

Modeling the dynamics of viral–host interaction during treatment of productively infected cells and free virus involving total immune response

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Abstract. Virus dynamics models are useful in interpreting and predicting the change in viral load over the time and the effect of treatment in emerging viral infections like HIV/AIDS, hepatitis B virus (HBV). We propose a mathematical model involving the role of total immune response (innate, CTL, and humoral) and treatment for productively infected cells and free virus to understand the dynamics of virus–host interactions. A threshold condition for the extinction or persistence of infection, i.e. basic reproductive number, in the presence of immune response (R_I) is established. We study the global stability of virus-free equilibrium and interior equilibrium using LaSalle’s principle and Lyapunov’s direct method. The global stability of virus-free equilibrium ensures the clearance of virus from the body, which is independent of initial status of subpopulations. Central manifold theory is used to study the behavior of equilibrium points at $R_I = 1$, i.e. when the basic reproductive number in the presence of immune response is one. A special case, when the immune response (IR) is not present, has also been discussed. Analysis of special case suggests that the basic reproductive number in the absence of immune response R_0 is greater than that of in the presence of immune response R_I , i.e. $R_0 > R_I$. It indicates that infection may be eradicated if $R_I < 1$. Numerical simulations are performed to illustrate the analytical results using MatLab and Mathematica.

Keywords: virus dynamics model, humoral immune response, CTL-mediated immune response, dynamical systems, viral infection.

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1 Introduction

1.1 Onset of viral infection

Diseases caused by viral infections have had a major impact on populations (e.g. hepatitis B virus, HIV/AIDS). Viruses may be present in the body either in a free state or as an intracellular parasite. Free viruses enter a cell in a receptor specific manner and infect the cell. Viral replication is possible only within a cell. The virus replicates within the cell by utilizing the cells own machinery. Inside the cell, a virus may either exist in a latent (inactive) form for a prolonged period or it may immediately adopt the host replication machinery and start producing multiple copies of itself. Once large number of virus particles have been produced inside the cell, they come out of the cell by destroying it. Now, these viruses are free to infect the other healthy cells. Upon infection, virus produces infected cells; all of these infected cells do not contribute in virus production, and some of them remains in latent stage and can produce virus once reactivated. Within the body, virus encounters an immune response, which prevents its spread from an infected cell to adjacent uninfected cells. The present model is being proposed to understand the dynamics of interaction between uninfected cells, productively infected cells, latently infected cells, free virus, and the effect of immune response with treatment of productively infected cells and free virus.

1.2 Mathematical models for HIV infection

In the literature, numerous mathematical models have been developed to study the dynamics of HIV infection [1, 4, 9, 17, 18, 24–26, 29, 41, 42]. The basic viral dynamics model has been studied in detail by researchers [1, 24]:

$$\frac{dx}{dt} = \lambda - \delta_0 x - \alpha x v, \quad \frac{dy}{dt} = \alpha x v - \delta_1 y, \quad \frac{dv}{dt} = k y - k_0 v. \quad (1)$$

In the above model, $x(t)$ is the number of uninfected cells, $y(t)$ is the number of infected cells, and $v(t)$ is the number of free virus at any time $t \geq 0$. Uninfected cells grow constantly at the rate λ and die out with the rate $\delta_0 x$. When free virus interacts with uninfected cells, it infects uninfected cells with infection rate constant α , and $\delta_1 y$ denotes the loss rate of infected cells. Virus is produced at the rate $k y$ via lysis of infected cells, and k_0 is clearance rate constant of virus.

1.2.1 Inclusion of effect of immune response

Immune response plays an important role to control viral infection as it fights against the virus and reduces the virus load. Nowak and Bangham [24] extended the basic virus dynamics model involving CTL (Cytotoxic T lymphocyte) component of immune response, which suggests that an active CTL immune response may reduce virus load. Vargas-De-León and Esteva [38] studied global stability of virus dynamics model with linear immune response. Further, Vargas-De-León [37] proposed a virus dynamics model with lytic and nonlytic immune responses. The effect of nonlinear immune attack rates

has been explored to understand the global dynamics of infection. It was shown that if the basic reproductive number $R_0 > 1$, then the virus will spread and persist within its cellular population, whereas if $R_0 < 1$, then the virus will not spread. They have also shown the importance of immune responses to control infection. Wang and Liu [41] proposed a class of delayed viral models with saturation infection rate and immune response. In their models, they considered the CTL response (which kills infected cells) and antibody response (which facilitates removal of viruses) separately to study the analytical behavior of systems. Roy et al. [29] studied the effect of CTL immune response on the dynamics of infected $CD4^+$ T cells, virus producing $CD4^+$ T cells, and virus by introducing a positive feedback parameters in the model. They also investigated an optimal control therapy using reverse transcriptase inhibitors (RTIs) that block new infection. Further, Dubey et al. [6] generalized the discussed model (1) by considering the effect of appropriate immune response on the infected cells and suggested that under some sufficient conditions, the number of uninfected cells can be maintained at an appropriate level. Hattaf et al. [13] studied the spread and transmission of HIV infection via: (i) virus-to-cell infection, and (ii) cell-to-cell transmission together with the adaptive immune response, which provides better understanding of HIV infection.

1.2.2 Inclusion of awareness and treatment

The spread of infectious diseases, especially, virus mediated may be controlled by providing appropriate awareness about the infection through media [21, 22, 30] and by treatment with appropriate therapeutic drugs [5]. Researchers have paid attention to drug therapy or treatment (cure) of targeted cells in virus dynamics models [11, 14–16, 20, 33–35, 40, 43]. Liu et al. [20] developed an HIV pathogenesis dynamics model considering cure rate. They incorporated the full logistic proliferation term for uninfected cells as well as infected cells in the model. In this study, they obtained a critical number (the smallest virus number released by per infected $CD4^+$ T cells) and have shown that this critical number increases with increase in cure rate and observed that the HIV infection can be controlled by increasing cure rate.

Hattaf et al. [12, 14] proposed and analyzed a virus dynamics model with general incidence rate and linear cure rate of the infected cells to uninfected cells. They have shown that the virus can be cleared and the disease dies out if the basic reproduction number is less than one. The model and results in [14] were further extended by Tian and Liu [35]. Gumel and Moghadas [11] studied the role of antiretroviral therapy in controlling the HIV infection. They investigated the immunological and therapeutic control of HIV and found the optimal level of antiretroviral therapy to eradicate HIV. Recently, Hill et al. [16] summarized that viral dynamics models have provided many important insights into dynamics of infection and have been extensively used to characterize the response of HIV to antiretroviral therapy. They addressed the important questions about the treatment and immunotherapy. For example, what is the efficacy of antiretroviral drugs, and how does antiretroviral efficacy influence treatment outcomes?

It is noticed that the above models focused on the cure of infected cells, while the cure or killing (via therapeutic drugs) of free virus is equally important to reduce the count of infected cells resulting in reduction of infection.

Considering the above points in view, we propose a five-dimensional virus dynamics model with saturated infection rate and immune response with treatment of infected cells as well as free virus. The main aim of this paper is to study the control of the replication of infected cells and free virus by considering immune response (innate, cellular and humoral) and appropriate treatment for both; the infected cells and free virus.

2 The mathematical model

It is reported in the virus dynamics models (see [10, 15, 16, 23, 25, 27, 28, 39]) that upon infection, a fraction of infected cells may be in latent state and thus do not take part in producing virus. However, latently infected cells become active upon stimulation and then join the other group of actively virus producing infected cells. In order to understand the interaction between uninfected cells ($x(t)$), productively infected cells ($y_1(t)$), latently infected cells ($y_2(t)$), virus ($v(t)$), and total immune response ($z(t)$) during treatment of both (productively infected cells and virus), we propose a mathematical model consisting of 5 ordinary differential equations

$$\begin{aligned}
 \frac{dx}{dt} &= \lambda - \delta_0 x - \frac{\alpha x v}{1 + \alpha_1 v}, \\
 \frac{dy_1}{dt} &= \frac{q \alpha x v}{1 + \alpha_1 v} - \delta_1 y_1 + \beta y_2 - \gamma_1 y_1 z - \theta_1 y_1, \\
 \frac{dy_2}{dt} &= \frac{(1 - q) \alpha x v}{1 + \alpha_1 v} - \delta_1 y_2 - \beta y_2, \\
 \frac{dv}{dt} &= k y_1 - k_0 v - \gamma_2 v z - \theta_2 v, \\
 \frac{dz}{dt} &= \mu - \mu_0 z + \mu_1 y_1 z + \mu_2 v z,
 \end{aligned} \tag{2}$$

$x(0) > 0, y_1(0) \geq 0, y_2(0) \geq 0, v(0) \geq 0, z(0) > 0$. In most of the previous work, it has been observed that immune response increases either due to infected cells (CTL immune response) [24, 37, 38] or virus (humoral immunity [18]). In this study, we assume that the immune response increases due to infected cells as well as virus (as considered in our previous study [4, 7, 8]). Keeping the above aspects in view, the virus dynamics can be governed by system (2) of five ordinary differential equations. The interaction of subpopulations can be visualized from schematic diagram of model (2) (Fig. 1). Here $x(t), y_1(t), y_2(t), v(t)$, and $z(t)$ represent the uninfected cells, productively infected cells, latently infected cells, free virus, and total immune response, respectively. Uninfected cells grow from the sources inside the body (thymus) at rate constant λ and die out at rate $\delta_0 x$. As shown in our previous work [4], the infection rate $f(t) = \alpha x(t)v(t)$ increases linearly with x or with v , which may not be realistic in real life. If we take the saturated incidence rate

$$f(t) = \frac{\alpha x v}{1 + \alpha_1 v}, \quad \alpha > 0, \alpha_1 \geq 0,$$

then it gives a rich dynamics of the system [4, 18, 32, 39]. Thus, we considered that free virus infects uninfected cells at saturated infection rate, which is given by Holling type II

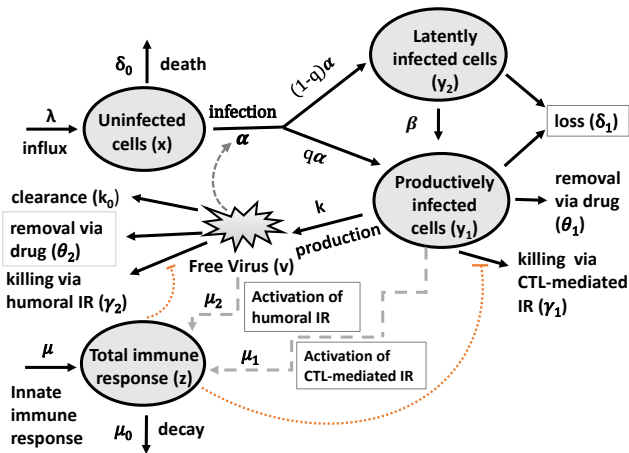


Figure 1. Schematic diagram of model (2). A mathematical model of viral dynamics augmented to include the total immune response (IR) during treatment of productively infected cells and free virus. Uninfected cells x , which proliferate at influx rate λ and die at rate δ_0 , get infected at rate α (dotted curved arrow) and divided into two types of infected cells: productively infected cells y_1 with fraction q and latently infected cells y_2 with fraction $1 - q$. Both type of infected cells loss at rate δ_1 , and latently infected cells get activated at rate β . Productively infected cells produce virions v at rate k . The total immune response z proliferates with innate immune response at rate μ and stimulates with CTL-mediated immune response (dashed elbow connector) at rate μ_1 via productively infected cells and with humoral immune response (dashed elbow connector) at rate μ_2 via virus and depletes at rate μ_0 . Productively infected cells and virus are cured or killed via drug at rates θ_1 and θ_2 , respectively, and are killed by CTL-mediated and humoral immune response at the rates γ_1 and γ_2 (dotted curved lines), respectively. Virus is cleared at rate k_0 .

functional response ($\alpha xv/(1 + \alpha_1 v)$, where α and α_1 are positive constants) [4, 18]. We also considered two states of infected cells [23, 39]: virus producing state (y_1), in this state, infected cells produce new virions; latently infected state (y_2), in this state, infected cells do not contribute in producing new virions, but can be reactivated to produce new virions. The probability that upon infection, a cell enters to the virus producing state is given by q , and $1 - q$ is the probability that upon infection, a cell enters to the latently infected state, and δ_1 notates the loss rate constant of these infected cells. The latently infected cells are getting reactivated at the rate constant β and join the virus producing infected cells to contribute in production of virus. Free virions are produced via lysis of productively infected cells at the rate constant k and get cleared from the body with the rate constant k_0 . We assumed that μ is the innate immune response of the body. When virus enters into the body and targets the uninfected cells to infect them, then the infected cell-specific lymphocytes (cellular immunity) proliferate at rate $\mu_1 y_1 z$, and the virus-specific lymphocytes (humoral immunity) proliferate at rate $\mu_2 v z$. The corresponding decrease in the number of productively infected cells and virus is given by rates $\gamma_1 y_1 z$ and $\gamma_2 v z$, respectively. The immune response decays at the rate $\mu_0 z$ due to natural factors. It is assumed that the productively infected cells and free virus are killed or removed with the rates $\theta_1 y_1$ and $\theta_2 v$ due to therapeutic drugs. In modeling, it has been assumed that drug acts on the productively infected cells by killing these cells or inducing these

cells to suicide by programmed cell death (PCD) or apoptosis. They do not re-enter the susceptible category as they are eliminated from the system. Total removal of virus from within cell to make it normal is not biologically possible, thus can not enter the susceptible class.

Remark 1. In the absence of immune response ($z = 0$) and drug therapy ($\theta_1 = \theta_2 = 0$), model (2) reduces to the model proposed in [39].

In the next section, we show that all the solutions of system (2) are positively invariant and bounded.

3 Boundedness and positivity of solutions of model (2)

In order to see the well-posedness of the model, from the first equation of model (2) we note that $dx/dt \geq -[\delta_0 + \alpha v/(1 + \alpha_1 v)]x$, which gives

$$x(t) \geq x(0) \exp \left[- \int_0^t \left(\delta_0 + \frac{\alpha v(s)}{1 + \alpha_1 v(s)} \right) ds \right].$$

Similarly, from other four equations we obtain

$$\begin{aligned} y_1(t) &\geq y_1(0) \exp \left[- \int_0^t (\delta_1 + \gamma_1 z(s) + \theta_1) ds \right], \\ y_2(t) &\geq y_2(0) \exp \left[- \int_0^t (\delta_1 + \beta) ds \right], \\ v(t) &\geq v(0) \exp \left[- \int_0^t (k_0 + \gamma_2 z(s) + \theta_2) ds \right], \\ z(t) &\geq z(0) \exp \left[\int_0^t (\mu_1 y_1(s) + \mu_2 v(s) - \mu_0) ds \right]. \end{aligned}$$

Thus, we state the following Lemma.

Lemma 1. *If $x(0) > 0, y_1(0) > 0, y_2(0) > 0, v(0) > 0$, and $z(0) > 0$, then all solutions of model (2) are positive.*

Now, in order to see the boundedness and invariance of system (2), from the first equation of model (2) we have $\dot{x} \leq \lambda - \delta_0 x$. Using elementary calculus, we get that $\limsup_{t \rightarrow \infty} x(t) \leq \lambda/\delta_0$. Further, $\dot{x} + \dot{y}_1 + \dot{y}_2 \leq \lambda - \delta(x + y_1 + y_2)$, where $\delta = \min\{\delta_0, \delta_1\}$. This implies

$$\limsup_{t \rightarrow \infty} (x(t) + y_1(t) + y_2(t)) \leq \frac{\lambda}{\delta}.$$

Again, we have $\dot{v} = ky_1 - k_0v - \gamma_2vz - \theta_2v \leq k\lambda/\delta - (k_0 + \theta_2)v$. This implies that

$$\limsup_{t \rightarrow \infty} v(t) \leq \frac{k\lambda}{\delta(k_0 + \theta_2)} =: v_m.$$

Now let $L = (\mu_1/\gamma_1)y_1 + (\mu_2/\gamma_2)v + z$. Differentiating L along all the solutions of system (2), we get

$$\begin{aligned} \dot{L} &= \frac{\mu_1 q \alpha x v}{\gamma_1(1 + \alpha_1 v)} + \frac{\mu_1 \beta}{\gamma_1} y_2 + \frac{\mu_2 k}{\gamma_2} y_1 + \mu \\ &\quad - \frac{\mu_1}{\gamma_1} (\delta_1 + \theta_1) y_1 - \frac{\mu_2}{\gamma_2} (k_0 + \theta_2) v - \mu_0 z \\ &\leq \mu_m - \delta_m L, \end{aligned}$$

where

$$\mu_m = \frac{\mu_1 q \alpha \lambda v_m}{\gamma_1 \delta (1 + \alpha_1 v_m)} + \frac{\lambda}{\delta} \left(\frac{\mu_1 \beta}{\gamma_1} + \frac{\mu_2 k}{\gamma_2} \right) + \mu,$$

and

$$\delta_m = \min\{\delta + \theta_1, k_0 + \theta_2, \mu_0\}.$$

This implies that

$$\limsup_{t \rightarrow \infty} L(t) \leq \frac{\mu_m}{\delta_m}.$$

Furthermore, $\dot{x} < 0$ if $x > \lambda/\delta_0$, $\dot{y}_1 < 0$ if $y_1 > \lambda/\delta$, $\dot{y}_2 < 0$ if $y_2 > \lambda/\delta$, $\dot{v} < 0$ if $v > v_m$, and $\dot{L} < 0$ if $L > \mu_m/\delta_m$. This shows that solutions of system (2) point towards the region Ω defined in Lemma (1). Hence Ω is positively invariant, and solutions of system (2) are bounded. Thus, we can state the following lemma.

Lemma 2. *The set $\Omega = \{(x, y_1, y_2, v, z) \in \mathbb{R}_+^5 : 0 < x + y_1 + y_2 \leq \lambda/\delta, 0 < v \leq v_m, 0 < z \leq \mu_m/\delta_m\}$ is positively invariant region of system (2).*

This proves that the model is biologically well behaved.

In the next section, first we find equilibrium points of system (2). Then determine the basic reproduction number of system (2). Afterwards, the local and global stability of the equilibrium points has been studied.

4 Stability analysis of model (2)

From model (2) it is clear that the system has two nonnegative equilibria:

- (i) Virus-free equilibrium (VFE) $E_0(x_0, 0, 0, 0, z_0)$, the point where infection is not present,
- (ii) Interior equilibrium (IE) $E_1(x^*, y_1^*, y_2^*, v^*, z^*)$, the equilibrium point where infection persists.

VFE is trivial and given by $E_0(x_0, 0, 0, 0, z_0) = E_0(\lambda/\delta_0, 0, 0, 0, \mu/\mu_0)$.

We use the next generation operator method [3,36] to determine the basic reproduction number. We are considering $y_1, y_2,$ and v to be the infection compartments. Let $X = (y_1, y_2, v)^T, F_1(X)$ is the nonnegative infection matrix (gain in infection terms), and $V_1(X)$ (the matrix for transfer terms between compartments) associated with system (2). Then we can rewrite system (2) as

$$\dot{X} = F_1(X) - V_1(X),$$

where

$$F_1(X) = \begin{bmatrix} \frac{q\alpha xv}{1+\alpha_1 v} + \beta y_2 \\ 0 \\ 0 \end{bmatrix} \quad \text{and} \quad V_1(X) = \begin{bmatrix} (\delta_1 + \theta_1 + \gamma_1 z)y_1 \\ (\delta_1 + \beta)y_2 - \frac{(1-q)\alpha xv}{1+\alpha_1 v} \\ (k_0 + \theta_2 + \gamma_2 z)v - ky_1 \end{bmatrix}.$$

The Jacobian of matrices $F_1(X)$ and $V_1(X)$ evaluated at VFE; $E_0(\lambda/\delta_0, 0, 0, 0, \mu/\mu_0)$ is given by

$$F_1 = \begin{bmatrix} 0 & \beta & \frac{q\alpha\lambda}{\delta_0} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad V_1 = \begin{bmatrix} \delta_1 + \theta_1 + \gamma_1 \frac{\mu}{\mu_0} & 0 & 0 \\ 0 & \delta_1 + \beta & -\frac{(1-q)\alpha\lambda}{\delta_0} \\ -k & 0 & k_0 + \theta_2 + \gamma_2 \frac{\mu}{\mu_0} \end{bmatrix}.$$

Then $\rho(F_1V_1^{-1})$ gives the spectral radius (largest eigenvalue) of the next generation matrix ($F_1V_1^{-1}$) as defined in [36]. Thus,

$$R_I = \rho(F_1V_1^{-1}) = \frac{\alpha\lambda k(q\delta_1 + \beta)}{(\delta_1 + \beta)\delta_0(\delta_1 + \theta_1 + \frac{\gamma_1\mu}{\mu_0})(k_0 + \theta_2 + \frac{\gamma_2\mu}{\mu_0})},$$

where R_I is the basic reproduction number in the presence of immune response. This can be defined as the average number of newly infected cells produced by single infected cell when introduced into a completely susceptible cells. It is apparent from the expression of the basic reproductive ratio (R_I) that it decreases with the increase in therapeutic drug (for both infected cells and virus) as well as with the improvement of immune response. In the present model, we consider immune response, so the given basic reproduction number is determined in the presence of immune response. Further, we can state the following theorem using the above results and Theorem 2 of [36].

Theorem 1. *The virus-free equilibrium E_0 is locally asymptotically stable if $R_I < 1,$ and unstable if $R_I > 1.$*

Local stability of virus-free equilibrium shows that the infection will die out if basic reproduction number is less than one and infection will further go on if basic reproduction number is more than one. To ensure that the virus-free equilibrium is independent of initial concentration of cells, there is a need to study the global stability, which is shown in the next theorem.

Theorem 2. *The virus-free equilibrium E_0 is globally asymptotically stable if $R_I < 1.$*

Proof. Let us define the following Lyapunov function:

$$L = y_1 + \frac{\beta}{\delta_1 + \beta}y_2 + \frac{\delta_1 + \theta_1 + \gamma_1 \frac{\mu}{\mu_0}}{k}v.$$

Taking the derivative of L along all the solutions of model (2), we get

$$\begin{aligned} \dot{L} &= \left[\frac{(q\delta_1 + \beta)\alpha xv}{(\delta_1 + \beta)(1 + \alpha_1 v)} - \frac{(\delta_1 + \theta_1 + \gamma_1 \frac{\mu}{\mu_0})(k_0 + \theta_2 + \gamma_2 z)}{k} v - \gamma_1 y_1 z + \frac{\mu}{\mu_0} \gamma_1 y_1 \right] \\ &\leq \left[\frac{(q\delta_1 + \beta)\alpha xv}{\delta_1 + \beta} - \frac{(\delta_1 + \theta_1 + \gamma_1 \frac{\mu}{\mu_0})(k_0 + \theta_2 + \gamma_2 z)}{k} v - \gamma_1 y_1 z + \frac{\mu}{\mu_0} \gamma_1 y_1 \right]. \end{aligned}$$

From VFE equation, $x = x_0 = \lambda/\delta_0$, and $z = z_0 = \mu/\mu_0$ we have

$$\dot{L} \leq \left[\frac{(q\delta_1 + \beta)\alpha \lambda}{\delta_0(\delta_1 + \beta)} - \frac{(\delta_1 + \theta_1 + \gamma_1 \frac{\mu}{\mu_0})(k_0 + \theta_2 + \gamma_2 \frac{\mu}{\mu_0})}{k} \right] v.$$

$R_I < 1$ implies that

$$\frac{(q\delta_1 + \beta)\alpha \lambda}{\delta_0(\delta_1 + \beta)} < \frac{(\delta_1 + \theta_1 + \gamma_1 \frac{\mu}{\mu_0})(k_0 + \theta_2 + \gamma_2 \frac{\mu}{\mu_0})}{k},$$

therefore, we obtain that $\dot{L} \leq 0$ if $R_I < 1$. Since the largest invariant set in $\{(x, y_1, y_2, v, z) \in \Omega: \dot{L} = 0\}$ is the singleton set $\{E_0\}$, by LaSalle’s invariance principle [19] this implies that E_0 is globally asymptotically stable. \square

Biologically, this theorem depicts that infection is cleared from the body if the average number of newly infected cells is less than one, which is independent of initial concentration of cells.

4.1 Existence of interior equilibrium $E_1(x^*, y_1^*, y_2^*, v^*, z^*)$

Equating equations of system (2) to zero, we note that x^*, y_1^*, y_2^*, v^* , and z^* are the positive solutions of the following algebraic equations:

$$\lambda - \delta_0 x - \frac{\alpha xv}{1 + \alpha_1 v} = 0, \tag{3}$$

$$\frac{q\alpha xv}{1 + \alpha_1 v} - \delta_1 y_1 - \gamma_1 y_1 z + \beta y_2 - \theta_1 y_1 = 0, \tag{4}$$

$$\frac{(1 - q)\alpha xv}{1 + \alpha_1 v} - \delta_1 y_2 - \beta y_2 = 0, \tag{5}$$

$$k y_1 - k_0 v - \gamma_2 v z - \theta_2 v = 0, \tag{6}$$

$$\mu - \mu_0 z + \mu_1 y_1 z + \mu_2 v z = 0. \tag{7}$$

After solving equations (3), (5), (6), we get

$$x = \frac{\lambda(1 + \alpha_1 v)}{\delta_0 + (\delta_0 \alpha_1 + \alpha)v}, \quad y_1 = \frac{k_0 + \theta_2 + \gamma_2 z}{k} v, \quad y_2 = \frac{(1 - q)\alpha \lambda v}{(\delta_1 + \beta)(\delta_0 + (\delta_0 \alpha_1 + \alpha)v)}.$$

Now, substituting these values of x, y_1, y_2 in equations (4) and (7), we get the following equations:

$$\frac{\mu_1 \gamma_2}{k} v z^2 + \left(\frac{\mu_1 (k_0 + \theta_2)}{k} + \mu_2 \right) v z - \mu_0 z + \mu = 0, \tag{8}$$

$$\gamma_1 \gamma_2 z^2 + B z + (\delta_1 + \theta_1)(k_0 + \theta_2) - \frac{\alpha \lambda k (q \delta_1 + \beta)}{(\delta_1 + \beta)(\delta_0 + (\delta_0 \alpha_1 + \alpha) v)} = 0, \tag{9}$$

where $B = (\delta_1 + \theta_1) \gamma_2 + (k_0 + \theta_2) \gamma_1 > 0$.

We solve equations (8) and (9) using isocline method. Let us consider

$$f_1(z, v) = \frac{\mu_1 \gamma_2}{k} v z^2 + \left(\frac{\mu_1 (k_0 + \theta_2)}{k} + \mu_2 \right) v z - \mu_0 z + \mu = 0, \tag{10}$$

$$f_2(z, v) = \gamma_1 \gamma_2 z^2 + B z + (\delta_1 + \theta_1)(k_0 + \theta_2) - \frac{\alpha \lambda k (q \delta_1 + \beta)}{(\delta_1 + \beta)(\delta_0 + (\delta_0 \alpha_1 + \alpha) v)} = 0. \tag{11}$$

From equation (10) we note the following:

- (i) When $v = 0, z = \mu / \mu_0 =: z_1$.
- (ii) When $v \rightarrow \infty$, we have either $z = 0$ or $z = -(\mu_1 (k_0 + \theta_2) + \mu_2 k) / (\mu_1 \gamma_2)$.
- (iii)
$$\frac{dz}{dv} = - \frac{\partial f_1 / \partial v}{\partial f_1 / \partial z} = - \frac{\mu_1 \gamma_2 z^2 + (\mu_1 (k_0 + \theta_2) + \mu_2 k) z}{(2 \mu_1 \gamma_2 z + \mu_2 k) v + (\mu_1 (k_0 + \theta_2) v - \mu_0 k)}.$$

Then $dz/dv < 0$ if $\lambda > \mu_0 \delta / \mu_1$, which is trivial from the persistence theory (see Lemma 2). This implies that z is decreasing function of v . Now, from equation (11) we note the following:

- (i) When $v = 0$, we have

$$\gamma_1 \gamma_2 z^2 + B z + (\delta_1 + \theta_1)(k_0 + \theta_2) - \frac{\alpha \lambda k (q \delta_1 + \beta)}{(\delta_1 + \beta) \delta_0} = 0, \tag{12}$$

which gives $z = (-B + \sqrt{B^2 - 4AC}) / (2A) =: z_2$, where $A = \gamma_1 \gamma_2, B = (\delta_1 + \theta_1) \gamma_2 + (k_0 + \theta_2) \gamma_1$, and $C = (\delta_1 + \theta_1)(k_0 + \theta_2) - \alpha \lambda k (q \delta_1 + \beta) / ((\delta_1 + \beta) \delta_0)$.

The above polynomial (12) has unique positive root if $C < 0$, i.e. if $R_0 > 1$, where $R_0 = (\alpha \lambda k (q \delta_1 + \beta)) / ((\delta_1 + \beta) \delta_0 (\delta_1 + \theta_1)(k_0 + \theta_2))$ is the basic reproduction number in the absence of immune response, which is computed in Section 5.

- (ii) Now, when $z = 0$, in equation (11), we have

$$v = \frac{1}{\delta_0 \alpha_1 + \alpha} \left(\frac{\alpha \lambda k (q \delta_1 + \beta)}{(\delta_1 + \beta)(\delta_1 + \theta_1)(k_0 + \theta_2)} - \delta_0 \right) = \frac{\delta_0}{\delta_0 \alpha_1 + \alpha} (R_0 - 1),$$

which is positive if $R_0 > 1$.

- (iii)
$$\frac{dz}{dv} = - \frac{\partial f_2 / \partial v}{\partial f_2 / \partial z} = - \frac{\frac{\alpha \lambda k (q \delta_1 + \beta)(\delta_0 \alpha_1 + \alpha)}{(\delta_1 + \beta)(\delta_0 + (\delta_0 \alpha_1 + \alpha) v)^2}}{2 \gamma_1 \gamma_2 z + B} < 0.$$

The above analysis shows that the two isoclines (10) and (11) intersects each other in the positive quadrant if $z_2 > z_1$, i.e. $R_I > 1$. Thus, the interior equilibrium exists if $R_I > 1$. This shows that if the number of newly infected cells produced by a single infected cell when all other cells are healthy is more than one, then infection persists and interior equilibrium exists.

4.2 Analysis at $R_I = 1$

To study the behaviour of the equilibrium points at $R_I = 1$, we use the center manifold theorem [2] as, at $R_I = 1$, linearization has a simple zero eigenvalue, hence linearization is inconclusive [31]. We made following assumptions to apply center manifold theorem to system (2).

Let $x = x_1, y_1 = x_2, y_2 = x_3, v = x_4$, and $z = x_5$, then system (2) can be rewrite as

$$\begin{aligned} \dot{x}_1 &= \lambda - \delta_0 x_1 - \frac{\alpha x_1 x_4}{1 + \alpha_1 x_4} = f_1, \\ \dot{x}_2 &= \frac{q\alpha x_1 x_4}{1 + \alpha_1 x_4} - \delta_1 x_2 + \beta x_3 - \gamma_1 x_2 x_5 - \theta_1 x_2 = f_2, \\ \dot{x}_3 &= \frac{(1 - q)\alpha x_1 x_4}{1 + \alpha_1 x_4} - \delta_1 x_3 - \beta x_3 = f_3, \\ \dot{x}_4 &= kx_2 - k_0 x_4 - \gamma_2 x_4 x_5 - \theta_2 x_4 = f_4, \\ \dot{x}_5 &= \mu - \mu_0 x_5 + \mu_1 x_2 x_5 + \mu_2 x_4 x_5 = f_5. \end{aligned} \tag{13}$$

At $R_I = 1$, we have α as bifurcation parameter, and this is given by

$$\alpha = \alpha^* = \frac{(\delta_1 + \beta)\delta_0(\delta_1 + \theta_1 + \frac{\gamma_1 \mu}{\mu_0})(k_0 + \theta_2 + \frac{\gamma_2 \mu}{\mu_0})}{\lambda k(q\delta_1 + \beta)}.$$

The linearization of the above system (13) at E_0 and for $\alpha = \alpha^*$ gives one simple zero eigenvalue, and other eigenvalues have negative real part, so central manifold theory was applied. We find the right eigenvector u of the Jacobian matrix at E_0 , and $\alpha = \alpha^*$ corresponding to the zero eigenvalue, which is given by $u = [u_1, u_2, u_3, u_4, u_5]^T$, where $u_1 = -\alpha^* x_0 / \delta_0, u_2 = (k_0 + \theta_2 + \gamma_2 z_0) / k, u_3 = (1 - q)\alpha^* x_0 / \delta_0, u_4 = 1, u_5 = (z_0(\mu_1(k_0 + \theta_2 + \gamma_2 z_0) + \mu_2 k)) / k$. The Jacobian matrix at E_0 and $\alpha = \alpha^*$ has a left eigenvector $w = [w_1, w_2, w_3, w_4, w_5]$, where $w_1 = 0, w_2 = 1, w_3 = \beta / (\delta_1 + \beta), w_4 = (\delta_1 + \theta_1 + \gamma_1 z_0) / k, w_5 = 0$. Further, the associated nonzero partial derivatives of the functions associated with system (13) at VFE E_0 and $\alpha = \alpha^*$ are:

$$\begin{aligned} \frac{\partial^2 f_2}{\partial x_1 \partial x_4} &= \frac{\partial^2 f_2}{\partial x_4 \partial x_1} = q\alpha^*, & \frac{\partial^2 f_2}{\partial x_4^2} &= -2q\alpha^* \alpha_1 x_0, & \frac{\partial^2 f_2}{\partial x_2 \partial x_5} &= \frac{\partial^2 f_2}{\partial x_5 \partial x_2} = -\gamma_1, \\ \frac{\partial^2 f_3}{\partial x_1 \partial x_4} &= \frac{\partial^2 f_3}{\partial x_4 \partial x_1} = (1 - q)\alpha^*, & \frac{\partial^2 f_3}{\partial x_4^2} &= -2(1 - q)\alpha^* \alpha_1 x_0, \\ \frac{\partial^2 f_4}{\partial x_4 \partial x_5} &= \frac{\partial^2 f_4}{\partial x_5 \partial x_4} = -\gamma_2, & \frac{\partial^2 f_2}{\partial x_4 \partial \alpha^*} &= qx_0, & \frac{\partial^2 f_3}{\partial x_4 \partial \alpha^*} &= (1 - q)x_0. \end{aligned}$$

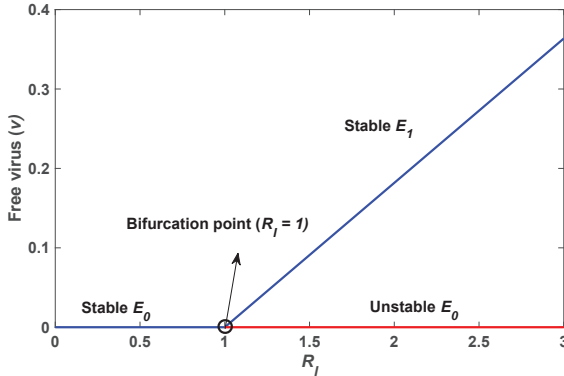


Figure 2. Plot of free virus versus basic reproduction number R_I .

From Theorem 4.1 of [2] the bifurcation constants a and b are given by

$$\begin{aligned}
 a &= \sum_{k,i,j=1}^5 w_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_0) \\
 &= -\frac{q\delta_1 + \beta}{\delta_0(\delta_1 + \beta)} (\alpha^* + 2\delta_0\alpha_1)\alpha^* x_0 - w_2 u_2 u_5 \gamma_1 - w_4 u_4 u_5 \gamma_2.
 \end{aligned}$$

For the given values of w_k 's, $k = 2, 3, 4$, and u_i, u_j 's, $i, j = 1, 2, 3, 4, 5$, $a < 0$, and

$$b = \sum_{k,i=1}^5 w_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \alpha^*}(E_0) = w_2(u_4 q x_0) + w_3(u_4(1 - q)x_0) = \frac{(q\delta_1 + \beta)x_0}{\delta_1 + \beta} > 0.$$

Thus, from Theorem 4.1(iv) of [2] we conclude the following result.

Theorem 3. *At $R_I = 1$, virus-free equilibrium changes its stability from stable to unstable, which shows that system (2) exhibits a transcritical bifurcation at $R_I = 1$ (Fig. 2).*

In Fig. 2, we plotted the V component of the steady states against R_I . When $R_I < 1$, only E_0 exists and is stable, and as R_I crosses 1, i.e. when R_I becomes greater than 1, a transcritical bifurcation of steady state E_0 occurs, and E_0 becomes unstable, while E_1 comes into existence.

In the next theorem, we show that E_1 is locally asymptotically stable under certain conditions.

Theorem 4. *The interior equilibrium $E_1(x^*, y_1^*, y_2^*, v^*, z^*)$ is locally asymptotically stable in \mathbb{R}_+^5 if the following inequalities hold true:*

$$3\alpha v^* x^* < 2\lambda(1 + \alpha_1 v^*), \tag{14}$$

$$\left(\frac{\mu_2 k}{\gamma_2 v^*} + \frac{\mu_1 q \alpha x^*}{\gamma_1 y_1^* (1 + \alpha_1 v^*)^2} \right)^2 < \frac{1}{4} \frac{\mu_1 \mu_2 P(k_0 + \theta_2 + \gamma_2 z^*)}{\gamma_1 \gamma_2 y_1^* v^*}, \tag{15}$$

$$3\gamma_2 \alpha^2 x^{*3} v^* < c_4 \lambda \mu_2 z^* (k_0 + \theta_2 + \gamma_2 z^*) (1 + \alpha_1 v^*)^4, \tag{16}$$

where

$$c_4 < \min \left\{ \frac{1}{3} \frac{\lambda \gamma_1 (1 + \alpha_1 v^*)^2 P y_1^*}{\mu_1 x^* z^* q^2 \alpha^2 v^{*2}}, \frac{1}{3} \frac{x^* P (\delta_1 + \beta)^2 \gamma_1 y_1^*}{\lambda \mu_1 z^* (1 - q)^2 \beta^2} \right\}, \quad P = \delta_1 + \theta_1 + \gamma_1 z^*.$$

Proof. Let $X = x - x^*, Y_1 = y_1 - y_1^*, Y_2 = y_2 - y_2^*, V = v - v^*$ and $Z = z - z^*$ be the small perturbations about the interior equilibrium E_1 . Using the above new variables, we linearize system (2) around the interior equilibrium E_1 . Then, in the linear model, we consider the following positive definite function:

$$W_1 = \frac{1}{2} X^2 + \frac{1}{2} c_1 Y_1^2 + \frac{1}{2} c_2 Y_2^2 + \frac{1}{2} c_3 V^2 + \frac{1}{2} c_4 Z^2,$$

where $c_1, c_2, c_3,$ and c_4 are positive constants to be chosen suitably.

Now differentiating W_1 with respect to time t along the solutions of linearized version of model (2), a little algebraic manipulation yields

$$\begin{aligned} \dot{W}_1 = & -\frac{1}{2} a_{11} X^2 + a_{12} X Y_1 - \frac{1}{2} a_{22} Y_1^2 - \frac{1}{2} a_{11} X^2 + a_{13} X Y_2 - \frac{1}{2} a_{33} Y_2^2 \\ & - \frac{1}{2} a_{11} X^2 + a_{14} X V - \frac{1}{2} a_{44} V^2 - \frac{1}{2} a_{22} Y_1^2 + a_{23} Y_1 Y_2 - \frac{1}{2} a_{33} Y_2^2 \\ & - \frac{1}{2} a_{22} Y_1^2 + a_{24} Y_1 V - \frac{1}{2} a_{44} V^2 - \frac{1}{2} a_{22} Y_1^2 + a_{25} Y_1 Z - \frac{1}{2} a_{55} Z^2 \\ & - \frac{1}{2} a_{33} Y_2^2 + a_{34} Y_2 V - \frac{1}{2} a_{44} V^2 - \frac{1}{2} a_{44} V^2 + a_{45} V Z - \frac{1}{2} a_{55} Z^2, \end{aligned}$$

where

$$\begin{aligned} a_{11} &= \frac{2}{3} \frac{\lambda}{x^*}, & a_{22} &= \frac{1}{2} c_1 P, & a_{33} &= \frac{2}{3} c_2 (\delta_1 + \beta), & a_{44} &= \frac{1}{2} c_3 (k_0 + \theta_2 + \gamma_2 z^*), \\ a_{55} &= c_4 \frac{\mu}{z^*}, & a_{12} &= \frac{c_1 q \alpha v^*}{1 + \alpha_1 v^*}, & a_{13} &= \frac{c_2 (1 - q) \alpha v^*}{1 + \alpha_1 v^*}, & a_{14} &= -\frac{\alpha x^*}{(1 + \alpha_1 v^*)^2}, \\ a_{23} &= c_1 \beta, & a_{24} &= \frac{c_1 q \alpha x^*}{(1 + \alpha_1 v^*)^2} + c_3 k, & a_{25} &= c_4 \mu_1 z^* - c_1 \gamma_1 y_1^*, \\ a_{34} &= \frac{c_2 (1 - q) \alpha x^*}{(1 + \alpha_1 v^*)^2}, & a_{45} &= c_4 \mu_2 z^* - c_3 \gamma_2 v^*. \end{aligned}$$

Sufficient conditions for \dot{W}_1 to be negative definite are given as follows:

$$a_{12}^2 < a_{11} a_{22}, \quad a_{13}^2 < a_{11} a_{33}, \quad a_{14}^2 < a_{11} a_{44}, \tag{17}$$

$$a_{23}^2 < a_{22} a_{33}, \quad a_{24}^2 < a_{22} a_{44}, \quad a_{25}^2 < a_{22} a_{55}, \tag{18}$$

$$a_{34}^2 < a_{33} a_{44}, \quad a_{45}^2 < a_{44} a_{55}. \tag{19}$$

By choosing $c_1 = c_4 \mu_1 z^* / (\gamma_1 y_1^*)$ and $c_3 = c_4 \mu_2 z^* / (\gamma_2 v^*)$ we note that conditions (18)₃ and (19)₂ are satisfied. Let us choose $c_2 = x^* (\delta_1 + \beta) / ((1 - q)^2 \lambda)$, then conditions (17)₃

and $(19)_1$ are equivalent, and we see that $(16) \Rightarrow (17)_3$ and $(19)_1$. Further, if we choose c_4 in such a manner that it satisfies the inequality

$$c_4 < \min \left\{ \frac{1}{3} \frac{\lambda \gamma_1 (1 + \alpha_1 v^*)^2 P y_1^*}{\mu_1 x^* z^* q^2 \alpha^2 v^{*2}}, \frac{1}{3} \frac{x^* P (\delta_1 + \beta)^2 \gamma_1 y_1^*}{\lambda \mu_1 z^* (1 - q)^2 \beta^2} \right\},$$

then conditions $(17)_1$ and $(18)_1$ are correspondingly satisfied. Further, we note that $(14) \Rightarrow (17)_2$ and $(15) \Rightarrow (18)_2$. Hence the theorem follows. \square

In the next theorem, we are able to find sufficient conditions for E_1 to be globally asymptotically stable.

Theorem 5. *Let the following inequalities hold in the interior of the positive orthant Ω :*

$$3\alpha v^* x^* < 2\lambda(1 + \alpha_1 v^*), \tag{20}$$

$$\left(\frac{\mu_2 k}{\gamma_2 v^*} + \frac{\mu_1 q \alpha x^*}{\gamma_1 y_1^* (1 + \alpha_1 v^*)} \right)^2 < \frac{1}{4} \frac{\mu_1 \mu_2 P (k_0 + \theta_2 + \gamma_2 z^*)}{\gamma_1 \gamma_2 y_1^* v^*}, \tag{21}$$

$$2\mu_1 \gamma_1 \mu_m^2 y_1^* < \mu \delta_m^2 P, \tag{22}$$

$$2\mu_2 \gamma_2 \mu_m^2 v^* < \mu \delta_m^2 (k_0 + \theta_2 + \gamma_2 z^*), \tag{23}$$

$$3\gamma_2 \alpha^2 \lambda^2 x^* v^* < m_4 \mu_2 z^* (k_0 + \theta_2 + \gamma_2 z^*) \delta_0^2 (1 + \alpha_1 v^*)^2, \tag{24}$$

where

$$m_4 < \min \left\{ \frac{1}{3} \frac{\lambda \gamma_1 y_1^* P (1 + \alpha_1 v_m)^2}{\mu_1 x^* z^* q^2 \alpha^2 v_m^2}, \frac{1}{3} \frac{x^* P (\delta_1 + \beta)^2 \gamma_1 y_1^*}{\lambda \mu_1 z^* (1 - q)^2 \beta^2} \right\}.$$

Then $E_1(x^*, y_1^*, y_2^*, v^*, z^*)$ is globally asymptotically stable with respect to all solutions in the interior of the positive orthant Ω .

Proof. We consider the following positive definite function about E_1 :

$$W_2 = \frac{1}{2}(x - x^*)^2 + \frac{m_1}{2}(y_1 - y_1^*)^2 + \frac{m_2}{2}(y_2 - y_2^*)^2 + \frac{m_3}{2}(v - v^*)^2 + \frac{m_4}{2}(z - z^*)^2,$$

where $m_1, m_2, m_3,$ and m_4 are positive constants to be chosen suitably.

Now differentiating W_2 with respect to time t along the solutions of model (2), we get

$$\begin{aligned} \dot{W}_2 = & -\frac{1}{2}b_{11}(x - x^*)^2 + b_{12}(x - x^*)(y_1 - y_1^*) - \frac{1}{2}b_{22}(y_1 - y_1^*)^2 \\ & - \frac{1}{2}b_{11}(x - x^*)^2 + b_{13}(x - x^*)(y_2 - y_2^*) - \frac{1}{2}b_{33}(y_2 - y_2^*)^2 \\ & - \frac{1}{2}b_{11}(x - x^*)^2 + b_{14}(x - x^*)(v - v^*) - \frac{1}{2}b_{44}(v - v^*)^2 \\ & - \frac{1}{2}b_{22}(y_1 - y_1^*)^2 + b_{23}(y_1 - y_1^*)(y_2 - y_2^*) - \frac{1}{2}b_{33}(y_2 - y_2^*)^2 \\ & - \frac{1}{2}b_{22}(y_1 - y_1^*)^2 + b_{24}(y_1 - y_1^*)(v - v^*) - \frac{1}{2}b_{44}(v - v^*)^2 \end{aligned}$$

$$\begin{aligned}
& -\frac{1}{2}b_{22}(y_1 - y_1^*)^2 + b_{25}(y_1 - y_1^*)(z - z^*) - \frac{1}{2}b_{55}(z - z^*)^2 \\
& -\frac{1}{2}b_{33}(y_2 - y_2^*)^2 + b_{34}(y_2 - y_2^*)(v - v^*) - \frac{1}{2}b_{44}(v - v^*)^2 \\
& -\frac{1}{2}b_{44}(v - v^*)^2 + b_{45}(v - v^*)(z - z^*) - \frac{1}{2}b_{55}(z - z^*)^2,
\end{aligned}$$

where

$$\begin{aligned}
b_{11} &= \frac{2}{3} \frac{\lambda}{x^*}, & b_{22} &= \frac{1}{2} m_1 P, & b_{33} &= \frac{2}{3} m_2 (\delta_1 + \beta), & b_{44} &= \frac{1}{2} m_3 (k_0 + \theta_2 + \gamma_2 z^*), \\
b_{55} &= m_4 \frac{\mu}{z^*}, & b_{12} &= \frac{m_1 q \alpha v}{1 + \alpha_1 v}, & b_{13} &= \frac{m_2 (1 - q) \alpha v^*}{1 + \alpha_1 v^*}, \\
b_{14} &= -\frac{\alpha x}{(1 + \alpha_1 v^*)(1 + \alpha_1 v)}, & b_{23} &= m_1 \beta, & b_{24} &= \frac{m_1 q \alpha x^*}{(1 + \alpha_1 v^*)(1 + \alpha_1 v)} + m_3 k, \\
b_{25} &= m_4 \mu_1 z - m_1 \gamma_1 y_1, & b_{34} &= \frac{m_2 (1 - q) \alpha x}{(1 + \alpha_1 v^*)(1 + \alpha_1 v)}, & b_{45} &= m_4 \mu_2 z - m_3 \gamma_2 v.
\end{aligned}$$

Sufficient conditions for \dot{W}_2 to be negative definite are given as follows:

$$b_{12}^2 < b_{11} b_{22}, \quad b_{13}^2 < b_{11} b_{33}, \quad b_{14}^2 < b_{11} b_{44}, \quad (25)$$

$$b_{23}^2 < b_{22} b_{33}, \quad b_{24}^2 < b_{22} b_{44}, \quad b_{25}^2 < b_{22} b_{55}, \quad (26)$$

$$b_{34}^2 < b_{33} b_{44}, \quad b_{45}^2 < b_{44} b_{55}. \quad (27)$$

Let us choose

$$m_1 = \frac{m_4 \mu_1 z^*}{\gamma_1 y_1^*}, \quad m_2 = \frac{x^* (\delta_1 + \beta)}{(1 - q)^2 \lambda}, \quad \text{and} \quad m_3 = \frac{m_4 \mu_2 z^*}{\gamma_2 v^*}.$$

Then we note that for chosen value of m_4 , conditions (25)₁ and (26)₁ are correspondingly satisfied. Further, (20) \Rightarrow (25)₂, (21) \Rightarrow (26)₂, (22) \Rightarrow (26)₃, (23) \Rightarrow (27)₂, (24) \Rightarrow (25)₃ and (27)₁. Hence the theorem follows. \square

Theorem 5 shows that by decreasing α and by increasing θ_1 and θ_2 , appropriately, conditions (20)–(24) may be satisfied. This shows that stability of the system increases by decreasing the infection rate of uninfected cells and by increasing the treatment rates of infected cells and virus at some appropriate levels.

5 A special case of model (2) without immune response

In the absence of immune response, model (2) reduces to the following model:

$$\begin{aligned}
\frac{dx}{dt} &= \lambda - \delta_0 x - \frac{\alpha x v}{1 + \alpha_1 v}, & \frac{dy_1}{dt} &= \frac{q \alpha x v}{1 + \alpha_1 v} - \delta_1 y_1 + \beta y_2 - \theta_1 y_1, \\
\frac{dy_2}{dt} &= \frac{(1 - q) \alpha x v}{1 + \alpha_1 v} - \delta_1 y_2 - \beta y_2, & \frac{dv}{dt} &= k y_1 - k_0 v - \theta_2 v.
\end{aligned} \quad (28)$$

Similar to model (2), this model (28) also exhibits two equilibria: (i) the virus-free equilibrium (VFE) $e_0(\lambda/\delta_0, 0, 0, 0)$ and (ii) the interior equilibrium (IE) $e_1(\bar{x}, \bar{y}_1, \bar{y}_2, \bar{v})$.

Using next generation operator method, as discussed in the previous section, the basic reproduction number R_0 can be computed, and we note that R_0 is given by $R_0 = \alpha\lambda k(q\delta_1 + \beta)/((\delta_1 + \beta)\delta_0(\delta_1 + \theta_1)(k_0 + \theta_2))$.

Under the similar analysis as done in the previous sections, one can prove the following theorem easily.

Theorem 6.

- (i) *The virus-free equilibrium e_0 is locally asymptotically stable if $R_0 < 1$, and e_0 is unstable if $R_0 > 1$.*
- (ii) *The virus-free equilibrium e_0 is globally asymptotically stable in Ω if $R_0 < 1$.*
- (iii) *Model (28) exhibits a transcritical bifurcation at $R_0 = 1$.*

5.1 Existence of interior equilibrium $e_1(\bar{x}, \bar{y}_1, \bar{y}_2, \bar{v})$

In case of interior equilibrium $e_1(\bar{x}, \bar{y}_1, \bar{y}_2, \bar{v})$, we note that $\bar{x}, \bar{y}_1, \bar{y}_2$ and \bar{v} are given by

$$\bar{x} = \frac{\lambda(1 + \alpha_1\bar{v})}{\delta_0 + (\delta_0\alpha_1 + \alpha)\bar{v}}, \quad \bar{y}_1 = \frac{k_0 + \theta_2}{k}\bar{v}, \quad \bar{y}_2 = \frac{(1 - q)\alpha\lambda\bar{v}}{(\delta_1 + \beta)(\delta_0 + (\delta_0\alpha_1 + \alpha)\bar{v})},$$

$$\bar{v} = \frac{1}{\delta_0\alpha_1 + \alpha} \left(\frac{\alpha\lambda k(q\delta_1 + \beta)}{(\delta_1 + \beta)(\delta_1 + \theta_1)(k_0 + \theta_2)} - \delta_0 \right).$$

It is clear that \bar{v} is positive if $R_0 = \alpha\lambda k(q\delta_1 + \beta)/(\delta_0(\delta_1 + \beta)(\delta_1 + \theta_1)(k_0 + \theta_2)) > 1$. This shows that the interior equilibrium in absence of immune response exists if $R_0 > 1$. The stability behaviour of the interior equilibrium e_1 can be studied in a similar manner as done in the previous section.

By comparing R_0 and R_I we note that $R_I < R_0$. This shows that rate of infection will be slow in the presence of immune response.

6 Simulation results

In this section, we present the numerical simulation results to elucidate the analytical findings. MatLab 7.10 and Mathematica 7.0 are used for simulation purposes.

6.1 Global stability and phase plane analysis of the subsystem

We note that the interior equilibrium $E_1(x^*, y_1^*, y_2^*, v^*, z^*)$ exists for the set of values of parameters given in Table 1, and $(x^*, y_1^*, y_2^*, v^*, z^*)$ are given as follows: $x^* = 948.6799$, $y_1^* = 1.2014$, $y_2^* = 0.5565$, $v^* = 0.2357$, and $z^* = 0.1260$.

We observe that all conditions given in Theorems 4 and 5 are satisfied. This shows that E_1 is locally as well as globally asymptotically stable for the set of values of parameters in Table 1.

Table 1. Description of parameters (units) used in model (2) and their values.

| Parameters (units) | Description | Values | Source |
|--|---|--------|-------------|
| λ ($\text{mm}^{-3}\text{d}^{-1}$) | Influx rate constant of $x(t)$ | 10 | [4, 33, 34] |
| δ_0 (d^{-1}) | Death rate constant of $x(t)$ | 0.01 | [4, 33, 34] |
| δ_1 (d^{-1}) | Loss rate constant of $y_1(t)$ and $y_2(t)$ | 0.015 | [33, 34] |
| k (d^{-1}) | Viral production rate constant | 0.08 | – |
| k_0 (d^{-1}) | Clearance rate constant of $v(t)$ | 0.02 | – |
| α ($\text{mm}^{-3}\text{d}^{-1}$) | Infection rate constant | 0.005 | – |
| α_1 ($\text{mm}^{-3}\text{d}^{-1}$) | Inhibition rate constant to infection | 5 | – |
| γ_1 (d^{-1}) | Killing rate constant of $y_1(t)$ by CTL IR | 0.2 | – |
| γ_2 (d^{-1}) | Killing rate constant of $v(t)$ by humoral IR | 0.3 | – |
| μ (d^{-1}) | Source rate of IR | 0.25 | – |
| μ_0 (d^{-1}) | Depletion rate constant of IR | 2 | – |
| μ_1 (d^{-1}) | Activation rate constant of CTL IR | 0.0035 | – |
| μ_2 (d^{-1}) | Activation rate constant of humoral IR | 0.052 | – |
| β (d^{-1}) | Activation rate constant of $y_2(t)$ | 0.4 | – |
| θ_1 (d^{-1}) | Drug effectiveness for $y_1(t)$ | 0.38 | – |
| θ_2 (d^{-1}) | Drug effectiveness for $v(t)$ | 0.35 | – |
| q | Probability of infected cell joining y_1 | 0.55 | [25] |

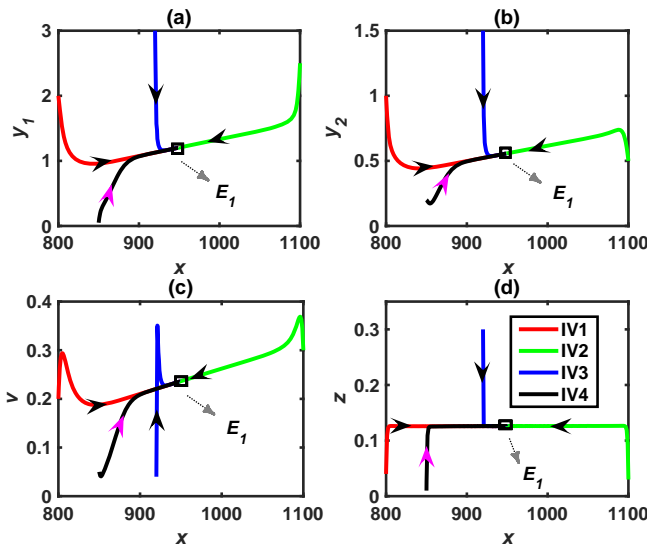


Figure 3. Global stability of the subsystem.

The phase plane analysis of the subsystem of model (2) in the xy_1 -, xy_2 -, xv -, and xz -planes are shown in Fig. 3. From these figure we note that all the trajectories initiating from different initial values converge to the same equilibrium point. The initial values are shown in the legend can be read as $IV1 \rightarrow [800, 2, 1, 0.2, 0.04]$, $IV2 \rightarrow [1100, 2.5, 0.5, 0.3, 0.03]$, $IV3 \rightarrow [920, 3, 1.5, 0.04, 0.05]$, and $IV4 \rightarrow [850, 0.05, 0.2, 0.05, 0.01]$. Since the system is globally asymptotically stable, therefore it is independent of initial status of the subpopulations.

6.2 Effect of saturated transmission rate on uninfected cells and productively infected cells

Figures 4(a) and 4(b) represent the effect of α on uninfected cells and productively infected cells, respectively. We observe that the concentration of uninfected cells is high (Fig. 4(a)) and that of productively infected cells is low (at zero level) for $\alpha = 0.001$ and, in this case, $R_I = 0.4598 < 1$. This shows that infection is no more at this stage. Further, the number of uninfected cells decreases with increase in α , which is obvious for real world scenarios when infection increases the number of uninfected or healthy cells declines. In Fig. 4(b), the number of productively infected cells increases with increase in infection rate α , which is also usual in real situations. Thus, infection can be controlled by controlling the spread of infection within the cells with the help of immune response and appropriate drugs. Figures 4(c) and 4(d) show the effect of α_1 , whereas α_1 changes reversibly with infection rate. In Fig. 4(c), we observe oscillations for small value of $\alpha_1 = 0.005$. In the expression for infection rate, when α_1 approaches zero, then this infection rate term $\alpha xv / (1 + \alpha_1 v)$ becomes bilinear, which is not realistic in case of large number of productively infected cells. It may be noted that behavior of productively infected cells is complementary to the behavior of uninfected cells, so similar explanation can be given for the oscillations in Fig. 4(d).

6.3 Effect of treatment and immune response on productively infected cells and free virus

The effect of therapeutic drugs θ_1 and θ_2 given to productively infected cells y_1 and free virus v are shown in Figs. 5(a) and 5(b), respectively. From these figures it follows that

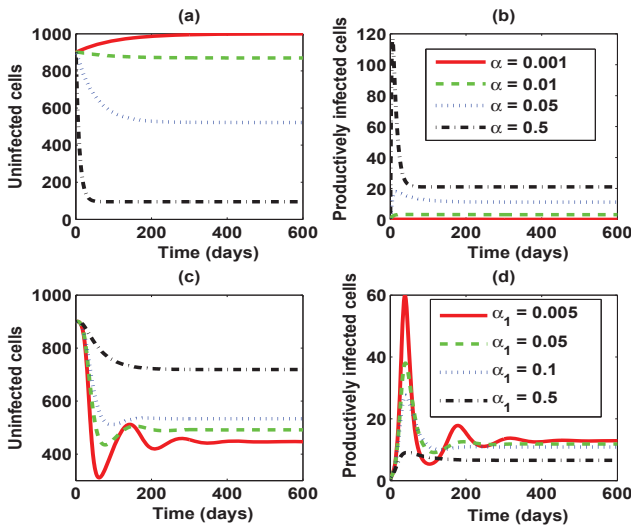


Figure 4. Effect of α and α_1 on uninfected cells (x) and productively infected cells (y_1), respectively.

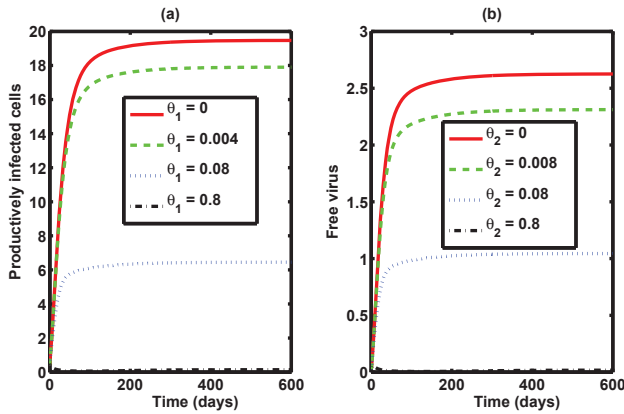


Figure 5. Effect of θ_1 on productively infected cells y_1 and effect of θ_2 on free virus v , respectively.

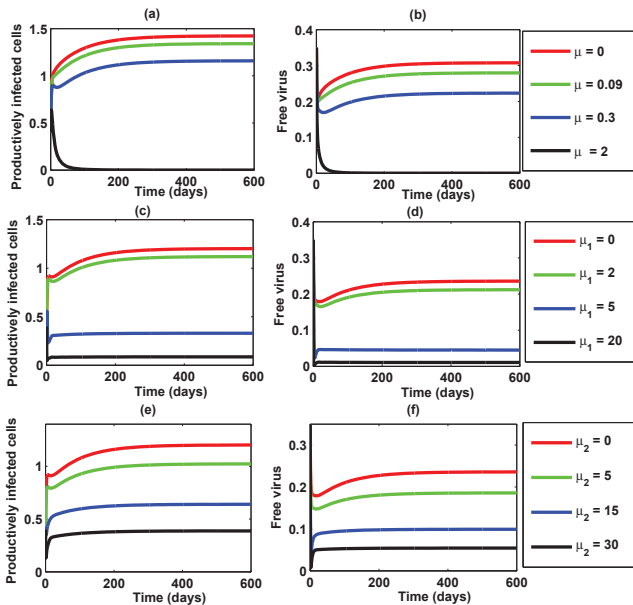


Figure 6. Effect of μ , μ_1 , μ_2 on productively infected cells (y_1) and free virus (v), respectively.

in the absence of treatment ($\theta_1 = \theta_2 = 0$), the number of productively infected cells and free virus are high. As efficacy of therapeutic drugs θ_1 and θ_2 increases, the number of productively infected cells and free virus decreases and settles down at their respective equilibrium levels. This highlights the efficacy of the drug in controlling the concentration of productively infected cells and free virus, respectively.

Figures 6(a) and 6(b) show that when immune response is not present, then trajectories settle at higher concentration of productively infected cells and free virus, while the

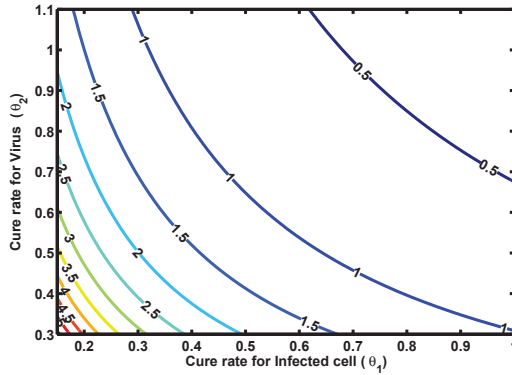


Figure 7. Variation of therapeutic drugs θ_1 and θ_2 on R_I .

concentration of the productively infected cells and free virus decreases with increase in immune response (μ) and approaches to zero for higher values of μ . In Figs. 6(c) and 6(d), the trajectories settle at high level for $\mu_1 = 0$, and for higher values of μ_1 , these trajectories are settled down at lower concentration of productively infected cells and free virus, but not approaching to zero as μ_1 is the increase in immune response due to stimulation from productively infected cells. Similar explanation can be given for Figs. 6(e) and 6(f), where μ_2 is the increase in immune response due to stimulation from free virus. It is interesting to note that if immune responses are at high levels, then productively infected cells and free virus can be brought back to zero level with adequate drugs, and thus, the infection may lead to reduction in viral load.

6.4 Variation of reproduction number

In the last figure (Fig. 7), we have shown the variation of R_I with respect to therapeutic drugs given to productively infected cells (θ_1) and virus (θ_2), respectively. We observe that for the less values of the therapeutic drug given to the productively infected cells ($\theta_1 = 0.15$) and that of viruses ($\theta_2 = 0.3$), the corresponding value of R_I is 5. It is apparent from Fig. 7 that if we increase the amount of therapeutic drug given to the productively infected cells ($\theta_1 = 1$) and virus ($\theta_2 = 1.1$), the corresponding value of R_I decreases, i.e. $R_I = 0.5$. This emphasize that combination of therapy is useful in reducing the viral load and, ultimately, to lower the infection.

7 Conclusions

In this paper, we constructed a virus dynamics model to understand the viral–host interaction and elucidate the effect of total immune response (innate, CTL, and humoral) together with the treatment given to the free virus as well as the productively infected cells. The model is comprised of 5-state variables, that is, uninfected cells, productively infected cells, latently infected cells, free virus, and total immune response. We performed stability

analysis of the model and observed that there exists two nonnegative equilibria: virus-free equilibrium (VFE, no persistent of virus) and interior equilibrium (IE, persistent of virus). From the global stability analysis of the virus-free equilibrium (VFE) it is depicted that the clearance of virus from the body is independent of initial status of subpopulations (Theorem 2). From the analysis of the model at $R_I = 1$ it is observed that VFE loses its stability from the stable state to unstable state, which gives birth to the transcritical bifurcation (Fig. 2), and the interior equilibrium exists for $R_I > 1$.

Simulation results show that the saturated infection rate gives realistic dynamics of transmission as bilinear infection rate leads to oscillatory behavior in subpopulations (Figs. 4(c) and 4(d)). The reduction in infection rate and increment in the effectiveness of therapy given to the productively infected cells and virus appropriately will lead to lower the count of infection and viral load. It is also shown that the number of new infection can be lowered via providing adequate treatment to both free virus and productively infected cells (Fig. 7). However, virus dynamics models suggest that the infection will extinct once the therapeutic drugs can target the latently infected cells, which lead to new infection upon activation.

The model also provides the insights into the dynamics of viral infection in absence of immune response. It is evident from the analysis of model (28) that the virus-free equilibrium (VFE) is globally asymptotically stable if $R_0 < 1$. The basic reproductive number in absence of immune response R_0 is greater than basic reproductive number in the presence of immune response R_I , i.e. $R_0 > R_I$. This implies that in the presence of immune response, the number of secondary infections will be less, which suggests that infection may be eradicated if $R_I < 1$. From the expression of R_I it is observed that the number of secondary infections decreases with the enhancement of immune response and drug efficacy. This shows that R_I may be made less than one by increasing drug efficacy and improving the immune conditions. Thus, increase in treatment is effective in controlling the number of productively infected cells and free viruses. In addition, action of immune response also reduces the virus load. It has also been shown in Fig. 7 that the reproduction number can be reduced by applying adequate combination of therapeutic drugs, which helps in reduction of viral load.

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