Global stability of virus dynamics model with capsids and two routes of infection

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Abstract: We study the global dynamics of within-host viral infection model with virus DNA- containing capsids. The effect of antibody immune response has been considered. The uninfected cell become infected due to its contacts with a virus or an infected cell. The incidence rate is given by saturation. The well-posedness of the model is establised. We utilise Lyapunov method and apply LaSalle's invariance principle to prove the global stability of the equilibria. We support our theoretical results by numerical simulations.

Keywords: viral infection; global stability; Lyapunov function; capsids; immune system; numerical simulations.

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1 Introduction

During last decades, many efforts have been made for mathematical modelling and analysis of viral infections. A proper model of virus dynamics could provide insights of a better understanding of the disease and clinical treatments used to fight against it. The basic virus dynamics model focused on exploring the relation between three main compartments, uninfected cells (s), infected cells producing viruses (y), and free viruses (p) and is given by Nowak and Bangham (1996):

$$\dot{s} = \varrho - \xi s - \delta s p, \tag{1}$$

$$\dot{y} = \delta s p - \epsilon y, \tag{2}$$

$$\dot{p} = \varkappa y - \vartheta p. \tag{3}$$

The generation and death rate constants of compartments (s, y, p) are give by $(\varrho, \delta, \varkappa)$ and $(\xi, \epsilon, \vartheta)$, respectively. The term δsp represents the incidence rate of infection. The parameters $\varrho, \delta, \varkappa, \xi, \epsilon$ and ϑ are positive. The model has been developed in order to describe within-host dynamics of many human viruses such as human immunodeficiency virus (HIV) (Nowak and Bangham, 1996; Perelson et al., 1997; Perelson and Nelson, 1999; Elaiw et al., 2014, 2018a, 2018b, 2019b; Zhao et al., 2013; Gibelli et al., 2017; Elaiw and Elnahary, 2019; Elaiw and Alshaikh, 2019; Elaiw and AlShamrani, 2018, 2019; Elaiw and Almuallem, 2015, 2016, 2019; Li and Wang, 2014; Prakash et al., 2019; Liu and Zhang, 2019; Bellomo and Tao, 2020; Wang et al., 2019), hepatitis B virus (HBV) (Wang et al., 2010; Yousfi et al., 2011; Chenar et al., 2018), hepatitis C virus (HCV) (Neumann et al., 1998; Zhang and Xu, 2017; Pan and Chakrabarty, 2018; Kitagawa et al., 2019), human T-cell leukemia virus (HTLV) (Li and Shu, 2012; Wang et al., 2018) and chikungunya virus (CHIKV) (Wang and Liu, 2017; Elaiw et al., 2018c, 2019a) etc.

Manna and Chakrabarty have formulated and analysed the following HBV infection model with HBV DNA-containing capsids (Manna and Chakrabarty, 2015):

$$\dot{s} = \varrho - \xi s - \delta sp, \tag{4}$$

$$\dot{y} = \delta sp - \epsilon y, \tag{5}$$

$$\dot{z} = \varkappa y - (\alpha + \gamma)z, \tag{6}$$

$$\dot{p} = \alpha z - \vartheta p, \tag{7}$$

where z is the concentration of the capsids. The capsids are produced at rate $\varkappa y$, die at rate γz and cause viral replication at rate αz, where γ and α are positive constants. Model (4)–(7) has been extended in Manna and Chakrabarty (2017), Manna (2017), Xu and Geng (2019) and Guo et al. (2018).

In Manna and Chakrabarty (2015, 2017), Manna (2017), Xu and Geng (2019) and Guo et al. (2018), it has been assumed that the uninfected cells become infected due to its contact with the virus (viral infection). The uninfected cells can be infected via two ways of transmissions, namely, the diffusion-limited virus-to-cell transmission and the direct cell-to-cell transfer using virological synapses (Shu et al., 2018). The cell-to-cell transmission has been recognised in several works (see e.g., Jolly and Sattentau (2004), Lehmann et al. (2011) and Sato et al. (1992)). Recent studies have reported that over 50% of viral infection is due to the cell-to-cell transmission (Iwami et al., 2015) and even with an antiretroviral therapy, the cell-to-cell spread of the virus can still permit ongoing replication (Sigal et al., 2011). Therefore, for some viruses, cell-to-cell transmission seems to be a more powerful and efficient means of virus propagation than the virus-to-cell transmission (Komarova et al., 2012). Several mathematical models of virus dynamics with two ways of infection have been developed by many researchers (see e.g., Culshaw et al. (2003), Lai and Zou (2014), Elaiw et al. (2019c), Hobiny et al. (2018), Elaiw and Raezah (2017) and Yang et al. (2015)). However, in these papers the virus DNA-containing capsids was not included.

In the present paper we formulated a viral infection model with virus DNA-containing capsids and with both virus-to-cell and cell-to-cell transmissions. The nonnegativity and boundedness of the solutions of the model were proven. We established the global stability of the equilibria by using Lyapunov method and applying LaSalle's invariance principle.

2 The model

In this section we extend model (4)–(7) by incorporating

- both virus-to-cell and cell-to-cell transmissions
- saturated incidence rate
- antibody immune response

$$\dot{s} = \varrho - \xi s - \frac{\delta_1 sp}{1 + \omega_1 p} - \frac{\delta_2 sy}{1 + \omega_2 y}, \tag{8}$$

$$\dot{y} = \frac{\delta_1 sp}{1 + \omega_1 p} + \frac{\delta_2 sy}{1 + \omega_2 y} - \epsilon y, \tag{9}$$

$$\dot{z} = \varkappa y - (\alpha + \gamma)z, \tag{10}$$

$$\dot{p} = \alpha z - \vartheta p - \mu u p, \tag{11}$$
$$\dot{u} = \beta + \rho u p - \tau u, \tag{12}$$

where u is the concentration of the antibodies. Antibodies attack the viruses at rate μup. The antibodies are generated at a constant rate β, proliferate at rate ρup and die at rate τu. Parameters $\omega_1 \geq 0$ and $\omega_2 \geq 0$ are the saturation constants. All the other parameters of the model are positive.

2.1 Basic properties

Lemma 1: There exist such positive numbers Δ_1, Δ_2 and Δ_3 that the compact set

$$\Gamma = \{(s, y, z, p, u) \in \mathbb{R}^5_{\geq 0} : 0 \leq s, y \leq \Delta_1, 0 \leq z, p \leq \Delta_2, 0 \leq u \leq \Delta_3\}$$

is positively invariant.

Proof: Since

$$\begin{aligned}
&\dot{s}\mid_{s=0} = \varrho > 0,\\
&\dot{y}\mid_{y=0} = \frac{\delta_1 s p}{1+\omega_1 p} \geq 0, \qquad \forall s, p \geq 0,\\
&\dot{z}\mid_{z=0} = \varkappa y \geq 0, \qquad \forall y \geq 0,\\
&\dot{p}\mid_{p=0} = \alpha z \geq 0, \qquad \forall z \geq 0,\\
&\dot{u}\mid_{u=0} = \beta > 0,
\end{aligned}$$

then $(u(t), y(t), z(t), p(t), u(t)) \in \mathbb{R}^5_{\geq 0}$ with $(u(0), y(0), z(0), p(0), u(0)) \in \mathbb{R}^5_{\geq 0}$. Define

$$\begin{aligned}
&\Theta_1(t) = s(t) + y(t),\\
&\Theta_2(t) = z(t) + p(t) + \frac{\mu}{\rho} u(t).
\end{aligned} \tag{13}$$

Then from equations (8)–(12) we get

$$\dot{\Theta}_1(t) = \varrho - \xi s(t) - \epsilon y(t) \leq \varrho - \upsilon_1 (s(t) + y(t)) = \varrho - \upsilon_1 \Theta_1(t),$$

where, $\upsilon_1 = min\{\xi, \epsilon\}$. Hence $\Theta_1(t) \leq \Delta_1$, if $\Theta_1(0) \leq \Delta_1$, where $\Delta_1 = \frac{\varrho}{\upsilon_1}$. It follows that $0 \leq s(t), y(t) \leq \Delta_1$ if $0 \leq s(0) + y(0) \leq \Delta_1$. Moreover, we have

$$\begin{aligned}
\dot{\Theta}_2(t) &= \varkappa y(t) - \gamma z(t) - \vartheta p(t) + \frac{\mu}{\rho}\beta - \frac{\tau\mu}{\rho} u(t)\\
&\leq \varkappa \Delta_1 + \frac{\mu}{\rho}\beta - \upsilon_2 \left(z(t) + p(t) + \frac{\mu}{\rho} u(t) \right)\\
&= \varkappa \Delta_1 + \frac{\mu}{\rho}\beta - \upsilon_2 \Theta_2(t),
\end{aligned}$$

where, $\upsilon_2 = min\{\gamma, \vartheta, \tau\}$. Hence $\Theta_2(t) \leq \Delta_2$, if $\Theta_2(0) \leq \Delta_2$, where $\Delta_2 = \frac{\varkappa\Delta_1 + \frac{\mu}{\rho}\beta}{\upsilon_2}$. Since $z(t), p(t)$ and $u(t)$ are all non-negative, then $0 \leq z(t), p(t) \leq \Delta_2$ and $u(t) \leq \Delta_3$ if $0 \leq z(0) + p(0) + \frac{\mu}{\rho} u(0) \leq \Delta_2$, where $\Delta_3 = \frac{\rho\Delta_2}{\mu}$. □

2.2 Equilibria

We define the basic reproduction number of equations (8)–(12) as:

$$\mathcal{R}_0 = \frac{\varrho[\delta_1 \varkappa \tau \alpha + \delta_2(\alpha+\gamma)(\vartheta\tau + \mu\beta)]}{\epsilon\xi(\vartheta\tau+\mu\beta)(\alpha+\gamma)}, \tag{14}$$

which represents the average number of secondary infections and it can be written as: $\mathcal{R}_0 = \mathcal{R}_{01} + \mathcal{R}_{02}$, where

$$\mathcal{R}_{01} = \frac{\varrho\delta_1\varkappa\tau\alpha}{\epsilon\xi(\vartheta\tau+\mu\beta)(\alpha+\gamma)},$$
$$\mathcal{R}_{02} = \frac{\varrho\delta_2}{\epsilon\xi}.$$

In fact, $\mathcal{R}_{01}$ is the average number of secondary viruses caused by a virus, that is the basic reproduction number corresponding to virus-to-cell infection mode, while $\mathcal{R}_{02}$ is the average number of secondary infected cells that caused by an infected cell, that is the basic reproduction number corresponding to cell-to-cell infection mode.

Lemma 2: *If $\mathcal{R}_0 \leq 1$, then system (8)–(12) has only one equilibrium Ω_0, and if $\mathcal{R}_0 > 1$, then the system has two equilibria Ω_0 and Ω_1.*

Proof: Let $\Omega(s, y, z, p, u)$ be any equilibrium satisfying:

$$0 = \varrho - \xi s - \frac{\delta_1 sp}{1+\omega_1 p} - \frac{\delta_2 sy}{1+\omega_2 y}, \tag{15}$$
$$0 = \frac{\delta_1 sp}{1+\omega_1 p} + \frac{\delta_2 sy}{1+\omega_2 y} - \epsilon y, \tag{16}$$
$$0 = \varkappa y - (\alpha+\gamma)z, \tag{17}$$
$$0 = \alpha z - \vartheta p - \mu u p, \tag{18}$$
$$0 = \beta + \rho u p - \tau u. \tag{19}$$

From equation (19) we get

$$u = \frac{\beta}{\tau - \rho p}. \tag{20}$$

Substituting from equation (20) into equation (18) we get

$$z = \frac{p(\vartheta + \mu u)}{\alpha} = \frac{p(\beta\mu - p\vartheta\rho + \vartheta\tau)}{\alpha(\tau - p\rho)}. \tag{21}$$

From equation (21) into equation (17) we get

$$y = \frac{z(\alpha+\gamma)}{\varkappa} = \frac{p(\alpha+\gamma)(\beta\mu - p\vartheta\rho + \vartheta\tau)}{\varkappa\alpha(\tau - p\rho)}. \tag{22}$$

Now if $p = 0$, then from equations (20)–(22) we have $u = \frac{\beta}{\tau}$ and $z = y = 0$. Substituting in equation (15) we get $s = \frac{\varrho}{\xi}$. In this case, we have only one possible equilibrium, that is the healthy equilibrium $\Omega_0 = (s_0, 0, 0, 0, u_0)$, where $s_0 = \frac{\varrho}{\xi}$ and $u_0 = \frac{\beta}{\tau}$.

If $p \neq 0$, then from equations (20)–(22) into equation (16) we get

$$s = \frac{\epsilon y(1+\omega_1 p)(1+\omega_2 y)}{p\delta_1 + y\delta_2 + py(\delta_2\omega_1 + \delta_1\omega_2)}. \tag{23}$$

Finally, from equations (20)–(23) into equation (15) we get

$$\frac{D_1p^4 + D_2p^3 + D_3p^2 + D_4p + D_5}{C_1p^2 + C_2p + C_3} = 0,$$

where

$$\begin{aligned}
D_1 &= -\vartheta^2\epsilon\rho^2(\alpha+\gamma)^2[\delta^2\omega_1 + (\delta_1\omega_2 + \xi\omega_1\omega_2)],\\
D_2 &= D_{21} + D_{22} + D_{23} + D_{24} + D_{25},\\
D_3 &= D_{31} + D_{32} + D_{33} + D_{34} + D_{35} + D_{36} + D_{37} + D_{38} + D_{39} + D_{310},\\
D_4 &= D_{41} + D_{42} + D_{43} + D_{44} + D_{45} + D_{46} + D_{47} + D_{48} + D_{49} + D_{410},\\
D_5 &= D_{51} + D_{52},\\
C_1 &= C_{11} + C_{12} + C_{13},\\
C_2 &= C_{21} + C_{22} + C_{23} + C_{24},\\
C_3 &= C_{31} + C_{32},
\end{aligned}$$

and

$$\begin{aligned}
D_{21} &= -\vartheta\rho\varkappa\alpha\rho\epsilon(\alpha+\gamma)\ (\delta_1 + \xi\omega_1),\\
D_{22} &= \vartheta\rho\varkappa\alpha\rho\varrho(\alpha+\gamma)(\delta_2\ \omega_1 + \delta_1\omega_2),\\
D_{23} &= 2\vartheta\rho\epsilon\mu\beta(\alpha+\gamma)^2[\delta_2\omega_1 + (\delta_1\omega_2 + \xi\omega_1\omega_2)],\\
D_{24} &= -\vartheta^2\rho\epsilon\delta_2(\alpha+\gamma)^2(\rho - 2\tau\omega_1),\\
D_{25} &= -\vartheta^2\rho\epsilon(\alpha+\gamma)^2[\xi\rho\omega_2 - 2\tau\omega_2(\delta_1 + \xi\omega 1)],\\
D_{31} &= \varkappa^2\alpha^2\varrho\delta_1\rho^2,\\
D_{32} &= -\vartheta^2\tau\epsilon(\alpha+\gamma)^2(\tau\delta_2\omega_1 - 2\delta_2\rho + \tau\delta_1\omega_2 - 2\xi\rho\omega_2 + \tau\xi\omega_1\omega_2),\\
D_{33} &= -\mu^2\epsilon\beta^2(\alpha+\gamma)^2(\delta_2\omega_1 + \delta_1\omega_2 + \xi\omega_1\omega_2),\\
D_{34} &= \varkappa\mu\alpha\beta\rho\epsilon(\alpha+\gamma)(\delta_1 + \xi\omega_1),\\
D_{35} &= -\varkappa\mu\alpha\beta\rho\varrho(\alpha+\gamma)(\delta_2\omega_1 + \delta_1\omega_2),\\
D_{36} &= \vartheta\rho^2\varkappa\alpha(\alpha+\gamma)(\varrho\delta_2 - \xi\ \epsilon),\\
D_{37} &= 2\vartheta\mu\rho\epsilon\beta(\alpha+\gamma)^2\ (\delta_2 + \xi\omega_2),\\
D_{38} &= -2\vartheta\tau\mu\epsilon\beta(\alpha+\gamma)^2[\delta_2\ \omega_1 + (\delta_1\omega_2 + \xi\omega_1\omega_2)],\\
D_{39} &= 2\vartheta\tau\varkappa\alpha\rho\epsilon(\alpha+\gamma)(\ \delta_1 + \xi\omega_1),\\
D_{310} &= -2\tau\vartheta\varkappa\alpha\rho\varrho(\alpha+\gamma)(\delta_2\omega_1 + \delta_1\omega_2),
\end{aligned}$$

$$\begin{aligned}
D_{41} &= -\vartheta^2\tau^2\epsilon(\alpha+\gamma)^2(\delta_2 + \xi\omega_2),\\
D_{42} &= -\mu\beta\varkappa\alpha\rho(\alpha+\gamma)(\varrho\delta_2 - \xi\epsilon),\\
D_{43} &= -\mu^2\epsilon\beta^2(\alpha+\gamma)^2(\delta_2 + \xi\omega_2),
\end{aligned}$$

$$D_{44} = -2\varkappa\alpha\vartheta\tau\rho(\alpha+\gamma)(\varrho\delta_2 - \xi\epsilon),$$
$$D_{45} = -2\vartheta\tau\mu\epsilon\beta(\alpha+\gamma)^2(\delta_2 + \xi\omega_2),$$
$$D_{46} = -\vartheta\tau^2\varkappa\alpha\epsilon(\alpha+\gamma)(\delta_1 + \xi\omega_1),$$
$$D_{47} = \vartheta\tau^2\varkappa\alpha\varrho(\alpha+\gamma)(\delta_2\omega_1 + \delta_1\omega_2),$$
$$D_{48} = -2\tau\varkappa^2\alpha^2\varrho\delta_1\rho,$$
$$D_{49} = -\tau\varkappa\alpha\mu\beta\epsilon(\alpha+\gamma)\ (\delta_1 + \xi\omega_1),$$
$$D_{410} = \tau\varkappa\alpha\mu\beta\varrho(\alpha+\gamma)(\delta_2\omega_1 + \delta_1\omega_2),$$
$$D_{51} = \tau\varkappa\alpha[\tau\varkappa\alpha\varrho\delta_1 - \vartheta\tau(\alpha+\gamma)(\xi\epsilon - \varrho\delta_2)],$$
$$D_{52} = -\mu\tau\varkappa\alpha\beta(\alpha+\gamma)(\xi\epsilon - \varrho\delta_2),$$

$$C_{11} = \alpha\varkappa\rho(\alpha\delta_2\vartheta\rho + \gamma\delta_2\vartheta\rho + \alpha\delta_1\varkappa\rho),$$
$$C_{12} = -\alpha\varkappa\rho(\alpha\beta\delta_2\mu\omega_1 + \beta\gamma\delta_2\mu\omega_1 + 2\alpha\delta_2\vartheta\tau\omega_1 + 2\gamma\delta_2\vartheta\tau\omega_1),$$
$$C_{13} = -\omega_2\alpha\varkappa\rho\delta_1(\alpha+\gamma)(\beta\mu + 2\vartheta\tau),$$
$$C_{21} = \alpha\varkappa\gamma\vartheta\tau(-2\delta_2\rho + \delta_2\tau\omega_1 + \delta_1\tau\omega_2),$$
$$C_{22} = \alpha^2\varkappa\beta\mu(-\delta_2\rho + \delta_2\tau\omega_1 + \delta_1\tau\omega_2),$$
$$C_{23} = \alpha\varkappa\beta\gamma\mu(-\delta_2\rho + \delta_2\tau\omega_1 + \delta_1\tau\omega_2),$$
$$C_{24} = \alpha^2\tau\varkappa(-2\delta_2\vartheta\rho - 2\delta_1\varkappa\rho + \delta_2\vartheta\tau\omega_1 + \delta_1\vartheta\tau\omega_2),$$
$$C_{31} = \alpha\varkappa\tau\beta\delta_2\mu(\alpha+\gamma),$$
$$C_{32} = \alpha\varkappa\tau((\alpha+\gamma)\delta_2\vartheta\tau + \alpha\delta_1\varkappa\tau).$$

Let us define a function $\Lambda(p)$ as:

$$\Lambda(p) = \frac{D_1p^4 + D_2p^3 + D_3p^2 + D_4p + D_5}{C_1p^2 + C_2p + C_3} = 0.$$

Then, we obtain

$$\Lambda(0) = \frac{\epsilon\xi(\alpha+\gamma)(\beta\mu + \vartheta\tau)(\mathcal{R}_0 - 1)}{\beta\delta_2\mu(\alpha+\gamma) + \delta_2\vartheta\tau(\alpha+\gamma) + \alpha\delta_1\varkappa\tau},$$
$$\lim_{p\to\frac{\tau}{\rho}+}\Lambda(p) = -\frac{\beta\epsilon\mu\tau(\alpha+\gamma)\{\delta_2(\rho+\tau\omega_1) + \delta_1\tau\omega_2 + \xi\omega_2(\rho+\tau\omega_1)\}}{\rho^2\alpha\varkappa(\delta_2\rho + \delta_2\tau\omega_1 + \delta_1\tau\omega_2)} < 0.$$

Therefore, if $\mathcal{R}_0 > 1$ then $\Lambda(0) > 0$ and $\exists p_1 \in (0, \frac{\tau}{\rho})$ such that $\Lambda(p_1) = 0$. It follows from equations (20)–(23) that

$$u_1 = \frac{\beta}{\tau - \rho p_1} > 0, \quad z_1 = \frac{p_1(\vartheta + \mu u_1)}{\alpha} > 0,$$
$$y_1 = \frac{z_1(\alpha+\gamma)}{\varkappa} > 0, \quad s_1 = \frac{y_1\epsilon(1+\omega_1p_1)(1+\omega_2y_1)}{p_1\delta_1 + y_1\delta_2 + p_1y_1(\delta_2\omega_1 + \delta_1\omega_2)} > 0.$$

Therefore, if $\mathcal{R}_0 > 1$, then the system has an infected equilibrium $\Omega_1 = (s_1, w_1, y_1, p_1, u_1)$. □

2.3 Global properties

The global stability of the equilibria will be established by constructing Lyapunov functions following the method presented in Korobeinikov (2004) and followed by Huang et al. (2010), Shu et al. (2013), Elaiw (2010), Elaiw and AlShamrani (2015a), Elaiw (2012), Elaiw and Azoz (2013), Elaiw and AlShamrani (2015b) and Elaiw and AlShamrani (2017). Define a function $G(\theta) = \theta - 1 - \ln\theta$.

Theorem 1: *If $\mathcal{R}_0 \leq 1$, then the equilibrium Ω_0 of system (8)–(12) is globally asymptotically stable.*

Proof: Define $L_0(s, y, z, p, u)$ as:

$$L_0(s,y,z,p,u) = s_0 G\left(\frac{s}{s_0}\right) + y + \frac{\delta_1 s_0 \alpha}{(\vartheta + \mu u_0)(\alpha+\gamma)} z + \frac{\delta_1 s_0}{\vartheta + \mu u_0} p + \frac{\mu \delta_1 s_0}{\rho(\vartheta+\mu u_0)} u_0 G\left(\frac{u}{u_0}\right).$$

Calculating $\frac{dL_0}{dt}$ along system (8)–(12) we obtain

$$\begin{aligned}\frac{dL_0}{dt} &= \left(1 - \frac{s_0}{s}\right)\left(\varrho - \xi s - \frac{\delta_1 s p}{1+\omega_1 p} - \frac{\delta_2 s y}{1+\omega_2 y}\right) + \frac{\delta_1 s p}{1+\omega_1 p} + \frac{\delta_2 s y}{1+\omega_2 y} - \epsilon y \\ &+ \frac{\delta_1 s_0 \alpha}{(\vartheta+\mu u_0)(\alpha+\gamma)}\Big(\varkappa y - (\alpha+\gamma) z\Big) + \frac{\delta_1 s_0}{\vartheta+\mu u_0}\Big(\alpha z - \vartheta p - \mu u p\Big) \\ &+ \frac{\mu\delta_1 s_0}{\rho(\vartheta+\mu u_0)}\left(1 - \frac{u_0}{u}\right)\Big(\beta + \rho u p - \tau u\Big) \\ &= \left(1 - \frac{s_0}{s}\right)\Big(\varrho - \xi s\Big) - \frac{\delta_1 s_0 \omega_1 p^2}{1+\omega_1 p} - \frac{\delta_2 s_0 \omega_2 y^2}{1+\omega_2 y} + \delta_2 s_0 y - \epsilon y \\ &+ \frac{\delta_1 s_0 \alpha}{(\vartheta+\mu u_0)(\alpha+\gamma)}\varkappa y + \frac{\mu\delta_1 s_0}{\rho(\vartheta+\mu u_0)}\left(1 - \frac{u_0}{u}\right)\Big(\beta - \tau u\Big)\end{aligned}$$

Substituting $\varrho = \xi s_0$ and $\beta = \tau u_0$ we get

$$\begin{aligned}\frac{dL_0}{dt} &= -\xi\frac{(s-s_0)^2}{s} - \frac{\delta_1 s_0 \omega_1 p^2}{1+\omega_1 p} - \frac{\delta_2 s_0 \omega_2 y^2}{1+\omega_2 y} \\ &+ \epsilon\left(\frac{\delta_2 s_0}{\epsilon} + \frac{\delta_1 s_0 \varkappa \alpha}{\epsilon(\vartheta+\mu u_0)(\alpha+\gamma)} - 1\right) y - \frac{\mu\delta_1 s_0 \tau}{\rho(\vartheta+\mu u_0)}\frac{(u-u_0)^2}{u} \\ &= -\xi\frac{(s-s_0)^2}{s} - \frac{\delta_1 s_0 \omega_1 p^2}{1+\omega_1 p} - \frac{\delta_2 s_0 \omega_2 y^2}{1+\omega_2 y} - \frac{\mu\delta_1 s_0 \tau}{\rho(\vartheta+\mu u_0)}\frac{(u-u_0)^2}{u} + \epsilon(\mathcal{R}_0 - 1) y.\end{aligned} \tag{24}$$

If $\mathcal{R}_0 \leq 1$, then for all $s, y, z, p, u > 0$ we have $\frac{dL_0}{dt} \leq 0$. It can be easily shown that $\frac{dL_0}{dt} = 0$ at Ω_0. Applying LaSalle's invariance principle we get Ω_0 is globally asymptotically stable. □

Theorem 2: *If $\mathcal{R}_0 > 1$, then the equilibrium Ω_1 of system (8)–(12) is globally asymptotically stable.*

Proof: Let

$$L_1(s,y,z,p,u) = s_1 G\left(\frac{s}{s_1}\right) + y_1 G\left(\frac{y}{y_1}\right) + \frac{\delta_1 s_1 p_1}{\varkappa y_1(1+\omega_1 p_1)} z_1 G\left(\frac{z}{z_1}\right) + \frac{\delta_1 s_1 p_1(\alpha+\gamma)}{\varkappa y_1 \alpha(1+\omega_1 p_1)} p_1 G\left(\frac{p}{p_1}\right) + \frac{\mu\delta_1 s_1 p_1(\alpha+\gamma)}{\rho\varkappa y_1 \alpha(1+\omega_1 p_1)} u_1 G\left(\frac{u}{u_1}\right).$$

Then

$$\begin{aligned}
\frac{dL_1}{dt} &= \left(1-\frac{s_1}{s}\right)\left(\varrho - \xi s - \frac{\delta_1 sp}{1+\omega_1 p} - \frac{\delta_2 sy}{1+\omega_2 y}\right) \\
&\quad + \left(1-\frac{y_1}{y}\right)\left(\frac{\delta_1 sp}{1+\omega_1 p} + \frac{\delta_2 sy}{1+\omega_2 y} - \epsilon y\right) \\
&\quad + \frac{\delta_1 s_1 p_1}{\varkappa y_1(1+\omega_1 p_1)}\left(1-\frac{z_1}{z}\right)\left(\varkappa y - (\alpha+\gamma)z\right) \\
&\quad + \frac{\delta_1 s_1 p_1(\alpha+\gamma)}{\varkappa y_1\alpha(1+\omega_1 p_1)}\left(1-\frac{p_1}{p}\right)\left(\alpha z - \vartheta p - \mu u p\right) \\
&\quad + \frac{\mu\delta_1 s_1 p_1(\alpha+\gamma)}{\rho\varkappa y_1\alpha(1+\omega_1 p_1)}\left(1-\frac{u_1}{u}\right)\left(\beta + \rho u p - \tau u\right) \\
&= \left(1-\frac{s_1}{s}\right)\left(\varrho - \xi s\right) + \frac{\delta_1 s_1 p}{1+\omega_1 p} + \frac{\delta_2 s_1 y}{1+\omega_2 y} \\
&\quad - \frac{\delta_1 sp}{1+\omega_1 p}\frac{y_1}{y} - \frac{\delta_2 s y_1}{1+\omega_2 y} - \epsilon y + \epsilon y_1 + \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1}\frac{y}{y_1} \\
&\quad - \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1}\frac{y z_1}{y_1 z} + \frac{\delta_1 s_1 p_1}{\varkappa y_1(1+\omega_1 p_1)}(\alpha+\gamma) z_1 \\
&\quad - \frac{\delta_1 s_1 p_1(\alpha+\gamma)}{\varkappa y_1(1+\omega_1 p_1)}\frac{z p_1}{p} - \frac{\delta_1 s_1 p_1(\alpha+\gamma)}{\varkappa y_1\alpha(1+\omega_1 p_1)}\vartheta p \\
&\quad + \frac{\delta_1 s_1 p_1(\alpha+\gamma)}{\varkappa y_1\alpha(1+\omega_1 p_1)}\vartheta p_1 + \frac{\delta_1 s_1 p_1(\alpha+\gamma)}{\varkappa y_1\alpha(1+\omega_1 p_1)}\mu u p_1 - \frac{\mu\delta_1 s_1 p_1(\alpha+\gamma)}{\varkappa y_1\alpha(1+\omega_1 p_1)} u_1 p \\
&\quad + \frac{\mu\delta_1 s_1 p_1(\alpha+\gamma)}{\rho\varkappa y_1\alpha(1+\omega_1 p_1)}\left(1-\frac{u_1}{u}\right)\left(\beta - \tau u\right).
\end{aligned}$$

We have

$$\varrho = \xi s_1 + \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1} + \frac{\delta_2 s_1 y_1}{1+\omega_1 p_1}, \;\; \epsilon y_1 = \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1} + \frac{\delta_2 s_1 y_1}{1+\omega_1 p_1},$$

$$\varkappa y_1 = (\alpha+\gamma) z_1, \;\; \vartheta p_1 = \alpha z_1 - \mu u_1 p_1, \;\; \beta = \tau u_1 - \rho u_1 p_1,$$

we get

$$\begin{aligned}\frac{dL_1}{dt} &= -\xi\frac{(s-s_1)^2}{s} + \left(1-\frac{s_1}{s}\right)\left(\frac{\delta_1 s_1 p_1}{1+\omega_1 p_1}\right.\\
&\quad \left.+ \frac{\delta_2 s_1 y_1}{1+\omega_2 y_1}\right) + \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1}\left(\frac{(1+\omega_1 p_1)p}{(1+\omega_1 p)p_1} - \frac{p}{p_1}\right)\\
&\quad + \frac{\delta_2 s_1 y_1}{1+\omega_2 y_1}\left(\frac{(1+\omega_2 y_1)y}{(1+\omega_2 y)y_1} - \frac{y}{y_1}\right) - \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1}\frac{s p y_1(1+\omega_1 p_1)}{s_1 p_1 y(1+\omega_1 p)}\\
&\quad - \frac{\delta_2 s_1 y_1}{1+\omega_2 y_1}\frac{s(1+\omega_2 y_1)}{s_1(1+\omega_2 y)} + \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1} + \frac{\delta_2 s_1 y_1}{1+\omega_2 y_1} - \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1}\frac{z_1 y}{z y_1}\\
&\quad + \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1} - \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1}\frac{z p_1}{z_1 p} + \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1} - 2\frac{\delta_1 s_1 p_1(\alpha+\gamma)}{\varkappa y_1\alpha(1+\omega_1 p_1)}\mu u_1 p_1\\
&\quad + \frac{\delta_1 s_1 p_1(\alpha+\gamma)}{\varkappa y_1\alpha(1+\omega_1 p_1)}\mu u p_1 + \frac{\delta_1 s_1 p_1(\alpha+\gamma)}{\varkappa y_1\alpha(1+\omega_1 p_1)}\mu u_1 p_1\frac{u_1}{u}\\
&\quad - \frac{\mu\delta_1 s_1 p_1\tau(\alpha+\gamma)}{\rho\varkappa y_1\alpha(1+\omega_1 p_1)}\frac{(u-u_1)^2}{u}. \end{aligned} \tag{25}$$

Equation (25) can be simplified as:

$$\begin{aligned}\frac{dL_1}{dt} &= -\xi\frac{(s-s_1)^2}{s} + \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1}\left[-1 + \frac{(1+\omega_1 p_1)p}{(1+\omega_1 p)p_1} - \frac{p}{p_1} + \frac{1+\omega_1 p}{1+\omega_1 p_1}\right]\\
&\quad + \frac{\delta_2 s_1 y_1}{1+\omega_2 y_1}\left[-1 + \frac{(1+\omega_2 y_1)y}{(1+\omega_2 y)y_1} - \frac{y}{y_1} + \frac{1+\omega_2 y}{1+\omega_2 y_1}\right]\\
&\quad + \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1}\left[5 - \frac{s_1}{s} - \frac{s p y_1(1+\omega_1 p_1)}{s_1 p_1 y(1+\omega_1 p)} - \frac{z_1 y}{z y_1} - \frac{z p_1}{z_1 p} - \frac{1+\omega_1 p}{1+\omega_1 p_1}\right]\\
&\quad + \frac{\delta_2 s_1 y_1}{1+\omega_2 y_1}\left[3 - \frac{s_1}{s} - \frac{s(1+\omega_2 y_1)}{s_1(1+\omega_2 y)} - \frac{1+\omega_2 y}{1+\omega_2 y_1}\right]\\
&\quad - \frac{\delta_1 s_1 p_1(\alpha+\gamma)}{\varkappa y_1\alpha(1+\omega_1 p_1)}\mu u_1 p_1\left[2 - \frac{u}{u_1} - \frac{u_1}{u}\right]\\
&\quad - \frac{\mu\delta_1 s_1 p_1\tau(\alpha+\gamma)}{\rho\varkappa y_1\alpha(1+\omega_1 p_1)}\frac{(u-u_1)^2}{u},\end{aligned}$$

and then,

$$\begin{aligned}\frac{dL_1}{dt} &= -\xi\frac{(s-s_1)^2}{s} - \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1}\left(\frac{\omega_1(p-p_1)^2}{(1+\omega_1 p)(1+\omega_1 p_1)p_1}\right)\\
&\quad - \frac{\delta_2 s_1 y_1}{1+\omega_2 y_1}\left(\frac{\omega_2(y-y_1)^2}{(1+\omega_2 y)(1+\omega_2 y_1)y_1}\right)\\
&\quad - \frac{\delta_1 s_1 p_1(\alpha+\gamma)}{\varkappa y_1\alpha(1+\omega_1 p_1)}\frac{\mu\beta}{\rho u_1}\frac{(u-u_1)^2}{u}\\
&\quad + \frac{\delta_1 s_1 p_1}{1+\omega_1 p_1}\left[5 - \frac{s_1}{s} - \frac{s p y_1(1+\omega_1 p_1)}{s_1 p_1 y(1+\omega_1 p)} - \frac{z_1 y}{z y_1} - \frac{z p_1}{z_1 p} - \frac{1+\omega_1 p}{1+\omega_1 p_1}\right]\\
&\quad + \frac{\delta_2 s_1 y_1}{1+\omega_2 y_1}\left[3 - \frac{s_1}{s} - \frac{s(1+\omega_2 y_1)}{s_1(1+\omega_2 y)} - \frac{1+\omega_2 y}{1+\omega_2 y_1}\right]\end{aligned}$$

Using the rule

$$\frac{1}{k}\sum_{j=1}^{k}\lambda_j \geq \sqrt[k]{\prod_{j=1}^{k}\lambda_j}, \qquad \text{where,} \qquad \lambda_j \geq 0,\ j=1,2,\ldots,k,$$

we get

$$\frac{s_1}{s} + \frac{spy_1(1+\omega_1 p_1)}{s_1 p_1 y(1+\omega_1 p)} + \frac{z_1 y}{z y_1} + \frac{z p_1}{z_1 p} + \frac{1+\omega_1 p}{1+\omega_1 p_1} \geq 5,$$

$$\frac{s_1}{s} + \frac{s(1+\omega_2 y_1)}{s_1(1+\omega_2 y)} + \frac{1+\omega_2 y}{1+\omega_2 y_1} \geq 5.$$

It follows that $\frac{dL_1}{dt} \leq 0$ and $\frac{dL_1}{dt} = 0$ at Ω_1. The global stability of Ω_1 is induced from LaSalle's invariance principle. □

3 Special cases

In this section we outline two special cases of model (8)–(12):

Case (I): If $\omega_1 = \omega_2 = 0$, then model (8)–(12) will reduce to the following model:

$$\dot{s} = \varrho - \xi s - \delta_1 sp - \delta_2 sy, \tag{26}$$
$$\dot{y} = \delta_1 sp + \delta_2 sy - \epsilon y, \tag{27}$$
$$\dot{z} = \varkappa y - (\alpha+\gamma)z, \tag{28}$$
$$\dot{p} = \alpha z - \vartheta p - \mu up, \tag{29}$$
$$\dot{u} = \beta + \rho up - \tau u. \tag{30}$$

and the basic reproduction number is the same as given by equation (14). Therefore, applying Theorems 1 and 2 to (26)–(30) immediately gives us the following results:

Corallary 1: *(i) If* $\mathcal{R}_0 \leq 1$, *then the equilibrium* Ω_0 *of system (26)–(30) is globally asymptotically stable,*

(ii) If $\mathcal{R}_0 > 1$, *then the equilibrium* Ω_1 *of system (26)–(30) is globally asymptotically stable.*

Case (II): If we neglect the capsids in the virus dynamics, then model (8)–(12) becomes

$$\dot{s} = \varrho - \xi s - \frac{\delta_1 sp}{1+\omega_1 p} - \frac{\delta_2 sy}{1+\omega_2 y}, \tag{31}$$
$$\dot{y} = \frac{\delta_1 sp}{1+\omega_1 p} + \frac{\delta_2 sy}{1+\omega_2 y} - \epsilon y, \tag{32}$$
$$\dot{p} = \varkappa y - \vartheta p - \mu up, \tag{33}$$
$$\dot{u} = \beta + \rho up - \tau u. \tag{34}$$

The basic reproduction number model (31)–(34) is given by $\widetilde{\mathcal{R}}_0 = \widetilde{\mathcal{R}}_{01} + \widetilde{\mathcal{R}}_{02}$, *where*

$$\widetilde{\mathcal{R}}_{01} = \frac{\varrho\delta_1\varkappa\tau}{\epsilon\xi(\vartheta\tau + \mu\beta)}, \quad \widetilde{\mathcal{R}}_{02} = \frac{\varrho\delta_2}{\epsilon\xi}.$$

Clearly

$$\mathcal{R}_0 = \frac{\alpha}{\alpha+\gamma}\widetilde{\mathcal{R}}_{01} + \widetilde{\mathcal{R}}_{02} < \widetilde{\mathcal{R}}_{01} + \widetilde{\mathcal{R}}_{02} = \widetilde{\mathcal{R}}_0.$$

It means that, the presence of capsids in the virus dynamics enhances the stability of the healthy equilibrium Ω_0.

Corallary 2 (Elaiw et al., 2019a)**:** *(i) If* $\widetilde{\mathcal{R}}_0 \leq 1$, *then the equilibrium* Ω_0 *of system (31)–(34) is globally asymptotically stable,*

(ii) If $\widetilde{\mathcal{R}}_0 > 1$, *then the equilibrium* Ω_1 *of system (31)–(34) is globally asymptotically stable.*

4 Numerical simulations

In this section, we solve system (8)–(12) numerically with different initial conditions. We simulate the system with values of the parameters given as: $\varrho = 2$, $\varkappa = 4$, $\mu = 0.5$, $\tau = 1$, $\alpha = 0.5$, $\xi = 0.1$, $\epsilon = 0.5$, $\vartheta = 0.1$, $\beta = 1.4$, $\rho = 0.2$, $\gamma = 0.2$. We assume that $\omega = \omega_1 = \omega_2$. The parameters δ_1, δ_2 and ω will be selected.

4.1 Stability of equilibria

System (8)–(12) will be solved with different initial values as:

IV1: $(s(0), y(0), z(0), p(0), u(0)) = (14.0, 1.0, 1.0, 1.0, 1.5)$,

IV2: $(s(0), y(0), z(0), p(0), u(0)) = (8.0, 2.0, 3.0, 3.0, 2.0)$,

IV3: $(s(0), y(0), z(0), p(0), u(0)) = (4.0, 3.5, 5.0, 6.0, 2.5)$.

In Figure 1 we want to confirm our global stability results given in Theorems 1 and 2, by showing that from any initial points (any disease stage) taken from a feasible set, the trajectory of the system will tend to one of the two equilibria of the system.

We fix $\omega = 0$ and choose the parameters δ_1 and δ_2 as follows:

Set (I): $\delta_1 = \delta_2 = 0.001$. With these data we get $\mathcal{R}_0 = 0.1829 < 1$. Figure 1 shows that, the solutions of the system with initials IV1-IV3 goes to $\Omega_0 = (20.0, 0, 0, 0, 1.4)$. This shows that, Ω_0 is globally asymptotically stable which supports Theorem 1.

Set (II): $\delta_1 = \delta_2 = 0.05$. Then, we calculate $\mathcal{R}_0 = 9.1429 > 1$. We found that the system has two equilibria $\Omega_0 = (20.0, 0, 0, 0, 1.4)$ and $\Omega_1 = (4.65, 3.06, 17.54, 3.53, 4.76)$. Figure 1 shows that in case of $\mathcal{R}_0 > 1$, the solutions converge to Ω_1 for all IV1-IV3. Thus the result Theorem 2 is numerically checked.

4.2 *Effect of saturation on the virus dynamics*

We consider the values of the parameters given above and take $\delta_1 = \delta_2 = 0.05$. We choose the following initial:

IV4: $(s(0), y(0), z(0), p(0), u(0)) = (12, 2.0, 10, 3.0, 3.4)$.

The variation of the states of the system with different values of ω is shown in Figure 2. It is clear that as the saturation parameter ω is increased, the number of uninfected cells are increased while the number of virus, infected cells, and antibodies are decreased.

Figure 1 The simulation of trajectories of system (8)–(12) with initial conditions IV1–IV3: (a) uninfected cells; (b) infected cells; (c) capsids; (d) free virus particles and (e) antibodies (see online version for colours)

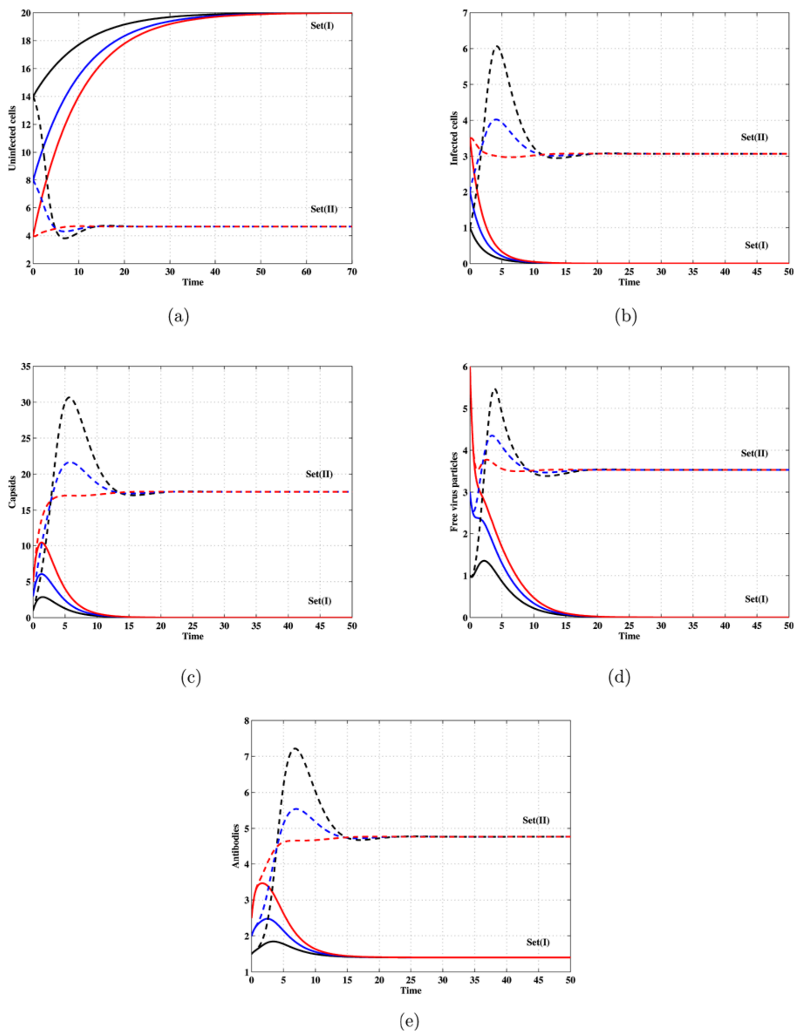
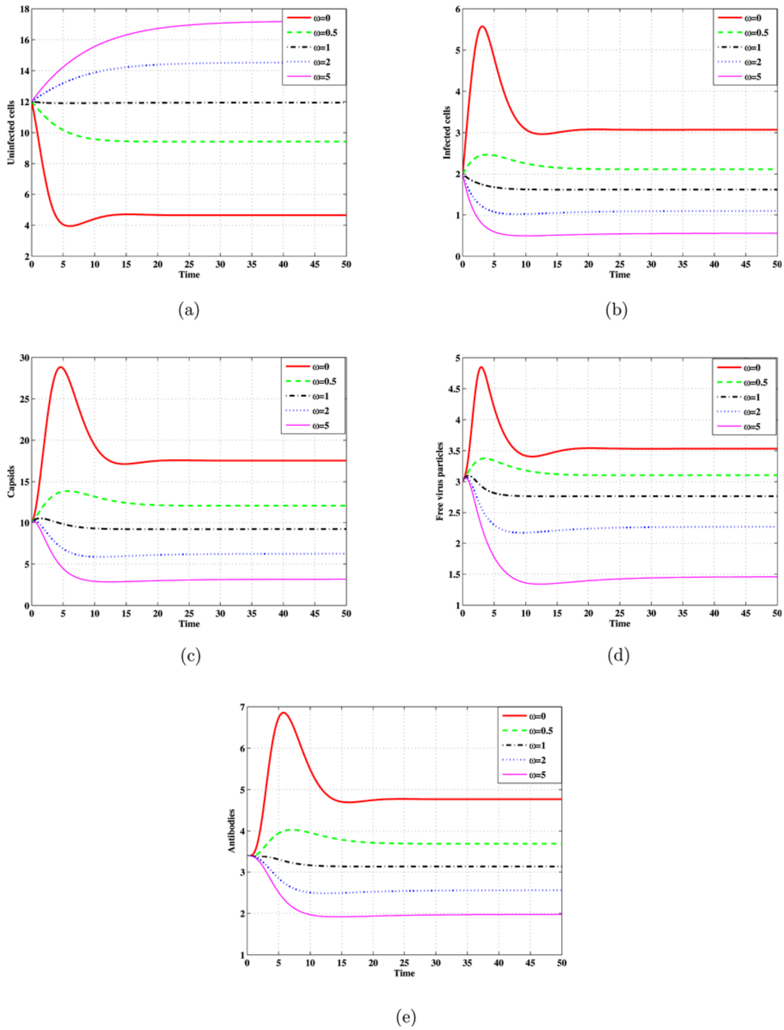


Figure 2 The simulation of trajectories of system (8)–(12) with different values of ω: (a) uninfected cells; (b) infected cells; (c) capsids; (d) free virus particles and (e) antibodies (see online version for colours)



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