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Global Stability of Generalized Within-host Chikungunya Virus Dynamics Models

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Abstract

This paper proposes two models of a general nonlinear within-host Chikungunya virus (CHIKV) dynamics. The production, incidence, proliferation and removal rates of all compartments are modeled by general nonlinear functions that satisfy a set of reasonable conditions. The second model takes into consideration two forms of infected host cells: (i) latently infected cells which do not produce the CHIKV, (ii) actively infected cells which generate the CHIKV particles. We show that all the solutions of the models are nonnegative and bounded. The global stability of the steady states of the models is proven by applying Lyapunov method and LaSalle's invariance principle. We perform numerical simulations to complement the obtained theoretical results.

Keywords: Within-host model; Chikungunya virus; General nonlinear function; Lyapunov function; Global stability

MSC 2010 No.: 34D20, 34D23, 37N25, 92B05

1. Introduction

Chikungunya virus (CHIKV) infection is an emerging and re-emerging mosquito-borne viral infection, which has become a serious public health issue in different regions worldwide (Intayot et al. (2019)). The CHIKV-imposed public health issue in these regions is increasing as a result of severity, prevalence and geographical distribution of the virus (Intayot et al. (2019)). The virus is endemic in subtropical and tropical countries in Africa and Asia. Since 1990, many countries from South and Central Americas have reported CHIKV infections with estimated 11,675 million cases. Recently, it was confirmed that people living in over 60 countries are now at the risk of CHIKV infection (Passos et al. (2020)).

CHIKV is an arbovirus that belongs to the Alphavirus genus of the Togaviridae family (Passos et al. (2020); Agusto (2017)). It is mainly transmitted by the bites of infected *Aedes aegypti* and *Aedes albopictus* mosquitoes (Intayot et al. (2019); Passos et al. (2020); Agusto (2017); Liu et al. (2020)). Both *Aedes aegypti* and *Aedes albopictus* mosquitoes are incriminated as the principal vector causing the transmission of CHIKV in Asia and Americas (Agarwal et al. (2016)). Usually, human-mosquito-human transmission cycle is maintained for CHIKV transmission. An *Aedes* female mosquito acquires the virus while taking blood meal from an infected person. After 7–12 days of virus incubation, the infected mosquito is capable of passing the virus to a healthy (susceptible) individuals through bite (Liu et al. (2020)). The virus attacks the monocytes and causes Chikungunya fever (Elaiw et al. (2018a)). The intrinsic incubation period in humans is 1–12 days after the infective bite and infected patients may appear viremia until 10 days (Liu et al. (2020)).

CHIKV infection is characterized by inflammation and pain of the musculoskeletal tissues accompanied by swelling in the joints and cartilage damage (Passos et al. (2020)). Generally, the symptoms are of short duration ranging from 2–12 days and infected individuals are expected to fully recover with permanent immunity (Agusto (2017)). Chikungunya-related death is very rare, although there are some cases where patients experience joint pains for many weeks following the initial infection (Intayot et al. (2019); Agusto (2017); Liu et al. (2020)). Currently, there are no CHIKV-specific vaccines or specific drugs to treat or prevent the viral infection. Supportive treatment is mainly used to relieve the symptoms, which is limited to the antipyretic, analgesic, corticoid and nonsteroidal anti-inflammatory drugs at present (Passos et al. (2020)). Hence, the principal strategy for controlling CHIKV outbreaks is vector control (Intayot et al. (2019)).

Several mathematical models of different viral infections have been developed in the last decade, particularly, Human immunodeficiency virus, Human T-lymphotropic virus, Hepatitis B virus, Hepatitis C virus, Dengue virus, Zika virus and CHIKV (see references Nowak and Bangham (1996); Bellomo and Tao (2020); Elaiw et al. (2018c); Elaiw and Ghaleb (2019); Perelson and Nelson (1999); Roy et al. (2013); Liu and Wang (2010); Elaiw (2010); Elaiw et al. (2019a); Neumann et al. (1998); Alade (2020); Elaiw et al. (2018d); Mann Manyombe et al. (2020); Hugo and Simanjilo (2019); Wang et al. (2010); Alade et al. (2020); Olaniyi (2018); Okyere et al. (2020); Elaiw et al. (2019b); Elaiw et al. (2018b); Wang and Li (2006); Wang et al. (2002); Cai et al. (2011); Abidemi et al. (2019); Abidemi et al. (2020a); Abidemi et al. (2020b); Song et al. (2020);

Wang and Liu (2017)), etc. These viral infection models enable us to understand the system regulating viral load dynamics, to estimate the strength of the immune responses and to provide estimate for drug efficacy that can lead to virus clearance. In particular, CHIKV which is mainly transmitted to humans by infected female mosquitoes (Aedes aegypti and Aedes albopictus). Most of the mathematical models of CHIKV presented in the literature describe the transmission dynamics of the virus in human and mosquito populations (Dumont and Chirleu (2010); Dumont and Tchuenche (2012); Dumont et al. (2008); Moulay et al. (2011); Moulay et al. (2012); Yakob and Clements (2013); Liu and Stechlinski (2015)). However, the mathematical modelling of the dynamics of within host CHIKV is very few. In Wang and Liu (2017), for instance, the authors presented a within host CHIKV dynamics model of four compartments: concentrations of uninfected cells, infected cells, CHIKV particles, and antibodies with respect to time. The incidence rate is given as a bilinear incidence rate. Such incidence rate does not give an accurate description of the viral infection (Huang et al. (2010)). Hence, there is the need for new within-host compartmental model which does not incorporate bilinear incidence rate.

Therefore, this paper proposes two new models to gain more insights into the transmission dynamics of within-host CHIKV infection. In the first model, we consider a general function as the intrinsic growth rate of uninfected cells for both production and natural mortality (see, e.g., Perelson and Nelson (1999); Wang and Li (2006); Smith and De Leenheer (2003)). The incidence rate is also given as a general nonlinear function that satisfies a set of reasonable conditions. The second model takes into account latently infected cells. These models improve the models presented in Wang and Liu (2017) and Elaiw et al. (2019c) and are given in a generalized form. In order to show the biological feasibility of our proposed models, we investigate the nonnegativity and boundedness of the solutions of the models. We derive the basic reproduction number $\mathcal{R}_0$, and construct appropriate Lyapunov functionals to establish the global stability of the models.

The rest of this work is organized as follows. In Section 2, the formulation and theoretical analysis of general within host CHIKV model are discussed. Development of general within host CHIKV model with latency as well as qualitative analysis of the model are considered in Section 3. Section 4 presents the numerical simulations of the proposed models. Lastly, the conclusion is drawn in Section 5.

2. General within host CHIKV model

We propose a general within host CHIKV dynamics model:

$$\dot{Z} = \psi(Z) - \Phi(Z,C), \tag{1}$$

$$\dot{U} = \Phi(Z,C) - \epsilon\varphi_1(U), \tag{2}$$

$$\dot{C} = b\varphi_1(U) - r\varphi_2(C) - \rho\varphi_2(C)\varphi_3(A), \tag{3}$$

$$\dot{A} = \lambda + m\varphi_2(C)\varphi_3(A) - \delta\varphi_3(A), \tag{4}$$

where the compartments $Z(t)$, $U(t)$, $C(t)$ and $A(t)$ denote uninfected cells concentration, infected cells concentration, CHIKV particles and antibodies at time t, respectively. The general functions

$\epsilon\varphi_1(U)$, $r\varphi_2(C)$ and $\delta\varphi_3(A)$ are the rates of death of infected cells, free CHIKV particles and antibodies, respectively. These rates are the generalized form of the linear death rates presented in the works by Wang and Liu (2017) and Elaiw et al. (2019c). The production and neutralization rates of CHIKV, and proliferation rate of antibodies are given by general functions in the forms $b\varphi_1(U)$, $\rho\varphi_2(C)\varphi_3(A)$ and $m\varphi_2(C)\varphi_3(A)$, respectively. The parameter λ is the production rate of the antibodies. The functions ψ, Φ, φ_1, φ_2, and φ_3 are continuously differentiable and satisfy the following assumptions (see references Hattaf and Yousfi (2016a)–Wang et al. (2016)):

(A1) (i) $Z_0 > 0$ such that $\psi(Z_0) = 0, \psi(Z) > 0$ for $Z \in [0, Z_0)$,

(ii) $\psi'(Z) < 0$ for all $Z > 0$,

(iii) $x, \bar{x} > 0$ such that $\psi(Z) \leq x - \bar{x}Z$ for all $Z \geq 0$.

(A2) (i) $\Phi(Z, C) > 0, \Phi(0, C) = \Phi(Z, 0) = 0$ for all $Z > 0, C > 0$,

(ii) $\frac{\partial\Phi(Z,C)}{\partial Z} > 0$, $\frac{\partial\Phi(Z,C)}{\partial C} > 0$, $\frac{\partial\Phi(Z,0)}{\partial C} > 0$ for all $Z > 0, C > 0$,

(iii) $\frac{d}{dZ}\left(\frac{\partial\Phi(Z,0)}{\partial C}\right) > 0$ for all $Z > 0$.

(A3) (i) $\varphi_j(n) > 0$ for all $n > 0$, $\varphi_j(0) = 0$, $j = 1, 2, 3$,

(ii) $\varphi_j'(n) > 0$ for all $n > 0$, $j = 1, 3$, $\varphi_2'(n) > 0$ for all $n \geq 0$,

(iii) there is $\alpha_j > 0$, $j = 1, 2, 3$, such that $\varphi_j(n) \geq \alpha_j n$ for all $n \geq 0$.

(A4) For all $Z, C > 0$, the function $\frac{\Phi(Z,C)}{\varphi_2(C)}$ is decreasing with respect to C.

Remark 2.1.

Assumptions (A1) and (A2) imply

$$(\psi(Z) - \psi(Z_0))\left(\frac{\partial\Phi(Z,0)}{\partial C} - \frac{\partial\Phi(Z_0,0)}{\partial C}\right) \leq 0. \tag{5}$$

From (A2), (A3), (A4) and applying L'Hopital's rule, we get

$$\frac{\Phi(Z,C)}{\varphi_2(C)} \leq \lim_{C\to 0^+}\frac{\Phi(Z,C)}{\varphi_2(C)} = \frac{1}{\varphi_2'(0)}\frac{\partial\Phi(Z,0)}{\partial C}. \tag{6}$$

From (A2) and (A4), we obtain

$$\left(\frac{\Phi(Z,C)}{\varphi_2(C)} - \frac{\Phi(Z,C_1)}{\varphi_2(C_1)}\right)(\Phi(Z,C) - \Phi(Z,C_1)) \leq 0,$$

which yields

$$\left(\frac{\Phi(Z,C)}{\Phi(Z,C_1)} - \frac{\varphi_2(C)}{\varphi_2(C_1)}\right)\left(1 - \frac{\Phi(Z,C_1)}{\Phi(Z,C)}\right) \leq 0.$$

2.1. Basic results

In this subsection, we investigate the nonnegativity, boundedness and steady states of the system (1)-(4). We define the compact set:

$$\hat{\Delta} = \{(Z, U, C, A) \in \mathbb{R}^4_{\geq 0} : 0 \leq Z, U \leq \breve{N}_1, 0 \leq C \leq \breve{N}_2, 0 \leq A \leq \breve{N}_3\}.$$

Lemma 2.1.

For system (1)-(4), there exist $\breve{N}_1, \breve{N}_2, \breve{N}_3 > 0$, such that $\hat{\Delta}$ is positively invariant.

Proof:

Since

$$\dot{Z}\Big|_{Z=0} = \psi(0) > 0, \qquad \dot{U}\Big|_{U=0} = \Phi(Z, C) \geq 0 \text{ for all } Z, C \geq 0,$$
$$\dot{C}\Big|_{C=0} = b\varphi_1(U) \geq 0 \text{ for all } U \geq 0, \qquad \dot{A}\Big|_{A=0} = \lambda > 0.$$

Hence, $\mathbb{R}^4_{\geq 0}$ is positively invariant with respect to system (1)-(4) .

Now, we define

$$K_1(t) = Z(t) + U(t) + \frac{\epsilon}{2b}C(t) + \frac{\epsilon\rho}{2bm}A(t), \tag{7}$$

then,

$$\begin{aligned}
\dot{K}_1(t) &= \psi(Z) - \frac{\epsilon}{2}\varphi_1(U) - \frac{\epsilon r}{2b}\varphi_2(C) + \frac{\epsilon\rho\lambda}{2bm} - \frac{\epsilon\rho\delta}{2bm}\varphi_3(A) \\
&\leq x - \bar{x}Z + \frac{\epsilon\rho\lambda}{2bm} - \frac{\epsilon}{2}\alpha_1 U - \frac{\epsilon r}{2b}\alpha_2 C - \frac{\epsilon\rho\delta}{2bm}\alpha_3 A \\
&\leq x + \frac{\epsilon\rho\lambda}{2bm} - \tilde{\sigma}_1\left(Z + U + \frac{\epsilon}{2b}C + \frac{\epsilon\rho}{2bm}A\right) \\
&= x + \frac{\epsilon\rho\lambda}{2bm} - \tilde{\sigma}_1 K_1(t),
\end{aligned}$$

where $\tilde{\sigma}_1 = \min\{\bar{x}, \frac{\epsilon}{2}\alpha_1, r\alpha_2, \delta\alpha_3\}$. Hence, $K_1(t) \leq \breve{N}_1$, if $K_1(0) \leq \breve{N}_1$, where $\breve{N}_1 = \frac{x}{\tilde{\sigma}_1} + \frac{\epsilon\rho\lambda}{2bm\tilde{\sigma}_1}$. It follows that $0 \leq Z(t), U(t) \leq \breve{N}_1$, $0 \leq C(t) \leq \breve{N}_2$ and $0 \leq A(t) \leq \breve{N}_3$ for all $t \geq 0$, if $Z(0) + U(0) + \frac{\epsilon}{2b}C(0) + \frac{\epsilon\rho}{2bm}A(0) \leq \breve{N}_1$, where $\breve{N}_2 = \frac{2b\breve{N}_1}{\epsilon}$ and $\breve{N}_3 = \frac{2br\breve{N}_1}{\epsilon\rho}$. Therefore, $Z(t), U(t)$, $C(t)$, and $A(t)$ are all bounded. ■

To investigate the steady states of the model, we solve the following system:

$$0 = \psi(Z) - \Phi(Z, C), \tag{8}$$
$$0 = \Phi(Z, C) - \epsilon\varphi_1(U), \tag{9}$$
$$0 = b\varphi_1(U) - r\varphi_2(C) - \rho\varphi_2(C)\varphi_3(A), \tag{10}$$
$$0 = \lambda + m\varphi_2(C)\varphi_3(A) - \delta\varphi_3(A). \tag{11}$$

Substituting the solutions of Equations (8), (9) and (11) into Equation (10) we obtain

$$\frac{b\Phi(Z,C)}{\epsilon} - \left(r + \frac{\rho\lambda}{\delta - m\varphi_2(C)}\right)\varphi_2(C) = 0. \tag{12}$$

In Equation (12), $C = 0$ is one of the solutions, which can be deduced from (A1)-(A3) that $Z = Z_0$, $U = 0$ and $A = A_0 = \varphi_3^{-1}\left(\frac{\lambda}{\delta}\right)$. This leads to a CHIKV-free steady state $E^0 = (Z_0, 0, 0, A_0)$.

Next, we assume that there exists $C_1 \in \left(0, \varphi_2^{-1}(\frac{\delta}{m})\right)$ which satisfies Equation (12). Equation (8) becomes

$$0 = \psi(Z) - \Phi(Z, C_1).$$

We define a function ϕ as:

$$\phi(Z) = \psi(Z) - \Phi(Z, C_1) = 0.$$

Then, we have $\phi(0) = \psi(0) > 0$ and $\phi(Z_0) = -\Phi(Z_0, C_1) < 0$. According to (A1)-(A2), ϕ is strictly decreasing function of Z. Thus, a unique $Z_1 \in (0, Z_0)$ exists, such that $\phi(Z_1) = 0$. From Equations (9) and (11), we get

$$U_1 = \varphi_1^{-1}\left(\frac{\Phi(Z_1, C_1)}{\epsilon}\right) > 0,\ A_1 = \varphi_3^{-1}\left(\frac{\lambda}{\delta - m\varphi_2(C_1)}\right) > 0. \tag{13}$$

This leads to the endemic steady state $E_1^0 = (Z_1, U_1, C_1, A_1)$. Then, by using the methods in Diekmann et al. (1990) and van den Driessche and Watmough (2002), the basic reproduction number $\mathcal{R}_0$ of system (1)-(4) can be defined as

$$\mathcal{R}_0 = \frac{b}{\epsilon\left(r + \rho\varphi_3(A_0)\right)\varphi_2'(0)}\frac{\partial\Phi(Z_0, 0)}{\partial C}.$$

2.2. Global stability

In this subsection, the global stability of the two steady states of system (1)-(4) are established by constructing appropriate Lyapunov functionals following the method presented in Ghosh et al. (2020) and Akanni et al. (2020). We use the function $H(v) = v - 1 - lnv$, and the notation $(Z, U, C, A) = (Z(t), U(t), C(t), A(t))$.

Theorem 2.1.

Suppose that $\mathcal{R}_0 \leq 1$ and assumptions (A1)-(A4) hold true, then E^0 is globally asymptotically stable (GAS).

Proof:

Define the function

$$G_0(Z,U,C,A) = Z - Z_0 - \int_{Z_0}^{Z}\lim_{C\to 0^+}\frac{\Phi(Z_0,C)}{\Phi(\vartheta,C)}d\vartheta + U + \frac{\epsilon}{b}C$$
$$+ \frac{\epsilon\rho}{bm}\left(A - A_0 - \int_{A_0}^{A}\frac{\varphi_3(A_0)}{\varphi_3(\vartheta)}d\vartheta\right).$$

Note that $G_0(Z,U,C,A) > 0$ for all $Z,U,C,A > 0$ and $G_0(Z_0,0,0,A_0) = 0$. Calculating $\frac{dG_0}{dt}$ along the system (1)-(4), we get

$$\begin{aligned}
\frac{dG_0}{dt} &= \left(1 - \lim_{C\to 0^+}\frac{\Phi(Z_0,C)}{\Phi(Z,C)}\right)(\psi(Z) - \Phi(Z,C)) + \Phi(Z,C) - \epsilon\varphi_1(U) \\
&\quad + \frac{\epsilon}{b}\left(b\varphi_1(U) - r\varphi_2(C) - \rho\varphi_2(C)\varphi_3(A)\right) \\
&\quad + \frac{\epsilon\rho}{bm}\left(1 - \frac{\varphi_3(A_0)}{\varphi_3(A)}\right)(\lambda + m\varphi_2(C)\varphi_3(A) - \delta\varphi_3(A)) \\
&= \psi(Z)\left(1 - \lim_{C\to 0^+}\frac{\Phi(Z_0,C)}{\Phi(Z,C)}\right) + \Phi(Z,C)\lim_{C\to 0^+}\frac{\Phi(Z_0,C)}{\Phi(Z,C)} - \frac{\epsilon}{b}r\varphi_2(C) \\
&\quad - \frac{\epsilon\rho}{b}\varphi_2(C)\varphi_3(A_0) + \frac{\epsilon\rho}{bm}\left(1 - \frac{\varphi_3(A_0)}{\varphi_3(A)}\right)(\lambda - \delta\varphi_3(A)) \\
&= \psi(Z)\left(1 - \frac{\partial\Phi(Z_0,0)/\partial C}{\partial\Phi(Z,0)/\partial C}\right) + \Phi(Z,C)\frac{\partial\Phi(Z_0,0)/\partial C}{\partial\Phi(Z,0)/\partial C} - \frac{\epsilon}{b}r\varphi_2(C) \\
&\quad - \frac{\epsilon\rho}{b}\varphi_2(C)\varphi_3(A_0) + \frac{\epsilon\rho}{bm}\left(1 - \frac{\varphi_3(A_0)}{\varphi_3(A)}\right)(\delta\varphi_3(A_0) - \delta\varphi_3(A)).
\end{aligned}$$

Since $\psi(Z_0) = 0$, then we have

$$\begin{aligned}
\frac{dG_0}{dt} &= (\psi(Z) - \psi(Z_0))\left(1 - \frac{\partial\Phi(Z_0,0)/\partial C}{\partial\Phi(Z,0)/\partial C}\right) - \frac{\epsilon\rho\delta}{bm}\frac{(\varphi_3(A) - \varphi_3(A_0))^2}{\varphi_3(A)} \\
&\quad + \frac{\epsilon(r + \rho\varphi_3(A_0))}{b}\left(\frac{b}{\epsilon(r + \rho\varphi_3(A_0))}\frac{\Phi(Z,C)}{\varphi_2(C)}\frac{\partial\Phi(Z_0,0)/\partial C}{\partial\Phi(Z,0)/\partial C} - 1\right)\varphi_2(C),
\end{aligned}$$

and from inequality (6) we get

$$\begin{aligned}
\frac{dG_0}{dt} &\le (\psi(Z) - \psi(Z_0))\left(1 - \frac{\partial\Phi(Z_0,0)/\partial C}{\partial\Phi(Z,0)/\partial C}\right) - \frac{\epsilon\rho\delta}{bm}\frac{(\varphi_3(A) - \varphi_3(A_0))^2}{\varphi_3(A)} \\
&\quad + \frac{\epsilon(r + \rho\varphi_3(A_0))}{b}\left(\frac{b}{\epsilon(r + \rho\varphi_3(A_0))\varphi_2'(0)}\frac{\partial\Phi(Z_0,0)}{\partial C} - 1\right)\varphi_2(C) \\
&= (\psi(Z) - \psi(Z_0))\left(1 - \frac{\partial\Phi(Z_0,0)/\partial C}{\partial\Phi(Z,0)/\partial C}\right) - \frac{\epsilon\rho\delta}{bm}\frac{(\varphi_3(A) - \varphi_3(A_0))^2}{\varphi_3(A)} \\
&\quad + \frac{\epsilon(r + \rho\varphi_3(A_0))}{b}(\mathcal{R}_0 - 1)\varphi_2(C).
\end{aligned}$$

Thus, if $\mathcal{R}_0 \le 1$, then $\frac{dG_0}{dt} \le 0$ for all $Z,C,A > 0$. Also, $\frac{dG_0}{dt} = 0$, when $Z = Z_0$, $A = A_0$, $C = 0$. Hence, by LaSalle's invariance principle (Khalil (1996)), E^0 is GAS. ■

Theorem 2.2.

If assumptions (A1)-(A4) hold true and E_1^0 exists, then E_1^0 is GAS.

Proof:

Define the function

$$\begin{aligned} G_1(Z,U,C,A) = Z - Z_1 - \int_{Z_1}^{Z} \frac{\Phi(Z_1,C_1)}{\Phi(\vartheta,C_1)} d\vartheta \\ + U - U_1 - \int_{U_1}^{U} \frac{\varphi_1(U_1)}{\varphi_1(\vartheta)} d\vartheta \\ + \frac{\epsilon}{b}\left(C - C_1 - \int_{C_1}^{C} \frac{\varphi_2(C_1)}{\varphi_2(\vartheta)} d\vartheta\right) \\ + \frac{\epsilon\rho}{bm}\left(A - A_1 - \int_{A_1}^{A} \frac{\varphi_3(A_1)}{\varphi_3(\vartheta)} d\vartheta\right). \end{aligned}$$

We have $G_1(Z,U,C,A) > 0$ for all $Z,U,C,A > 0$ and $G_1(Z_1,U_1,C_1,A_1) = 0$. Calculating $\frac{dG_1}{dt}$ along the system (1)-(4), we get

$$\begin{aligned} \frac{dG_1}{dt} = &\left(1 - \frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right)(\psi(Z) - \Phi(Z,C)) \\ &+ \left(1 - \frac{\varphi_1(U_1)}{\varphi_1(U)}\right)(\Phi(Z,C) - \epsilon\varphi_1(U)) \\ &+ \frac{\epsilon}{b}\left(1 - \frac{\varphi_2(C_1)}{\varphi_2(C)}\right)(b\varphi_1(U) - r\varphi_2(C) - \rho\varphi_2(C)\varphi_3(A)) \\ &+ \frac{\epsilon\rho}{bm}\left(1 - \frac{\varphi_3(A_0)}{\varphi_3(A)}\right)(\lambda + m\varphi_2(C)\varphi_3(A) - \delta\varphi_3(A)). \end{aligned}$$

Applying

$$\psi(Z_1) = \epsilon\varphi_1(U_1),\ \lambda = \delta\varphi_3(A_1) - m\varphi_2(C_1)\varphi_3(A_1),$$

we obtain

$$\begin{aligned} \frac{dG_1}{dt} = &(\psi(Z) - \psi(Z_1))\left(1 - \frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right) + \epsilon\varphi_1(U_1)\left(1 - \frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right) \\ &+ \Phi(Z,C)\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)} - \Phi(Z,C)\frac{\varphi_1(U_1)}{\varphi_1(U)} + \epsilon\varphi_1(U_1) - \epsilon\varphi_1(U)\frac{\varphi_2(C_1)}{\varphi_2(C)} \\ &- \frac{\epsilon}{b}r\varphi_2(C) + \frac{\epsilon}{b}r\varphi_2(C_1) + \frac{\epsilon\rho}{b}\varphi_2(C_1)\varphi_3(A) - \frac{\epsilon\rho}{b}\varphi_2(C_1)\varphi_3(A_1) \\ &+ \frac{\epsilon\rho}{b}\varphi_2(C_1)\varphi_3(A_1)\frac{\varphi_3(A_1)}{\varphi_3(A)} - \frac{\epsilon\rho}{b}\varphi_2(C)\varphi_3(A_1) \\ &+ \frac{\epsilon\rho}{bm}\left(1 - \frac{\varphi_3(A_1)}{\varphi_3(A)}\right)(\delta\varphi_3(A_1) - \delta\varphi_3(A)). \end{aligned}$$

Using the conditions for E_1^0:

$$\Phi(Z_1,C_1) = \epsilon\varphi_1(U_1) = \frac{\epsilon}{b}r\varphi_2(C_1) + \frac{\epsilon\rho}{b}\varphi_2(C_1)\varphi_3(A_1),$$

we get

$$\begin{aligned}
\frac{dG_1}{dt} &= (\psi(Z)-\psi(Z_1))\left(1-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right)+3\epsilon\varphi_1(U_1)-\epsilon\varphi_1(U_1)\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\\
&\quad+\epsilon\varphi_1(U_1)\frac{\Phi(Z,C)}{\Phi(Z,C_1)}-\epsilon\varphi_1(U_1)\frac{\Phi(Z,C)\varphi_1(U_1)}{\Phi(Z_1,C_1)\varphi_1(U)}-\epsilon\varphi_1(U_1)\frac{\varphi_2(C_1)\varphi_1(U)}{\varphi_2(C)\varphi_1(U_1)}\\
&\quad-\epsilon\varphi_1(U_1)\frac{\varphi_2(C)}{\varphi_2(C_1)}-\frac{2\epsilon\rho}{b}\varphi_2(C_1)\varphi_3(A_1)+\frac{\epsilon\rho}{b}\varphi_2(C_1)\varphi_3(A)\\
&\quad+\frac{\epsilon\rho}{b}\varphi_2(C_1)\varphi_3(A_1)\left(\frac{\varphi_3(A_1)}{\varphi_3(A)}\right)-\frac{\epsilon\rho\delta}{bm}\left(1-\frac{\varphi_3(A_1)}{\varphi_3(A)}\right)(\varphi_3(A)-\varphi_3(A_1)). \qquad (14)
\end{aligned}$$

Equation (14) can be simplified as:

$$\begin{aligned}
\frac{dG_1}{dt} &= (\psi(Z)-\psi(Z_1))\left(1-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right)\\
&\quad+\epsilon\varphi_1(U_1)\left(\frac{\Phi(Z,C)}{\Phi(Z,C_1)}-\frac{\varphi_2(C)}{\varphi_2(C_1)}-1+\frac{\Phi(Z,C_1)\varphi_2(C)}{\Phi(Z,C)\varphi_2(C_1)}\right)\\
&\quad+\epsilon\varphi_1(U_1)\left[4-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}-\frac{\Phi(Z,C)\varphi_1(U_1)}{\Phi(Z_1,C_1)\varphi_1(U)}-\frac{\varphi_2(C_1)\varphi_1(U)}{\varphi_2(C)\varphi_1(U_1)}-\frac{\Phi(Z,C_1)\varphi_2(C)}{\Phi(Z,C)\varphi_2(C_1)}\right]\\
&\quad-\frac{\epsilon\rho}{b}\varphi_2(C_1)\varphi_3(A_1)\left(2-\frac{\varphi_3(A)}{\varphi_3(A_1)}-\frac{\varphi_3(A_1)}{\varphi_3(A)}\right)-\frac{\epsilon\rho\delta}{bm}\frac{(\varphi_3(A)-\varphi_3(A_1))^2}{\varphi_3(A)}\\
&= (\psi(Z)-\psi(Z_1))\left(1-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right)\\
&\quad+\epsilon\varphi_1(U_1)\left(\frac{\Phi(Z,C)}{\Phi(Z,C_1)}-\frac{\varphi_2(C)}{\varphi_2(C_1)}\right)\left(1-\frac{\Phi(Z,C_1)}{\Phi(Z,C)}\right)\\
&\quad+\epsilon\varphi_1(U_1)\left[4-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}-\frac{\Phi(Z,C)\varphi_1(U_1)}{\Phi(Z_1,C_1)\varphi_1(U)}-\frac{\varphi_2(C_1)\varphi_1(U)}{\varphi_2(C)\varphi_1(U_1)}-\frac{\Phi(Z,C_1)\varphi_2(C)}{\Phi(Z,C)\varphi_2(C_1)}\right]\\
&\quad-\frac{\epsilon\rho\lambda}{bm\varphi_3(A_1)}\frac{(\varphi_3(A)-\varphi_3(A_1))^2}{\varphi_3(A)}. \qquad (15)
\end{aligned}$$

The first two terms of (15) are less than or equal to zero according to assumptions (A1)-(A4) and Remark 2.1. Also, based on the relation between geometrical and arithmetical means, we have

$$4\le\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}+\frac{\Phi(Z,C)\varphi_1(U_1)}{\Phi(Z_1,C_1)\varphi_1(U)}+\frac{\varphi_2(C_1)\varphi_1(U)}{\varphi_2(C)\varphi_1(U_1)}+\frac{\Phi(Z,C_1)\varphi_2(C)}{\Phi(Z,C)\varphi_2(C_1)}.$$

Then $\frac{dG_1}{dt}\le 0$ and $\frac{dG_1}{dt}=0$ if $Z=Z_1$, $U=U_1$, $C=C_1$ and $A=A_1$. By the LaSalle's invariance principle, E_1^0 is GAS. ∎

3. General Within Host CHIKV Model with Latency

We propose a general within host CHIKV model with latently infected cells (Y) and actively infected cells (U) as:

$$\dot{Z} = \psi(Z) - \Phi(Z, C), \tag{16}$$

$$\dot{Y} = (1-g)\Phi(Z, C) - (\omega + \kappa)\xi(Y), \tag{17}$$

$$\dot{U} = g\Phi(Z, C) + \kappa\xi(Y) - \epsilon\varphi_1(U), \tag{18}$$

$$\dot{C} = b\varphi_1(U) - r\varphi_2(C) - \rho\varphi_2(C)\varphi_3(A), \tag{19}$$

$$\dot{A} = \lambda + m\varphi_2(C)\varphi_3(A) - \delta\varphi_3(A), \tag{20}$$

where $0 < g < 1$. The latently infected cells (Y) are activated at rate $\kappa\xi(Y)$ and die at rate $\omega\xi(Y)$, where ω and κ are positive constants. Functions ψ, Φ, φ_1, φ_2, and φ_3 are assumed to satisfy assumptions (A1)-(A4). The function $\xi(Y)$ also satisfies the condition:

Assumption A5.

(i) $\xi(Y) > 0$ for $Y > 0$, $\xi(0) = 0$, (ii) $\xi'(Y) > 0$ for $Y > 0$, (iii) there is $\alpha_4 > 0$ such that $\xi(Y) \geq \alpha_4 Y$ for $Y \geq 0$.

3.1. Basic results

We define the compact set:

$$\tilde{\Delta} = \{(Z, Y, U, C, A) \in \mathbb{R}^5_{\geq 0} : 0 \leq Z, Y, U \leq \bar{N}_1, 0 \leq C \leq \bar{N}_2, 0 \leq A \leq \bar{N}_3\}.$$

Lemma 3.1.

For system (16)-(20), there exist $\bar{N}_1, \bar{N}_2, \bar{N}_3 > 0$, such that $\tilde{\Delta}$ is positively invariant.

Proof:

Since

$$\begin{aligned}
\dot{Z}\Big|_{Z=0} &= \psi(0) > 0,\\
\dot{Y}\Big|_{Y=0} &= (1-g)\Phi(Z, C) \geq 0 \ \text{ for all } Z, C \geq 0,\\
\dot{U}\Big|_{U=0} &= g\Phi(Z, C) + A\xi(Y) \geq 0 \ \text{ for all } Z, C, Y \geq 0,\\
\dot{C}\Big|_{C=0} &= b\varphi_1(U) \geq 0 \ \text{ for all } U \geq 0,\\
\dot{A}\Big|_{A=0} &= \lambda > 0.
\end{aligned}$$

Hence, $\mathbb{R}^5_{\geq 0}$ is positively invariant with respect to system (16)-(20).

Next, let

$$K_2(t) = Z(t) + Y(t) + U(t) + \frac{\epsilon}{2b}C(t) + \frac{\epsilon\rho}{2bm}A(t), \tag{21}$$

then,

$$\begin{aligned}\dot{K}_2(t) &= \psi(Z) - \omega\xi(Y) - \frac{\epsilon}{2}\varphi_1(U) - \frac{\epsilon}{2b}r\varphi_2(C) + \frac{\epsilon\rho\lambda}{2bm} - \frac{\epsilon\rho\delta}{2bm}\varphi_3(A)\\ &\le x - \bar{x}Z + \frac{\epsilon\rho\lambda}{2bm} - \omega\alpha_4 Y - \frac{\epsilon}{2}\alpha_1 U - \frac{\epsilon}{2b}r\alpha_2 C - \frac{\epsilon\rho\delta}{2bm}\alpha_3 A\\ &\le x + \frac{\epsilon\rho\lambda}{2bm} - \tilde{\sigma}_2\left(Z + Y + U + \frac{\epsilon}{2b}C + \frac{\epsilon\rho}{2bm}A\right)\\ &= x + \frac{\epsilon\rho\lambda}{2bm} - \tilde{\sigma}_2 K_2(t),\end{aligned}$$

where $\tilde{\sigma}_2 = \min\{\bar{x}, \omega\alpha_4, \frac{\epsilon}{2}\alpha_1, r\alpha_2, \delta\alpha_3\}$. Hence, $K_2(t) \le \bar{N}_1$, if $K_2(0) \le \bar{N}_1$, where $\bar{N}_1 = \frac{x}{\tilde{\sigma}_2} + \frac{\epsilon\rho\lambda}{2bm\tilde{\sigma}_2}$. It follows that $0 \le Z(t), Y(t), U(t) \le \bar{N}_1$, $0 \le C(t) \le \bar{N}_2$ and $0 \le A(t) \le \bar{N}_3$ for all $t \ge 0$, if $Z(0) + Y(0) + U(0) + \frac{\epsilon}{2b}C(0) + \frac{\epsilon\rho}{2bm}A(0) \le \bar{N}_1$, where $\bar{N}_2 = \frac{2b\bar{N}_1}{\epsilon}$ and $\bar{N}_3 = \frac{2rb\bar{N}_1}{\epsilon\rho}$. Therefore, $Z(t), Y(t), U(t), C(t)$ and $A(t)$ are all bounded. ∎

To investigate the steady states of the model (16)-(20), we solve the following system:

$$0 = \psi(Z) - \Phi(Z, C), \tag{22}$$

$$0 = (1-g)\Phi(Z, C) - (\omega + \kappa)\xi(Y), \tag{23}$$

$$0 = g\Phi(Z, C) + \kappa\xi(Y) - \epsilon\varphi_1(U), \tag{24}$$

$$0 = b\varphi_1(U) - r\varphi_2(C) - \rho\varphi_2(C)\varphi_3(A), \tag{25}$$

$$0 = \lambda + m\varphi_2(C)\varphi_3(A) - \delta\varphi_3(A). \tag{26}$$

From Equations (23) and (24), we obtain

$$\xi(Y) = \frac{(1-g)\Phi(Z, C)}{(\omega + \kappa)},\ \varphi_1(U) = \frac{(\omega g + \kappa)\Phi(Z, C)}{\epsilon(\omega + \kappa)}. \tag{27}$$

Substituting Equations (26) and (27) into (25) we get

$$\frac{b(\omega g + \kappa)\Phi(Z, C)}{\epsilon(\omega + \kappa)} - \left(r + \frac{\rho\lambda}{\delta - m\varphi_2(C)}\right)\varphi_2(C) = 0. \tag{28}$$

Applying (A1)-(A3) into Equation (28), we have $C = 0$ as one of the solutions. This leads to a CHIKV-free steady state $E^* = (Z_0, 0, 0, 0, A_0)$, where $Z = Z_0$, $Y = 0$, $U = 0$ and $A = A_0 = \varphi_3^{-1}\left(\frac{\lambda}{\delta}\right)$. Next, we assume that there exists $C_1 \in \left(0, \varphi_2^{-1}(\frac{\delta}{m})\right)$ which satisfies Equation (28). Equation (22) becomes

$$0 = \psi(Z) - \Phi(Z, C_1).$$

We define a function Π as:

$$\Pi(Z) = \psi(Z) - \Phi(Z, C_1) = 0.$$

Then, we have $\Pi(0) = \psi(0) > 0$ and $\Pi(Z_0) = -\Phi(Z_0, C_1) < 0$. According to (A1)-(A2), Π is strictly decreasing function of Z. Thus, a unique $Z_1 \in (0, Z_0)$ exists, such that $\Pi(Z_1) = 0$. From Equations (23), (24) and (26), we obtain

$$\begin{aligned} Y_1 &= \xi^{-1}\left(\frac{(1-g)\Phi(Z_1, C_1)}{(\omega+\kappa)}\right) > 0, \\ U_1 &= \varphi_1^{-1}\left(\frac{(\omega g+\kappa)\Phi(Z_1, C_1)}{\epsilon(\omega+\kappa)}\right) > 0, \\ A_1 &= \varphi_3^{-1}\left(\frac{\lambda}{\delta - m\varphi_2(C_1)}\right) > 0. \end{aligned} \tag{29}$$

This leads to the endemic steady state $E_1^* = (Z_1, Y_1, U_1, C_1, A_1)$. The basic reproduction number $\mathcal{R}_0^Y$ of system (16)-(20) can be expressed as

$$\mathcal{R}_0^Y = \frac{b(\omega g+\kappa)}{\epsilon\left(\omega+\kappa\right)\left(r+\rho\varphi_3\left(A_0\right)\right)\varphi_2'(0)}\frac{\partial\Phi\left(Z_0, 0\right)}{\partial C}.$$

3.2. Global stability

Theorem 3.1.

Suppose that $\mathcal{R}_0^Y \leq 1$ and assumptions (A1)-(A5) hold true. Then E^* is GAS.

Proof:

Let consider the function

$$\begin{aligned} G_0^Y(Z, Y, U, C, A) = Z - Z_0 &- \int_{Z_0}^{Z} \lim_{C\to 0^+}\frac{\Phi(Z_0, C)}{\Phi(\vartheta, C)}d\vartheta \\ &+ \frac{\kappa}{\omega g+\kappa}Y + \frac{\omega+\kappa}{\omega g+\kappa}U + \frac{\epsilon(\omega+\kappa)}{b(\omega g+\kappa)}C \\ &+ \frac{\epsilon\rho(\omega+\kappa)}{bm(\omega g+\kappa)}\left(A - A_0 - \int_{A_0}^{A}\frac{\varphi_3(A_0)}{\varphi_3(\vartheta)}d\vartheta\right). \end{aligned}$$

Calculating $\dfrac{dG_0^Y}{dt}$ along the system (16)-(20), we get

$$\begin{aligned} \frac{dG_0^Y}{dt} = &\left(1 - \lim_{C\to 0^+}\frac{\Phi(Z_0, C)}{\Phi(Z, C)}\right)(\psi(Z) - \Phi(Z, C)) + \frac{\kappa}{\omega g+\kappa}\left((1-g)\Phi(Z, C) - (\omega+\kappa)\xi(Y)\right) \\ &+ \frac{\omega+\kappa}{\omega g+\kappa}\left(g\Phi(Z, C) + \kappa\xi(Y) - \epsilon\varphi_1(U)\right) \\ &+ \frac{\epsilon(\omega+\kappa)}{b(\omega g+\kappa)}\left(b\varphi_1(U) - r\varphi_2(C) - \rho\varphi_2(C)\varphi_3(A)\right) \\ &+ \frac{\epsilon\rho(\omega+\kappa)}{bm(\omega g+\kappa)}\left(1 - \frac{\varphi_3(A_0)}{\varphi_3(A)}\right)\left(\lambda + m\varphi_2(C)\varphi_3(A) - \delta\varphi_3(A)\right) \end{aligned}$$

$$\begin{aligned}\frac{dG_0^Y}{dt} = &\left(1 - \lim_{C\to 0^+}\frac{\Phi(Z_0,C)}{\Phi(Z,C)}\right)\psi(Z)\\ &+ \Phi(Z,C)\left(\lim_{C\to 0^+}\frac{\Phi(Z_0,C)}{\Phi(Z,C)}\right)\\ &- \frac{\epsilon(\omega+\kappa)}{b(\omega g+\kappa)}r\varphi_2(C)\\ &- \frac{\epsilon\rho(\omega+\kappa)}{b(\omega g+\kappa)}\varphi_2(C)\varphi_3(A_0)\\ &+ \frac{\epsilon\rho(\omega+\kappa)}{bm(\omega g+\kappa)}\left(1-\frac{\varphi_3(A_0)}{\varphi_3(A)}\right)(\lambda-\delta\varphi_3(A))\end{aligned}$$

$$\begin{aligned}\frac{dG_0^Y}{dt} &= (\psi(Z)-\psi(Z_0))\left(1-\frac{\partial\Phi(Z_0,0)/\partial C}{\partial\Phi(Z,0)/\partial C}\right) + \Phi(Z,C)\frac{\partial\Phi(Z_0,0)/\partial C}{\partial\Phi(Z,0)/\partial C}\\ &\quad - \frac{\epsilon(\omega+\kappa)}{b(\omega g+\kappa)}(r+\rho\varphi_3(A_0))\varphi_2(C)\\ &\quad + \frac{\epsilon\rho(\omega+\kappa)}{bm(\omega g+\kappa)}\left(1-\frac{\varphi_3(A_0)}{\varphi_3(A)}\right)(\delta\varphi_3(A_0)-\delta\varphi_3(A))\\ &\le (\psi(Z)-\psi(Z_0))\left(1-\frac{\partial\Phi(Z_0,0)/\partial C}{\partial\Phi(Z,0)/\partial C}\right)\\ &\quad - \frac{\epsilon\rho(\omega+\kappa)\delta}{bm(\omega g+\kappa)}\frac{(\varphi_3(A)-\varphi_3(A_0))^2}{\varphi_3(A)}\\ &\quad + \left(\lim_{C\to 0^+}\frac{\Phi(Z,C)}{\varphi_2(C)}\frac{\partial\Phi(Z_0,0)/\partial C}{\partial\Phi(Z,0)/\partial C} - \frac{\epsilon(\omega+\kappa)}{b(\omega g+\kappa)}(r+\rho\varphi_3(A_0))\right)\varphi_2(C)\\ &= (\psi(Z)-\psi(Z_0))\left(1-\frac{\partial\Phi(Z_0,0)/\partial C}{\partial\Phi(Z,0)/\partial C}\right) - \frac{\epsilon\rho(\omega+\kappa)\delta}{bm(\omega g+\kappa)}\frac{(\varphi_3(A)-\varphi_3(A_0))^2}{\varphi_3(A)}\\ &\quad + \frac{\epsilon(\omega+\kappa)(r+\rho\varphi_3(A_0))}{b(\omega g+\kappa)}\left(\frac{b(\omega g+\kappa)}{\epsilon(\omega+\kappa)(r+\rho\varphi_3(A_0))\varphi_2'(0)}\frac{\partial\Phi(Z_0,0)}{\partial C}-1\right)\varphi_2(C)\\ &= (\psi(Z)-\psi(Z_0))\left(1-\frac{\partial\Phi(Z_0,0)/\partial C}{\partial\Phi(Z,0)/\partial C}\right) - \frac{\epsilon\rho(\omega+\kappa)\delta}{bm(\omega g+\kappa)}\frac{(\varphi_3(A)-\varphi_3(A_0))^2}{\varphi_3(A)}\\ &\quad + \frac{\epsilon(\omega+\kappa)(r+\rho\varphi_3(A_0))}{b(\omega g+\kappa)}\left(\mathcal{R}_0^Y-1\right)\varphi_2(C). \end{aligned} \tag{30}$$

From Remark 2.1 we have, if $\mathcal{R}_0^Y \le 1$, then $\frac{dG_0^Y}{dt} \le 0$ for all $Z, C, A > 0$. Furthermore, $\frac{dG_0^Y}{dt} = 0$, when $Z = Z_0$, $A = A_0$, $C = 0$. Applying LaSalle's invariance principle, we get that E^* is GAS. ■

Theorem 3.2.

If assumptions (A1)-(A5) hold true and E_1^* exists, then E_1^* is GAS.

Proof:

Define the function

$$\begin{aligned}
G_1^Y(Z,Y,U,C,A) = {} & Z - Z_1 - \int_{Z_1}^{Z} \frac{\Phi(Z_1,C_1)}{\Phi(\vartheta,C_1)} d\vartheta + \frac{\kappa}{\omega g+\kappa}\left(Y - Y_1 - \int_{Y_1}^{Y} \frac{\xi(Y_1)}{\xi(\vartheta)} d\vartheta\right) \\
& + \frac{\omega+\kappa}{\omega g+\kappa}\left(U - U_1 - \int_{U_1}^{U} \frac{\varphi_1(U_1)}{\varphi_1(\vartheta)} d\vartheta\right) \\
& + \frac{\epsilon(\omega+\kappa)}{b(\omega g+\kappa)}\left(C - C_1 - \int_{C_1}^{C} \frac{\varphi_2(C_1)}{\varphi_2(\vartheta)} d\vartheta\right) \\
& + \frac{\epsilon\rho(\omega+\kappa)}{bm(\omega g+\kappa)}\left(A - A_1 - \int_{A_1}^{A} \frac{\varphi_3(A_1)}{\varphi_3(\vartheta)} d\vartheta\right).
\end{aligned}$$

Calculating $\dfrac{dG_1^Y}{dt}$ along the system (16)-(20), we get

$$\begin{aligned}
\frac{dG_1^Y}{dt} = {} & \left(1 - \frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right)(\psi(Z) - \Phi(Z,C)) \\
& + \frac{\kappa}{\omega g+\kappa}\left(1 - \frac{\xi(Y_1)}{\xi(Y)}\right)((1-g)\Phi(Z,C) - (\omega+\kappa)\xi(Y)) \\
& + \frac{\omega+\kappa}{\omega g+\kappa}\left(1 - \frac{\varphi_1(U_1)}{\varphi_1(U)}\right)(g\Phi(Z,C) + \kappa\xi(Y) - \epsilon\varphi_1(U)) \\
& + \frac{\epsilon(\omega+\kappa)}{b(\omega g+\kappa)}\left(1 - \frac{\varphi_2(C_1)}{\varphi_2(C)}\right)(b\varphi_1(U) - r\varphi_2(C) - \rho\varphi_2(C)\varphi_3(A)) \\
& + \frac{\epsilon\rho(\omega+\kappa)}{bm(\omega g+\kappa)}\left(1 - \frac{\varphi_3(A_1)}{\varphi_3(A)}\right)(\lambda + m\varphi_2(C)\varphi_3(A) - \delta\varphi_3(A)).
\end{aligned}$$

Applying

$$\psi(Z_1) = \Phi(Z_1,C_1),\ \lambda = \delta\varphi_3(A_1) - m\varphi_2(C_1)\varphi_3(A_1),$$

we obtain

$$\begin{aligned}
\frac{dG_1^Y}{dt} = {} & (\psi(Z) - \psi(Z_1))\left(1 - \frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right) + \Phi(Z_1,C_1)\left(1 - \frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right) + \Phi(Z,C)\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)} \\
& - \frac{\kappa(1-g)}{\omega g+\kappa}\Phi(Z,C)\frac{\xi(Y_1)}{\xi(Y)} + \frac{\kappa(\omega+\kappa)}{\omega g+\kappa}\xi(Y_1) - \frac{(\omega+\kappa)g}{\omega g+\kappa}\Phi(Z,C)\frac{\varphi_1(U_1)}{\varphi_1(U)} \\
& - \frac{\kappa(\omega+\kappa)}{\omega g+\kappa}\frac{\xi(Y)\varphi_1(U_1)}{\varphi_1(U)} + \frac{\epsilon(\omega+\kappa)}{\omega g+\kappa}\varphi_1(U_1) - \frac{\epsilon(\omega+\kappa)}{\omega g+\kappa}\frac{\varphi_2(C_1)\varphi_1(U)}{\varphi_2(C)} \\
& - \frac{\epsilon(\omega+\kappa)}{b(\omega g+\kappa)}r\varphi_2(C) + \frac{\epsilon(\omega+\kappa)}{b(\omega g+\kappa)}r\varphi_2(C_1) + \frac{\epsilon\rho(\omega+\kappa)}{b(\omega g+\kappa)}\varphi_2(C_1)\varphi_3(A) \\
& - \frac{\epsilon\rho(\omega+\kappa)}{b(\omega g+\kappa)}\varphi_2(C_1)\varphi_3(A_1) + \frac{\epsilon\rho(\omega+\kappa)}{b(\omega g+\kappa)}\varphi_2(C_1)\varphi_3(A_1)\left(\frac{\varphi_3(A_1)}{\varphi_3(A)}\right) \\
& - \frac{\epsilon\rho(\omega+\kappa)}{b(\omega g+\kappa)}\varphi_2(C)\varphi_3(A_1) + \frac{\epsilon\rho(\omega+\kappa)}{bm(\omega g+\kappa)}\left(1 - \frac{\varphi_3(A_1)}{\varphi_3(A)}\right)(\delta\varphi_3(A_1) - \delta\varphi_3(A)).
\end{aligned}$$

Using the conditions:

$$(1-g)\Phi(Z_1,C_1)=(\omega+\kappa)\xi(Y_1),\ g\Phi(Z_1,C_1)+\kappa\xi(Y_1)=\epsilon\varphi_1(U_1),$$
$$b\varphi_1(U_1)=r\varphi_2(C_1)+\rho\varphi_2(C_1)\varphi_3(A_1),$$

we get

$$\begin{aligned}\frac{\epsilon\,(\omega+\kappa)}{\omega g+\kappa}\varphi_1(U_1)&=\Phi(Z_1,C_1)=\frac{\kappa(1-g)}{\omega g+\kappa}\Phi(Z_1,C_1)+\frac{(\omega+\kappa)\,g}{\omega g+\kappa}\Phi(Z_1,C_1),\\ \frac{\epsilon(\omega+\kappa)}{b(\omega g+\kappa)}r\varphi_2(C_1)&=\Phi(Z_1,C_1)-\frac{\epsilon\rho(\omega+\kappa)}{b(\omega g+\kappa)}\varphi_2(C_1)\varphi_3(A_1),\end{aligned}$$

and

$$\begin{aligned}\frac{dG_1^Y}{dt}&=(\psi(Z)-\psi(Z_1))\left(1-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right)+\Phi(Z_1,C_1)\left(\frac{\Phi(Z,C)}{\Phi(Z,C_1)}-\frac{\varphi_2(C)}{\varphi_2(C_1)}\right)\\
&+\frac{\kappa(1-g)}{\omega g+\kappa}\Phi(Z_1,C_1)\left(1-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right)\\
&+\frac{(\omega+\kappa)\,g}{\omega g+\kappa}\Phi(Z_1,C_1)\left(1-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right)\\
&-\frac{\kappa(1-g)}{\omega g+\kappa}\Phi(Z_1,C_1)\frac{\Phi(Z,C)\xi(Y_1)}{\Phi(Z_1,C_1)\xi(Y)}+\frac{\kappa(1-g)}{\omega g+\kappa}\Phi(Z_1,C_1)\\
&-\frac{(\omega+\kappa)\,g}{\omega g+\kappa}\Phi(Z_1,C_1)\frac{\Phi(Z,C)\varphi_1(U_1)}{\Phi(Z_1,C_1)\varphi_1(U)}\\
&-\frac{\kappa(1-g)}{\omega g+\kappa}\Phi(Z_1,C_1)\frac{\varphi_1(U_1)\xi(Y)}{\varphi_1(U)\xi(Y_1)}\\
&+\frac{\kappa(1-g)}{\omega g+\kappa}\Phi(Z_1,C_1)+\frac{(\omega+\kappa)\,g}{\omega g+\kappa}\Phi(Z_1,C_1)\\
&-\frac{\kappa(1-g)}{\omega g+\kappa}\Phi(Z_1,C_1)\frac{\varphi_2(C_1)\varphi_1(U)}{\varphi_2(C)\varphi_1(U_1)}\\
&-\frac{(\omega+\kappa)\,g}{\omega g+\kappa}\Phi(Z_1,C_1)\frac{\varphi_2(C_1)\varphi_1(U)}{\varphi_2(C)\varphi_1(U_1)}+\frac{\kappa(1-g)}{\omega g+\kappa}\Phi(Z_1,C_1)\\
&+\frac{(\omega+\kappa)\,g}{\omega g+\kappa}\Phi(Z_1,C_1)\\
&-\frac{2\epsilon\rho(\omega+\kappa)}{b(\omega g+\kappa)}\varphi_2(C_1)\varphi_3(A_1)+\frac{\epsilon\rho(\omega+\kappa)}{b(\omega g+\kappa)}\varphi_2(C_1)\varphi_3(A)\\
&+\frac{\epsilon\rho(\omega+\kappa)}{b(\omega g+\kappa)}\varphi_2(C_1)\varphi_3(A_1)\left(\frac{\varphi_3(A_1)}{\varphi_3(A)}\right)\\
&-\frac{\epsilon\rho(\omega+\kappa)\delta}{bm(\omega g+\kappa)}\frac{(\varphi_3(A)-\varphi_3(A_1))^2}{\varphi_3(A)}.\end{aligned}\tag{31}$$

Equation (31) can be simplified as:

$$\begin{aligned}
\frac{dG_1^Y}{dt} &= (\psi(Z)-\psi(Z_1))\left(1-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right)\\
&+\Phi(Z_1,C_1)\left(\frac{\Phi(Z,C)}{\Phi(Z,C_1)}-\frac{\varphi_2(C)}{\varphi_2(C_1)}-1+\frac{\Phi(Z,C_1)\varphi_2(C)}{\Phi(Z,C)\varphi_2(C_1)}\right)\\
&+\frac{\kappa(1-g)}{\omega g+\kappa}\Phi(Z_1,C_1)\left[5-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}-\frac{\Phi(Z,C)\xi(Y_1)}{\Phi(Z_1,C_1)\xi(Y)}-\frac{\varphi_1(U_1)\xi(Y)}{\varphi_1(U)\xi(Y_1)}\right.\\
&\left.-\frac{\varphi_2(C_1)\varphi_1(U)}{\varphi_2(C)\varphi_1(U_1)}-\frac{\Phi(Z,C_1)\varphi_2(C)}{\Phi(Z,C)\varphi_2(C_1)}\right]\\
&+\frac{(\omega+\kappa)\,g}{\omega g+\kappa}\Phi(Z_1,C_1)\left[4-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}-\frac{\Phi(Z,C)\varphi_1(U_1)}{\Phi(Z_1,C_1)\varphi_1(U)}\right.\\
&\left.-\frac{\varphi_2(C_1)\varphi_1(U)}{\varphi_2(C)\varphi_1(U_1)}-\frac{\Phi(Z,C_1)\varphi_2(C)}{\Phi(Z,C)\varphi_2(C_1)}\right]\\
&-\frac{\epsilon\rho(\omega+\kappa)}{b(\omega g+\kappa)}\varphi_2(C_1)\varphi_3(A_1)\left(2-\frac{\varphi_3(A)}{\varphi_3(A_1)}-\frac{\varphi_3(A_1)}{\varphi_3(A)}\right)\\
&-\frac{\epsilon\rho(\omega+\kappa)\delta}{bm(\omega g+\kappa)}\frac{(\varphi_3(A)-\varphi_3(A_1))^2}{\varphi_3(A)},\\
\frac{dG_1^Y}{dt} &= (\psi(Z)-\psi(Z_1))\left(1-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}\right)\\
&+\Phi(Z_1,C_1)\left(\frac{\Phi(Z,C)}{\Phi(Z,C_1)}-\frac{\varphi_2(C)}{\varphi_2(C_1)}\right)\left(1-\frac{\Phi(Z,C_1)}{\Phi(Z,C)}\right)\\
&+\frac{\kappa(1-g)}{\omega g+\kappa}\Phi(Z_1,C_1)\left[5-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}-\frac{\Phi(Z,C)\xi(Y_1)}{\Phi(Z_1,C_1)\xi(Y)}-\frac{\varphi_1(U_1)\xi(Y)}{\varphi_1(U)\xi(Y_1)}\right.\\
&\left.-\frac{\varphi_2(C_1)\varphi_1(U)}{\varphi_2(C)\varphi_1(U_1)}-\frac{\Phi(Z,C_1)\varphi_2(C)}{\Phi(Z,C)\varphi_2(C_1)}\right]\\
&+\frac{(\omega+\kappa)\,g}{\omega g+\kappa}\Phi(Z_1,C_1)\left[4-\frac{\Phi(Z_1,C_1)}{\Phi(Z,C_1)}-\frac{\Phi(Z,C)\varphi_1(U_1)}{\Phi(Z_1,C_1)\varphi_1(U)}\right.\\
&\left.-\frac{\varphi_2(C_1)\varphi_1(U)}{\varphi_2(C)\varphi_1(U_1)}-\frac{\Phi(Z,C_1)\varphi_2(C)}{\Phi(Z,C)\varphi_2(C_1)}\right]\\
&-\frac{\epsilon\rho(\omega+\kappa)\lambda}{bm(\omega g+\kappa)\varphi_3(A_1)}\frac{(\varphi_3(A)-\varphi_3(A_1))^2}{\varphi_3(A)}.
\end{aligned}\tag{32}$$

Clearly, $\frac{dG_1^Y}{dt}\leq 0$ and $\frac{dG_1^Y}{dt}=0$ if $Z=Z_1$, $Y=Y_1$, $U=U_1$, $C=C_1$ and $A=A_1$. By the LaSalle's invariance principle, E_1^* is GAS. ∎

4. Numerical Simulations

In this section, numerical simulations for the systems (1)-(4) and (16)-(20) are carried out to validate our global stability results. We have used MATLAB for all the computations.

Example 4.1.

We consider

$$\dot{Z} = \gamma - qZ + \pi Z\left(1 - \frac{Z}{Z_{\max}}\right) - \frac{\beta ZC}{1 + a_1 Z + a_2 C}, \tag{33}$$

$$\dot{U} = \frac{\beta ZC}{1 + a_1 Z + a_2 C} - \epsilon U, \tag{34}$$

$$\dot{C} = bU - rC - \rho CA, \tag{35}$$

$$\dot{A} = \lambda + mCA - \delta A, \tag{36}$$

where $\beta, \gamma, \pi, q, a_1, a_2, Z_{\max} > 0$. In the concentration of uninfected cells, the generation rate constant is denoted as γ, maximum proliferation rate as πZ, natural death rate as qZ and $Z_{\max}$ as the maximum level of uninfected cells concentration in the body. The intrinsic growth rate of uninfected cells is defined as

$$\psi(Z) = \gamma - qZ + \pi Z\left(1 - \frac{Z}{Z_{\max}}\right),$$

and we assume that $\pi < q$ (Smith and De Leenheer (2003)). Then, we have $\psi(0) = \gamma > 0$ and $\psi(Z_0) = 0$, where

$$Z_0 = \frac{Z_{\max}}{2\pi}\left(\pi - q + \sqrt{(\pi - q)^2 + \frac{4\gamma\pi}{Z_{\max}}}\right).$$

Moreover, it follows that

$$\psi'(Z) = -q + \pi - \frac{2\pi Z}{Z_{\max}} < 0.$$

Clearly, $\psi(Z) > 0$ for all $Z \in [0, Z_0)$. Thus, (A1) holds true.

Next, the incidence rate of infection is defined as

$$\Phi(Z, C) = \frac{\beta ZC}{1 + a_1 Z + a_2 C}.$$

Clearly, $\Phi(Z, C) > 0, \Phi(0, C) = \Phi(Z, 0) = 0$ for all $Z, C > 0$. Then, for $Z > 0$ and $C > 0$, we have

$$\frac{\partial \Phi(Z, C)}{\partial Z} = \frac{\beta C(1 + a_2 C)}{(1 + a_1 Z + a_2 C)^2} > 0,$$

$$\frac{\partial \Phi(Z, C)}{\partial C} = \frac{\beta Z(1 + a_1 Z)}{(1 + a_1 Z + a_2 C)^2} > 0,$$

$$\frac{\partial \Phi(Z, 0)}{\partial C} = \frac{\beta Z}{(1 + a_1 Z)} > 0,$$

$$\frac{d}{dZ}\left(\frac{\partial \Phi(Z, 0)}{\partial C}\right) = \frac{\beta}{(1 + a_1 Z)^2} > 0.$$

Thus, (A2) is satisfied. Then, we have $\varphi_i(n) = \alpha_i n > 0$, $i = 1, 2, 3$ for all $n > 0$, $\varphi_i(0) = 0$, and $\varphi_i'(n) = \alpha_i > 0$. Thus, (A3) holds true. Also, for all $Z, C > 0$,

$$\frac{\Phi(Z,C)}{\varphi_2(C)} = \frac{\beta Z}{(1 + a_1 Z + a_2 C)},$$
$$\frac{\partial}{\partial C}\left(\frac{\Phi(Z,C)}{\varphi_2(C)}\right) = -\frac{\beta Z a_2}{(1 + a_1 Z + a_2 C)^2} < 0.$$

Thus, (A4) is also satisfied. With these, system (33)-(36) agrees with the global stability results in Theorems 2.1-2.2. The basic reproduction number $\mathcal{R}_0$ for system (33)-(36) is defined as

$$\mathcal{R}_0 = \frac{b}{\epsilon(r + \rho A_0)} \frac{\partial \Phi(Z_0, 0)}{\partial C} = \frac{b}{\epsilon(r + \rho A_0)} \frac{\beta Z_0}{(1 + a_1 Z_0)}.$$

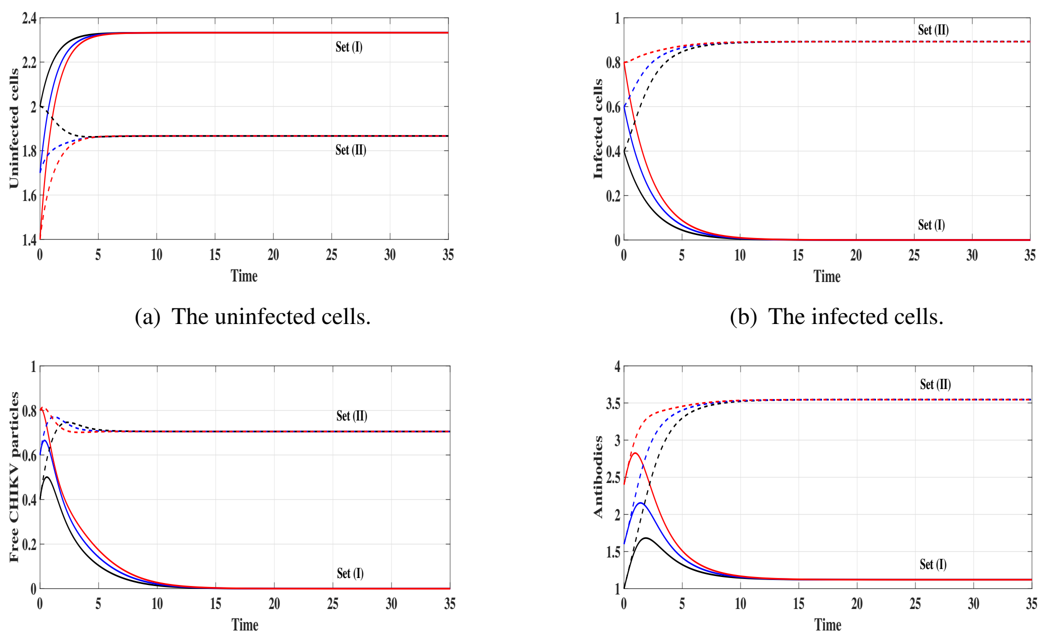
We consider three different initial values to show the numerical results for system (33)-(36). The initial values are

IV_1: $Z_0 = 2.0, U_0 = 0.4, C_0 = 0.4$ and $A_0 = 1.0$,

IV_2: $Z_0 = 1.7, U_0 = 0.6, C_0 = 0.6$ and $A_0 = 1.6$,

IV_3: $Z_0 = 1.4, U_0 = 0.8, C_0 = 0.8$ and $A_0 = 2.4$.

The following values of parameters are used: $\gamma = 1.826$, $r = 0.4418$, $\delta = 1.251$, $a_1 = 1.0$, $a_2 = 3.0$, $m = 1.2129$, $\epsilon = 0.4441$, $\lambda = 1.402$, $\rho = 0.5964$, $b = 2.02$, $q = 0.7979$, $Z_{\max} = 2.7462$, $\pi = 0.1$, $\beta =$varied.



(a) The uninfected cells. (b) The infected cells.

(c) The free CHIKV particles. (d) The antibodies.

Figure 1. The evolution of the steady states of system (33)–(36)

Set (I): Here, $\beta = 0.005$ and we calculate $\mathcal{R}_0 = 0.0143 < 1$. In Figure 1, the solutions of the system with the initial values $\mathbf{I}V_1 - \mathbf{I}V_3$ return to the CHIKV-free steady state $E^0 = (2.3325, 0, 0, 1.1207)$. This shows the consistency of the numerical results with the result of Theorem 2.1, that E^0 is GAS. In this case, the CHIKV will be removed.

Set (II): We take $\beta = 1.5$, and $\mathcal{R}_0 = 4.3015 > 1$. Figure 1 shows the compatibility of our numerical results with the result of Theorem 2.2. We can easily see that the solutions of the system with the initial values $\mathbf{I}V_1 - \mathbf{I}V_3$ tend to the endemic steady state $E_1^0 = (1.8667, 0.8925, 3.5450, 0.7053)$. Hence, E_1^0 exists and it is GAS.

Example 4.2.

We consider

$$\dot{Z} = \gamma - qZ + \pi Z\left(1 - \frac{Z}{Z_{\max}}\right) - \frac{\beta ZC}{1 + a_1 Z + a_2 C}, \tag{37}$$

$$\dot{Y} = (1-g)\frac{\beta ZC}{1 + a_1 Z + a_2 C} - (\omega + \kappa)Y, \tag{38}$$

$$\dot{U} = g\frac{\beta ZC}{1 + a_1 Z + a_2 C} + \kappa Y - \epsilon U, \tag{39}$$

$$\dot{C} = bU - rC - \rho CA, \tag{40}$$

$$\dot{A} = \lambda + mCA - \delta A. \tag{41}$$

The parameters and variables are the same as given in Example 4.1. Similar to Example 4.1 above, one can show that assumptions (A1)-(A4) satisfy the model (37)-(41). In this example, we chose $\xi(Y) = Y$. Thus, (A5) is satisfied, which shows that the global stability results in Theorems 3.1-3.2 are applicable. The basic reproduction number $\mathcal{R}_0^Y$ for model (37)-(41) is given by

$$\mathcal{R}_0^Y = \frac{b(\omega g + \kappa)}{\epsilon(\omega + \kappa)(r + \rho A_0)}\frac{\partial \Phi(Z_0, 0)}{\partial C} = \frac{b\beta(\omega g + \kappa)Z_0}{\epsilon(\omega + \kappa)(r + \rho A_0)\,(1 + a_1 Z_0)}.$$

Next, let us consider the following initial values to show the numerical results for system (37)-(41):

$\mathbf{I}V_4$: $Z_0 = 2.0, Y_0 = 0.2, U_0 = 0.4, C_0 = 0.4$ and $A_0 = 1.0$,

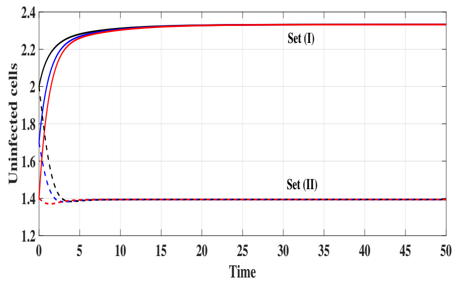
$\mathbf{I}V_5$: $Z_0 = 1.7, Y_0 = 0.4, U_0 = 0.6, C_0 = 0.6$ and $A_0 = 1.6$,

$\mathbf{I}V_6$: $Z_0 = 1.4, Y_0 = 0.6, U_0 = 0.8, C_0 = 0.8$ and $A_0 = 2.4$.

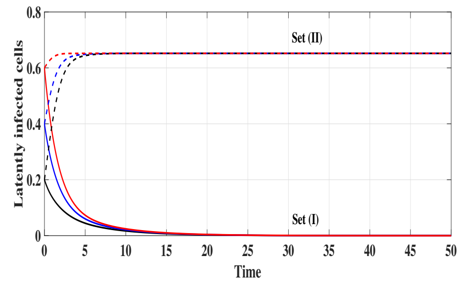
We use the following values of parameters: $g = 0.5$, $\kappa = 0.1$, $\omega = 0.5$, $\beta =$ varied. The other parameters are the same as given in Example 4.1.

Set (I): Here, $\beta = 0.3$, and we calculate $\mathcal{R}_0^Y = 0.5018 < 1$. Figure 2 clearly shows that, the solutions of the system with the initial values $\mathbf{I}V_4 - \mathbf{I}V_6$ finally approach the CHIKV-free steady state $E^* = (2.3325, 0, 0, 0, 1.1207)$. This validates Theorem 3.1 that E^* is GAS.

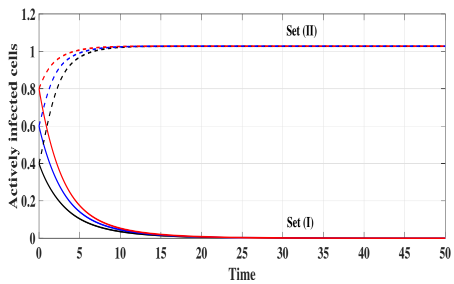
Set (II): We take $\beta = 3.5$. This gives $\mathcal{R}_0^Y = 5.8548 > 1$. We compute the steady state $E_1^* = (1.3940, 0.6520, 1.0277, 3.9641, 0.7398)$. When $\mathcal{R}_0^Y > 1$, the solutions of the system with the initial values $\mathbf{I}V_4 - \mathbf{I}V_6$ tend to E_1^*. In this set, E_1^* exists and it is GAS. This proves the validity of Theorem 3.2.



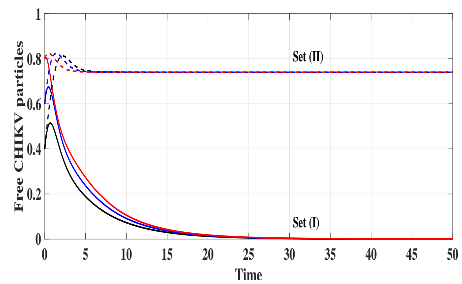
(a) The uninfected cells.



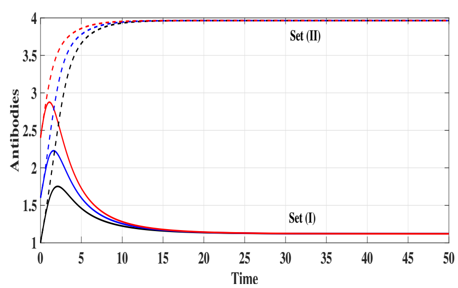
(b) The latently infected cells.



(c) The actively infected cells.



(d) The free CHIKV particles.



(e) The antibodies.

Figure 2. The evolution of the steady states of system (37)–(41)

5. Conclusion

In this work, we have presented two models of a generalized within-host CHIKV dynamics. The first model considered a class of infected cells while the second model considered two classes of infected cells that are actively and latently infected cells. We have investigated the well-posedness of the models by studying the nonnegativity and boundedness of the solutions. Under a set of reasonable conditions on the general nonlinear functions, we have constructed suitable Lyapunov functionals to prove the global stability of the steady states of the models which fully determined by the basic reproduction number $\mathcal{R}_0$. In addition, our proposed models have extended and generalized some existing models in the literature. These proposed models can also be extended by incorporating two routes of infection (i.e., CHIKV-to-cell infection and cell-to-cell transmission) which we shall consider in our future work.

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