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Research Article

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Global properties of virus dynamics with B-cell impairment

Abstract: In this paper we construct a class of virus dynamics models with impairment of B-cell functions. Two forms of the incidence rate have been considered, saturated and general. The well-posedness of the models is justified. The models admit two equilibria which are determined by the basic reproduction number R_0. The global stability of each equilibrium is proven by utilizing Lyapunov function and LaSalle's invariance principle. The theoretical results are illustrated by numerical simulations.

1 Introduction

The study of within-host virus dynamics using mathematical modeling has been an interesting topic to research in the last decades. A proper model could provide insights of a better understanding of the virus dynamics and clinical treatments used to fight against it. In an infection process, the interaction between viruses and cells can be seen as an ecological system within the infected host. A wide of mathematical models focused on exploring the interaction between three basic compartments, uninfected cells (U), infected cells producing viruses (I) and viruses (P). A basic model of virus dynamics was originally developed by Nowak and Bangham [1] which has become highly used by experimentalists and theorists (see e.g., Nowak and May [2]). The model presented in [1] is given by:

$$\dot{U} = \varrho - \gamma U - \omega UP, \tag{1}$$

$$\dot{I} = \omega UP - \beta I, \tag{2}$$

$$\dot{P} = \varkappa I - \xi P, \tag{3}$$

where U, I and P are the concentrations of uninfected cells, infected cells and viruses, respectively. The parameters ϱ, γ, ω, β, $\varkappa$ and ξ are positive. The full description of the model was given in [1]. A huge number of papers have been published as extension of the basic model (see, e.g., [3–22]).

The immune response plays a critical role in controlling the virus spreading. The specificity and memory in adaptive immune responses are the responsibility of lymphocytes. B cells and T cells are the two main types of lymphocytes. The function of T cells is to recognize and kill infected cells, while the function of B

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cells is to produce antibodies which bind to virus particles and mark it as a foreign structure for elimination by other cells of the immune system. Antibody alone can neutralize, and thus protect against, viruses [23]. The virus dynamics model with B cell immune response was presented by Murase et al. [24] as

$$\dot{U} = \varrho - \gamma U - \omega UP, \tag{4}$$

$$\dot{I} = \omega UP - \beta I, \tag{5}$$

$$\dot{P} = \varkappa I - \xi P - \rho PC, \tag{6}$$

$$\dot{C} = \varepsilon PC - \mu C, \tag{7}$$

where C is the concentration of B cells. Many extended models are developed with B cell immune response (see, e.g., [25–36]).

In certain circumstances, some viruses can suppress immune response or even destroy it especially when the load of viruses is too high. Models with T cell immune impairment were studied several times (see, e.g., [37–40]). In addition, there are factors affect B cell function and cause the impairment of B cell [41–43]. These factors include the following; malnutrition, tumors, cytotoxic drugs, irradiation, aging, trauma, some diseases (e.g., diabetes) and immunosuppression by microbes, e.g., malaria, measles virus but especially HIV [23]. In a very recent work, Miao et al. [44] have proposed a virus dynamics model which includes: humoral impairment, time delay, reaction-diffusion, and logistic growth of the target cells. Due to the complexity of the model presented in [44], the global stability analysis of the model's equilibria did not studied. Studying the global stability of equilibria for virus dynamics models will give us a detailed information and enhances our understanding about the virus dynamics. Therefore, many mathematician have paid great efforts to study global stability of systems in virology (see, e.g., [7–19] and [45–54]) and epidemiology (see, e.g., [55–57]).

In [44], the incidence rate of infection is given by bilinear. In reality, the bilinear incidence may not accurate to characterize the virus dynamics during different stages of infection especially when the concentration of the viruses is high [8]. Therefore, in the present paper, we propose viral infection model with B-cell impairment and with two nonlinear forms of the incidence rate, saturation and general. We show that the solutions of the model are nonnegative and bounded. The global stability of the equilibria is established by constructing Lyapunov functions and applying LaSalle's invariance principle.

2 Model with saturation

In this section we propose a virus dynamics model including B-cell impairment and saturated incidence as:

$$\dot{U} = \varrho - \gamma U - \frac{\omega UP}{1 + \alpha P}, \tag{8}$$

$$\dot{I} = \frac{\omega UP}{1 + \alpha P} - \beta I, \tag{9}$$

$$\dot{P} = \varkappa I - \xi P - \rho PC, \tag{10}$$

$$\dot{C} = \varepsilon P - \mu C - \vartheta CP, \tag{11}$$

where, ϑPC is the B-cell impairment rate and $\alpha \geq 0$ is a saturation constant.

2.1 Basic properties

We define the compact set

$$\Omega = \left\{ (U, I, P, C) \in \mathbb{R}^4_{\geq 0} : 0 \leq U \leq s_1, 0 \leq I \leq s_1, 0 \leq P \leq s_2, 0 \leq C \leq s_3 \right\} \tag{12}$$

where $s_i > 0$, $i = 1, 2, 3$.

Proposition 1. The set Ω is positively invariant for model (8)-(11).

Proof. We have

$$\dot{U}\mid_{U=0} = \varrho > 0,$$

$$\dot{I}\mid_{I=0} = \frac{\omega UP}{1 + \alpha P} \geq 0, \qquad \text{when } U, P \geq 0,$$

$$\dot{P}\mid_{P=0} = \varkappa I \geq 0, \qquad \text{when } I \geq 0,$$

$$\dot{C}\mid_{C=0} = \varepsilon P \geq 0, \qquad \text{when } P \geq 0.$$

Thus $\mathbb{R}^4_{\geq 0}$ is positively invariant for model (8)-(11). Let $F(t) = U + I + \frac{\beta}{2\varkappa}P + \frac{\beta\xi}{4\varepsilon\varkappa}C$, then

$$\dot{F}(t) = \varrho - \gamma U - \frac{\omega UP}{1 + \alpha P} + \frac{\omega UP}{1 + \alpha P} - \beta I + \frac{\beta}{2}I - \frac{\beta\xi}{2\varkappa}P - \frac{\beta\rho}{2\varkappa}PC + \frac{\beta\xi}{4\varkappa}P - \frac{\beta\xi\mu}{4\varepsilon\varkappa}C - \frac{\beta\xi\vartheta}{4\varepsilon\varkappa}PC$$

$$= \varrho - \gamma U - \frac{\beta}{2}I - \frac{\beta\xi}{4\varkappa}P - \left(\frac{\beta\rho}{2\varkappa} + \frac{\beta\xi\vartheta}{4\varepsilon\varkappa}\right)PC - \frac{\beta\xi\mu}{4\varepsilon\varkappa}C$$

$$\leq \varrho - \gamma U - \frac{\beta}{2}I - \frac{\beta\xi}{4\varkappa}P - \frac{\beta\xi\mu}{4\varepsilon\varkappa}C$$

$$\leq \varrho - \sigma\left(U + I + \frac{\beta}{2\varkappa}P + \frac{\beta\xi}{4\varepsilon\varkappa}C\right)$$

$$= \varrho - \sigma F(t),$$

where $\sigma = \min\left\{\gamma, \frac{\beta}{2}, \frac{\xi}{2}, \mu\right\}$. Then,

$$F(t) \leq \frac{\varrho}{\sigma} + \left(F(0) - \frac{\varrho}{\sigma}\right)e^{-\sigma t}.$$

Then, $0 \leq F(t) \leq s_1$, if $F(0) \leq s_1$ for $t \geq 0$ where $s_1 = \frac{\varrho}{\sigma}$. Hence, $0 \leq U(t), I(t) \leq s_1, 0 \leq P(t) \leq s_2$ and $0 \leq C(t) \leq s_3$ for all $t \geq 0$ if $U(0) + I(0) + \frac{\beta}{2\varkappa}P(0) + \frac{\beta\xi}{4\varepsilon\varkappa}C(0) \leq s_1$, where $s_2 = \frac{2\varkappa s_1}{\beta}$ and $s_3 = \frac{4\varepsilon\varkappa s_1}{\beta\xi}$. This guarantees that the solutions of the model are bounded. □

The basic infection reproduction number for model (8)-(11) is given by:

$$R_0 = \frac{\varrho\omega\varkappa}{\beta\xi\gamma}.$$

Lemma 1. Consider model (8)-(11), we have
(i) if $R_0 \leq 1$, then the model has only one equilibrium point EP_0,
(ii) if $R_0 > 1$, then the model has two equilibria EP_0 and EP_1.

Proof.
At any equilibrium $EP(U, I, P, C)$ we have

$$\varrho - \gamma U - \frac{\omega UP}{1 + \alpha P} = 0, \tag{13}$$

$$\frac{\omega UP}{1 + \alpha P} - \beta I = 0, \tag{14}$$

$$\varkappa I - \xi P - \rho PC = 0, \tag{15}$$

$$\varepsilon P - \mu C - \vartheta CP = 0. \tag{16}$$

From equations (13)-(16) we get an infection-free equilibrium $EP_0 = (U_0, 0, 0, 0)$, where $U_0 = \frac{\varrho}{\gamma}$ and a unique endemic equilibrium $EP_1 = (U_1, I_1, P_1, C_1)$, where

$$U_1 = \frac{\varrho(1 + \alpha P_1)}{\gamma + \alpha\gamma P_1 + \omega P_1}, \quad I_1 = \frac{\varrho\omega P_1(1 + \alpha P_1)}{\beta(\gamma + \alpha\gamma P_1 + \omega P_1)}, \quad P_1 = \frac{-b + \sqrt{b^2 - 4ac}}{2a}, \quad C_1 = \frac{\varepsilon P_1}{\vartheta P_1 + \mu},$$

where

$$a = \beta\xi\gamma\alpha\vartheta + \beta\xi\vartheta\omega + \beta\gamma\rho\varepsilon\alpha + \beta\rho\varepsilon\omega,$$
$$b = \beta\xi\gamma\vartheta + \beta\xi\gamma\mu\alpha + \beta\rho\varepsilon\gamma + \beta\xi\mu\omega - \varrho\omega\vartheta\varkappa,$$
$$c = \beta\xi\gamma\mu\left(1 - R_0\right).$$

Then the equilibrium EP_1 exists when $R_0 > 1$. □

2.2 Global properties

Define a function $G(u) = u - 1 - \ln u$. Clearly $G(u) \geq 0$, for $u > 0$ and $G(1) = 0$. The global stability analysis of the two equilibria of model (8)-(11) will be established in the next theorems.

Theorem 1. Let $R_0 < 1$, then the infection-free equilibrium EP_0 of model (8)-(11) is globally asymptotically stable.

Proof. Construct a Lyapunov function $L_0(U, I, P, C)$ as

$$L_0 = U_0 G\left(\frac{U}{U_0}\right) + I + \frac{\beta}{\varkappa}P + \frac{\beta\xi}{\varepsilon\varkappa}\left(1 - R_0\right)C.$$

Calculating $\dfrac{dL_0}{dt}$ as:

$$\frac{dL_0}{dt} = \left(1 - \frac{U_0}{U}\right)\left(\varrho - \gamma U - \frac{\omega UP}{1 + \alpha P}\right) + \frac{\omega UP}{1 + \alpha P} - \beta I + \frac{\beta}{\varkappa}\left(\varkappa I - \xi P - \rho PC\right) + \frac{\beta\xi}{\varepsilon\varkappa}\left(1 - R_0\right)\left(\varepsilon P - \mu C - \vartheta CP\right)$$

$$= -\gamma\left(1 - \frac{U_0}{U}\right)\left(U - U_0\right) - \frac{\beta\rho}{\varkappa}PC - \frac{\beta\xi\vartheta}{\varepsilon\varkappa}\left(1 - R_0\right)PC + \left(\frac{\omega U_0}{1 + \alpha P} - \frac{\beta\xi}{\varkappa} + \frac{\beta\xi}{\varkappa}\left(1 - R_0\right)\right)P - \frac{\beta\xi\mu}{\varepsilon\varkappa}\left(1 - R_0\right)C$$

$$= -\frac{\gamma(U - U_0)^2}{U} - \left(\frac{\beta\rho}{\varkappa} + \frac{\beta\xi\vartheta}{\varepsilon\varkappa}\left(1 - R_0\right)\right)PC - \frac{\beta\xi\mu}{\varepsilon\varkappa}\left(1 - R_0\right)C - \frac{\beta\xi\alpha R_0}{\varkappa(1 + \alpha P)}P^2.$$

Since $R_0 < 1$, then for all $U, P, C > 0$ we have $\dfrac{dL_0}{dt} \leq 0$. Moreover, $\dfrac{dL_0}{dt} = 0$ when $U(t) = U_0$ and $P(t) = C(t) = 0$. Let $D_0 = \left\{(U, I, P, C) : \dfrac{dL_0}{dt} = 0\right\}$ and M_0 be the largest invariant subset of D_0. The trajectory of model (8)-(11) tends to M_0 [58]. All the elements of M_0 satisfy $U(t) = U_0$ and $P(t) = C(t) = 0$. Then Eq. (10) we get

$$\dot{P}(t) = 0 = \varkappa I(t), \quad \Rightarrow I(t) = 0.$$

Hence, $M_0 = \{EP_0\}$. From LaSalle's invariance principle, we derive that if $R_0 < 1$, then EP_0 is globally asymptotically stable. □

Theorem 2. Let $R_0 > 1$, then the endemic equilibrium EP_1 of model (8)-(11) is globally asymptotically stable.

Proof. Construct a Lyapunov function $L_1(U, I, P, C)$ as

$$L_1 = U_1 G\left(\frac{U}{U_1}\right) + I_1 G\left(\frac{I}{I_1}\right) + \frac{\beta}{\varkappa}P_1 G\left(\frac{P}{P_1}\right) + \frac{\beta\rho}{2\varkappa(\varepsilon - \vartheta C_1)}\left(C - C_1\right)^2.$$

Note that from the equilibrium condition Eq. (16) that

$$\varepsilon - \vartheta C_1 = \frac{\mu C_1}{P_1} > 0.$$

Then $\dfrac{dL_1}{dt}$ is given by:

$$\frac{dL_1}{dt} = \left(1 - \frac{U_1}{U}\right)\left(\varrho - \gamma U - \frac{\omega UP}{1 + \alpha P}\right) + \left(1 - \frac{I_1}{I}\right)\left(\frac{\omega UP}{1 + \alpha P} - \beta I\right)$$

$$+ \frac{\beta}{\varkappa}\left(1 - \frac{P_1}{P}\right)(\varkappa I - \xi P - \rho PC) + \frac{\beta\rho}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)(\varepsilon P - \mu C - \vartheta CP)$$

$$= \left(1 - \frac{U_1}{U}\right)(\varrho - \gamma U) + \frac{\omega U_1 P}{1 + \alpha P} - \frac{\omega UP}{1 + \alpha P}\frac{I_1}{I} + \beta I_1 - \frac{\beta\xi}{\varkappa}P - \frac{\beta\rho}{\varkappa}PC - \beta\frac{P_1}{P}I + \frac{\beta\xi}{\varkappa}P_1$$

$$+ \frac{\beta\rho}{\varkappa}P_1 C + \frac{\beta\rho}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)(\varepsilon P - \mu C - \vartheta CP).$$

From the equilibrium conditions, we have:

$$\varrho = \gamma U_1 + \frac{\omega U_1 P_1}{1 + \alpha P_1},$$

$$\beta I_1 = \frac{\omega U_1 P_1}{1 + \alpha P_1},$$

$$\varkappa I_1 = \xi P_1 + \rho P_1 C_1,$$

$$\varepsilon P_1 = \mu C_1 + \vartheta P_1 C_1.$$

Utilizing the conditions of EP_1, we get

$$\frac{dL_1}{dt} = \left(1 - \frac{U_1}{U}\right)\left(\gamma U_1 + \frac{\omega U_1 P_1}{1 + \alpha P_1} - \gamma U\right) + \frac{\omega U_1 P}{1 + \alpha P} - \frac{\omega UP}{1 + \alpha P}\frac{I_1}{I}$$

$$+ \frac{\omega U_1 P_1}{1 + \alpha P_1} - \frac{\beta\xi}{\varkappa}P - \frac{\beta\rho}{\varkappa}PC - \beta\frac{P_1}{P}I + \frac{\beta\xi}{\varkappa}P_1 + \frac{\beta\rho}{\varkappa}P_1 C$$

$$+ \frac{\beta\rho}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)(\varepsilon P - \mu C - \vartheta CP - \varepsilon P_1 + \mu C_1 + \vartheta C_1 P_1).$$

Simplifying the result, we obtain

$$\frac{dL_1}{dt} = -\frac{\gamma(U - U_1)^2}{U} + \frac{\omega U_1 P_1}{1 + \alpha P_1}\left(2 - \frac{U_1}{U}\right) + \frac{\omega U_1 P}{1 + \alpha P} - \frac{\omega UP}{1 + \alpha P}\frac{I_1}{I}$$

$$- \frac{\beta\xi}{\varkappa}(P - P_1) - \frac{\beta\rho}{\varkappa}(P - P_1)C - \frac{\omega U_1 P_1}{1 + \alpha P_1}\frac{P_1 I}{PI_1}$$

$$+ \frac{\beta\rho}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)(\varepsilon P - \mu C - \vartheta CP - \varepsilon P_1 + \mu C_1 + \vartheta C_1 P_1 + \vartheta C_1 P - \vartheta C_1 P)$$

$$+ \frac{\beta\rho}{\varkappa}(P - P_1)C_1 - \frac{\beta\rho}{\varkappa}(P - P_1)C_1$$

$$= -\frac{\gamma(U - U_1)^2}{U} + \frac{\omega U_1 P_1}{1 + \alpha P_1}\left(2 - \frac{U_1}{U} - \frac{P_1 I}{PI_1}\right) + \frac{\omega U_1 P_1}{1 + \alpha P_1}\frac{P(1 + \alpha P_1)}{P_1(1 + \alpha P)}$$

$$- \frac{\omega U_1 P_1}{1 + \alpha P_1}\frac{(1 + \alpha P_1)}{(1 + \alpha P)}\frac{UPI_1}{U_1 P_1 I} - \frac{\beta}{\varkappa}(P - P_1)(\xi + \rho C_1)$$

$$- \frac{\beta\rho}{\varkappa}(P - P_1)(C - C_1) + \frac{\beta\rho\varepsilon}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)(P - P_1)$$

$$- \frac{\beta\rho\mu}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)^2 - \frac{\beta\rho\vartheta}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)^2 P - \frac{\beta\rho\vartheta C_1}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)(P - P_1)$$

$$= -\frac{\gamma(U - U_1)^2}{U} + \frac{\omega U_1 P_1}{1 + \alpha P_1}\left(3 - \frac{U_1}{U} - \frac{P_1 I}{PI_1} - \frac{(1 + \alpha P_1)UPI_1}{(1 + \alpha P)U_1 P_1 I}\right)$$

$$+ \frac{\omega U_1 P_1}{1 + \alpha P_1}\frac{P(1 + \alpha P_1)}{P_1(1 + \alpha P)} - \frac{\omega U_1 P_1}{1 + \alpha P_1}\frac{P}{P_1} - \frac{\beta\rho}{\varkappa}(P - P_1)(C - C_1)$$

$$+ \frac{\beta\rho(\varepsilon - \vartheta C_1)}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)(P - P_1) - \frac{\beta\rho(\mu + \vartheta P)}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)^2$$

$$= -\frac{\gamma(U - U_1)^2}{U} + \frac{\omega U_1 P_1}{1 + \alpha P_1}\left(4 - \frac{U_1}{U} - \frac{P_1 I}{PI_1} - \frac{(1 + \alpha P_1)UPI_1}{(1 + \alpha P)U_1 P_1 I} - \frac{1 + \alpha P}{1 + \alpha P_1}\right)$$

$$- \frac{\beta\rho(\mu + \vartheta P)}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)^2 + \frac{\omega U_1 P_1}{1 + \alpha P_1}\left(\frac{P(1 + \alpha P_1)}{P_1(1 + \alpha P)} - \frac{P}{P_1} - 1 + \frac{1 + \alpha P}{1 + \alpha P_1}\right)$$

$$= -\frac{\gamma(U - U_1)^2}{U} + \frac{\omega U_1 P_1}{1 + \alpha P_1}\left(4 - \frac{U_1}{U} - \frac{P_1 I}{PI_1} - \frac{(1 + \alpha P_1)UPI_1}{(1 + \alpha P)U_1 P_1 I} - \frac{1 + \alpha P}{1 + \alpha P_1}\right)$$

$$- \frac{\beta \rho (\mu + \vartheta P)}{\varkappa (\varepsilon - \vartheta C_1)} (C - C_1)^2 - \frac{\alpha \omega U_1 (P - P_1)^2}{(1 + \alpha P)(1 + \alpha P_1)^2}.$$

Using geometrical mean (GM) and arithmetical mean (AM) inequality

$$AM \geq GM, \tag{17}$$

we get

$$4 \leq \frac{U_1}{U} + \frac{P_1 I}{P I_1} + \frac{(1 + \alpha P_1) U P I_1}{(1 + \alpha P) U_1 P_1 I} + \frac{1 + \alpha P}{1 + \alpha P_1}.$$

Thus for all $U, I, P, C > 0$ we have $\frac{dL_1}{dt} \leq 0$. In addition $\frac{dL_1}{dt} = 0$ when $U = U_1$, $I = I_1$, $P = P_1$ and $C = C_1$. Let $D_1 = \left\{ W_1(U, I, P, C) : \frac{dL_1}{dt} = 0 \right\}$ and M_1 be the largest invariant subset of D_1. Clearly $M_1 = \{EP_1\}$. Applying LaSalle's invariance principle we obtain that if $R_0 > 1$, then EP_1 is globally asymptotically stable. $\square$

3 Model with general incidence rate

In this section we propose a model with more general incidence rate function $\Theta(U, P)$ as:

$$\dot{U} = \varrho - \gamma U - \Theta(U, P), \tag{18}$$

$$\dot{I} = \Theta(U, P) - \beta I, \tag{19}$$

$$\dot{P} = \varkappa I - \xi P - \rho P C, \tag{20}$$

$$\dot{C} = \varepsilon P - \mu C - \vartheta P C, \tag{21}$$

We need the following Assumptions of the function $\Theta(U, P)$:

(A1) $\Theta(U, P)$ is continuously differentiable, $\Theta(U, P) > 0$, and $\Theta(0, P) = \Theta(U, 0) = 0$ for all $U > 0$ and $P > 0$,

(A2) $\dfrac{\partial \Theta(U, P)}{\partial U} > 0$, $\dfrac{\partial \Theta(U, P)}{\partial P} > 0$, and $\dfrac{\partial \Theta(U, 0)}{\partial P} > 0$ for all $U > 0$ and $P > 0$,

(A3) $\dfrac{d}{dU} \left(\dfrac{\partial \Theta(U, 0)}{\partial P} \right) > 0$ for all $U > 0$,

(A4) $\dfrac{\Theta(U, P)}{P}$ is decreasing with respect to P for all $P > 0$.

One can show that the set Ω given by Eq. (12) is positively invariant for model (18)-(21).

Lemma 2. Assume that Assumptions (A1)-(A4) are satisfied, then there exists a threshold parameter $R_0^G > 0$ such that:
(i) if $R_0^G < 1$, then the model has only one equilibrium point EP_0; and
(ii) if $R_0^G > 1$, then the model has two equilibria EP_0 and EP_1.

Proof. At any equilibrium $EP(U, I, P, C)$ we have

$$\varrho - \gamma U - \Theta(U, P) = 0, \tag{22}$$

$$\Theta(U, P) - \beta I = 0, \tag{23}$$

$$\varkappa I - \xi P - \rho P C = 0, \tag{24}$$

$$\varepsilon P - \mu C - \vartheta C P = 0. \tag{25}$$

From Eq. (25), we have

$$C = \frac{\varepsilon P}{\mu + \vartheta P}, \tag{26}$$

and from Eq. (24), we get

$$I = \frac{\xi P}{\varkappa} + \frac{\rho \varepsilon}{\varkappa} \left(\frac{P^2}{\mu + \vartheta P} \right). \tag{27}$$

Now from Eqs. (27) and (22)-(23), we obtain

$$U = \frac{\varrho}{\gamma} - \left(\frac{\beta\xi}{\gamma\varkappa} P + \frac{\beta\rho\varepsilon}{\gamma\varkappa} \left(\frac{P^2}{\mu + \vartheta P} \right) \right). \tag{28}$$

Let

$$\Psi(P) = \frac{\varrho}{\gamma} - \frac{\beta\xi}{\gamma\varkappa} P - \frac{\beta\rho\varepsilon}{\gamma\varkappa} \left(\frac{P^2}{\mu + \vartheta P} \right).$$

Therefore, we can write U as $U = \Psi(P)$. Note that $\Psi(0) = \frac{\varrho}{\gamma}$.

From Eqs. (27) and (22)-(23), we have

$$\Theta(\Psi(P), P) - \beta \left[\frac{\xi P}{\varkappa} + \frac{\rho\varepsilon}{\varkappa} \left(\frac{P^2}{\mu + \vartheta P} \right) \right] = 0. \tag{29}$$

Observe that, $P = 0$ is a solution of Eq. (29). Then from Eqs. (26)-(28), we have $U = U_0$, $I = 0$, and $C = 0$. Then we get an infection-free equilibrium $EP_0 = (U_0, 0, 0, 0)$.

Let

$$H(P) = \Theta(\Psi(P), P) - \beta \left[\frac{\xi P}{\varkappa} + \frac{\rho\varepsilon}{\varkappa} \left(\frac{P^2}{\mu + \vartheta P} \right) \right],$$

then $H(0) = 0$. Let $\overline{P}$ be such that $\Psi(\overline{P}) = 0$, i.e.,

$$U_0 - \frac{\beta\xi}{\gamma\varkappa} \overline{P} - \frac{\beta\rho\varepsilon}{\gamma\varkappa} \left(\frac{\overline{P}^2}{\mu + \vartheta\overline{P}} \right) = 0,$$

which gives

$$(\beta\rho\varepsilon + \beta\xi\vartheta)\overline{P}^2 + (\beta\xi\mu - \gamma\varkappa\vartheta U_0)\overline{P} - \gamma\varkappa\mu U_0 = 0. \tag{30}$$

Thus, the positive solution of Eq. (30) is given by

$$\overline{P} = \frac{(\gamma\varkappa\vartheta U_0 - \beta\xi\mu) + \sqrt{(\beta\xi\mu - \gamma\varkappa\vartheta U_0)^2 + 4\gamma\varkappa\mu U_0(\beta\rho\varepsilon + \beta\xi\vartheta)}}{2(\beta\rho\varepsilon + \beta\xi\vartheta)}.$$

We can see that

$$H(\overline{P}) = \Theta(0, \overline{P}) - \beta \left[\frac{\xi\overline{P}}{\varkappa} + \frac{\rho\varepsilon}{\varkappa} \left(\frac{\overline{P}^2}{\mu + \vartheta\overline{P}} \right) \right] = -\beta \left[\frac{\xi\overline{P}}{\varkappa} + \frac{\rho\varepsilon}{\varkappa} \left(\frac{\overline{P}^2}{\mu + \vartheta\overline{P}} \right) \right] < 0.$$

Moreover,

$$H'(P) = \frac{\partial\Theta(U, P)}{\partial P} + \Psi'(P) \frac{\partial\Theta(U, P)}{\partial U} - \frac{\beta\xi}{\varkappa} - \frac{\beta\rho\varepsilon \left(2\mu P + \vartheta P^2 \right)}{\varkappa(\mu + \vartheta P)^2}.$$

Assumption (A1) implies that $\dfrac{\partial\Theta(U_0, 0)}{\partial U} = 0$, then

$$H'(0) = \frac{\partial\Theta(U_0, 0)}{\partial P} - \frac{\beta\xi}{\varkappa} = \frac{\beta\xi}{\varkappa} \left(\frac{\varkappa}{\beta\xi} \frac{\partial\Theta(U_0, 0)}{\partial P} - 1 \right).$$

Therefore, if $\dfrac{\varkappa}{\beta\xi} \dfrac{\partial\Theta(U_0, 0)}{\partial P} > 1$, then $H'(0) > 0$ and $\exists P_1 \in (0, \overline{P})$ such that $H(P_1) = 0$. Let us define

$$R_0^G = \frac{\varkappa}{\beta\xi} \frac{\partial\Theta(U_0, 0)}{\partial P},$$

which represents the basic reproduction number. Now, let

$$g(U) = \varrho - \gamma U - \Theta(U, P_1) = 0.$$

Then we have $g(0) = \varrho > 0$ and $g(U_0) = -\Theta(U_0, P_1) < 0$. Assumption (A2) implies that $g(U)$ is a strictly decreasing function of U, and then there exists a unique $U_1 \in (0, U_0)$ such that $g(U_1) = 0$. Moreover, from Eqs. (26) and (27), we have

$$C_1 = \frac{\varepsilon P_1}{\mu + \vartheta P_1} > 0,$$

$$I_1 = \frac{\xi P_1}{\varkappa} + \frac{\rho\varepsilon}{\varkappa} \left(\frac{P_1^2}{\mu + \vartheta P_1} \right) > 0.$$

Therefore, an endemic equilibrium $EP_1 = (U_1, I_1, P_1, C_1)$ exists if $R_0^G > 1$.   □

3.1 Global stability of equilibria

The global stability analysis of the two equilibria of model (18)-(21) will be investigated in this section.

Theorem 3. Let $R_0^G > 1$, then the infection-free equilibrium EP_0 of model (18)-(21) is globally asymptotically stable.

Proof. Construct a Lyapunov function $Z_0(U, I, P, C)$ as

$$Z_0 = U - U_0 - \int_{U_0}^{U} \lim_{P \to 0^+} \frac{\Theta(U_0, P)}{\Theta(\eta, P)} d\eta + I + \frac{\beta}{\varkappa} P + \frac{\beta\xi}{\varepsilon\varkappa} \left(1 - R_0^G\right) C.$$

Calculating $\dfrac{dZ_0}{dt}$ as:

$$\frac{dZ_0}{dt} = \left(1 - \lim_{P \to 0^+} \frac{\Theta(U_0, P)}{\Theta(U, P)}\right) (\varrho - \gamma U - \Theta(U, P)) + \Theta(U, P) - \beta I + \frac{\beta}{\varkappa} (\varkappa I - \xi P - \rho PC)$$

$$+ \frac{\beta\xi}{\varepsilon\varkappa} \left(1 - R_0^G\right) (\varepsilon P - \mu C - \vartheta PC)$$

$$= \left(1 - \lim_{P \to 0^+} \frac{\Theta(U_0, P)}{\Theta(U, P)}\right) (\varrho - \gamma U) + \Theta(U, P) \lim_{P \to 0^+} \frac{\Theta(U_0, P)}{\Theta(U, P)} - \frac{\beta\xi}{\varkappa} P - \frac{\beta\rho}{\varkappa} PC$$

$$+ \frac{\beta\xi}{\varkappa} \left(1 - R_0^G\right) P - \frac{\beta\xi\mu}{\varepsilon\varkappa} \left(1 - R_0^G\right) C - \frac{\beta\xi\vartheta}{\varepsilon\varkappa} \left(1 - R_0^G\right) PC$$

$$= (\varrho - \gamma U) \left(1 - \lim_{P \to 0^+} \frac{\Theta(U_0, P)}{\Theta(U, P)}\right) + \Theta(U, P) \lim_{P \to 0^+} \frac{\Theta(U_0, P)}{\Theta(U, P)} - \frac{\beta\xi R_0^G}{\varkappa} P - \frac{\beta\xi\mu}{\varepsilon\varkappa} \left(1 - R_0^G\right) C$$

$$- \left[\frac{\beta\rho}{\varkappa} + \frac{\beta\xi\vartheta}{\varepsilon\varkappa} \left(1 - R_0^G\right)\right] PC$$

$$= \gamma U_0 \left(1 - \frac{U}{U_0}\right) \left(1 - \frac{\partial\Theta(U_0, 0)/\partial P}{\partial\Theta(U, 0)/\partial P}\right) + \frac{\beta\xi R_0^G}{\varkappa} \left[\frac{\varkappa\Theta(U, P)}{\beta\xi R_0^G P} \frac{\partial\Theta(U_0, 0)/\partial P}{\partial\Theta(U, 0)/\partial P} - 1\right] P$$

$$- \frac{\beta\xi\mu}{\varepsilon\varkappa} \left(1 - R_0^G\right) C - \left[\frac{\beta\rho}{\varkappa} + \frac{\beta\xi\vartheta}{\varepsilon\varkappa} \left(1 - R_0^G\right)\right] PC.$$

From the Assumptions, we have the first term is less than or equal to zero. In addition,

$$\frac{\Theta(U, P)}{P} \le \lim_{P \to 0^+} \frac{\Theta(U, P)}{P} = \frac{\partial\Theta(U, 0)}{\partial P},$$

for all $U > 0$. Then

$$\frac{\varkappa\Theta(U, P)}{\beta\xi R_0^G P} \frac{\partial\Theta(U_0, 0)/\partial P}{\partial\Theta(U, 0)/\partial P} \le \frac{\varkappa}{\beta\xi R_0^G} \frac{\partial\Theta(U_0, 0)}{\partial P} = 1.$$

It implies that

$$\frac{dZ_0}{dt} \le \gamma U_0 \left(1 - \frac{U}{U_0}\right) \left(1 - \frac{\partial\Theta(U_0, 0)/\partial P}{\partial\Theta(U, 0)/\partial P}\right) - \frac{\beta\xi\mu}{\varepsilon\varkappa} \left(1 - R_0^G\right) C - \left[\frac{\beta\rho}{\varkappa} + \frac{\beta\xi\vartheta}{\varepsilon\varkappa} \left(1 - R_0^G\right)\right] PC.$$

Therefore, if $R_0^G < 1$, then $\dfrac{dZ_0}{dt} \le 0$ for all $U, P, C > 0$. Similar to the proof of Theorem 1, one can show that EP_0 is globally asymptotically stable. $\square$

Theorem 4. Let $R_0^G > 1$, then the endemic equilibrium EP_1 of model (18)-(21) is globally asymptotically stable.

Proof. Define $Z_1(U, I, P, C)$ as

$$Z_1 = U - U_1 - \int_{U_1}^{U} \frac{\Theta(U_1, P_1)}{\Theta(\eta, P_1)} d\eta + I_1 G\left(\frac{I}{I_1}\right) + \frac{\beta}{\varkappa} P_1 G\left(\frac{P}{P_1}\right) + \frac{\beta\rho}{2\varkappa(\varepsilon - \vartheta C_1)} (C - C_1)^2.$$

Then $\dfrac{dZ_1}{dt}$ can be calculated as:

$$
\frac{dZ_1}{dt} = \left(1 - \frac{\Theta(U_1, P_1)}{\Theta(U, P_1)}\right)(\varrho - \gamma U - \Theta(U, P)) + \left(1 - \frac{I_1}{I}\right)(\Theta(U, P) - \beta I)
$$

$$
+ \frac{\beta}{\varkappa}\left(1 - \frac{P_1}{P}\right)(\varkappa I - \xi P - \rho PC) + \frac{\beta\rho}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)(\varepsilon P - \mu C - \vartheta PC).
$$

Using the equilibrium condition, $\varepsilon P_1 - \mu C_1 - \vartheta P_1 C_1 = 0$, we have

$$
\frac{dZ_1}{dt} = \left(1 - \frac{\Theta(U_1, P_1)}{\Theta(U, P_1)}\right)(\varrho - \gamma U) + \Theta(U, P)\frac{\Theta(U_1, P_1)}{\Theta(U, P_1)} - \frac{I_1}{I}\Theta(U, P) + \beta I_1
$$

$$
- \frac{\beta\xi}{\varkappa}P - \frac{\beta\rho}{\varkappa}PC - \beta\frac{P_1}{P}I + \frac{\beta\xi}{\varkappa}P_1 + \frac{\beta\rho}{\varkappa}P_1 C
$$

$$
+ \frac{\beta\rho}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)(\varepsilon P - \mu C - \vartheta PC - \varepsilon P_1 + \mu C_1 + \vartheta P_1 C_1 + \vartheta PC_1 - \vartheta PC_1)
$$

$$
+ \frac{\beta\rho}{\varkappa}(P - P_1)C_1 - \frac{\beta\rho}{\varkappa}(P - P_1)C_1
$$

$$
= \left(1 - \frac{\Theta(U_1, P_1)}{\Theta(U, P_1)}\right)(\varrho - \gamma U) + \Theta(U, P)\frac{\Theta(U_1, P_1)}{\Theta(U, P_1)} - \frac{I_1}{I}\Theta(U, P) + \beta I_1 - \frac{\beta\xi}{\varkappa}P
$$

$$
- \frac{\beta\rho}{\varkappa}PC - \beta\frac{P_1}{P}I + \frac{\beta\xi}{\varkappa}P_1 + \frac{\beta\rho}{\varkappa}P_1 C + \frac{\beta\rho\varepsilon}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)(P - P_1)
$$

$$
- \frac{\beta\rho\mu}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)^2 - \frac{\beta\rho\vartheta P}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)^2
$$

$$
- \frac{\beta\rho\vartheta C_1}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)(P - P_1) + \frac{\beta\rho}{\varkappa}(P - P_1)C_1 - \frac{\beta\rho}{\varkappa}(P - P_1)C_1.
$$

From the equilibrium conditions, we have

$$
\beta I_1 = \Theta(U_1, P_1),
$$

$$
\varrho = \gamma U_1 + \beta I_1.
$$

Applying these conditions, we obtain

$$
\frac{dZ_1}{dt} = \left(1 - \frac{\Theta(U_1, P_1)}{\Theta(U, P_1)}\right)(\gamma U_1 + \beta I_1 - \gamma U) + \beta I_1\frac{\Theta(U, P)}{\Theta(U, P_1)} - \frac{I_1}{I}\Theta(U, P) + \beta I_1 - \frac{\beta\xi}{\varkappa}(P - P_1)
$$

$$
- \frac{\beta\rho}{\varkappa}(P - P_1)C - \beta\frac{P_1}{P}I + \frac{\beta\rho(\varepsilon - \vartheta C_1)}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)(P - P_1) - \frac{\beta\rho(\mu + \vartheta P)}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)^2
$$

$$
+ \frac{\beta\rho}{\varkappa}(P - P_1)C_1 - \frac{\beta\rho}{\varkappa}(P - P_1)C_1
$$

$$
= \left(1 - \frac{\Theta(U_1, P_1)}{\Theta(U, P_1)}\right)(\gamma U_1 - \gamma U) + \beta I_1\left(2 - \frac{\Theta(U_1, P_1)}{\Theta(U, P_1)}\right) + \beta I_1\frac{\Theta(U, P)}{\Theta(U, P_1)} - \beta I_1\frac{I_1\Theta(U, P)}{I\Theta(U_1, P_1)}
$$

$$
- \frac{\beta}{\varkappa}(P - P_1)(\xi + \rho C_1) - \frac{\beta\rho}{\varkappa}(P - P_1)(C - C_1) - \beta I_1\frac{P_1 I}{P I_1} + \frac{\beta\rho}{\varkappa}(C - C_1)(P - P_1)
$$

$$
- \frac{\beta\rho(\mu + \vartheta P)}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)^2
$$

$$
= \left(1 - \frac{\Theta(U_1, P_1)}{\Theta(U, P_1)}\right)(\gamma U_1 - \gamma U) + \beta I_1\left(3 - \frac{\Theta(U_1, P_1)}{\Theta(U, P_1)} - \frac{I_1\Theta(U, P)}{I\Theta(U_1, P_1)} - \frac{P_1 I}{P I_1}\right)
$$

$$
+ \beta I_1\left(\frac{\Theta(U, P)}{\Theta(U, P_1)} - \frac{P}{P_1}\right) - \frac{\beta\rho(\mu + \vartheta P)}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)^2
$$

$$
= \left(1 - \frac{\Theta(U_1, P_1)}{\Theta(U, P_1)}\right)(\gamma U_1 - \gamma U) + \beta I_1\left[4 - \frac{\Theta(U_1, P_1)}{\Theta(U, P_1)} - \frac{I_1\Theta(U, P)}{I\Theta(U_1, P_1)} - \frac{P_1 I}{P I_1} - \frac{P\Theta(U, P_1)}{P_1\Theta(U, P)}\right]
$$

$$
+ \beta I_1\left[\frac{\Theta(U, P)}{\Theta(U, P_1)} - \frac{P}{P_1} - 1 + \frac{P\Theta(U, P_1)}{P_1\Theta(U, P)}\right] - \frac{\beta\rho(\mu + \vartheta P)}{\varkappa(\varepsilon - \vartheta C_1)}(C - C_1)^2
$$

$$
= \gamma U_1\left(1 - \frac{U}{U_1}\right)\left(1 - \frac{\Theta(U_1, P_1)}{\Theta(U, P_1)}\right) + \beta I_1\left[4 - \frac{\Theta(U_1, P_1)}{\Theta(U, P_1)} - \frac{I_1\Theta(U, P)}{I\Theta(U_1, P_1)} - \frac{P_1 I}{P I_1} - \frac{P\Theta(U, P_1)}{P_1\Theta(U, P)}\right]
$$

$$+ \beta I_1 \left(\frac{\Theta(U, P)}{\Theta(U, P_1)} - \frac{P}{P_1} \right) \left(1 - \frac{\Theta(U, P_1)}{\Theta(U, P)} \right) - \frac{\beta \rho (\mu + \vartheta P)}{\varkappa (\varepsilon - \vartheta C_1)} (C - C_1)^2 .$$

From Assumptions (A2) and (A4) we have

$$\left(1 - \frac{U}{U_1} \right) \left(1 - \frac{\Theta(U_1, P_1)}{\Theta(U, P_1)} \right) \leq 0,$$

$$\left(\frac{\Theta(U, P)}{\Theta(U, P_1)} - \frac{P}{P_1} \right) \left(1 - \frac{\Theta(U, P_1)}{\Theta(U, P)} \right) \leq 0.$$

Therefore, using inequality (17) we get that for all $U, I, P, C > 0$ we have $\frac{dZ_1}{dt} \leq 0$ and $\frac{dZ_1}{dt} = 0$ if and only if $U = U_1, I = I_1, P = P_1$ and $C = C_1$. Applying LaSalle's invariance principle, we obtain that if $R_0^G > 1$, then EP_1 is globally asymptotically stable. □

4 Numerical simulations

We conduct numerical simulations for model (18)-(21) with specific incidence rate function

$$\Theta(U, P) = \frac{\omega U P}{1 + \alpha_1 P + \alpha_2 U}.$$

Then we get following model with Beddington-DeAngelis functional response:

$$\dot{U} = \varrho - \gamma U - \frac{\omega U P}{1 + \alpha_1 P + \alpha_2 U}, \tag{31}$$

$$\dot{I} = \frac{\omega U P}{1 + \alpha_1 P + \alpha_2 U} - \beta I, \tag{32}$$

$$\dot{P} = \varkappa I - \xi P - \rho P C, \tag{33}$$

$$\dot{C} = \varepsilon P - \mu C - \vartheta P C, \tag{34}$$

where ω is a positive parameter, while α_1 and α_2 are non-negative parameters. We note that if $\alpha_1 = \alpha_2 = 0$, then we obtain a model with bilinear incidence, if $\alpha_1 \neq 0$ and $\alpha_2 = 0$, then we get saturated incidence which given in model (8)-(11), and if $\alpha_1 = 0$ and $\alpha_2 \neq 0$, then we obtain Holling type-II. We can easily see that $\Theta(U, P)$ is continuously differentiable function. Moreover, $\Theta(U, P)$ satisfying the following conditions:

We have

$$\frac{\partial \Theta(U, P)}{\partial U} = \frac{\omega P + \alpha_1 \omega P^2}{(1 + \alpha_1 P + \alpha_2 U)^2}, \quad \frac{\partial \Theta(U, P)}{\partial P} = \frac{\omega U + \alpha_2 \omega U^2}{(1 + \alpha_1 P + \alpha_2 U)^2},$$

then $\Theta(U, P)$ is continuously differentiable. Moreover, $\Theta(U, P) > 0$, and $\Theta(0, P) = \Theta(U, 0) = 0$ for all $U > 0$ and $P > 0$. Thus (A1) is satisfied.

Since $\frac{\partial \Theta(U, P)}{\partial U} > 0$, $\frac{\partial \Theta(U, P)}{\partial P} > 0$, and $\frac{\partial \Theta(U, 0)}{\partial P} = \frac{\omega U}{1 + \alpha_2 U} > 0$ for all $U > 0$, then (A2) is satisfied.

We have

$$\frac{d}{dU} \left(\frac{\partial \Theta(U, 0)}{\partial P} \right) = \frac{\omega}{(1 + \alpha_2 U)^2} > 0 \text{ for all } U \geq 0,$$

then (A3) is satisfied.

Finally we have

$$\frac{\partial}{\partial P} \left(\frac{\Theta(U, P)}{P} \right) = \frac{-\alpha_1 \omega U}{(1 + \alpha_1 P + \alpha_2 U)^2} < 0, \quad \text{for all } P \geq 0,$$

then (A4) is also satisfied.

The basic reproduction number of model (31)-(34) is given by

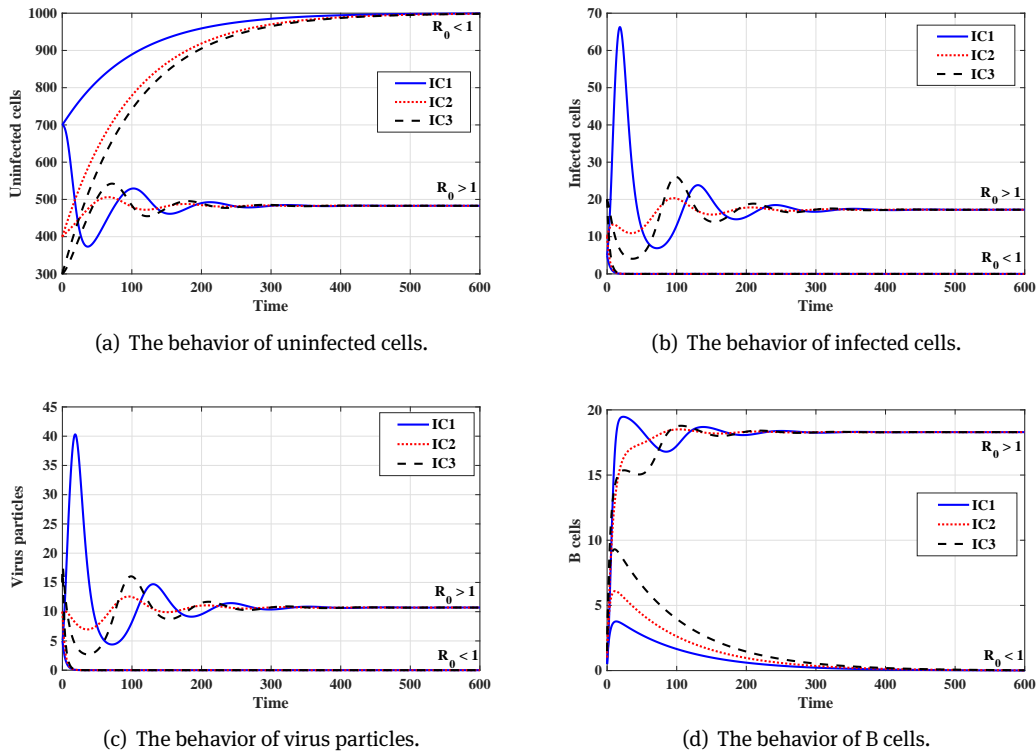$$R_0^G = \frac{\varkappa \omega U_0}{\beta \xi (1 + \alpha_2 U_0)}.$$

(a) The behavior of uninfected cells.

(b) The behavior of infected cells.

(c) The behavior of virus particles.

(d) The behavior of B cells.

Figure 1: Solution trajectories of system (31)-(34) in case $\alpha_1 = \alpha_2 = 0$.

(a) The behavior of uninfected cells.

(b) The behavior of infected cells.

(c) The behavior of virus particles.

(d) The behavior of B cells.
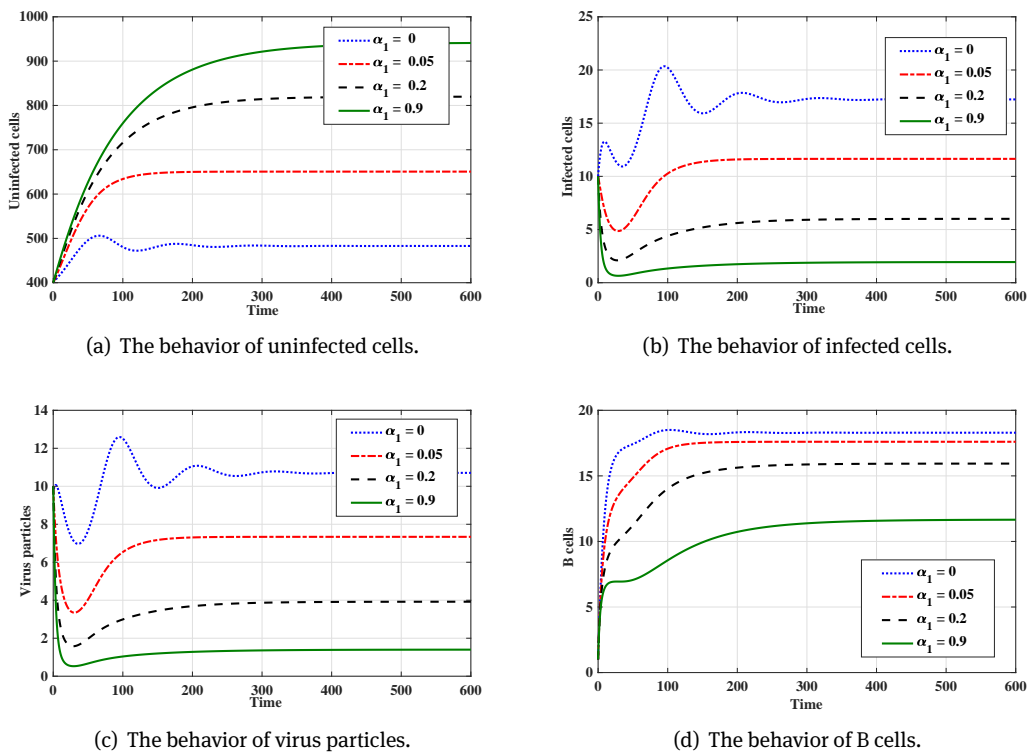
Figure 2: Solution trajectories of system (31)-(34) for different values of α_1 when $\alpha_2 = 0$.

(a) The behavior of uninfected cells.

(b) The behavior of infected cells.

(c) The behavior of virus particles.

(d) The behavior of B cells.
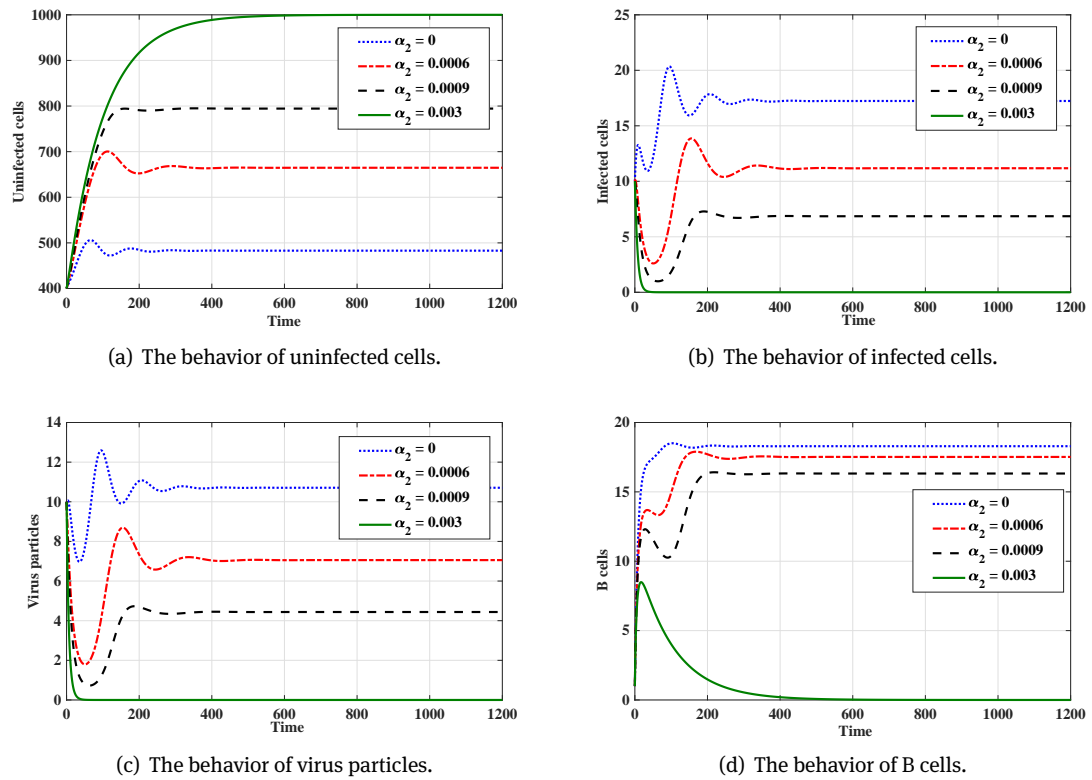
Figure 3: Solution trajectories of system (31)-(34) for different values of α_2 when $\alpha_1 = 0$.

(a) The behavior of uninfected cells.

(b) The behavior of infected cells.

(c) The behavior of virus particles.
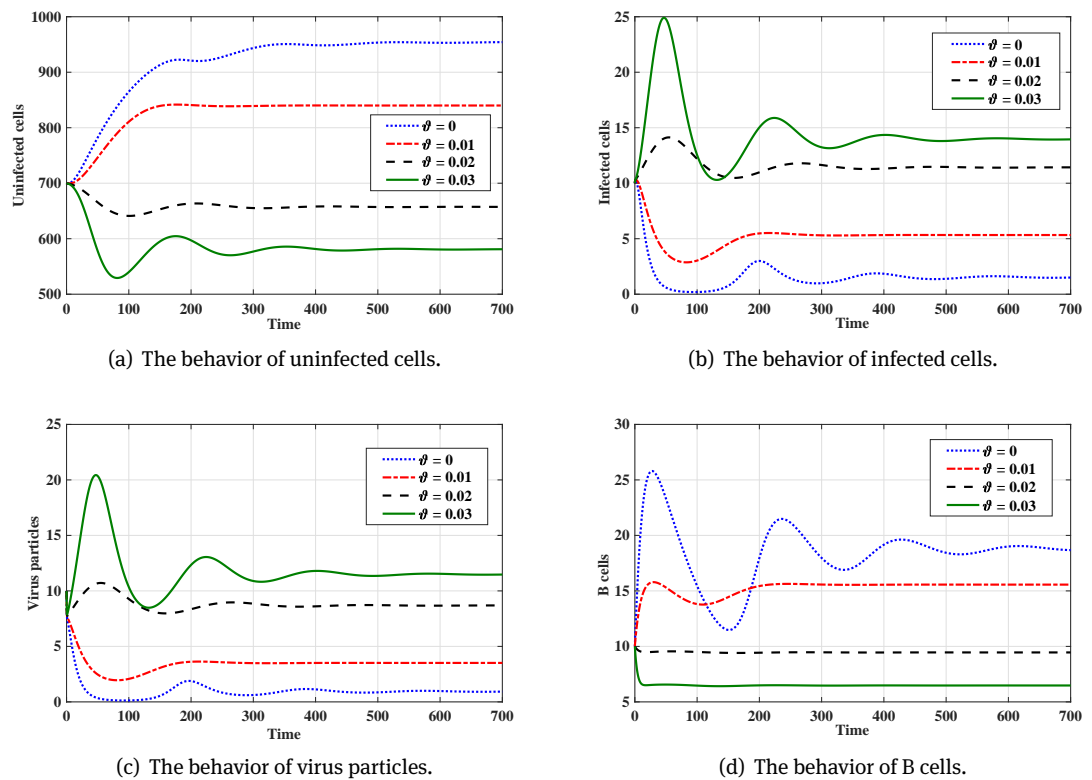

(d) The behavior of B cells.

Figure 4: Solution trajectories of system (31)-(34) for different values of ϑ.

In the numerical simulations we fix the values of parameters $\varrho = 10$, $\varkappa = \xi = 3$, $\rho = 0.1$, $\mu = \gamma = 0.01$, $\beta = 0.3$, $\varepsilon = 0.2$ and vary ω and ϑ

Case(1): Effect of ω on the stability of equilibria.

For this case, we take $\alpha_1 = \alpha_2 = 0$ and $\vartheta = 0.01$. We choose three different initial conditions as:

IC1: $U(0) = 700$, $I(0) = 5$, $P(0) = 5$, $C(0) = 0.5$,

IC2: $U(0) = 400$, $I(0) = 10$, $P(0) = 10$, $C(0) = 1$,

IC3: $U(0) = 300$, $I(0) = 20$, $P(0) = 15$, $C(0) = 1.5$.

We consider two values of the parameter ω as:

(i) $\omega = 0.0001$, then we compute $R_0^G = 0.3333 < 1$. Figure 1 shows that, for all IC1-IC3, the solution of the model tends to $EP_0 = (1000, 0, 0, 0)$. It means that, EP_0 is globally asymptotically stable.

(ii) $\omega = 0.001$, then we compute $R_0^G = 3.3333 > 1$. Figure 1, shows that the solutions of the model converge to the equilibrium $EP_1 = (482.9, 17.23, 10.7, 18.29)$ for all IC1-IC3. Then, EP_1 is globally asymptotically stable.

Case(2): Effect of the saturation infection on the virus dynamics.

In this case, we take $\alpha_2 = 0$ and $\vartheta = 0.01$. We choose $\omega = 0.001$, and α_1 varied. Moreover we consider the initial condition IC2. Figure 2 shows that as α_1 is increased, the concentrations of the uninfected target cells is increased, while the the concentration of infected cells, virus particles and B cells are decreased. We note that the parameter α_1 has no effect on the stability of equilibria

Case(3): Effect of Holling type-II.

For this case, we take $\alpha_1 = 0$, $\omega = 0.001$, and $\vartheta = 0.01$ then $\Theta(U, P)$ represents the Holling type-II. Let us choose the initial condition IC2. We suggest different values of α_2 to see its effect on the model as we can see in Figure 3. Moreover, we have the following cases:

(i) EP_1 is globally asymptotically stable when $0 \le \alpha_2 < 0.0023$,

(ii) EP_0 is globally asymptotically stable when $\alpha_2 > 0.0023$.

This means that α_2 can play the role of controller which can be designed to stabilize the system around the infection-free equilibrium EP_0.

Case(4): Effect of the B cell impairment parameter ϑ.

In this case, we take $\alpha_1 = 0.01$ and $\alpha_2 = 0.002$. We choose $\omega = 0.001$, and ϑ varied. Moreover, we consider the following initial condition

IC4: $U(0) = 700$, $I(0) = 10$, $P(0) = 10$, $C(0) = 10$.

Figure 4 shows that as ϑ is increased, the concentrations of infected cells and virus particles are increased, while the concentration of uninfected cells is decreased. We note that the parameter ϑ has no effect on the stability of equilibria.

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