbf{A_1})\ f(0,v) = 0,\ \textit{for all } v \geq 0 \textit{ and } g(0,y) = 0,\ \textit{for all } y \geq 0, \\ &(\mathbf{A_2})\ \frac{\partial f}{\partial x}(x,v) > 0 \textit{ and } \frac{\partial g}{\partial x}(x,y) > 0,\ \textit{for all } x > 0,\ y \geq 0 \textit{ and } v \geq 0, \\ &(\mathbf{A_3})\ \frac{\partial f}{\partial v}(x,v) \leq 0 \textit{ and } \frac{\partial g}{\partial y}(x,y) \leq 0,\ \textit{for all } x \geq 0,\ y \geq 0 \textit{ and } v \geq 0. \end{aligned}$$

In this work, the results of [11, 12, 25, 31] will be generalized and improved. The authors of [11, 12, 25, 31] analyzed systems formulated using ordinary derivatives. System (1) in the present work generalizes these previous models:

- When $f(x,v) = \beta_1 x$ and $g(x,y) = \beta_2 x$, System (1) reduces to the model presented in [25]. That study established the global dynamics using Lyapunov's second method and LaSalle's invariance principle.
- If $g(x,y) = 0$ and the humoral immunity term is absent ($w = 0$), System (1) simplifies to the models studied in [12, 31]. The global stability of the

Table 1: Biological interpretation of variables and parameters in system (1)

Variable/Parameter	Description
$x(t)$	Concentrations of uninfected target cells at time t
$y(t)$	Concentrations of infected cells at time t
$v(t)$	Concentrations of viruses at time t
$w(t)$	Concentrations of antibody cells at time t
λ	Source rate of host cells
d	Decay rate of healthy cells
α	Cure rate of infected cells
a	Death rate of infected cells
k	Virion production rate
u	Death rate of virus
q	Clearance rate of virus
g	Activation rate of antibody cells
h	Death rate of antibody cells

endemic equilibrium in those works was proven by precluding periodic solutions and applying the Poincaré–Bendixson theorem for competitive systems, which required additional hypotheses on the functions and parameters.

- Similarly, by setting $w = 0$, System (1) becomes equivalent to the model in [11]. The global dynamics of its rest points were analyzed using the same methods as in [12, 31].

In our study, the results about the global stability of the model will be given with fewer assumptions and are more accurate.

The Caputo fractional derivative of order β of a function $f \in \mathbb{C}^n$ is given by

$$D^{\beta} f(t) = \frac{1}{\Gamma(n-\beta)} \int_a^t \frac{f^{(n)}(s)}{(t-s)^{\beta+1-n}} ds, \quad n-1 < \beta < n,$$

with $n \in \mathbb{N}$, $\beta, a, t \in \mathbb{R}$, $a > 0$ and $t > a$.

In the following lemma, a Volterra-type Lyapunov function is obtained for fractional-order epidemic systems ([32]). Applying this lemma, the global stability of equilibria will be proven in Section 3.

Lemma 1.1. *Let $X(.)$ be a continuous and differentiable function with $X(t) \in \mathbb{R}_{\geq 0}$. Then, for any time instant $t \geq t_0$, one has*

$$D^{\beta}\left[X(t) - X^* - X^* \ln \frac{X(t)}{X^*}\right] \leq \left(1 - \frac{X^*}{X(t)}\right) D^{\beta} X(t), \qquad X^* \in \mathbb{R}_{\geq 0}, \qquad \forall \beta \in (0,1).$$

The paper is organized as follows. In Section 2 some basic properties of the model such as positivity and boundedness of solutions will be given and after obtaining the basic reproduction number, the conditions for the existence of equilibrium points are stated. In Section 3 , some stability analyses of the infection-free equilibrium, immune-free equilibrium and chronic equilibrium are presented. We propose some numerical simulations to confirm of theoretical results in Section 4 and in the last section, a discussion about the results will be given.

2 Basic Properties of Model

In this section, some properties about the solutions of (1) will be presented. By the similar arguments in [13], the boundedness and positivity of solutions will be shown. The equilibrium points and reproduction numbers will also be calculated.

Proposition 2.1. *The solutions of system (1) are positive and uniformly bounded for all $t > 0$.*

If $v = 0$, then $y = 0$ and $w = 0$. In this situation, system has the infection-free equilibrium $\mathbf{E_0} = (x_0, 0, 0, 0) = \left(\frac{\lambda}{d}, 0, 0, 0\right)$. To obtain the basic reproduction number, the next generation matrix method will be applied. Consider the equations associated with the infection

$$D^{\beta} y(t) = v f(x,v) + y g(x,y) - ay - \alpha y = \mathbf{A}_1 - \mathbf{B}_1,$$
$$D^{\beta} v(t) = ky - uv - qvw = \mathbf{A}_2 - \mathbf{B}_2,$$

where $\mathbb{A}_1 = v f(x,v) + y g(x,y)$, $\mathbb{B}_1 = ay + \alpha y$, $\mathbb{A}_2 = 0$ and $\mathbb{B}_2 = qvw + uv - ky$. Therefore,

$$\mathbf{F} = \begin{pmatrix} \frac{\partial \mathbb{A}_1}{\partial y}(\mathbf{E_0}) & \frac{\partial \mathbb{A}_1}{\partial v}(\mathbf{E_0}) \\ \\ \frac{\partial \mathbb{A}_2}{\partial y}(\mathbf{E_0}) & \frac{\partial \mathbb{A}_2}{\partial v}(\mathbf{E_0}) \end{pmatrix} = \begin{pmatrix} g(x_0,0) & f(x_0,0) \\ \\ 0 & 0 \end{pmatrix},$$

$$\mathbf{V} = \begin{pmatrix} \frac{\partial \mathbb{B}_1}{\partial y}(\mathbf{E_0}) & \frac{\partial \mathbb{B}_1}{\partial v}(\mathbf{E_0}) \\ \frac{\partial \mathbb{B}_2}{\partial y}(\mathbf{E_0}) & \frac{\partial \mathbb{B}_2}{\partial v}(\mathbf{E_0}) \end{pmatrix} = \begin{pmatrix} a+\alpha & 0 \\ -k & u \end{pmatrix}.$$

The basic reproduction number is given by $\mathbf{R_0} = \rho(\mathbf{FV^{-1}})$, where $\rho(\mathbb{M})$ is the spectral radius of the matrix $\mathbb{M}$. In this case

$$\mathbf{R_0} = \frac{k}{(a+\alpha)u} f(x_0, 0) + \frac{1}{a+\alpha} g(x_0, 0) = \mathbf{R_{01}} + \mathbf{R_{02}}.$$

To Find the other rest points of (1), by attention to the equilibrium conditions, we have

$$w = 0 \quad or \quad w = \frac{h}{g}.$$

We have the following cases:
Case 1: If $w = 0$, then from system (1) it can be written that

$$v_1 = \frac{k}{u} y_1, \quad y_1 = \frac{1}{a}(\lambda - dx_1)$$

where $0 < x_1 < x_0$. Using the second equation of (1) and equilibrium conditions, the following function on interval $[0, x_0]$ can be defined:

$$\mathbf{H}(x) = \frac{k}{au} f\left(x, \frac{k}{au}(\lambda - dx)\right) + \frac{1}{a} g\left(x, \frac{1}{a}(\lambda - dx)\right) - \frac{a+\alpha}{a}.$$

Therefore, from $(\mathbf{A_1})$

$$\begin{aligned} \mathbf{H}(0) &= -\frac{a+\alpha}{a} < 0, \\ \mathbf{H}(x_0) &= \frac{a+\alpha}{a}\left(\frac{k}{(a+\alpha)u} f(x_0, 0) + \frac{1}{a+\alpha} g(x_0, 0) - 1\right) \\ &= \frac{a+\alpha}{a}(\mathbf{R_0} - 1). \end{aligned}$$

If $\mathbf{R_0} > 1$, then $\mathbf{H}(x)$ has at least one root in $[0, x_0]$. Note that

$$\mathbf{H}'(x) = \frac{k}{au}\left(\frac{\partial f}{\partial x} - \frac{kd}{au}\frac{\partial f}{\partial v}\right) + \frac{1}{a}\left(\frac{\partial g}{\partial x} - \frac{d}{a}\frac{\partial g}{\partial y}\right).$$

From $(\mathbf{A_2})$ and $(\mathbf{A_3})$, it can be concluded that $\mathbf{H}'(x) > 0$. Thus, if $\mathbf{R_0} > 1$, then (1) has a unique immune-free equilibrium $\mathbf{E_1} = (x_1, y_1, v_1, 0)$ with $0 < x < x_0$, $y_1 = \frac{1}{a}\left(\lambda - dx_1\right)$, $v_1 = \frac{k}{u} y_1$ and $w_1 = 0$.

Remark 2.2. By attention to the above argument, it is easy to see that if $\mathbf{R_0} < 1$, then $\mathbf{H}(x_0) < 0$. Hence, there is no positive equilibrium with $0 < x < x_0$. If $\mathbf{R_0} = 1$, then $\mathbf{H}(x_0) = 0$ and $\mathbf{E_0} = \mathbf{E_1}$

Case 2: Now assume that $w \neq 0$. Thus, $v = \dfrac{h}{g}$. From equilibrium conditions,

$$y = \frac{1}{a}\Big(\lambda - dx\Big),$$
$$w = \frac{g}{hq}\left[\frac{k}{a}\Big(\lambda - dx\Big) - \frac{uh}{g}\right].$$

Since $w > 0$, we have

$$\frac{k}{a}\Big(\lambda - dx\Big) - \frac{uh}{g} > 0,$$

which implies that

$$0 < x < \frac{\lambda}{d} - \frac{auh}{kdg} = \bar{x}.$$

In addition to $\mathbf{R_0}$, we need another threshold number ($\mathbf{R_{Hom}}$) which is called humoral immune response reproduction rate. As in [13], $\mathbf{R_{Hom}}$ has the following definition

$$\mathbf{R_{Hom}} = \frac{gv_1}{h}.$$

This number shows the threshold level of virus which is required to initiate the antibody cells response. By the second equation of (1) and equilibrium conditions, we can define the following function on interval $[0, \bar{x}]$:

$$\mathbf{J}(x) = \frac{h}{g}f\Big(x, \frac{h}{g}\Big) + \frac{1}{a}\Big(\lambda - dx\Big)g\Big(x, \frac{1}{a}(\lambda - dx)\Big) - \frac{a+\alpha}{a}\Big(\lambda - dx\Big).$$

It is clear that, $\mathbf{J}(0) = -\dfrac{a+\alpha}{a}\lambda < 0$. If $\mathbf{R_{Hom}} < 1$, then $v_1 < \dfrac{h}{g}$, $y_1 < \dfrac{uh}{kg}$ and $x_1 > \bar{x}$. Therefore,

$$\mathbf{J}(\bar{x}) < \frac{h}{g}\left(f(x_1, v_1) + \frac{u}{k}g(x_1, y_1) - (\alpha + a)\frac{u}{k}\right) = 0.$$

Hence, if $\mathbf{R_{Hom}} < 1$, then chronic equilibrium $\mathbf{E_2}$ dose not exist. Now, assume that $\mathbf{R_{Hom}} > 1$. In this case, $v_1 > \dfrac{h}{g}$, $y_1 > \dfrac{uh}{kg}$ and $x_1 < \bar{x}$. Therefore,

$$\mathbf{J}(\bar{x}) > \frac{h}{g}\left(f(x_1, v_1) + \frac{u}{k}g(x_1, y_1) - (\alpha + a)\frac{u}{k}\right) = 0.$$

Thus, it can be concluded that function $\mathbf{J}$ has roots in $[0, \bar{x}]$. Also,

$$\mathbf{J}'(x) = \frac{h}{g}\frac{\partial f}{\partial x} + \frac{1}{a}(\lambda - dx)\left(\frac{\partial g}{\partial x} - \frac{d}{a}\frac{\partial g}{\partial y}\right) - \frac{d}{a}\mathbf{S}(x)$$

where

$$\mathbf{S}(x) = g\left(x, \frac{1}{a}(\lambda - dx)\right) - (\alpha + a).$$

$\mathbf{S}(x)$ satisfies the following conditions,

$$\begin{aligned} &\mathbf{S}(0) = -(\alpha + a) < 0, \\ &\mathbf{S}(\bar{x}) = g\left(\bar{x}, \frac{uh}{kg}\right) - (\alpha + a), \\ &\mathbf{S}'(x) = \frac{\partial g}{\partial x} - \frac{d}{a}\frac{\partial g}{\partial y} > 0. \end{aligned} \tag{2}$$

By attention to (2), if $\mathbf{S}(\bar{x}) < 0$, then $\mathbf{S}(x) < 0$. From $(\mathbf{A_2})$ and $(\mathbf{A_3})$, it can be concluded that $\mathbf{J}'(x) > 0$. Thus, if $\mathbf{R_0} > 1$ and $\mathbf{R_{Hom}} > 1$ and $\mathbf{S}(\bar{x}) < 0$, then (1) has a unique chronic equilibrium $\mathbf{E_2} = (x_2, y_2, v_2, w_2)$ with $0 < x_2 < \bar{x}$, $y_2 = \frac{1}{a}\left(\lambda - dx_2\right)$, $v_2 = \frac{h}{g}$ and $w_2 = \frac{g}{hq}\left[\frac{k}{a}\left(\lambda - dx_2\right) - \frac{uh}{g}\right]$.

Remark 2.3. If we consider $g(x, y)$ as famous incidence functions such as mass action, saturated mass action, Beddington-DeAngelis and Crowley-Martin, then the condition $\mathbf{S}(\bar{x}) < 0$ can be written as an inequality which depends on $\bar{x}$ with upper bound $\hat{x}$. Therefore, for the uniqueness of chronic equilibrium $\mathbf{E_2}$, we assume that the range of uninfected target cells (x) is in the interval $[0, \min\{\bar{x}, \hat{x}\}]$.

3 Sensitivity Analysis of $\mathbf{R_0}$

To obtain the sensitivity analysis of $\mathbf{R_0}$, we use the partial derivative of $\mathbf{R_0}$ with respect to parameters. We have the relations $f(x_0, 0) > 0$ and $g(x_0, 0) > 0$.

Also, all parameters of system (1) are positive. Hence, it can be written that

$$\begin{aligned}
\frac{\partial \mathbf{R_0}}{\partial k} &= \frac{f(x_0,0)}{(a+\alpha)u} > 0,\\
\frac{\partial \mathbf{R_0}}{\partial a} &= -\frac{ku}{(a+\alpha)^2u^2}f(x_0,0) - \frac{1}{(a+\alpha)^2}g(x_0,0) < 0,\\
\frac{\partial \mathbf{R_0}}{\partial \alpha} &= -\frac{ku}{(a+\alpha)^2u^2}f(x_0,0) - \frac{1}{(a+\alpha)^2}g(x_0,0) < 0,\\
\frac{\partial \mathbf{R_0}}{\partial u} &= -\frac{k}{(a+\alpha)u^2} < 0.
\end{aligned}$$

By above relations, it can be concluded that $\mathbf{R_0}$ increases with k and decreases with a, α, u.

In the special cases for $f(x,v)$ and $g(x,y)$, the other relations about the sensitivity analysis of $\mathbf{R_0}$ with respect to the new parameters can be added. In Section 5, this work will be shown.

4 Global Stability

In this section, by applying suitable Lyapunov functions the global stability of infection-free equilibrium, immune-free equilibrium and chronic equilibrium will be presented. First, the global stability of infection-free equilibrium $\mathbf{E_0}$ will be shown.

Theorem 4.1. *If $\mathbf{R_0} \leq 1$, then infection-free equilibrium $\mathbf{E_0}$ is globally asymptotically stable.*

Proof. Consider the following Lyapunov function:

$$\begin{aligned}
\mathbf{L_0}(x,y,z) = x - x_0 - x_0 \ln\left(\frac{x}{x_0}\right) + y + \frac{f(x_0,0)}{u}v + \frac{qf(x_0,0)}{gu}w\\
+ \frac{\alpha}{2(a+d)x_0}(x - x_0 + y)^2.
\end{aligned}$$

Computing the time derivative of $\mathbf{L_0}$ along the solution of (1) and using Lemma 1.1, we have

$$\begin{aligned} D^\beta \mathbf{L_0} &\leq \left(1-\frac{x_0}{x}\right)D^\beta x + D^\beta y + \frac{f(x_0,0)}{u}D^\beta v + \frac{qf(x_0,0)}{gu}D^\beta w \\ &\quad + \frac{\alpha}{(a+d)x_0}(x-x_0+y)(D^\beta x + D^\beta y) \\ &= \left(1-\frac{x_0}{x}\right)(\lambda - dx - vf(x,v) - yg(x,y) + \alpha y) \\ &\quad + (vf(x,v) + yg(x,y) - ay - \alpha y) + \frac{f(x_0,0)}{u}(ky - uv - qvw) \\ &\quad + \frac{qf(x_0,0)}{gu}(gvw - hw) + \frac{\alpha}{(a+d)x_0}(x-x_0+y)(\lambda - dx - ay). \end{aligned}$$

From equilibrium conditions we have $\lambda = dx_0$. Therefore,

$$\begin{aligned} D^\beta \mathbf{L_0} &\leq \left(1-\frac{x_0}{x}\right)[-vf(x,v) - yg(x,y) - d(x-x_0) + \alpha y] \\ &\quad + (vf(x,v) + yg(x,y) - ay - \alpha y) + \frac{f(x_0,0)}{u}(ky - uv - qvw) \\ &\quad + \frac{qf(x_0,0)}{gu}(gvw - hw) - \frac{\alpha}{(a+d)x_0}[(x-x_0+y][ay + d(x-x_0)]. \end{aligned}$$

On the other hand,

$$\alpha\left(1-\frac{x_0}{x}\right)y = -\alpha y\frac{(x-x_0)^2}{xx_0} + \frac{\alpha}{x_0}(x-x_0)y.$$

Thus, we have

$$\begin{aligned} D^\beta \mathbf{L_0} &\leq -\left(dx_0 + \alpha y + \frac{\alpha dx}{a+d}\right)\frac{(x-x_0)^2}{xx_0} - \frac{a\alpha y^2}{(a+d)x_0} \\ &\quad - \frac{qhf(x_0,0)}{gu}w + (a+\alpha)y(\mathbf{R_0} - 1). \end{aligned}$$

If $\mathbf{R_0} \leq 1$, then $D^\beta \mathbf{L_0} \leq 0$. Hence, the infection-free equilibrium $\mathbf{E_0}$ is stable, when $\mathbf{R_0} \leq 1$. On the other hand, $D^\beta \mathbf{L_0} = 0$ if and only if $x = x_0, y = 0, v = 0$ and $w = 0$. From Krasovskii-LaSalle principle ([20]), it can concluded that the infection-free equilibrium $\mathbf{E_0}$ is globally asymptotically stable. □

To illustrate our main result about the global stability of immune-free equilibrium and chronic equilibrium, we need the following conditions on incidence

rate functions $f(x,v)$ and $g(x,y)$.
($\mathbf{C_1}$) For any positive equilibrium $(x_*, y_*, v_*, w_*) \in \mathbb{R}^3_{>0}$, suppose that

$$x_* f(x,v) - x f(x_*, v_*) = \mathbf{M}(x,v)(v - v_*)$$
$$x_* v f(x,v) - x v_* f(x_*, v_*) = \mathbf{N}(x,v)(v - v_*)$$

where $\mathbf{M}(x,v) < 0$ for all $x, v > 0$ and $\mathbf{N}(x,v) > 0$ for all $x, v > 0$.
($\mathbf{C_2}$) For any positive equilibrium $(x_*, y_*, v_*, w_*) \in \mathbb{R}^3_{>0}$, suppose that

$$x_* g(x,y) - x g(x_*, y_*) = \mathbf{P}(x,y)(y - y_*)$$
$$x_* y g(x,y) - x y_* g(x_*, y_*) = \mathbf{Q}(x,y)(y - y_*)$$

where $\mathbf{P}(x,y) < 0$ for all $x, y > 0$ and $\mathbf{Q}(x,y) > 0$ for all $x, y > 0$.

Remark 4.2. A straightforward computation confirms that conditions $\mathbf{C_1}$ and $\mathbf{C_2}$ are met for incidence rate functions, including mass action, saturated mass action, density dependence, Beddington–DeAngelis, and Crowley–Martin.

Theorem 4.3. *Suppose that* ($\mathbf{C_1}$) *and* ($\mathbf{C_2}$) *hold. If* $\mathbf{R_0} > 1$, $\mathbf{R_{Hom}} \leq 1$ *and* $dx_1 - \alpha y_1 \geq 0$, *then immune-free equilibrium* $\mathbf{E_1}$ *is globally asymptotically stable.*

Proof. Consider the Lyapunov function as

$$\begin{aligned}\mathbf{L_1}(x,y,z) = {} & x - x_1 - x_1 \ln\left(\frac{x}{x_1}\right) + y - y_1 - y_1 \ln\left(\frac{y}{y_1}\right) \\ & + \frac{v_1 f(x_1, v_1)}{k y_1}\left[v - v_1 - v_1 \ln\left(\frac{v}{v_1}\right)\right] + \frac{q f(x_1, v_1)}{g u} w \\ & + \frac{\alpha}{2(a+d)x_1}(x - x_1 + y - y_1)^2.\end{aligned}$$

The following relations hold in $\mathbf{E_1}$

$$\begin{aligned} & \lambda - d x_1 - v_1 f(x_1, v_1) - y_1 g(x_1, y_1) + \alpha y_1 = 0, \\ & v_1 f(x_1, v_1) + y_1 g(x_1, y_1) - a y_1 - \alpha y_1 = 0, \\ & k y_1 - u v_1 = 0. \end{aligned} \tag{3}$$

Taking time derivative of $\mathbf{L_1}$ along the solutions of (1) and using Lemma 1.1,

it can be written that

$$\begin{aligned}
D^{\beta}\mathbf{L_1} \leq & \left(1-\frac{x_1}{x}\right)D^{\beta}x+\left(1-\frac{y_1}{y}\right)D^{\beta}y+\frac{v_1 f(x_1,v_1)}{ky_1}\left(1-\frac{v_1}{v}\right)D^{\beta}v \\
& +\frac{qf(x_1,v_1)}{gu}D^{\beta}w+\frac{\alpha}{(a+d)x_1}[x-x_1+y-y_1](D^{\beta}x+D^{\beta}y) \\
= & \left(1-\frac{x_1}{x}\right)(\lambda-dx-vf(x,v)-yg(x,y)+\alpha y) \\
& +\left(1-\frac{y_1}{y}\right)(vf(x,v)+yg(x,y)-ay-\alpha y) \\
& +\frac{v_1 f(x_1,v_1)}{ky_1}\left(1-\frac{v_1}{v}\right)(ky-uv-qvw)+\frac{qf(x_1,v_1)}{gu}(gvw-hw) \\
& +\frac{\alpha}{(a+d)x_1}[x-x_1+y-y_1](\lambda-dx-ay).
\end{aligned}$$

From relation (3), we have

$$\begin{aligned}
D^{\beta}\mathbf{L_1} \leq & \left(1-\frac{x_1}{x}\right)[v_1 f(x_1,v_1)+y_1 g(x_1,y_1)-vf(x,v)-yg(x,y) \\
& -d(x-x_1)+\alpha(y-y_1)] \\
& +\left(1-\frac{y_1}{y}\right)\left(vf(x,v)+yg(x,y)-\frac{yv_1 f(x_1,v_1)}{y_1}-yg(x_1,y_1)\right) \\
& +\frac{v_1 f(x_1,v_1)}{ky_1}\left(1-\frac{v_1}{v}\right)\left(ky-\frac{ky_1 v}{v_1}\right)+\frac{qf(x_1,v_1)}{gu}(gvw-hw) \\
& -\frac{\alpha}{(a+d)x_1}[x-x_1+y-y_1][d(x-x_1)+a(y-y_1)].
\end{aligned}$$

On the other hand,

$$\alpha\left(1-\frac{x_1}{x}\right)(y-y_1)=-\alpha(y-y_1)\frac{(x-x_1)^2}{xx_1}+\frac{\alpha}{x_1}(x-x_1)(y-y_1).$$

Thus,

$$
\begin{aligned}
D^{\beta}\mathbf{L_1} \leq & -\left[dx_1 - \alpha y_1 + \alpha y + \frac{\alpha d x}{a+d}\right]\frac{(x-x_1)^2}{xx_1} - \frac{\alpha a}{(a+d)x_1}(y-y_1)^2 \\
& + v_1 f(x_1,v_1)\left[-1 - \frac{v}{v_1} + \frac{x_1 v f(x,v)}{x v_1 f(x_1,v_1)} + \frac{x f(x_1,v_1)}{x_1 f(x,v)}\right] \\
& + v_1 f(x_1,v_1)\left[4 - \frac{x_1}{x} - \frac{y v_1}{y_1 v} - \frac{y_1 v f(x,v)}{y v_1 f(x_1,v_1)} - \frac{x f(x_1,v_1)}{x_1 f(x,v)}\right] \\
& + y_1 g(x_1,y_1)\left[-1 - \frac{y}{y_1} + \frac{x_1 y g(x,y)}{x y_1 g(x_1,y_1)} + \frac{x g(x_1,y_1)}{x_1 g(x,y)}\right] \\
& + y_1 g(x_1,y_1)\left[3 - \frac{x_1}{x} - \frac{g(x,y)}{g(x_1,y_1)} - \frac{x g(x_1,y_1)}{x_1 g(x,y)}\right] \\
& + \frac{qh f(x_1,v_1)}{gu}(\mathbf{R_{Hom}} - 1)w.
\end{aligned}
$$

From conditions ($\mathbf{C_1}$) and ($\mathbf{C_2}$), it can be written that

$$
\begin{aligned}
-1 - \frac{v}{v_1} + \frac{x_1 v f(x,v)}{x v_1 f(x_1,v_1)} + \frac{x f(x_1,v_1)}{x_1 f(x,v)} & \\
= & \frac{[x_1 f(x,v) - x f(x_1,v_1)][x_1 v f(x,v) - x v_1 f(x_1,v_1)]}{x x_1 v_1 f(x,v) f(x_1,v_1)} \\
= & \frac{\mathbf{M}(x,v)\mathbf{N}(x,v)(v-v_1)^2}{x x_1 v_1 f(x,v) f(x_1,v_1)} \leq 0
\end{aligned}
$$

and

$$
\begin{aligned}
-1 - \frac{y}{y_1} + \frac{x_1 y g(x,y)}{x y_1 g(x_1,y_1)} + \frac{x g(x_1,y_1)}{x_1 g(x,y)} & \\
= & \frac{[x_1 g(x,y) - x g(x_1,y_1)][x_1 y g(x,y) - x y_1 g(x_1,y_1)]}{x x_1 y_1 g(x,y) g(x_1,y_1)} \\
= & \frac{\mathbf{P}(x,y)\mathbf{Q}(x,y)(y-y_1)^2}{x x_1 y_1 g(x,y) g(x_1,y_1)} \leq 0.
\end{aligned}
$$

We know that the arithmetic mean is greater or equal to geometric mean, thus it can be obtained that

$$
\begin{aligned}
4 - \frac{x_1}{x} - \frac{y v_1}{y_1 v} - \frac{y_1 v f(x,v)}{y v_1 f(x_1,v_1)} - \frac{x f(x_1,v_1)}{x_1 f(x,v)} \leq 0, \\
3 - \frac{x_1}{x} - \frac{g(x,y)}{g(x_1,y_1)} - \frac{x g(x_1,y_1)}{x_1 g(x,y)} \leq 0.
\end{aligned}
$$

If $dx_1 - \alpha y_1 \geq 0$, then $D^\beta \mathbf{L_1} \leq 0$. Hence, the immune-free equilibrium $\mathbf{E_1}$ is stable when $\mathbf{R_{Hom}} \leq 1$ and $dx_1 - \alpha y_1 \geq 0$. On the other hand, $D^\beta \mathbf{L_1} = 0$ if and only if $x = x_1, y = y_1, v = v_1$ and $w = w_1$. From Krasovskii-LaSalle principle ([20]), it can be concluded that the immune-free equilibrium $\mathbf{E_1}$ is globally asymptotically stable. □

Theorem 4.4. *Suppose that* $(\mathbf{C_1})$ *and* $(\mathbf{C_2})$ *hold. If* $\mathbf{R_0} > 1$, $\mathbf{R_{Hom}} > 1$ *and* $dx_2 - \alpha y_2 \geq 0$, *then chronic equilibrium* $\mathbf{E_2}$ *is globally asymptotically stable.*

Proof. Consider the following Lyapunov function as

$$\begin{aligned}\mathbf{L_2}(x,y,z) = {} & x - x_2 - x_2 \ln\left(\frac{x}{x_2}\right) + y - y_2 - y_2 \ln\left(\frac{y}{y_2}\right) \\ & + \frac{v_2 f(x_2,v_2)}{k y_2}\left[v - v_2 - v_2 \ln\left(\frac{v}{v_2}\right)\right] \\ & + \frac{q f(x_2,v_2)}{g u}\left[w - w_2 - w_2 \ln\left(\frac{w}{w_2}\right)\right] \\ & + \frac{\alpha}{2(a+d)x_2}(x - x_2 + y - y_2)^2.\end{aligned}$$

The following relations hold in $\mathbf{E_2}$

$$\begin{aligned} & \lambda - dx_2 - v_2 f(x_2,v_2) - y_2 g(x_2,y_2) + \alpha y_2 = 0, \\ & v_2 f(x_2,v_2) + y_2 g(x_2,y_2) - a y_2 - \alpha y_2 = 0, \\ & k y_2 - u v_2 - q v_2 w_2 = 0, \\ & g v_2 w_2 - h w_2 = 0. \end{aligned} \tag{4}$$

Taking time derivative of $\mathbf{L_2}$ along the solutions of (1) and using Lemma 1.1, it can be written that

$$\begin{aligned} D^\beta \mathbf{L_2} \leq {} & \left(1 - \frac{x_2}{x}\right) D^\beta x + \left(1 - \frac{y_2}{y}\right) D^\beta y + \frac{v_2 f(x_2,v_2)}{k y_2}\left(1 - \frac{v_2}{v}\right) D^\beta v \\ & + \frac{q f(x_2,v_2)}{g u} D^\beta w + \frac{\alpha}{(a+d)x_2}[x - x_2 + y - y_2](D^\beta x + D^\beta y) \\ = {} & \left(1 - \frac{x_2}{x}\right)(\lambda - dx - v f(x,v) - y g(x,y) + \alpha y) \\ & + \left(1 - \frac{y_2}{y}\right)(v f(x,v) + y g(x,y) - a y - \alpha y) \\ & + \frac{v_2 f(x_2,v_2)}{k y_2}\left(1 - \frac{v_2}{v}\right)(k y - u v - q v w) \end{aligned}$$

$$+\frac{qf(x_2,v_2)}{gu}\left(1-\frac{w_2}{w}\right)(gvw-hw)$$
$$+\frac{\alpha}{(a+d)x_2}[x-x_2+y-y_2](\lambda-dx-ay).$$

From relation (4), we have

$$\begin{aligned}D^{\beta}\mathbf{L_2}\leq&\left(1-\frac{x_2}{x}\right)[v_2f(x_2,v_2)+y_2g(x_2,y_2)-vf(x,v)-yg(x,y)\\&-d(x-x_2)+\alpha(y-y_2)]\\&+\left(1-\frac{y_2}{y}\right)\left(vf(x,v)+yg(x,y)-\frac{yv_2f(x_2,v_2)}{y_2}-yg(x_2,y_2)\right)\\&+\frac{v_2f(x_2,v_2)}{ky_2}\left(1-\frac{v_2}{v}\right)\left(ky-\frac{ky_2v}{v_2}\right)\\&+\frac{qf(x_2,v_2)}{gu}\left(1-\frac{w_2}{w}\right)(gvw-hw)\\&-\frac{\alpha}{(a+d)x_2}[x-x_2+y-y_2][d(x-x_2)+a(y-y_2)].\end{aligned}$$

On the other hand,

$$\alpha\left(1-\frac{x_2}{x}\right)(y-y_2)=-\alpha(y-y_2)\frac{(x-x_2)^2}{xx_2}+\frac{\alpha}{x_2}(x-x_2)(y-y_2).$$

Thus,

$$\begin{aligned}D^{\beta}\mathbf{L_2}\leq&-\left[dx_2-\alpha y_2+\alpha y+\frac{\alpha dx}{a+d}\right]\frac{(x-x_2)^2}{xx_2}-\frac{\alpha a}{(a+d)x_2}(y-y_2)^2\\&+v_2f(x_2,v_2)\left[-1-\frac{v}{v_2}+\frac{x_2vf(x,v)}{xv_2f(x_2,v_2)}+\frac{xf(x_2,v_2)}{x_2f(x,v)}\right]\\&+v_2f(x_2,v_2)\left[4-\frac{x_2}{x}-\frac{yv_2}{y_2v}-\frac{y_2vf(x,v)}{yv_2f(x_2,v_2)}-\frac{xf(x_2,v_2)}{x_2f(x,v)}\right]\\&+y_2g(x_2,y_2)\left[-1-\frac{y}{y_2}+\frac{x_2yg(x,y)}{xy_2g(x_2,y_2)}+\frac{xg(x_2,y_2)}{x_2g(x,y)}\right]\\&+y_2g(x_2,y_2)\left[3-\frac{x_2}{x}-\frac{g(x,y)}{g(x_2,y_2)}-\frac{xg(x_2,y_2)}{x_2g(x,y)}\right].\end{aligned}$$

From conditions ($\mathbf{C_1}$) and ($\mathbf{C_2}$), it can be written that

$$\begin{aligned}
&-1-\frac{v}{v_2}+\frac{x_2vf(x,v)}{xv_2f(x_2,v_2)}+\frac{xf(x_2,v_2)}{x_2f(x,v)}\\
&\quad=\frac{[x_2f(x,v)-xf(x_2,v_2)][x_2vf(x,v)-xv_2f(x_2,v_2)]}{xx_2v_2f(x,v)f(x_2,v_2)}\\
&\quad=\frac{\mathbf{M}(x,v)\mathbf{N}(x,v)(v-v_2)^2}{xx_2v_2f(x,v)f(x_2,v_2)}\leq 0
\end{aligned}$$

and

$$\begin{aligned}
&-1-\frac{y}{y_2}+\frac{x_2yg(x,y)}{xy_2g(x_2,y_2)}+\frac{xg(x_2,y_2)}{x_2g(x,y)}\\
&\quad=\frac{[x_2g(x,y)-xg(x_2,y_2)][x_2yg(x,y)-xy_2g(x_2,y_2)]}{xx_2y_2g(x,y)g(x_2,y_2)}\\
&\quad=\frac{\mathbf{P}(x,y)\mathbf{Q}(x,y)(y-y_2)^2}{xx_2y_2g(x,y)g(x_2,y_2)}\leq 0.
\end{aligned}$$

On the other hand, the arithmetic mean is greater or equal to geometric mean, thus it can be obtained that

$$\begin{aligned}
&4-\frac{x_2}{x}-\frac{yv_2}{y_2v}-\frac{y_2vf(x,v)}{yv_2f(x_2,v_2)}-\frac{xf(x_2,v_2)}{x_2f(x,v)}\leq 0,\\
&3-\frac{x_2}{x}-\frac{g(x,y)}{g(x_2,y_2)}-\frac{xg(x_2,y_2)}{x_2g(x,y)}\leq 0.
\end{aligned}$$

If $dx_2-\alpha y_2\geq 0$, then $D^\beta\mathbf{L_2}\leq 0$. Hence, the chronic equilibrium $\mathbf{E_2}$ is stable, when $\mathbf{R_{Hom}}>1$ and $dx_2-\alpha y_2\geq 0$. On the other hand, $D^\beta\mathbf{L_2}=0$ if and only if $x=x_2, y=y_2, v=v_2$ and $w=w_2$. From Krasovskii-LaSalle principle ([20]), it can be concluded that the chronic equilibrium $\mathbf{E_2}$ is globally asymptotically stable. □

Remark 4.5. While Theorems 3.2 and 3.3 provide useful sufficient conditions, it is important to note that these conditions are not necessary. Moreover, the additional conditions in Theorems 3.2 and 3.3 namely, $dx_i-\alpha y_i\geq 0$ for $i=1,2$, which implies $\lambda-v_if(x_i,v_i)-y_ig(x_i,y_i)\geq 0$ specify that at equilibrium, the regenerative capacity of uninfected cells exceeds the rate at which they are lost to infection. This is a biologically plausible assumption for maintaining a stable, non-trivial healthy cell population.

5 Numerical Simulations

In this section, the numerical simulation of (1) will be presented. To do this, using MATLAB and FDE12 method, the global stability of equilibrium points

will be shown. Since the functions $f(x,v)$ and $g(x,y)$ are general, in simulation these functions must be specified. Consider the following system

$$\begin{aligned} D^{\beta}x(t) &= \lambda - dx - \frac{m_1 xv}{1+\eta_1 v} - \frac{m_2 xy}{1+\eta_2 y} + \alpha y, \\ D^{\beta}y(t) &= \frac{m_1 xv}{1+\eta_1 v} + \frac{m_2 xy}{1+\eta_2 y} - ay - \alpha y, \\ D^{\beta}v(t) &= ky - uv - qvw, \\ D^{\beta}w(t) &= gvw - hw, \end{aligned} \tag{5}$$

where $f(x,v) = \dfrac{m_1 x}{1+\eta_1 v}$ and $g(x,y) = \dfrac{m_2 x}{1+\eta_2 y}$, which are type of saturated mass action functional response. For the functions $f(x,v)$ and $g(x,y)$, we have

$$\begin{aligned} x_* f(x,v) - xf(x_*,v_*) &= -\frac{m_1\eta_1 x x_*}{(1+\eta_1 v)(1+\eta_1 v_*)}(v-v_*), \\ x_* v f(x,v) - xv_* f(x_*,v_*) &= \frac{m_1 x x_*}{(1+\eta_1 v)(1+\eta_1 v_*)}(v-v_*), \\ x_* g(x,y) - xg(x_*,y_*) &= -\frac{m_2\eta_2 x x_*}{(1+\eta_2 y)(1+\eta_2 y_*)}(y-y_*), \\ x_* y g(x,y) - xy_* g(x_*,y_*) &= \frac{m_2\eta_2 x x_*}{(1+\eta_2 y)(1+\eta_2 y_*)}(y-y_*). \end{aligned}$$

Hence, theses function meet the conditions $(\mathbf{C_1})$ and $(\mathbf{C_2})$. In this case, we use the parameters in Table 1 and different values of fractional derivative order β.

Table 2: Parameter Values used for simulation (5)

Parameter	Description	values	source
λ	Source rate of host cells	10	[25]
d	Decay rate of healthy cells	0.01	[25]
m_1	Viral infectivity rate	0.0001, 0.0012	Assumed
γ_1	Positive parameter that describes the effects of capture rate	0.00005	Assumed
m_2	Infected cells infectivity rate	0.00016, 0.0016	Assumed
γ_2	Positive parameter that describes the effects of capture rate	0.00005	Assumed
α	Cure rate of infected cells	0.01	[25]
a	Death rate of infected cells	0.8	[13]
k	Virion production rate	0.2	[13]
u	Clearance rate of virus	2.4	[30]
q	Death rate of virus by antibody cells	0.01	[7]
g	Activation rate of antibody cells	0.03,0.125	[13]
h	Death rate of virus	2	[13]

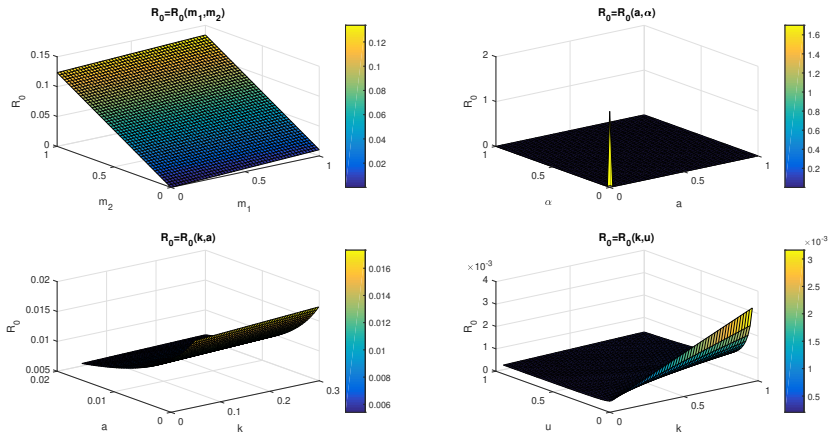


Figure 1: Plot of the basic reproduction number $\mathbf{R_0}$, in terms of various parameters involved in model (5)

The basic reproduction number for system (5) has the following form,

$$\mathbf{R_0} = \frac{km_1x_0}{(a+\alpha)u} + \frac{m_2x_0}{a+\alpha}.$$

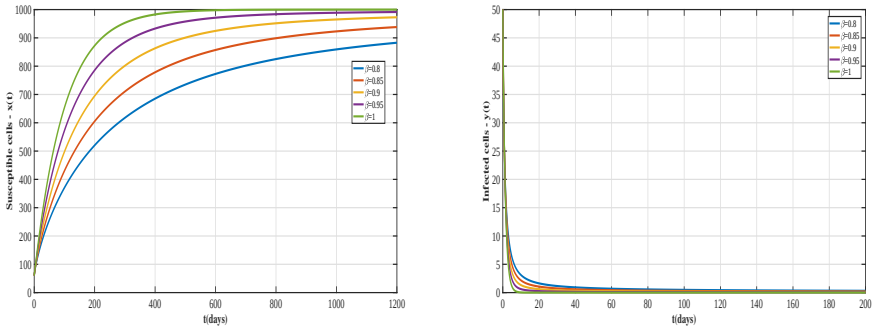
In this case, we have the new sensitivity analysis of $\mathbf{R_0}$ with respect to m_1 and m_2,

$$\frac{\partial \mathbf{R_0}}{\partial m_1} = \frac{kx_0}{(a+\alpha)u} > 0,$$
$$\frac{\partial \mathbf{R_0}}{\partial m_2} = \frac{x_0}{a+\alpha} > 0.$$

In Figure 1, plot of the basic reproduction number $\mathbf{R_0}$, in terms of various parameters has been given.

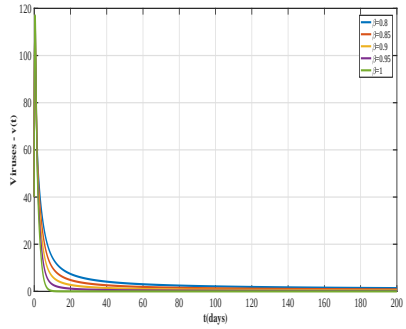
By choosing $m_1 = 0.0001$, $m_2 = 0.00016$ and $g = 0.03$, we have $\mathbf{R_0} = 0.7119$. In this case, by Theorem 4.1 it can be concluded that the solutions of (1) with any positive initial conditions tend to infection-free equilibrium point $\mathbf{E_0} = (1000, 0, 0, 0)$. Hence, the infection-free equilibrium point $\mathbf{E_0}$ is globally asymptotically stable (See Figure 2).

If we put $m_1 = 0.0012$, $m_2 = 0.0016$ and $g = 0.03$, we have $\mathbf{E_1} = (123.0133, 10.9635, 45.6754, 0)$, $\mathbf{R_0} = 8.1481$ and $\mathbf{R_{Hom}} = 0.6851 < 1$. Also, for the immune-free equilibrium point the condition $dx_1 - \alpha y_1 = 1.1205 > 0$ is

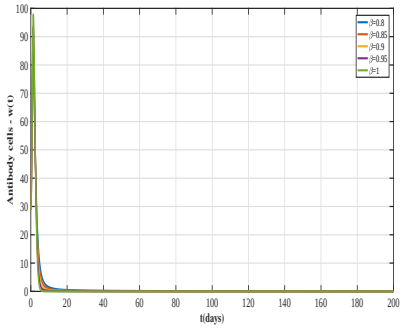


(a) Susceptible cells - $x(t)$

(b) Infected cells - $y(t)$



(c) Viruses - $v(t)$



(d) Antibody cells - $w(t)$

Figure 2: Solution trajectories as functions of time, tending to stable equilibrium $\mathbf{E_0}$

satisfied. By attention to Theorem 4.3, it can be concluded that the immune-free equilibrium point $\mathbf{E_1}$ is globally asymptotically stable (See Figure 3).

By considering $m_1 = 0.0012$, $m_2 = 0.0016$ and $g = 0.125$, we have $\mathbf{E_2} = (226.1049, 9.6737, 16, 364.6043)$, $\mathbf{R_0} = 8.1481$ and $\mathbf{R_{Hom}} = 2.8745 > 1$. The condition $dx_2 - \alpha y_2 = 2.1643 > 0$ is also established. By Theorem 4.4, we have the globally asymptotic stability of chronic equilibrium point $\mathbf{E_2}$ (See Figure 4). By choosing $\beta = 0.90$ and $\beta = 1$, the numerical values of solution presented in Tables 3 and 4.

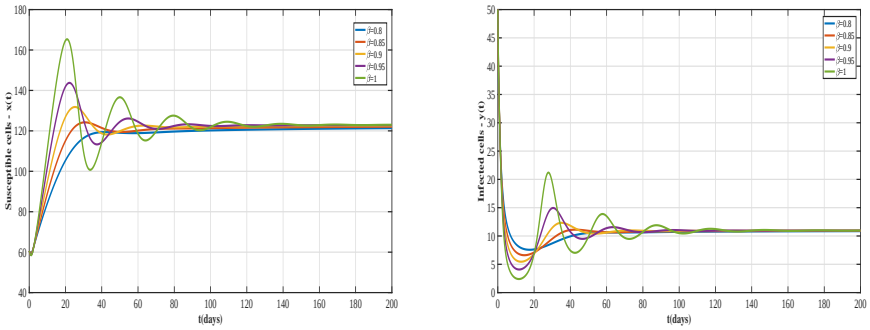
Now, we want to show the effect of cure rate on dynamical behavior of system (1). By choosing the fix fractional order $\beta = 0.95$ and different values of α, namely, $\alpha = 0, 2, 3, 4, 6$, it can be concluded that chronic state of illness

Table 3: The values of $x(t), y(t), v(t)$ and $w(t)$ with fractional order $\beta = 0.90$ in the steady state $\mathbf{E_2}$.

t(days)	$x(t)$	$y(t)$	$v(t)$	$w(t)$
1	60	50	40	30
2	63.4597	26.4056	15.8070	1.5162×10^3
3	69.4256	15.7519	12.7900	1.0227×10^3
4	75.4972	10.4468	12.1759	634.4994
⋮	⋮	⋮	⋮	⋮
97	216.6453	9.0990	16.0445	327.3738
98	216.8091	9.1100	16.0345	328.0967
99	216.9680	9.1208	16.0425	328.7978
100	217.1222	9.1312	16.0415	329.4780

Table 4: The values of $x(t), y(t), v(t)$ and $w(t)$ with fractional order $\beta = 1$ in the steady state $\mathbf{E_2}$.

t(days)	$x(t)$	$y(t)$	$v(t)$	$w(t)$
1	60	50	40	30
2	62.6818	26.7183	14.5942	1.6488×10^3
3	69.2024	13.8947	10.9714	1.0363×10^3
4	76.4605	7.6061	10.1083	519.4653
⋮	⋮	⋮	⋮	⋮
97	225.7728	9.6453	16.0030	362.7192
98	225.7959	9.6473	16.0028	362.8504
99	225.8175	9.6491	16.0026	362.97241
100	225.8375	9.6508	16.0024	363.0860



(a) Susceptible cells - $x(t)$ **(b)** Infected cells - $y(t)$

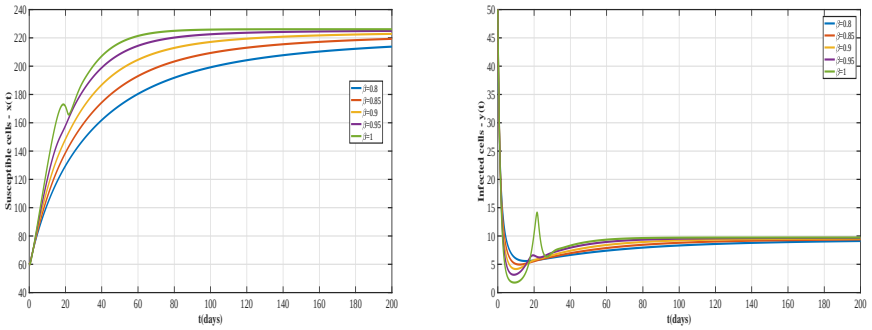
(c) Viruses - $v(t)$ **(d)** Antibody cells - $w(t)$

Figure 3: Solution trajectories as functions of time, tending to stable equilibrium $\mathbf{E_1}$

tend to infection-free state. By attention to this argument, if we control the amount of cure rate, then we have a pretty level in the control of infection (See Figure 5).

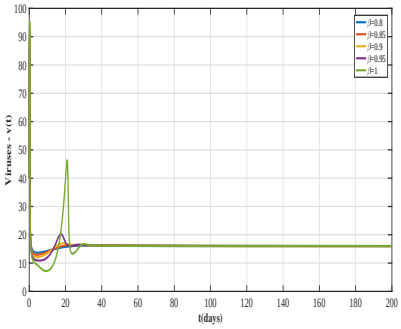
6 Discussions and Conclusions

In this paper, a generalized viral infection model with Caputo fractional derivative, cure rate and humoral immunity was studied. By considering certain conditions on two threshold numbers, basic reproduction number ($\mathbf{R_0}$) and humoral immune response reproduction rate ($\mathbf{R_{Hom}}$), the existence, uniqueness

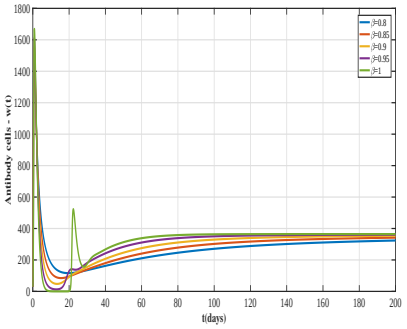


(a) Susceptible cells - $x(t)$

(b) Infected cells - $y(t)$



(c) Viruses - $v(t)$

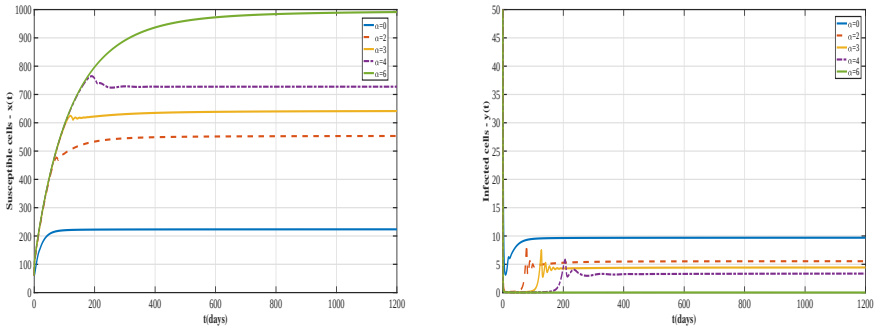


(d) Antibody cells - $w(t)$

Figure 4: Solution trajectories as functions of time, tending to stable equilibrium $\mathbf{E_2}$

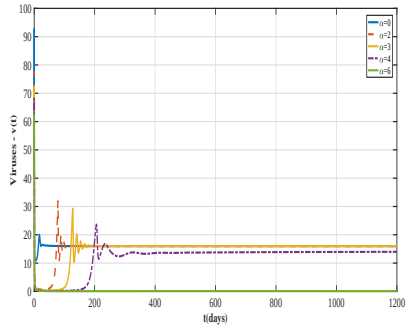
and global stability of equilibria were studied. For the global stability of equilibria, Lyapunov's second method, Krasovskii-LaSalle principle and Lemma 1.1 were applied. We proved that if $\mathbf{R_0} \leq 1$, then infection-free equilibrium point $\mathbf{E_0} = (x_0, 0, 0, 0)$ is globally asymptotically stable. Also, if $\mathbf{R_0} > 1$, $\mathbf{R_{Hom}} \leq 1$ and $dx_1 - \alpha y_1 \geq 0$, then immune-free equilibrium $\mathbf{E_1} = (x_1, y_1, v_1, 0)$ is globally asymptotically stable. Finally, we proved that if $\mathbf{R_0} > 1$, $\mathbf{R_{Hom}} > 1$ and $dx_2 - \alpha y_2 \geq 0$, then chronic equilibrium point $\mathbf{E_2} = (x_2, y_2, v_2, w_2)$ is globally asymptotically stable. To illustrate our analytical results, numerical simulation of model was provided in Section 5.

The results of this paper improve and extend the results about the global stability of equilibria in [11, 12, 31]. Also, the results of the paper [25] are

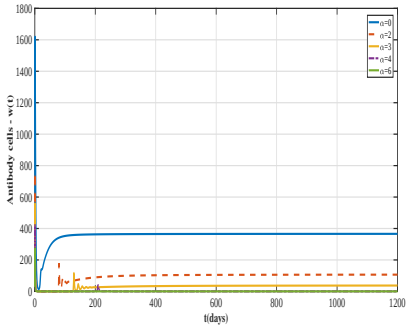


(a) Susceptible cells - $x(t)$

(b) Infected cells - $y(t)$



(c) Viruses - $v(t)$



(d) Antibody cells - $w(t)$

Figure 5: Dynamical behavior of (1) with different values of cure rate (α)

extend.

This study lays the groundwork for several important avenues of future research:

1- Advanced Drug Efficacy Modeling: While our model incorporates basic treatment effects, a critical next step is to develop more sophisticated strategies for optimizing drug efficacy. This includes simulating combination therapies, adherence variability, and the evolution of drug resistance to identify regimens that maximize long-term viral suppression and immune recovery.

2- Stochastic and Fractional Dynamics: The deterministic nature of our model overlooks the inherent randomness in disease spread. A valuable extension would be to formulate a stochastic fractional-order model. This approach would more realistically represent chance events in transmission and the vari-

able success of interventions, providing a more robust tool for risk assessment and policy planning.

We hope that our results help specialists in the field of infectious diseases and give new methods for physicians in the study of illnesses.

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