Dynamics of the Generalized Tumor-Virotherapy Model with Time Delay Effect

Sarud Udomchalermpat, Sanoe Koonpraseart and Ekkachai Kunnawuttipreechachan

***Abstract*—In this work, we analyze dynamics of the generalized tumor-virotherapy model. Firstly, we investigate equilibria of the model and find stability conditions on the model's parameters for each equilibrium. We also determine the conditions for the existence of a Hopf bifurcation, which shows the oscillatory of the solutions. The behavior of the model is shown with well-known biologically admissible growth functions, such as logistic, Gompertz and von Bertalanffy functions. Finally, we illustrate various classes of numerical simulations to support the analytical results.**

***Index Terms*—virotherapy, tumor, growth function, Hopf bifurcation.**

I. Introduction

CANCER is one of leading causes of death worldwide, accounting for nearly eight million deaths per year[1]. It is a generic term for a large class of diseases that can affect any part of human body. An important problem in medicine is to develop methods for controlling tumor growth. Comprehensive reviews of cancer biology can be found in standard textbooks, such as [2] - [3].

An improved understanding of the dynamics of cancerous tumor growth may help physicians and cancer researchers to develop better medical prognosis for patients with more effective treatment plans. Mathematical modeling is one of the most successful methodologies in theoretical cancer research. In developing models, experimental data is used to create mathematical equations that describe the tumor growth. For the case of cancer, useful models for tumor growth can be obtained by differential equation models of population growth, where the populations could be divided into two groups of populations, i.e. infected and uninfected cell populations [3] - [4].

There are many different therapeutic methods developed for cancer treatment such as surgery, radiation and chemotherapy. Recently, a promising new therapeutic treatment for cancer is *virotherapy*. This treatment is based on the use of selected viruses which can replicate in and kill cancer cells without harming normal cells. One example of this type of virus is the *oncolytic* virus [5].

Many researchers (see, e.g., [4], [6]) have used mathematical models to study dynamics and effects of virotherapy on cancer progression. One of the most popular models is introduced by Wodarz [5] as

$$\begin{aligned} \dot{x} &= rx\left(1-\frac{x+y}{k}\right)-\delta x-\beta xy, \\ \dot{y} &= \beta xy+sy\left(1-\frac{x+y}{k}\right)-ay. \end{aligned} \tag{1}$$

Here x is the number of uninfected cell populations and y is the number of infected cell populations at time t. The definitions of model's parameters are given in Table I.

TABLE I
DEFINITIONS OF THE MODEL'S PARAMETERS .

Parameters	Meaning	Unit
t	Time	day
r	The rate of tumor growth	day^{-1}
s	The growth rate of infected cells	day^{-1}
δ	The rate at which the immune system destroys tumor cells	day^{-1}
β	The transmission rate of viral infection which spreads in tumor cells	number.mLday^{-1}
a	The rate at which the virus destroys infected tumor cells	day^{-1}
k	The maximum possible number of uninfected and infected cells in a tumor	number.mL^{-1}

In addition, many researchers (see, e.g., [7], [8], [9]) have used mathematical models with time delay to study dynamics of cancer growth. Oyama [10] has shown that the existence of a time delay in a virotherapy stage is important, which affect treament process. More examples of the importance of the time delay can be found in [11]–[12]. These authors have shown that the length of the time delay can depend on types of cancer and oncolytic virus.

For delay differential equations, Ashyani [6] has studied the dynamics of the modified delay model of Eq. (1) for the tumor growth including a time delay for the death of infected cells in virotheraphy. The model is presented by

$$\begin{aligned} \dot{x} &= rx\left(1-\frac{x+y}{k}\right)-\delta x-\beta xy, \\ \dot{y} &= \beta xy+sy\left(1-\frac{x+y}{k}\right)-ay(t-\tau), \end{aligned} \tag{2}$$

where $ay(t-\tau)$ is the rate in which the infected cells die due to infection with a constant delay τ representing the time of infection to death.

In (2), it is assumed that the growth of the cell populations in the tumor can be modeled by the logistic function with a basic growth rate r. However, there are many other interesting growth rates in biological models. In general, model (2) can be generalized with a general growth function G as the following pair of differential equations,

$$\begin{aligned} \dot{x} &= rxG(x,y)-\delta x-\beta xy, \\ \dot{y} &= \beta xy+syG(x,y)-ay(t-\tau), \end{aligned} \tag{3}$$

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Sarud Udomchalermpat is with Department of Mathematics, Faculty of Applied Science, King Mongkut's University of Technology North Bangkok, Thailand (e-mail: rud19@hotmail.com).

Sanoe Koonpraseart is with Department of Mathematics, Faculty of Applied Science, King Mongkut's University of Technology North Bangkok, Thailand (e-mail: sanoe.k@sci.kmutnb.ac.th).

Ekkachai Kunnawuttipreechachan is with Department of Mathematics, Faculty of Applied Science, King Mongkut's University of Technology North Bangkok, Thailand (e-mail: ekkachai.k@sci.kmutnb.ac.th).

where $\tau \geq 0$ and all parameters are non-negative.

The function G in (3) represents a *per capita* fraction of a tumor growth depending on the total number of uninfected and virus-infected tumor cells. In (3), we assume that $\delta < r$. If $\delta > r$, then a biological meaning is that immune system can destroy all of tumor cells in the body. Hence, virotherapy will not be needed. Moreover, we also assume that and the oncolytic virus can destroy tumor cells faster than immune cells. Consequently, the immune system cannot interrupt the virotherapy process. The initial conditions of (3) is given by

$$x(0) = x_0 > 0 \quad and \quad y(0) = y_0 > 0.$$

In general, there are many different growth models expressed by one-dimensional differential equations published in previous literature (see, e.g., [3]). One approach is to consider a tumor as a population of cells and uses ordinary differential equations to model this population (see, e.g., [13]). Some classical fractions for population growth laws in biological models are as follows

$$\begin{aligned} &\text{Logistic law:} && G(x,y) = 1 - \Big(\frac{x+y}{k}\Big), \\ &\text{Gompertz law:} && G(x,y) = 1 - \ln\Big(\frac{x+y}{k}\Big), \\ &\text{von Bertalanffy law:} && G(x,y) = \frac{k-(x+y)^{\frac{1}{3}}}{k(x+y)^{\frac{1}{3}}}, \end{aligned}$$

where where $k > 0$ represents maximum carrying capacity.

In this study the assumptions of the growth fraction G in model (3) are stated as follows:

(A1) G is a continuous and differentiable function,

(A2) G is a positive function,

(A3) G_x and G_y are strictly negative for non-nega--tive x and y.

In this paper, we aim to investigate the equilibria and prove the non-negativity of (3). The linearization method is used to analyze the local stability. We will study the behavior of generalized tumor-virotherapy model (3) with well-known growth fraction, such as logistic, Gompertz and von Bertalanffy functions. Finally, numerical simulations are carried out using mathematical software with biologically reasonable parameter values to illustrate model's behavior and support the analytical results.

II. Model's Equilibria

In this section, we investigate all equilibria (x^*, y^*) of (3) by setting $\dot{x} = \dot{y} = 0$, $x(t) = x^*$ and $y(t) = y(t-\tau) = y^*$. Hence, the equilibria are the roots of the following system:

$$rx^*G(x^*,y^*) - \delta x^* - \beta x^* y^* = 0, \tag{4}$$

$$\beta x^* y^* + s y^* G(x^*,y^*) - a y^* = 0. \tag{5}$$

From (4) - (5), It is not difficult to see that $x^* = y^* = 0$ is a solution, then the *trivial equilibrium*

$$E_1 = (x_1^*, y_1^*) = (0,0),$$

is an equilibrium of (3). Moreover, by setting $x^* = 0$, we obtain the second equilibrium,

$$E_2 = (0, y_2^*),$$

where y_2^* satisfies $G(0,y_2^*) = a/s$. The equilibrium E_2 is called *free-uninfected equilibrium.*

Next, by setting $y^* = 0$, we obtain the *free-infected equilibrium*,

$$E_3 = (x_3^*, 0),$$

where x_3^* satisfies $G(x_3^*, 0) = \delta/r$.

If $x^* \neq 0$ and $y^* \neq 0$, then we obtain the *interior equilibrium* $E_4(x_4^*, y_4^*)$, where

$$x_4^* = \frac{a - sG(x_4^*, y_4^*)}{\beta} \quad and \quad y_4^* = \frac{rG(x_4^*, y_4^*) - \delta}{\beta}. \tag{6}$$

Note that x_4^* and y_4^* are positive provided that

$$\frac{\delta}{r} < G(x_4^*, y_4^*) < \frac{a}{s}. \tag{7}$$

After simplifying (6), we then have the relation between x_4^* and y_4^* as

$$y_4^* = \frac{r(a - \beta x_4^*) - s\delta}{s\beta}.$$

For biological meaning, the trivial equilibrium E_1 means that the tumor does not exist. Hence, the tumor is eventually destroyed and the treatment is successful. In addition, the free-uninfected equilibrium E_2 represents that all tumor cells become infected cells. In this case, the tumor cells do not respond the virotherapy treatment. Moreover, the free-infected equilibrium E_3 means that all tumor cells are uninfected after virotherapy. It represents that the treatment is not successful. Finally, the interior equilibrium E_4 means that both uninfected and infected tumor cells still exist. This case is the most interesting case for biological sense. The stability of the equilibrium means that the tumor population is less than the carrying capacity k.

In the next section, we will analyze and find the conditions for stability of each equilibrium for the model (3).

III. Stability of the Model's Equilibria

To study the local stability for each equilibrium of the model (3), we used advantages of Lemma 3.1 for the conditions of all roots of the characteristic equation for a delay differential equation have negative real part.

Lemma 3.1 [14] *Let* $m, n \in$ R. *The conditions for all roots* λ_i *of (8)*

$$\lambda_i = m + ne^{-\lambda_i \tau}. \tag{8}$$

is as follows.

1) *If* $n \geq 0$ *and* $m + n < 0$*, then all roots of (8) have negative real part for all* $\tau \geq 0$.
2) *If* $n < 0$ *and* $m < n$*, then all eigenvalues have negative real part for all* $\tau \geq 0$.
3) *If* $n < 0$ *and* $-n > |m|$*, then there exists* $\tau_0 > 0$*, such that all eigenvalues have negative real part for all* $\tau \in [0, \tau_0)$.

Next, the local stability for each equilibrium is analyzed by the linearization method. The linearized equation of (3) at the equilibrium (x^*, y^*) is given by

$$\dot{W}(t) = \begin{bmatrix} w_{11} & w_{12} \\ w_{21} & w_{22} \end{bmatrix} W(t) + \begin{bmatrix} 0 & 0 \\ 0 & -a \end{bmatrix} W(t-\tau), \tag{9}$$

where $W(t) = \begin{bmatrix} x(t) - x^* \\ y(t) - y^* \end{bmatrix}$ and

$$\begin{aligned}
w_{11} &= rx^*G_x(x^*, y^*) + rG(x^*, y^*) - \delta - \beta y^*, \\
w_{12} &= rx^*G_y(x^*, y^*) - \beta x^*, \\
w_{21} &= \beta y^* + sy^*G_x(x^*, y^*), \\
w_{22} &= \beta x^* + sy^*G_y(x^*, y^*) + sG(x^*, y^*).
\end{aligned}$$

Note that (9) is used to examine the characteristic equation of the model (3), which will be useful for analyze the stability.

A. Stability of E_1

From (9), the characteristic equation of the model (3) at $E_1 = (0, 0)$ is

$$\begin{vmatrix} rG(0,0) - \delta - \lambda & 0 \\ 0 & sG(0,0) - ae^{-\lambda\tau} - \lambda \end{vmatrix} = 0. \quad (10)$$

The eigenvalues related to (10) are

$$\begin{aligned}
\lambda_1 &= rG(0,0) - \delta, \\
\lambda_2 &= sG(0,0) - ae^{-\lambda_2\tau}. \quad (11)
\end{aligned}$$

The stability property of the model (3) at E_1 are stated as the following theorem.

Theorem 3.1 *The conditions for stability properties of (3) at E_1 can be stated as follows.*

1) *If $0 < G(0,0) \leq 1$ and $G(0,0) < \min\{\frac{\delta}{r}, \frac{a}{s}\}$, then the equilibrium E_1 is locally asymptotically stable for $\tau \geq 0$, otherwise it is unstable.*
2) *If $G(0,0) > 1$, then the equilibrium E_1 is unstable for $\tau \geq 0$.*
3) *The Hopf bifurcation cannot be occurred at E_1.*

Proof: From the assumption (A2), we have $G(0,0) > 0$ and $\delta/r < 1$.

In the case that $0 < G(0,0) \leq 1$, if $G(0,0) < \delta/r < 1$, then λ_1 in (11) is negative real number. On the contrary, if $G(0,0) > \delta/r > 1$, then λ_1 is positive real number. From Lemma 3.1, we compare the eigenvalues in (8) with λ_2 in (11). It can be seen that $m = sG(0,0)$ and $n = -a$. By the second condition of Lemma 3.1, if $G(0,0) < a/s$, then λ_2 is negative real number. On the contrary, if $G(0,0) > a/s$, then λ_2 is positive real number. As the results, we can conclude that if $G(0,0) < \min\{\frac{\delta}{r}, \frac{a}{s}\}$, then the equilibrium E_1 is locally asymptotically stable.

In case that $G(0,0) > 1$, it can be seem that λ_1 in (11) is positive real number. Then the equilibrium E_1 is unstable.

Next, we analyze the Hopf bifurcation at E_1. Let $0 < G(0,0) < \delta/r$, then λ_1 in (11) is negative number. From the third condition of Lemma 3.1, we have

$$0 < G(0,0) < \frac{a}{s}. \quad (12)$$

Suppose that $\omega \in \mathrm{R}^+$ and let $\lambda_2 = \mathrm{i}\omega$ be roots of (11). It follows that

$$\begin{aligned}
i\omega &= sG(0,0) - ae^{-i\omega\tau}, \\
&= sG(0,0) - a(\cos\omega\tau - i\sin\omega\tau). \quad (13)
\end{aligned}$$

Comparing real and imaginary parts from both sides of (13), we have

$$\begin{aligned}
sG(0,0) &= a\cos\omega\tau \quad (14) \\
\omega &= a\sin\omega\tau. \quad (15)
\end{aligned}$$

Hence, (14) and (15) can be simplified as

$$\omega^2 = a^2 - s^2G^2(0,0). \quad (16)$$

From $0 < G(0,0) < \delta/r$, we find that

$$a^2 - s^2G^2(0,0) < 0. \quad (17)$$

Hence, (16) and (17) show that $\omega \notin \mathrm{R}^+$. Then the proof is complete.

Next, we prove global stability of the tumor-free equilibrium without time delay by using a Lyapunov function.

Theorem 3.2 *The tumor free equilibrium E_1 is globally asymptotically stable for $\tau = 0$, if the condition $G(0,0) < \min\{\frac{\delta}{r}, \frac{a}{s}\}$ is fulfilled.*

Proof: We introduce a function of the form $V(x,y) = x+y$, which is positive-definite and continuously differentiable for all positive bounded values of $x + y$, i.e., $V(0,0) = 0$ and $V(x,y) > 0, \forall x > 0$ and $\forall y > 0$ [15]. Hence, the time derivative of the Lyapunov function V satisfies

$$\begin{aligned}
\dot{V} &= \dot{x} + \dot{y} \\
&= rxG(x,y) - \delta x + syG(x,y) - ay \\
&= x(rG(x,y) - \delta) + y(sG(x,y) - a) \\
&\leq x(rG(0,0) - \delta) + y(sG(0,0) - a).
\end{aligned}$$

If $G(0,0) < \frac{\delta}{r}$ and $G(0,0) < \frac{a}{s}$, then $\dot{V} \leq 0$. Therefore, the equilibrium E_1 is globally stable. The condition for E_1 is globally asymptotically stable is

$$G(0,0) < \min\left\{\frac{\delta}{r}, \frac{a}{s}\right\}. \quad (18)$$

We note that condition (18) is only a sufficient condition for global stability but we have not proved that the conditions are also necessary conditions for global stability of the tumor free equilibrium E_1.

B. Stability of E_2

From (9), the characteristic equation of (3) at $E_2 = (0, y_2^*)$ is

$$\begin{vmatrix} a_{11} - \lambda & 0 \\ a_{21} & a_{22} - ae^{-\lambda\tau} - \lambda \end{vmatrix} = 0, \quad (19)$$

where

$$\begin{aligned}
a_{11} &= rG(0, y_2^*) - \delta - \beta y_2^*, \\
a_{21} &= \beta y_2^* + sy_2^*G_x(0, y_2^*), \\
a_{22} &= sy_2^*G_y(0, y_2^*) + sG(0, y_2^*).
\end{aligned}$$

The eigenvalues of (19) with the condition $G(0, y_2^*) = a/s$ are

$$\begin{aligned}
\lambda_1 &= \frac{ra}{s} - \delta - \beta y_2^*, \\
\lambda_2 &= sy_2^*G_y(0, y_2^*) + a - ae^{-\lambda_2\tau}. \quad (20)
\end{aligned}$$

If $y_2^* < (ra - \delta s)/\beta s$, then the equilibrium E_2 is unstable for $\tau \geq 0$. On the contrary, if $y_2^* > (ra - \delta s)/\beta s$, then λ_1 is negative real number.

Next, consider $\lambda_2 = sy_2^*G_y(0, y_2^*) + a - ae^{-\lambda_2\tau}$. From Lemma 3.1 and assumption (A3), we compare the eigenvalue of (8) in Lemma 3.1 with λ_2 in (20). It can see that $m = sy_2^*G_y(0, y_2^*) + a$ and $n = -a$, then stability property of the equilibrium E_2 are stated as follows.

Theorem 3.3 *If $y_2^* > (ra - \delta s)/\beta s$ and $G_y(0, y_2^*) < 0$, then the equilibrium E_2 is asymptotically stable for all $\tau \geq 0$, and it does not exhibit a Hopf bifurcation.*

Proof: To show that Hopf bifurcation at E_2 can not be occurred, the third condition of Lemma 3.1 shows that

$$\frac{-2a}{sy_2^*} < G_y(0, y_2^*) < 0. \quad (21)$$

Suppose that $\omega \in \mathrm{R}^+$ and let $\lambda_2 = \mathrm{i}\omega$ be a root of (20). It follows that

$$\begin{aligned} i\omega &= sy_2^* G_y(0, y_2^*) + a - ae^{-i\omega\tau}, \\ &= sy_2^* G_y(0, y_2^*) + a - a(\cos\omega\tau - i\sin\omega\tau). \quad (22) \end{aligned}$$

Comparing the real and imaginary parts from both sides of (22), we have

$$\begin{aligned} sy_2^* G_y(0, y_2^*) + a &= a\cos\omega\tau \quad (23) \\ \omega &= a\sin\omega\tau. \quad (24) \end{aligned}$$

Hence, (22) and (23) can be simplified as

$$\omega^2 = sy_2^* G_y(0, y_2^*)(sy_2^* G_y(0, y_2^*) + 2a). \quad (25)$$

From condition (21), it can be seen that

$$sy_2^* G_y(0, y_2^*)(sy_2^* G_y(0, y_2^*) + 2a) < 0. \quad (26)$$

Hence, (25) and (26) show that $\omega \notin \mathrm{R}^+$. As the results, there is no Hopf bifurcation for E_2.

C. Stability of E_3

From (9), the characteristic equation of (3) at $E_3 = (x_3^*, 0)$ is

$$\begin{vmatrix} b_{11} - \lambda & b_{12} \\ b_{21} & b_{22} - ae^{-\lambda\tau} - \lambda \end{vmatrix} = 0, \quad (27)$$

where

$$\begin{aligned} b_{11} &= rx_3^* G_x(x_3^*, 0), \\ b_{12} &= rx_3^* G_y(x_3^*, 0) - \beta x_3^*, \\ b_{22} &= \beta x_3^* + sG(x_3^*, 0). \end{aligned}$$

The eigenvalues of (27) with the condition $G(x_3^*, 0) = \delta/r$ are

$$\begin{aligned} \lambda_1 &= rx_3^* G_x(x_3^*, 0), \\ \lambda_2 &= \beta x_3^* + \frac{s\delta}{r} - ae^{-\lambda_2\tau}. \quad (28) \end{aligned}$$

From the assumption (A3), λ_1 in (28) is negative real number. Compare with the eigenvalue in (8) in Lemma 3.1 with λ_2 in (28). By the second and third conditions in Lemma 3.1, it can be seen that if $m = \beta x_3^* + \frac{s\delta}{r}$ and $n = -a$, then the stability property of E_3 are stated as the following theorem.

Theorem 3.4 *If $0 < x_3^* < \frac{ar - s\delta}{\beta r}$, then the free-infected equilibrium E_3 is locally asymptotically stable for $\tau \in [0, \tau_0)$, otherwise it is unstable.*

Proof: Suppose that $\omega \in \mathrm{R}^+$ and let $\lambda_2 = \mathrm{i}\omega$ be a root of (28). It follows that

$$\begin{aligned} i\omega &= \beta x_3^* + \frac{s\delta}{r} - ae^{-i\omega\tau}, \\ &= \beta x_3^* + \frac{s\delta}{r} - a(\cos\omega\tau - i\sin\omega\tau). \quad (29) \end{aligned}$$

Comparing real and imaginary parts from both sides of (29), we have

$$\begin{aligned} \beta x_3^* + \frac{s\delta}{r} &= a\cos\omega\tau \quad (30) \\ \omega &= a\sin\omega\tau. \quad (31) \end{aligned}$$

Hence, (30) and (31) can be simplified as

$$\omega^2 = a^2 - (\beta x_3^* + \frac{s\delta}{r})^2.$$

If $0 < x_3^* < \frac{ar - s\delta}{\beta r}$, then

$$\omega = \sqrt{a^2 - (\beta x_3^* + \frac{s\delta}{r})^2}. \quad (32)$$

We also find τ_k, which are roots of (30) as

$$\tau_k = \frac{1}{\omega} \arccos\left(\frac{\beta x_3^* r + s\delta}{ar} + 2k\pi\right), \quad (33)$$

then $\tau_0 = \frac{1}{\omega} \arccos\left(\frac{\beta x_3^* r + s\delta}{ar}\right)$.

Next, the condition for Hopf bifurcation occurrence of (3) at E_3 is provided that $\mathrm{Re}\left(\frac{d\lambda}{d\tau}\right) > 0$. Consider the characteristic equation (27):

$$\lambda^2 - (b_{11} + b_{22})\lambda + b_{11}b_{22} + a(\lambda - b_{11})e^{-\lambda\tau} = 0. \quad (34)$$

Let λ be a function of τ, i.e. $\lambda = \lambda(\tau)$. Differentiate both sides of (34) with respect to τ, it follows that

$$\begin{aligned} \left(\frac{d\lambda}{d\tau}\right)^{-1} &= \frac{2\lambda - (b_{11} + b_{22})}{-\lambda^3 - (b_{11} + b_{22})\lambda^2 - b_{11}b_{22}\lambda} - \frac{\tau}{\lambda} \\ &\quad + \frac{1}{(\lambda + b_{11})\lambda} \quad (35) \end{aligned}$$

Suppose that

$$\lambda(\tau_0) = \alpha(\tau_0) + i\omega(\tau_0).$$

Let $\mathrm{Re}(\lambda(\tau_0)) = 0$ and $\mathrm{Im}(\lambda(\tau_0)) = \omega$, then $\alpha(\tau_0) = 0$ and $\lambda(\tau_0) = \mathrm{i}\omega$. From (35), we can show that

$$\begin{aligned} \left(\frac{d\lambda}{d\tau}\right)^{-1} &= \frac{i2\omega - (b_{11} + b_{22})}{i\omega^3 - (b_{11} - b_{22})\omega^2 - ib_{11}b_{22}\omega} - \frac{\tau}{i\omega} \\ &\quad + \frac{1}{-\omega^2 + ib_{11}\omega} \quad (36) \end{aligned}$$

Consider only the real part of (36). It follows that

$$Re\left(\left(\frac{d\lambda}{d\tau}\right)^{-1}\Big|_{\tau=\tau_0}\right) = \frac{\omega^2(\omega^2 + b_{11}^2)}{\left((b_{11} + b_{22})^2\omega^4 + (b_{11}b_{22}\omega - \omega^3)^2\right)}.$$

Hence, $\mathrm{Re}\left(\frac{d\lambda}{d\tau}\Big|_{\tau=\tau_0}\right)$ is positive, which is a condition for τ_0 is a Hopf bifurcation point and the bifurcation occurs as $\tau = \tau_0$.

D. Stability of E_4

From (9), the characteristic equation of (3) at the interior equilibrium $E_4 = (x_4^*, y_4^*)$ is

$$\begin{vmatrix} c_{11} - \lambda & c_{12} \\ c_{21} & c_{22} - ae^{-\lambda\tau} - \lambda \end{vmatrix} = 0, \quad (37)$$

where

$$\begin{aligned} c_{11} &= rx_4^*G_x(x_4^*,y_4^*) + rG(x_4^*,y_4^*) - \delta - \beta y_4^*,\\ c_{12} &= rx_4^*G_y(x_4^*,y_4^*) - \beta x_4^*,\\ c_{21} &= \beta y_4^* + sy_4^*G_x(x_4^*,y_4^*),\\ c_{22} &= \beta x_4^* + sy_4^*G_y(x_4^*,y_4^*) + sG(x_4^*,y_4^*). \end{aligned}$$

From (37), characteristic equation with the condition (7) is

$$\begin{aligned} &\lambda^2 + (\beta(y_4^* - x_4^*) - rX - sY + \delta)\lambda\\ &+\big[r\beta x_4^*X + (rsG(x_4^*,y_4^*) - \delta s - \beta s y_4^*)Y\\ &-\delta\beta x_4^* + rsx_4^*G_x(x_4^*,y_4^*)G(x_4^*,y_4^*)\\ &-\beta x_4^*y_4^*(rG_y(x_4^*,y_4^*) + sG_x(x_4^*,y_4^*))\big]\\ &+a(\lambda - rX + \beta y_4^* + \delta)e^{-\lambda\tau} = 0, \end{aligned}$$

where

$$\begin{aligned} X &= x_4^*G_x(x_4^*,y_4^*) + G(x_4^*,y_4^*),\\ Y &= y_4^*G_y(x_4^*,y_4^*) + G(x_4^*,y_4^*). \end{aligned}$$

The characteristic equation of (37) is

$$\lambda^2 + C\lambda + B + a(\lambda - A)e^{-\lambda\tau} = 0, \quad (38)$$

where

$$\begin{aligned} A &= \beta y_4^* - rX + \delta,\\ B &= r\beta x_4^*X + (rsG(x_4^*,y_4^*) - \delta s - \beta s y_4^*)Y\\ &\quad + rsx_4^*G_x(x_4^*,y_4^*)G(x_4^*,y_4^*) - \delta\beta x_4^*\\ &\quad - \beta x_4^*y_4^*(rG_y(x_4^*,y_4^*) + sG_x(x_4^*,y_4^*)),\\ C &= \beta(y_4^* - x_4^*) - rX - sY + \delta. \end{aligned} \quad (39)$$

For the case that $\tau = 0$, then the characteristic equation of (38) is

$$\lambda^2 + (C + a)\lambda + B - aA = 0.$$

The eigenvalues are

$$\lambda_{1,2} = \frac{-(C + a) \pm \sqrt{(C + a)^2 - 4(B - aA)}}{2}. \quad (40)$$

Therefore, the stability condition of non-delay case for E_4 are stated by the following theorem.

Theorem 3.5 *Let A, B and C are defined in (39). The stability conditions of model (3) at E_4 can be stated as follows.*

1) *If $B - aA > 0$, then the equilibrium E_4 is locally asymptotically stable when $C + a > 0$ and unstable when $C + a < 0$.*
2) *If $B - aA < 0$, then the equilibrium E_4 is a saddle point.*

Let τ be the bifurcation parameter. In the next section we will investigate additional conditions and evaluate the formula in which $\tau = \tau_0$ becomes the Hopf bifurcation point.

IV. Existence of Periodic Solution of E_4

In this section, we analyze the bifurcation of E_4 of (3) where $\tau > 0$. From (38), the characteristic equation is

$$\lambda^2 + C\lambda + B + a(\lambda - A)e^{-\lambda\tau} = 0. \quad (41)$$

Suppose that $\omega \in \mathrm{R}^+$ and let $\lambda = \mathrm{i}\omega$ be a root of (41). It follows that

$$\begin{aligned} &(B - \omega^2 + a\omega\sin\omega\tau + aA\cos\omega\tau)\\ &+(C\omega - aA\sin\omega\tau + a\omega\cos\omega\tau)i = 0. \end{aligned} \quad (42)$$

Comparing the real and imaginary parts from both sides of (42), we have

$$a\omega\sin\omega\tau + aA\cos\omega\tau = \omega^2 - B \quad (43)$$

$$aA\sin\omega\tau - a\omega\cos\omega\tau = C\omega \quad (44)$$

From (43) and (44) can be simplified as

$$a^2\omega^2 + a^2A^2 = (B - \omega^2)^2 + C^2\omega^2. \quad (45)$$

Then, solving for ω from (45), then

$$\omega^2 = \frac{1}{2}\Big[(a^2 + 2B - C^2) \pm\sqrt{(a^2 - C^2)(a^2 + 4B - C^2) + 4a^2A^2}\Big]. \quad (46)$$

Hence, the conditions for non-zero value of ω are $C^2 < 2B + a^2$ and $|A| < B/a$.

The solutions of (43) and (44) are

$$\sin\omega\tau = \frac{\omega^3 + (AC - B)\omega}{a(\omega^2 + A^2)}, \quad \cos\omega\tau = \frac{(A - C)\omega^2 - AB}{a(\omega^2 + A^2)}. \quad (47)$$

Finally, from (47), the value of τ is given by

$$\tau_k = \frac{1}{\omega}\cos^{-1}\left(\frac{(A - C)\omega^2 - AB}{a(\omega^2 + A^2)} + 2k\pi\right), \quad (48)$$

where $k = 0, 1, 2, \ldots.$ Condition (48) represents the bifurcation points of the model (3). We will next investigate whether the first bifurcation point τ_0 is a Hopf bifurcation point. The necessary conditions are that $\lambda(\tau_0)$ is purely imaginary number and $\mathrm{Re}\left(\left.\frac{d\lambda}{d\tau}\right|_{\tau=\tau_0}\right) > 0$.

Theorem 4.1 *Let A, B and C be defined in (39). If $(C^2 - a^2 + \frac{2}{3}B^2)^2 > \frac{4}{9}(4a^2A^2 + B^2)$, then the model (3) undergoes a Hopf bifurcation at the interior equilibrium E_4, where $\tau = \tau_0$ is defined in (48).*

Proof: Consider the characteristic equation

$$\lambda^2 + C\lambda + B + a(\lambda - A)e^{-\lambda\tau} = 0. \quad (49)$$

Let λ be a function of τ, i.e. $\lambda = \lambda(\tau)$. Differentiate both sides of (49) with respect to τ, it follows that

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{2\lambda + C}{-\lambda^3 - C\lambda^2 - B\lambda} - \frac{\tau}{\lambda} + \frac{1}{(\lambda + A)\lambda} \quad (50)$$

Suppose that

$$\lambda(\tau_0) = \alpha(\tau_0) + i\omega(\tau_0).$$

Let $\mathrm{Re}(\lambda(\tau_0)) = 0$ and $\mathrm{Im}(\lambda(\tau_0)) = \omega$ then $\alpha(\tau_0) = 0$ and $\lambda(\tau_0) = \mathrm{i}\omega$. From (50), we can show that

$$\left.\left(\frac{d\lambda}{d\tau}\right)^{-1}\right|_{\tau=\tau_0} = \frac{i2\omega + C}{i\omega^3 + C\omega^2 - iB\omega} - \frac{\tau}{i\omega} + \frac{1}{-\omega^2 + iA\omega}$$

Simplifying above equation, the real part is

$$Re\left(\left(\frac{d\lambda}{d\tau}\right)^{-1}\Bigg|_{\tau=\tau_0}\right) = \frac{(C^2+2B)-(2\omega^2+a^2)}{a^2(\omega^2+A^2)}. \quad (51)$$

We can see that $\mathrm{Re}\left(\left(\frac{d\lambda}{d\tau}\right)^{-1}\Bigg|_{\tau=\tau_0}\right) > 0$ if and only if

$$C^2+2B > 2\omega^2+a^2. \quad (52)$$

From (46),

$$\omega^2 = \frac{(a^2+2B-C^2)}{2} \frac{\pm\sqrt{(C^2-2B-a^2)^2-4(B^2-a^2A^2)}}{2}.$$

Then condition (52) becomes

$$(C^2-a^2+\frac{2}{3}B^2)^2 > \frac{4}{9}(4a^2A^2+B^2). \quad (53)$$

Therefore, the value of $\mathrm{Re}\left(\frac{d\lambda}{d\tau}\Bigg|_{\tau=\tau_0}\right)$ is positive under the condition (53). Thus τ_0 is the first Hopf bifurcation point with bifurcation occurring as τ increases.

Note that the hypotheses for Hopf bifurcation are satisfied at $\tau=\tau_0$ with the condition (53). This leads us to state the following theorem.

Theorem 4.2 *The conditions for stability properties of (3) at E_4 are stated as follows.*

1) *If $\tau<\tau_0$, then the interior equilibrium E_4 is locally asymptotically stable.*
2) *If $\tau>\tau_0$, then the equilibrium E_4 is unstable.*
3) *If $\tau=\tau_0$ and $(C^2-a^2+\frac{2}{3}B^2)^2 > \frac{4}{9}(4a^2A^2+B^2)$, then τ_0 is the Hopf bifurcation point.*

V. Applications and Numerical Examples

In this section, we apply the analytical results to investigate the model (3) with logistic, Gompertz and von Bertalanffy growth functions. For each of these growth functions, the numerical simulations are shown with biologically reasonable values of parameters to explain dynamics of the tumor-virotherapy model.

A. The logistic growth law

For the special case of (3) with the logistic growth function $G(x,y)=1-(x+y)/k$. The model (3) becomes

$$\begin{aligned}\dot{x} &= rx\left(1-\frac{x+y}{k}\right)-\delta x-\beta xy,\\ \dot{y} &= \beta xy+sy\left(1-\frac{x+y}{k}\right)-ay(t-\tau).\end{aligned} \quad (54)$$

For equilibrium E_1, we get $G(0,0)=1$. From Theorem 3.1, E_1 is unstable for all $\tau\geq 0$.

For the equilibrium E_2, we have $G(0,y_2^*)=a/s$ and then $y_2^*=k(s-a)/s$. The condition $s>a$ provides positive equilibrium. We also find that $G_y(0,y_2^*)=-1/k$. From Theorem 3.2, if $k>(ra-\delta s)/\beta(s-a)$ and $s>a$, then the equilibrium E_2 is locally asymptotically stable for all $\tau\geq 0$.

For equilibrium E_3, we have $G(x_3^*,0)=\delta/r$ and therefore $x_3^*=k(r-\delta)/r$ is positive if $r>\delta$. From Theorem 3.3, we can state the conditions of stability as follows.

1) If $0<k<\frac{ar-s\delta}{\beta(r-\delta)}$, then the equilibrium E_3 is locally asymptotically stable for $\tau\in[0,\tau_0)$, and it is unstable for $\tau>\tau_0$.
2) If $k>\frac{ar-s\delta}{\beta(r-\delta)}$, then the equilibrium E_3 is unstable for all $\tau\geq 0$.

Finally, to support the results, we present some numerical simulations generated for the first choice of parameter values from [6],

$$r=0.2, \delta=0.01, \beta=0.1, s=1, a=2, k=70, \quad (55)$$

and we assume that the initial conditions are $x(t)=12$ and $y(t)=2$, where $t\in[-\tau,0]$.

Using the conditions in Theorems 3.1 - 3.4 and Theorem 4.2, we would expect the followings:

1) The equilibrium E_1 is unstable for all $\tau\geq 0$ when $G(0,0)=1$,

2) the equilibrium E_2 does not exist when $s=1<a=2$.

3) The equilibrium E_3 exists if $r=0.2>\delta=0.01$.

4) If $k=70>(ar-\delta s)/\beta(r-\delta)\approx 20.5263$, then the equilibrium E_3 is unstable for all $\tau\geq 0$.

5) If $C+a=0.5571428594>0$ and $B-aA=0.1600599079>0$, then the equilibrium E_4 is locally asymptotically stable for all $\tau=0$.

6) From (46) and (48), the Hopf bifurcation point $\tau_0\approx 0.2998$.

Numerical solutions of (54) are shown in Figures 1 and 2 with different values of τ to support the theoretical results in previous sections and the conditions in Theorem 4.2. Figure 1 illustrates the numerical solutions of (54) near the bifurcation point $\tau_0\approx 0.2998$. We can see that the solutions in Figure 1 converge to the positive equilibrium $E_4=(11.96,1.53)$ when $\tau=0.25<\tau_0$. On the other hand, in Figure 2, the solutions are oscillated about the equilibrium $E_4=(11.96,1.53)$ when $\tau=0.30>\tau_0$.

The second set of parameter is obtained from [6],

$$r=0.2, \delta=0.1, \beta=0.1, s=1.001, a=1, k=29, \quad (56)$$

and we assume that the initial conditions are $x(t)=3$ and $y(t)=2$, where $t\in[-\tau,0]$.

Numerical solutions of (54) are shown in Figures 3 and 4 with different values of τ to support the theoretical results in previous sections. We can see that the solutions in Figure 3 and Figure 4 converge to the positive equilibrium $E_4=(0.45,0.89)$.

The third set of parameter is obtained from [6],

$$r=0.1, \delta=1, \beta=5, s=2, a=3, k=5, \quad (57)$$

and we assume that the initial conditions are $x(t)=3$ and $y(t)=2$ where $t\in[-\tau,0]$.

Numerical solutions of (54) are shown in Figures 5 with the values of $\tau=0$ to support the theoretical results in previous sections. We can see that the solutions in Figure 5 converge to the positive equilibrium $E_1=(0,0)$.

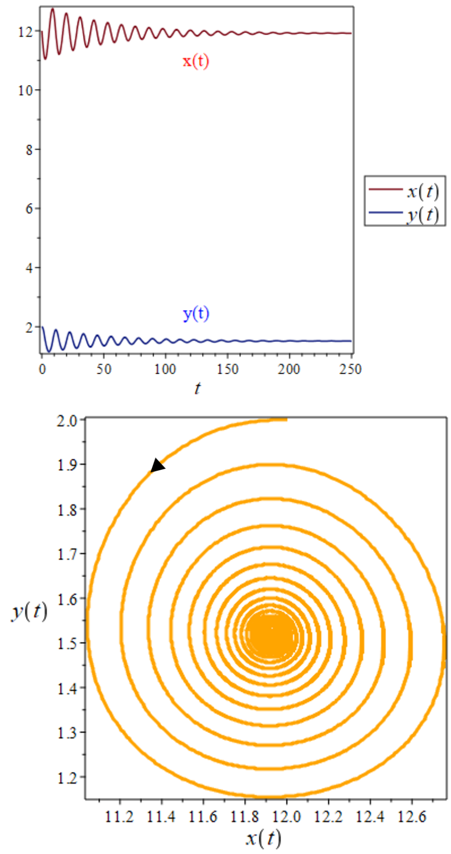

Fig. 1. Numerical solutions of (54) converge to E_4 where $\tau = 0.25 < \tau_0$ with parameter values in (55).

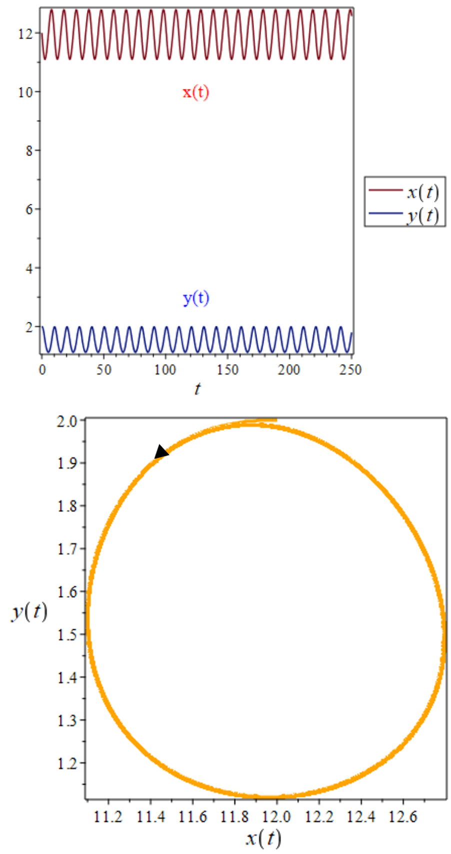

Fig. 2. Numerical solutions of (54) oscillate about E_4 where $\tau = 0.30 > \tau_0$ with parameter values in (55).

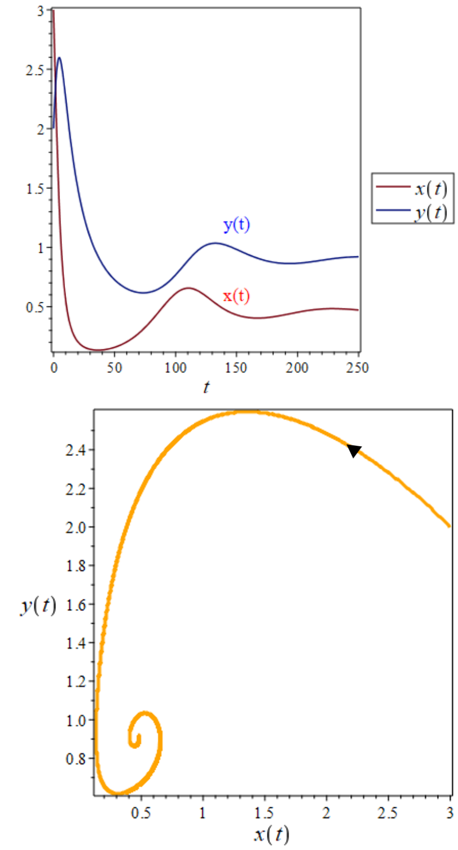

Fig. 3. Numerical solutions of (54) converge to E_4 where $\tau = 0$ with parameter values in (56).

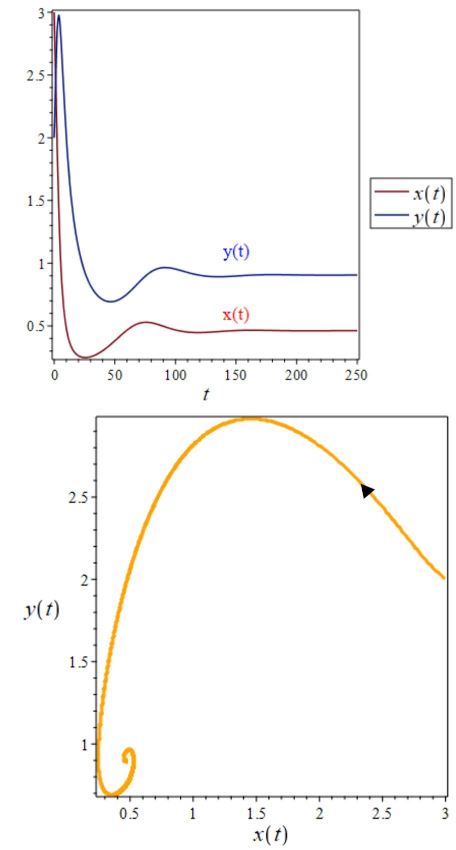

Fig. 4. Numerical solutions of (54) converge to E_4 where $\tau = 0.50$ with parameter values in (56).

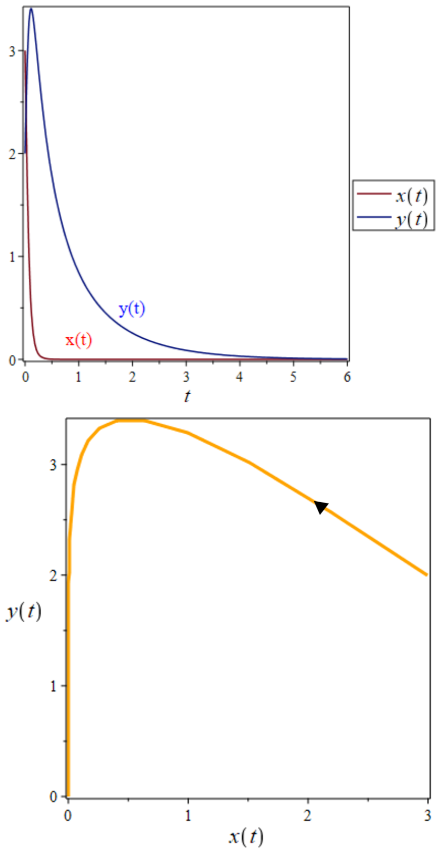

Fig. 5. Numerical solutions of (54) converge to E_1 where $\tau = 0$ with parameter values in (57).

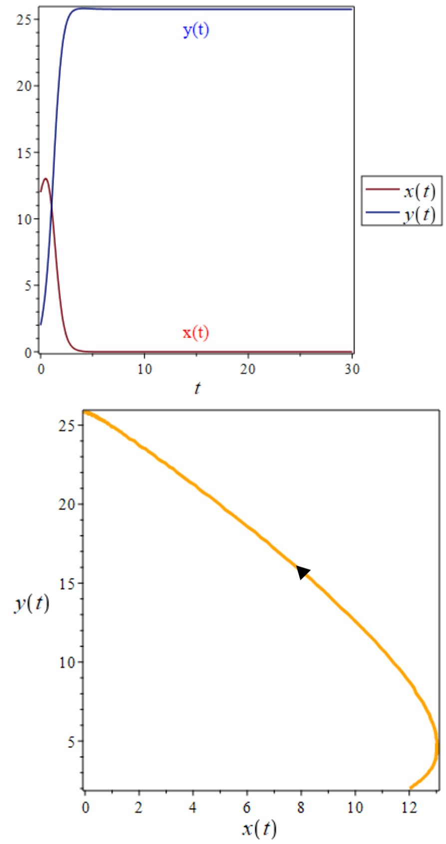

Fig. 6. Numerical solutions of (58) converge to E_2 where $\tau = 0$ with parameter values in (55).

B. The Gompertz growth law

For the special choice of the Gompertz growth function $G(x, y) = 1 - ln\big((x + y)/k\big)$, equation (3) becomes

$$\begin{aligned} \dot{x} &= rx\left(1 - \ln\left(\frac{x+y}{k}\right)\right) - \delta x - \beta xy, \\ \dot{y} &= \beta xy + sy\left(1 - \ln\left(\frac{x+y}{k}\right)\right) - ay(t-\tau). \end{aligned} \quad (58)$$

For equilibrium E_1, we find that $G(0, 0)$ does not define, then E_1 does not exist.

For the equilibrium E_2, we have $G(0, y_2^*) = a/s$ and then $y_2^* = ke^{\frac{s-a}{s}}$. From Theorem 3.2, if $k > (ar - s\delta)/\beta se^{\frac{s-a}{s}}$ and $s/a < 2$, then the equilibrium E_2 is locally asymptotically stable for $\tau \geq 0$.

For equilibrium E_3, we have $G(x_3^*, 0) = \delta/r$ and therefore $x_3^* = ke^{\frac{r-\delta}{r}}$. From Theorem 3.3, we can state the conditions of stability as follows

1) If $0 < k < \frac{ar-s\delta}{\beta re^{\frac{r-\delta}{r}}}$, then the equilibrium E_3 is asymptotically stable for $\tau \in [0, \tau_0)$, and it is unstable for $\tau > \tau_0$.
2) If $k > \frac{ar-s\delta}{\beta re^{\frac{r-\delta}{r}}}$, then the equilibrium E_3 is unstable for all $\tau \geq 0$.

Finally, to support the results, we present some numerical results with parameter values in (55).

Using the conditions in Theorems 3.2 - 3.4, we would expect the followings:

1) we find that $k = 70 > (ar - s\delta)/\beta se^{\frac{s-a}{s}} \approx 10.6013$ and $\frac{s}{a} = \frac{1}{2} < 2$, and therefore the equilibrium E_2 is locally asymptotically stable for all $\tau \geq 0$.

2) If $k = 70 > \frac{ar-s\delta}{\beta re^{\frac{r-\delta}{r}}} \approx 7.5414$, then the equilibrium E_3 is unstable for all $\tau \geq 0$.

3) If x_4^* and y_4^* are complex number, then the equilibrium E_4 does not exist.

Numerical solutions of (58) are shown in Figures 6 and 7 with different values of τ to support the theoretical results in previous sections and the conditions in Theorem 3.2. We can see that the solutions in Figures 6 and 7 converge to the positive equilibrium $E_2 = (0, 26.12)$.

The second set of parameter (56), the numerical solutions of (58) are shown in Figures 8 and 9 with different values of τ to support the theoretical results in previous sections and the conditions in Theorem 3.2. We can see that the solutions in Figures 8 and 9 converge to the positive equilibrium $E_2 = (0, 29.10)$.

C. The Von Bertalanffy growth law

For the special choice of the von Bertalanffy growth function $G(x, y) = \frac{k-(x+y)^{\frac{1}{3}}}{k(x+y)^{\frac{1}{3}}}$, equation (3) becomes

$$\begin{aligned} \dot{x} &= rx\left(\frac{k-(x+y)^{\frac{1}{3}}}{k(x+y)^{\frac{1}{3}}}\right) - \delta x - \beta xy, \\ \dot{y} &= \beta xy + sy\left(\frac{k-(x+y)^{\frac{1}{3}}}{k(x+y)^{\frac{1}{3}}}\right) - ay(t-\tau). \end{aligned} \quad (59)$$

For equilibrium E_1, we find that $G(0, 0)$ does not define, then E_1 does not exist.

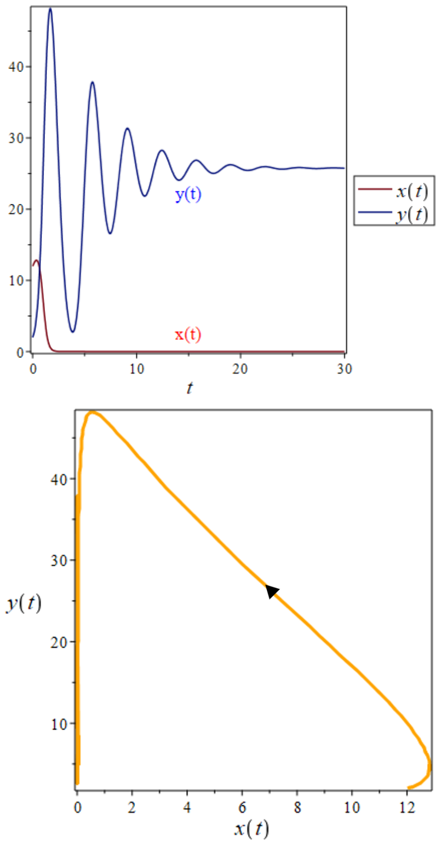

Fig. 7. Numerical solutions of (58) converge to E_2 where $\tau = 0.52$ with parameter values in (55).

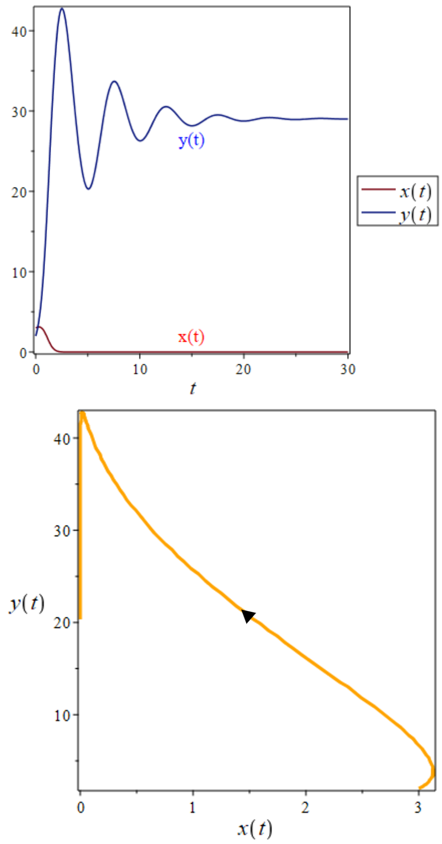

Fig. 9. Numerical solutions of (58) converge to E_2 where $\tau = 1.1$ with parameter values in (56).

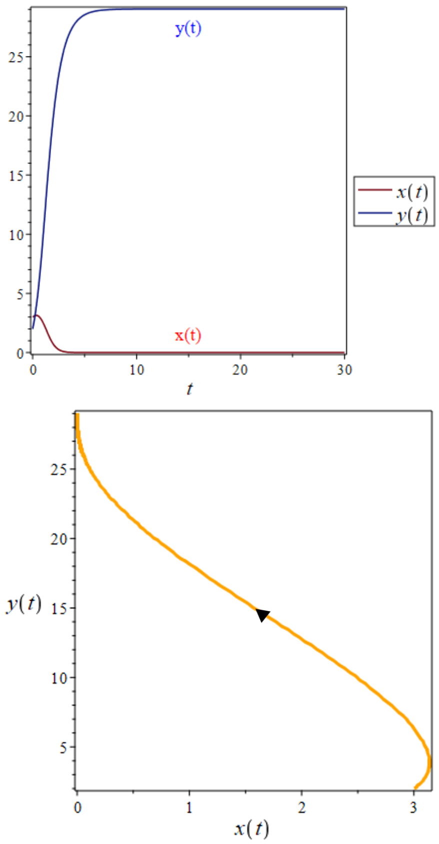

Fig. 8. Numerical solutions of (58) converge to E_2 where $\tau = 0$ with parameter values in (56).

For equilibrium E_2, we have $G(0, y_2^*) = a/s$ and then $y_2^* = (sk/(ak+s))^3$. From Theorem 3.2, if $(sk/(ak+s))^3 > (ra-\delta s)/\beta s$ and $k > s/a$, then the equilibrium E_2 is locally asymptotically stable for all $\tau \geq 0$.

For equilibrium E_3, we have $G(x_3^*, 0) = \delta/r$ and therefore $x_3^* = (rk/(\delta k + r))^3$. From Theorem 3.3, we can state the conditions of stability as follows

1) If $0 < \left(\frac{rk}{\delta k+r}\right)^3 < \frac{ar-s\delta}{\beta r}$, then the equilibrium E_3 is asymptotically stable for $\tau \in [0, \tau_0)$, and it is unstable for $\tau > \tau_0$.
2) If $\left(\frac{rk}{\delta k+r}\right)^3 > \frac{ar-s\delta}{\beta r}$, then the equilibrium E_3 is unstable for all $\tau \geq 0$.

Finally, to support the results, we present some numerical results with parameter values in (55).

Using the conditions in Theorems 3.2 - 3.4 and 4.2, we would expect the followings:

1) If $(sk/(ak+s))^3 \approx 0.1224 < (ra-\delta s)/\beta s = 3.9$, then the equilibrium E_2 is unstable for all $\tau \geq 0$.

2) If $\left(\frac{rk}{\delta k+r}\right)^3 \approx 3,764.0604 > \frac{ar-s\delta}{\beta r} = 19.5$, then the equilibrium E_3 is is unstable for all $\tau \geq 0$.

3) If $C + a = 0.2998301325 > 0$ and $B - aA = 0.9923030155 > 0$, then the equilibrium E_4 is locally asymptotically stable for all $\tau = 0$.

4) The Hopf bifurcation point τ_0 is evaluated by (46) and (48), then we have $\tau_0 \approx 0.2685$.

Numerical solutions of (59) are shown in Figures 10 and 11 with different values of τ to support the theoretical results in previous sections and the conditions in Theorem 4.2. Figure 10 illustrates the numerical solutions of (59) near the bifurcation point $\tau_0 \approx 0.2685$. We can see that the

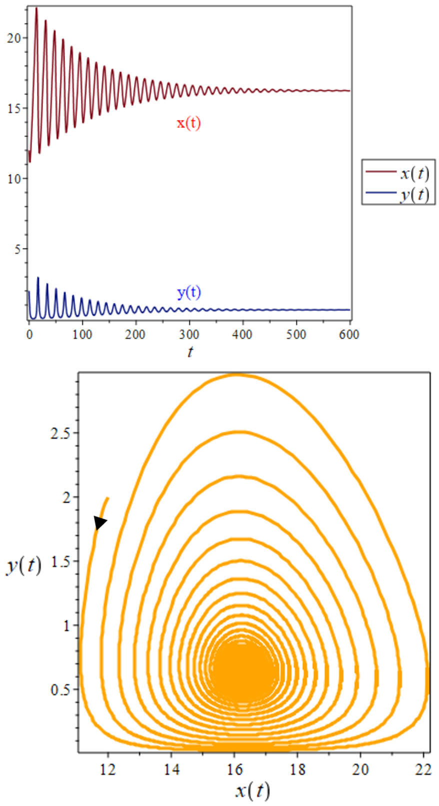

Fig. 10. Numerical solutions of (59) converge to E_4 where $\tau = 0.22 < \tau_0$ with parameter values in (55).

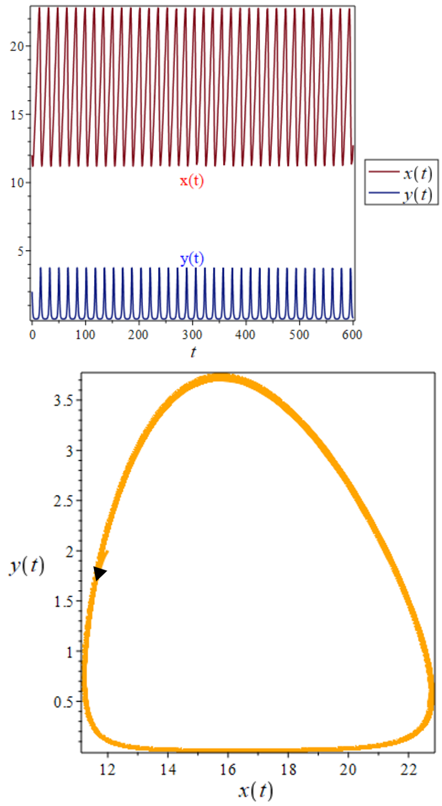

Fig. 11. Numerical solutions of (59) oscillate about E_4 where $\tau = 0.269 > \tau_0$ with parameter values in (55).

solutions in Figure 10 converge to the positive equilibrium $E_4 = (16.31, 0.68)$ when $\tau = 0.22 < \tau_0$. On the other hand, in Figure 11, the solutions are oscillated about the equilibrium $E_4 = (11.96, 1.53)$ when $\tau = 0.269 > \tau_0$.

The second set of parameter (56), the numerical solutions of (59) are shown in Figures 12 and 13 with different values of τ to support the theoretical results in previous sections. We can see that the solutions in Figures 12 and 13 converge to the positive equilibrium $E_4 = (4.25, 0.15)$.

VI. Conclusion

In this paper, the main aim is to analyze dynamics of generalized tumor-virotherapy model (3). In the analytical part, we stated the equilibria of model (3) and the conditions for biological meaning of each equilibrium. We also determined the conditions of stability properties of the model (3) about the equilibria in Theorems 3.1 - 3.5. The theorem for the existence of the Hopf bifurcation was stated in Theorem 4.1, and the behaviors of the stability properties about the Hopf bifurcation points τ_0 were provided in Theorem 4.2.

In applications and numerical examples, we applied the analytical results to the logistic, Gompertz and von Bertalanffy growth functions, which are special cases of model (3). Finally, we presented some numerical simulations with the first set of parameter values in (55). For the logistic and von Bertalanffy functions, the results show the behaviors of the solutions before and after the Hopf bifurcation points τ_0 which both uninfected and infected tumor cells were existed in Figures 1-2 and Figures 10-11. For Gompertz function, the results show that the solutions converge to the equilibrium which represent that all of tumor cells are infected cells

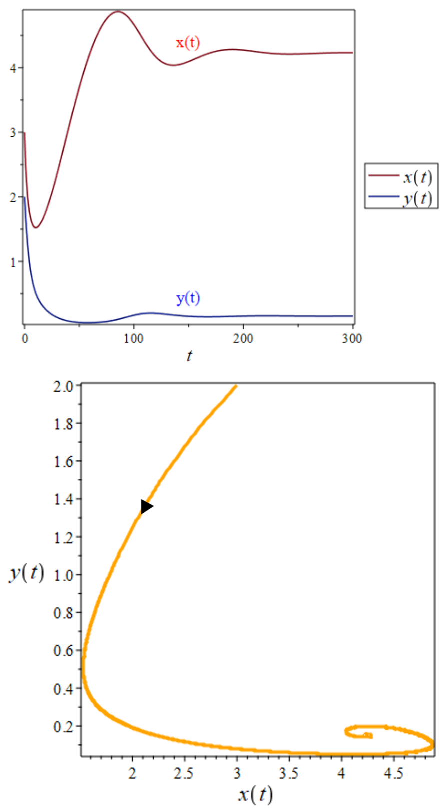

Fig. 12. Numerical solutions of (59) converge to E_4 where $\tau = 0$ with parameter values in (56).

in Figures 6-7. Moreover, the numerical results with the second set of parameter values in (56). For all classes of the growth functions, the results show in Figure 3-4, Figure

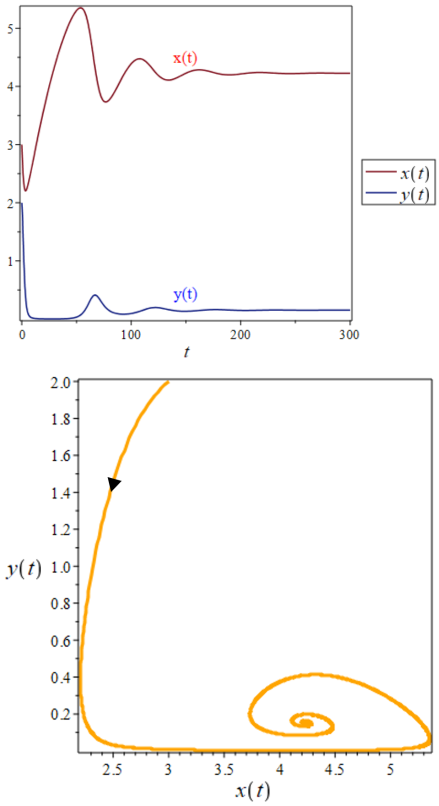

Fig. 13. Numerical solutions of (59) converge to E_4 where $\tau = 0.70$ with parameter values in (56).

8-9 and Figure 12-13 that the solutions always converge to the equilibrium. In addition, we show the numerical results with the third set of parameter values in (57). For the logistic function, the solutions always converge to trivial equilibrium as shown in Figure 5.

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