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Dynamic Analysis of a Tumor Treatment Model Using Oncolytic Virus and Chemotherapy with Saturated Infection Rate

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Abstract. Virotherapy is one of the most promising therapies in the treatment of tumors which may be further combined with chemotherapy to accelerate the healing rate. In this article, we propose a mathematical model for the treatment of tumors using oncolytic virus and chemotherapy. This model takes the form of nonlinear ordinary differential equations describing the interactions between uninfected tumor cells, infected tumor cells, an oncolytic virus, and chemotherapy. It is assumed that the rate of infection between uninfected tumor cells and infected tumor cells is in a saturated form. The saturation effect takes into account the fact that the number of contacts between them reaches the maximum value when the immune system works to stop the virus. The dynamical analysis, which includes the existence of equilibrium points, and its stability analysis is investigated. The analysis result shows that the system has three equilibrium points: tumor-free equilibrium point, virus-free equilibrium point and endemic equilibrium point. It is proven that these equilibrium points are conditionally stable. The numerical simulations show the successful combination of chemotherapy and virotherapy using an oncolytic virus in eliminating the tumor cells.

Keywords: tumor, oncolytic virus, chemotherapy, saturated infected rate, stability analysis

1. Introduction

A tumor is one of the deadliest diseases in the world. It is a group of diseases characterized by uncontrolled cell growth. The tumor can attack the surrounding tissue and spread to other body parts [1]. This disease can be caused by environmental factors, genetic, radiation, viruses, alcoholism, and others. Traditional tumor treatments used to fight against the tumor are surgery, chemotherapy, and radiotherapy [2]. Traditional treatment however not only kills tumor cells but also damage human body normal cells at the same time [3]. Some common side of using traditional treatment involves hair loss, fatigue, nausea, and decrease blood cell count [4]. The development of science in the field of genetic engineering, has found treatment using oncolytic virus. An oncolytic virus is a kind of tumor killer virus, which can infect and lyse tumor cells and spread through the tumor while leaving normal cells largely unharmed [5]. An oncolytic virus can be replicated in the infected tumor cells. When an infected tumor cell is lysed, it can burst out a mass of new oncolytic viruses. Then, new viruses can

infect much more neighboring tumor cells [6]. The interaction between virus and tumor cells is very complex. The first mathematical models of oncolytic virus therapy considered ordinary differential equations that describe the basic interaction between two types of tumor (uninfected and infected).

In 2001, Wodarz proposed a mathematical model, which describes the interaction between two types of tumor cells (uninfected and infected) with bilinear infection rate [7]. In 2006, Novozhilov et al. modified the Wodarz model by changing the bilinear infection rate to standard infection rate [8]. In 2003, Wodarz modified his previous model by adding virus population [9]. In 2006, Dingli et al. modified the model proposed by Wodarz by adding the assumption that the death rate of uninfected tumor cells is contained in the logistic growth rate. Furthermore, the natural death rate and the other death rate of tumor cells caused by virus infection are considered as a unity called uninfected tumor cells death rate [10]. In 2008, Dingli et al. modified their previous model by adding two assumptions, namely the process of fusion between tumor cells and an oncolytic virus is resulting infected tumor cells and each virus is assumed to be dead after infecting tumor cell [11]. Then, Tian modified the model proposed by Dingli et al. by adding a parameter that represents the burst size of new viruses coming out from the lysis of infected tumor cells [12]. In 2011, Agarwal modified the model proposed by Novozhilov et al. by changing the standard infection rate into saturated rate [13]. Malinzi et al. in 2017, extend models by presenting by Tian et al. Malinzi et al. (2017) develop a mathematical model which combines virotherapy and chemotherapy treatments. The model includes uninfected tumor cells, infected tumor cells, free virus particles, and chemotherapy drug [14]. Virus infection of the tumor is considered to be of Michaelis-Menten form.

In this paper, we modify the dynamics model of Malinzi et al. by changing the Michaelis-Menten infection rate into a saturated rate. In section 2, we introduce a mathematical model. The condition for the existence of equilibrium point and stability are analyzed in Section 3. Next, the numerical simulations are presented in Section 5. Finally, conclusions are presented in section 5.

2. Mathematical Model

In this section, we propose and formulate our new mathematical model describing the growth of the tumor and its interaction with the oncolytic virus and chemotherapy with a saturated rate. This model contains four variables, namely, uninfected tumor cell population $U(t)$, infected tumor cell population $I(t)$, free virus particles population $V(t)$, and chemotherapy population $C(t)$. The model is given by the following nonlinear system of differential equations.

$$
\begin{aligned}
\frac{dU}{dt} &= rU\left(1 - \frac{U+I}{K}\right) - \frac{\beta UV}{U+I+\alpha} - \frac{\delta_U UC}{K_c+C}, \\
\frac{dI}{dt} &= \frac{\beta UV}{U+I+\alpha} - \delta I - \frac{\delta_I IC}{K_c+C}, \\
\frac{dV}{dt} &= b\delta I - \frac{\beta UV}{U+I+\alpha} - \gamma V, \\
\frac{dC}{dt} &= \mu - \psi C,
\end{aligned}
\tag{1}
$$

with initial conditions : $U(0) = U_o, I(0) = I_o, V(0) = V_o, C(0) = C_o$. The constant $U(0), I(0), V(0), C(0)$ we assume to be non-negative and all parameter model $r, K, \beta, \alpha, \delta_U, \delta_i, K_c, \delta, b, \gamma, \mu$ consider positive. The term $rU\left(1 - \frac{U+I}{K}\right)$ represents tumor growth with rate r and K is carrying capacity or maximum tumor size so that $U + I \leq K$. The term $\frac{\beta UV}{U+I+\alpha}$ represents infected tumor cells by an oncolytic virus which are limited maximum tumor size and immune response. β is the infection rate and α response immune. Drug effect to the uninfected and infected tumor cells is respectively described by the terms $\frac{\delta_U UC}{K_c+C}$ and $\frac{\delta_i IC}{K_c+C}$, where δ_U, δ_i are lysis rate and K_c are Michaelis-Menten constants. Virus production is dependent on its burst size, that is the larger the burst size, the higher the number of viruses produced. Virus production is taken to be $b\delta I$, where b is virus burst size and δ is the infected tumor cell natural death rate. Virus deactivation in the body tissue is represented by γV

where γ is the rate of decay. Term μ represents drug injection, and ψC is the natural drug concentration decay, where ψ is the rate of decay.

3. Analysis Model

In this section, we will discuss the equilibrium points and stability of the system (1). An equilibrium point is a point at which variable of a system remains unchanged over time. In order to get the possible equilibrium, setting the right sides of all equation of system (1) equal to zero.

$$ru\left(1-\frac{U+I}{K}\right)-\frac{\beta UV}{U+I+\alpha}-\frac{\delta_U UC}{K_c+C}=0,$$
$$\frac{\beta UV}{U+I+\alpha}-\delta I-\frac{\delta_I IC}{K_c+C}=0,$$
$$b\delta I-\frac{\beta UV}{U+I+\alpha}-\gamma V=0,$$
$$\mu-\psi C=0.$$

(2)

The system (2) has three positive equilibrium points, namely a tumor-free equilibrium point $E_0=\left(0,0,0,\frac{\mu}{\psi}\right)$, virus-free equilibrium point $E_1=\left(K\left(1-\frac{\delta_u C}{r(K_c+C)}\right),0,0,\frac{\mu}{\psi}\right)$, and an endemic equilibrium point $E^*=(U^*,I^*,V^*,C^*)$, where $I=\frac{\beta UA-DU\gamma-D\alpha\gamma}{D\gamma}$, $V=\frac{\beta UA^2-ADU\gamma-AD\alpha\gamma}{D\gamma^2}$, and U^* is determined by

$$aU^2+bU-c=0,$$

with
$$a=\frac{r\beta A}{KD\gamma},$$
$$b=\frac{\beta A}{\gamma}-\frac{\alpha r}{K}-r-D+\frac{\delta_u C}{K_c+C},$$
$$c=-\left(\delta+\frac{\delta_i C}{K_c+C}\right)\alpha,$$
$$A=b\delta-\delta-\frac{\delta_i C}{K_c+C},$$
$$D=\left(\delta+\frac{\delta_i C}{K_c+C}\right).$$

The complicated form of equilibrium point E_1 and E^* needs the investigation on its existence. The result of the investigations is briefly stated in the following proposition.

1. The equilibrium point E_1 exists when $r(\psi K_c+\mu)>\delta_u\mu$.

2. The equilibrium point E^* exists when $b\delta>\delta+\frac{\delta_i C}{K_c+C}$.

The investigation of the local stability of equilibrium points of a nonlinear system is performed by linearizing the system around the point. This process is resulting in a Jacobian matrix of the system, which can be used to determine the stability by considering the eigenvalue of the matrix. When all of the eigenvalues are negative then the equilibrium point is stable. Otherwise, it is unstable. The Jacobian matrix of the system (1) is

$$J(E)=\begin{bmatrix} r\left(1-\frac{2U+I}{K}\right)-\frac{\beta V(I+\alpha)}{(U+I+\alpha)^2}-\frac{\delta_U C}{K_C+C} & -\frac{RU}{K}+\frac{\beta UV}{(U+I+\alpha)^2} & -\frac{\beta U}{U+I+\alpha} & -\frac{\delta_U UK_C}{(K_C+C)^2} \\ \frac{\beta V(I+\alpha)}{(U+I+\alpha)^2} & -\frac{\beta UV}{(U+I+\alpha)^2}-\delta-\frac{\delta_I C}{K_C+C} & \frac{\beta U}{U+I+\alpha} & -\frac{\delta_I IK_C}{(K_C+C)^2} \\ -\frac{\beta V(I+\alpha)}{(U+I+\alpha)^2} & b\delta+\frac{\beta UV}{(U+I+\alpha)^2} & -\frac{\beta U}{U+I+\alpha}-\gamma & 0 \\ 0 & 0 & 0 & -\psi \end{bmatrix}.$$

3.1. Behavior of tumor-free equilibrium point

The Jacobian matrix evaluated at $E_0=\left(0,0,0,\frac{\mu}{\psi}\right)$ is

$$J(E_0) = \begin{bmatrix} r - \frac{\delta_U C}{K_C + C} & 0 & 0 & 0 \\ 0 & -\delta - \frac{\delta_I C}{K_C + C} & 0 & 0 \\ 0 & b\delta & -\gamma & 0 \\ 0 & 0 & 0 & -\psi \end{bmatrix}. \tag{3}$$

The eigenvalue is $\lambda_1 = r - \frac{\delta_U \frac{\mu}{\psi}}{K_C + \frac{\mu}{\psi}}$, $\lambda_2 = -\delta - \frac{\delta_I \frac{\mu}{\psi}}{K_C + \frac{\mu}{\psi}}$, $\lambda_3 = -\gamma$, and $\lambda_4 = -\psi$. Since λ_2, λ_3, λ_4 are

negative, then E_0 will be locally asymptotically stable if $r < \frac{\delta_U \frac{\mu}{\psi}}{K_C + \frac{\mu}{\psi}}$.

3.2. Behavior of virus-free equilibrium point

The Jacobian matrix evaluated at $E_1 = \left(K\left(1 - \frac{\delta_u C}{r(K_c + C)}\right), 0, 0, \frac{\mu}{\psi} \right)$ is

$$J(E_1) = \begin{bmatrix} \frac{\delta_U \frac{\mu}{\psi}(r-1)}{K_C + \frac{\mu}{\psi}} - r - \lambda & \frac{\delta_U \frac{\mu}{\psi}}{K_C + \frac{\mu}{\psi}} - r & \frac{\beta K \left(\delta_U \frac{\mu}{\psi} - r\left(K_C + \frac{\mu}{\psi}\right)\right)}{\left((\alpha+K)r\left(K_C + \frac{\mu}{\psi}\right)\right) - K\delta_U \frac{\mu}{\psi}} & \frac{\delta_U K_C K\left(r\left(K_C + \frac{\mu}{\psi}\right) - \delta_U \frac{\mu}{\psi}\right)}{r\left(K_C + \frac{\mu}{\psi}\right)^3} \\ 0 & -\delta - \frac{\delta_I \frac{\mu}{\psi}}{K_C + \frac{\mu}{\psi}} - \lambda & \frac{\beta K\left(r\left(K_C + \frac{\mu}{\psi}\right) - \delta_U \frac{\mu}{\psi}\right)}{\left((\alpha+K)r\left(K_C + \frac{\mu}{\psi}\right)\right) - K\delta_U \frac{\mu}{\psi}} & 0 \\ 0 & b\delta & \frac{\beta K\left(\delta_U \frac{\mu}{\psi} - r\left(K_C + \frac{\mu}{\psi}\right)\right)}{\left((\alpha+K)r\left(K_C + \frac{\mu}{\psi}\right)\right) - K\delta_U \frac{\mu}{\psi}} - \gamma - \lambda & 0 \\ 0 & 0 & 0 & -\psi - \lambda \end{bmatrix}. \tag{4}$$

The characteristic polynomial of the matrix $J(E_1)$ takes the following forms :

$$P(\lambda) = (-\psi - \lambda)\left(\frac{\delta_U \frac{\mu}{\psi}(r-1)}{K_C + \frac{\mu}{\psi}} - r - \lambda\right)(a_1\lambda^2 + a_1\lambda + a_3) = 0, \tag{5}$$

where

$a_1 = 1$,

$$a_2 = \gamma + \frac{\delta_I \frac{\mu}{\psi}}{K_C + \frac{\mu}{\psi}} - \delta - \frac{\beta K\left(\delta_U \frac{\mu}{\psi} - r\left(K_C + \frac{\mu}{\psi}\right)\right)}{\left((\alpha+K)r\left(K_C + \frac{\mu}{\psi}\right)\right) - K\delta_U \frac{\mu}{\psi}},$$

$$a_3 = \frac{\beta K\left(\delta_U \frac{\mu}{\psi} - r\left(K_C + \frac{\mu}{\psi}\right)\right)}{\left((\alpha+K)r\left(K_C + \frac{\mu}{\psi}\right)\right) - K\delta_U \frac{\mu}{\psi}}\left(\delta - \delta\frac{\beta K\left(r\left(K_C + \frac{\mu}{\psi}\right) - \delta_U \frac{\mu}{\psi}\right)}{\left((\alpha+K)r\left(K_C + \frac{\mu}{\psi}\right)\right) - K\delta_U \frac{\mu}{\psi}} - \frac{\delta_I \frac{\mu}{\psi}}{K_C + \frac{\mu}{\psi}}\right) + \gamma\left(\frac{\delta_I \frac{\mu}{\psi}}{K_C + \frac{\mu}{\psi}} - \delta\right).$$

The eigenvalue of the matrix $J(E_1)$ are

$$\lambda_1 = -\psi, \qquad \lambda_2 = \frac{\delta_U \frac{\mu}{\psi}(r-1)}{K_C + \frac{\mu}{\psi}} - r, \qquad \lambda_3 = \frac{-(a_2) - \sqrt{(a_2)^2 - 4a_3}}{2}, \qquad \lambda_4 = \frac{-(a_2) + \sqrt{(a_2)^2 - 4a_3}}{2}.$$

The eigenvalue λ_1 and λ_3 are both negative for all non-negative parameter values, while eigenvalue λ_2 can be negative if $\frac{\delta_U \frac{\mu}{\psi}(r-1)}{K_C + \frac{\mu}{\psi}} < r$ and eigenvalue λ_4 can be negative if

$$(a_2) + 4(a_3) < (a_2),$$
$$\gamma > b\left(\frac{b\delta c}{(a-\delta)} + 1\right),$$

Then λ_4 are negative. Hence all four eigenvalues are negative, so E_1 is locally stable.

3.3. Behavior of endemic equilibrium point

The Jacobian matrix at $E^* = (U^*, I^*, V^*, C^*)$ is

$$J(E^*) = \begin{bmatrix} r\left(1-\frac{2U^*+I^*}{K}\right)-\frac{\beta V^*(I+\alpha)}{(U^*+I^*+\alpha)^2}-\frac{\delta_U C}{K_C+C} & -\frac{RU^*}{K}+\frac{\beta U^*V^*}{(U^*+I^*+\alpha)^2} & -\frac{\beta U^*}{U^*+I^*+\alpha} & -\frac{\delta_U U^* K_C}{(K_C+C)^2} \\ \frac{\beta V^*(V^*+\alpha)}{(U^*+I^*+\alpha)^2} & -\frac{\beta U^*V^*}{(U^*+I^*+\alpha)^2}-\delta-\frac{\delta_I C}{K_C+C} & \frac{\beta U^*}{U^*+I^*+\alpha} & -\frac{\delta_I I K_C}{(K_C+C)^2} \\ -\frac{\beta V^*(V^*+\alpha)}{(U^*+I^*+\alpha)^2} & b\delta+\frac{\beta U^*V^*}{(U^*+I^*+\alpha)^2} & -\frac{\beta U^*}{U^*+I^*+\alpha}-\gamma & 0 \\ 0 & 0 & 0 & -\psi \end{bmatrix}. \qquad (6)$$

The characteristic equation associated with $J(E^*)$ is given by

$$(-\psi-\lambda)(m_0\lambda^3+m_1\lambda^2+m_2\lambda+m_3)=0,$$

where :

$A = \frac{\beta V^*(I+\alpha)}{(U^*+I^*+\alpha)^2}+\frac{\delta_U C}{K_C+C}+\frac{\delta_I C}{K_C+C}+\frac{\beta U^*V^*}{(U^*+I^*+\alpha)^2}+\delta-r\left(1-\frac{2U^*+I^*}{K}\right),$

$B = \frac{\beta U^*V^*}{(U^*+I^*+\alpha)^2}+\delta+\frac{\delta_I C}{K_C+C},$

$C = \frac{\beta V^*(I+\alpha)}{(U^*+I^*+\alpha)^2}+\frac{\delta_U C}{K_C+C}-r\left(1-\frac{2U^*+I^*}{K}\right),$

$D = \frac{\beta V^*(I+\alpha)}{(U^*+I^*+\alpha)^2}\left(\frac{RU^*}{K}-\frac{\beta U^*V^*}{(U^*+I^*+\alpha)^2}\right),$

$M = \frac{U^*+I^*+\alpha}{\beta U^*},$

$m_0 = 1,$

$m_1 = \frac{1}{M}\left(\frac{U^*+I^*+\alpha}{\beta U^*}A+\frac{U^*+I^*+\alpha}{\beta U^*}\gamma+1\right),$

$m_2 = \frac{1}{M}\left(A+\frac{U^*+I^*+\alpha}{\beta U^*}\gamma A+\frac{U^*+I^*+\alpha}{\beta U^*}BC+\frac{U^*+I^*+\alpha}{\beta U^*}D-b\delta-\frac{\beta U^*V^*}{(U^*+I^*+\alpha)^2}-\frac{\beta V^*(i^*+\alpha)}{(U^*+I^*+\alpha)^2}\right)\lambda,$

$m_3 = \frac{1}{M}\left((BC+D)\left(1+\frac{U^*+I^*+\alpha}{\beta U^*}\gamma\right)+\left(b\delta+\frac{\beta U^*V^*}{(U^*+I^*+\alpha)^2}\right)\left(r\left(1-\frac{2U^*+I^*}{K}\right)-\frac{\delta_U C}{K_C+C}\right)+\left(\frac{\beta V^*(i^*+\alpha)}{(U^*+I^*+\alpha)^2}\right)\left(-\frac{RU^*}{K}-\delta-\frac{\delta_I C}{K_C+C}\right)\right).$

Eigenvalue $\lambda_1 = -\psi$, which have negative real parts. Thus, we only need to consider the remaining three eigenvalues, which can be obtained by the following equation,

$$m_0\lambda^3+m_1\lambda^2+m_2\lambda+m_3=0 \qquad (7)$$

According to the Routh-Hurwitz criteria [15], the eigenvalues of equation (7) have negative real parts if and only if $m_1 > 0, m_3 > 0$, and $m_1 m_2 - m_3 > 0$.

4. Numerical Simulation

In this section, we present a numerical simulation of the model (1). The numerical simulations of the model equations are illustrated using MATLAB. The first simulation is aimed to show the stability of equilibrium $E_0 = \left(0,0,0,\frac{\mu}{\psi}\right)$, the second simulations show the stability of equilibrium $E_1 = \left(K\left(1-\frac{\delta_u\frac{\mu}{\psi}}{r\left(K_c+\frac{\mu}{\psi}\right)}\right),0,0,\frac{\mu}{\psi}\right)$, the third simulations show the stability when $E^* = (U^*, I^*, V^*, C^*)$ exist, and fourth simulations show the effect of different virus burst size rate. For tumor free condition $E_0 = \left(0,0,0,\frac{\mu}{\psi}\right)$, we use parameters values: $r = 0.1, K = 2139, \beta = 0.01, \alpha = 0.5, \delta_u = 50, K_c = 10000, \delta = 0.5, \delta_i = 60, b = 0.5, \gamma = 0.1, \mu = 150, \psi = 4.17.$ Based on previous analysis, since $r = 0.1 < 0.1792114696 = \frac{\delta_U\frac{\mu}{\psi}}{K_C+\frac{\mu}{\psi}}$ then $E_0 = (0,0,0,36)$ is locally asymptotically stable as shown in Figure 1.

The result of the numerical simulation provided in Figure 1 shows that the initial condition converges to the equilibrium point E_0.

The second simulation is executed to show the local stability of equilibrium point $E_1 = \left(K \left(1 - \frac{\delta_u \frac{\mu}{\psi}}{r \left(K_c + \frac{\mu}{\psi} \right)} \right), 0, 0, \frac{\mu}{\psi} \right)$. The simulation is made using a set of parameters as follow : $r = 0.206$, $K = 2000$, $\beta = 0.712$, $\alpha = 0.5$, $\delta_u = 40$, $K_c = 10000$, $\delta = 1$, $\delta_i = 60$, $b = 1$, $\gamma = 0.001$, $\mu = 203$, $\psi = 4.17$. In this case, since $\gamma = 0.001 > 0.00068483 = \left(\frac{b \delta c}{(a - \delta)} + 1 \right)$ then E_1 is locally asymptotically stable as shown in Figure 2. The result of the numerical simulation provided in Figure 2 shows that the initial condition converges to the equilibrium point $E_1 = (119, 0, 0, 49)$.

The third simulation is conducted to investigate the stability of $E^* = (U^*, I^*, V^*, C^*)$. Based on the previous analysis, we get these parameters as a condition for the existence of an endemic equilibrium point. We use the following parameters : $r = 1.8$, $K = 10000$, $\beta = 0.00085$, $\alpha = 0.5$, $\delta_u = 0.2$, $K_c = 10000$, $\delta = 0.2$, $\delta_i = 0.8$, $\gamma = 0.0001$, $b = 1.2$, $\mu = 20$, $\psi = 0.14$. An endemic equilibrium point $E^* = (8459, 1319, 379000, 143)$ is locally asymptotically stable since it satisfies the Routh-Hurwitz criterion where $m_1 = 0.02956768848 > 0$, $m_3 = 0.000005016214500 > 0$, $m_1 m_2 - m_3 = 0.01078110345 > 0$. The result of the numerical simulation provided in Figure 3 shows that the solution converges to the equilibrium point $E^* = (8459, 1319, 379000, 143)$.

The last simulation is executed to show the effect of different burst size. We use different parameter value for $b = 1.2$, $b = 1.5$ and $b = 1.7$. The result of the numerical simulation provided in Figure 4. The Figure shows that increasing virus burst size causes the densities of uninfected cells decrease, whereas the densities of infected cells will increase.
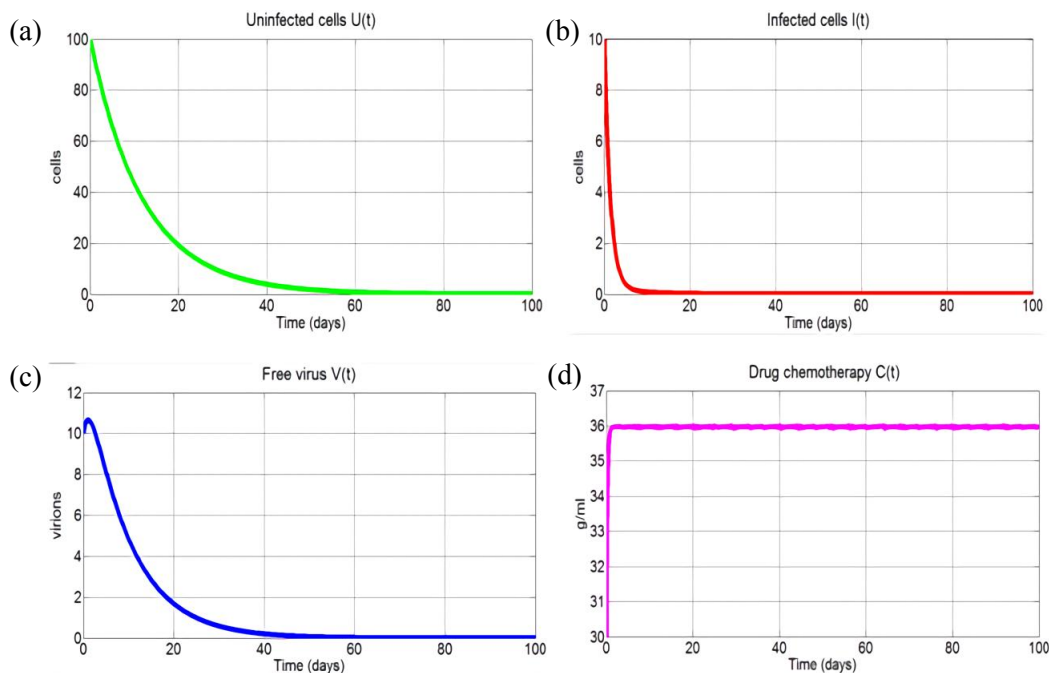
Figure 1. The stability of equilibrium point E_0. The initial condition (a) $U(0) = 100$, (b) $I(0) = 10$, (c) $V(0) = 10$, (d) $C(0) = 30$.
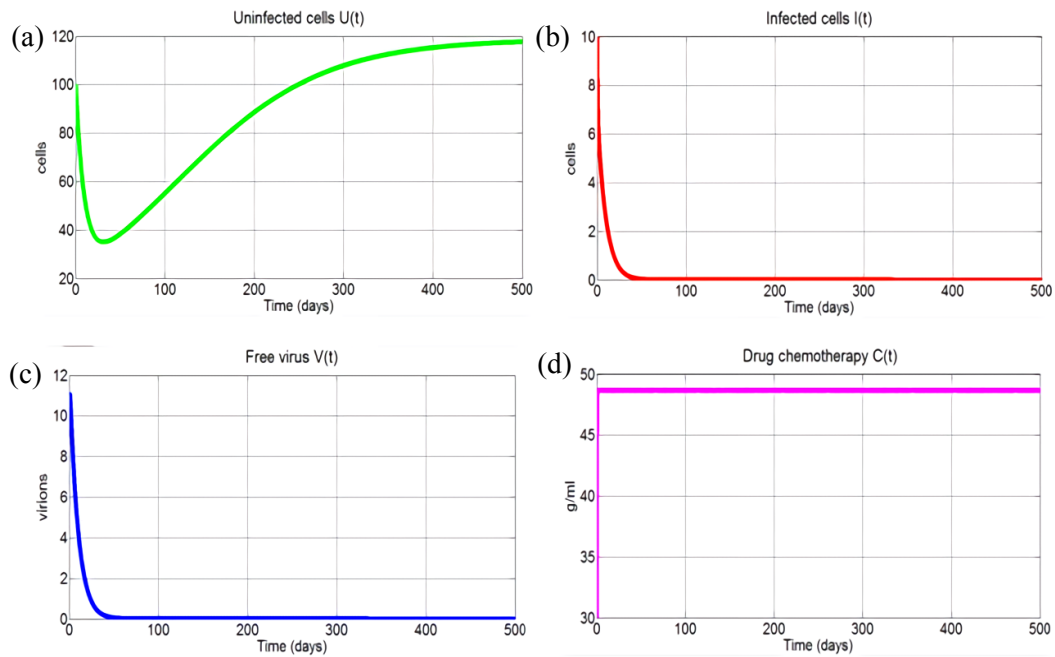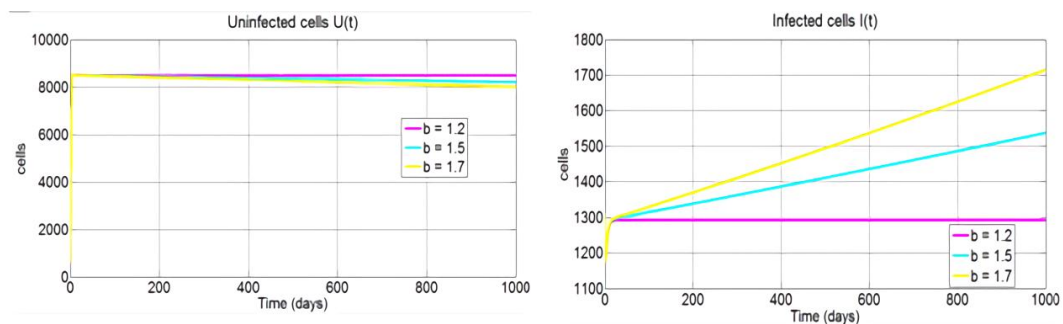
Figure 2. The stability of equilibrium point E_1. The initial condition (a) $U(0) = 100$, (b) $I(0) = 10$, (c) $V(0) = 10$, (d) $C(0) = 30$.
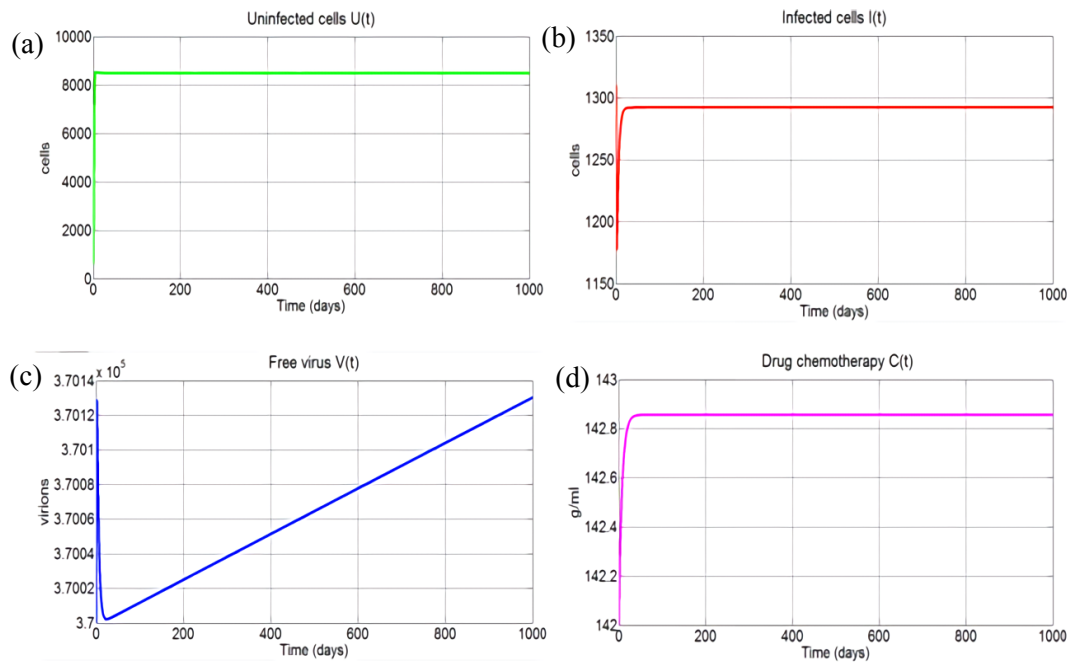
Figure 3. The stability of equilibrium point E^*. The initial condition (a) $U(0) = 600$, (b) $I(0) = 1310$, (c) $V(0) = 370000$, (d) $C(0) = 142$.

Figure 4. The effect of different value of virus burst size.

5. Conclusion

This paper introduces a new mathematical model of tumor therapy with oncolytic virus and chemotherapy with a saturated rate. The dynamical analysis shows that the model has three equilibrium points, namely tumor-free equilibrium, virus free equilibrium, and an endemic equilibrium point. The tumor-free equilibrium point and virus-free is locally asymptotically stable under certain condition, and an endemic equilibrium point is locally asymptotically stable if it satisfies Routh-Hurwitz criterion. From the simulation, it is also found that increasing the burst size of virus will decrease density of tumor.

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