Riv. Mat. Univ. Parma, Vol. **12** (2021), 221-238

Hajimohammad Mohammadinejad, Saeed Jani
and Omid RabieiMotlagh

Mathematical analysis for oncolytic virotherapy

Abstract. In this paper, we introduce a mathematical model for cancer virotherapy. The model simulates the coeffects of tumor cells and CTLs by considering the time delay of the viral lytic cycle. This delay has been recently seen in some clinical observations when the tumor size changes with a time delay after the virus injection. We investigate the stability of equilibrium points of the model and the corresponding biological interpretation. The model simulates some aspects of the phenomenon which have not been recorded by the former models. For example, a Hopf bifurcation occurs in the delayed model showing an oscillation in the size of the tumor. We indicate natural limitations of the therapy process; for example, the oncolytic virus must be modified such that the time of the delay of the lytic cycle is less than the Hopf bifurcation value.

Keywords. Hopf bifurcation, Stability, Cancer virotherapy.

Mathematics Subject Classification: 37N25, 97M99, 34K20.

1 - Introduction

The growing spread of cancers has always led researchers to look for new treatments for this complex disease. Although clinical and theoretical studies have identified ways to treat or control different cancers, some patients have not yet received promising therapies. Traditional cancer treatments (surgery, chemotherapy, and radiation) treat many cancer patients, but in some cases, these treatments are ineffective or may cause problems for the patient. For example, in brain tumors, the surgeon may remove a part of healthy brain tissue

Received: August 4, 2020; accepted in revised form: June 14, 2021.

that can be very dangerous for the patient. Moreover, during chemotherapy, tumor cells become drug-resistant, making it impossible to obtain complete therapy. Such limitations in cancer treatment have led researchers to look for new ways to treat cancer.

One of the fascinating and relatively new ideas of cancer treatment is virotherapy. The strategy in virotherapy is to use specific viruses to infect the tumor so that the tumor cells die from the infection. After injecting into the tumor, the viruses multiply and infect more tumor cells. These viruses are called oncolytic viruses. There are two kinds of oncolytic viruses: wild oncolytic viruses and gene-modified viruses. Wild oncolytic viruses with natural oncolytic activity in human tumors, like Myxomaviruses, Bovine herpesvirus 4, Reovirus, Newcastle disease virus (NDV), Coxsackievirus, Vesicular stomatitis virus (VSV), and Parvoviruses have shown limited oncolytic efficacy in clinical trials. Gene-modified viruses such as Adenovirus, Herpes simplex, and Vaccinia that are engineered to achieve a selective oncolysis have great potency of oncolysis. [**1**, **2**, **3**, **4**]. For history on oncolytic virotherapy, see [**1**] and [**5**].

The idea of eliminating the tumors by the viruses was introduced at the beginning of the twentieth century. (The first reported cancer remission due to the viral infection was described in 1904 for a woman with myelogenous leukemia after being infected with influenza). For several years, research in this field was limited due to technology and virology limitations [**6**, **7**, **8**, **9**, **10**]. Over the last 50 years, thanks to rapid growth in genetic engineering and virology, this therapeutic method has been studied by researchers, and promising results are obtained. After decades of research, virotherapy has recently reached clinical application and uses in combination with other therapeutic methods. Some studies that confirm the influence of virotherapy in cancer treatment include [**11**, **12**, **13**, **14**, **15**, **16**].

Although clinical and theoretical studies of virotherapy have shown promising results, this therapeutic method has not yet yielded the expected results. Cancer cells, viruses, and the immune system influence the virotherapy, and each can be very complex. So, it is hard to provide a clear picture of the dynamics of virotherapy. Recently, for a better understanding of virotherapy dynamics and to see all the possible outcomes, researchers use mathematical modeling and analysis. The presented models are expressed in terms of ordinary differential equations [**17**, **18**, **19**, **21**, **22**, **43**], partial differential equations [**20**, **23**, **24**] and delayed differential equations [**25**, **26**, **27**, **28**, **29**, **30**, **31**, **32**, **33**, **34**, **44**].

One of the basic models for cancer virotherapy proposed by Wodarz includes the dynamics between the tumor, virus, and virus-specific CTLs. Cytotoxic T Lymphocytes (CTLs) are the immune system elements that can detect the virus on infected cells and kill the infected cells. So, in virotherapy, the tumor

cells are destroyed in two ways: Some of the tumor cells die directly from the infection, and some are identified and removed by the virus-specific CTLs after the infection. Wodarz presented the following model [**35**]:

$$\begin{cases} \dfrac{dx}{dt} = rx(1 - \dfrac{x+y}{K}) - dx - \beta xv \\ \dfrac{dy}{dt} = \beta xy + sy(1 - \dfrac{x+y}{K}) - ay - p_v y z_v \\ \dfrac{dz_v}{dt} = c_v y z_v - b z_v. \end{cases}$$

This model consists of three variables: uninfected tumor cells (x), infected tumor cells (y), and virus-specific CTLs (z_v). The tumor grows in a logistic model at a rate r, and die at a rate d by the immune system. The maximum size or space that the tumor is allowed to occupy is given by its carrying capacity K. The virus spreads to tumor cells at a rate of β. Infected tumor cells are killed by the virus at a rate of a and grow in a logistic fashion at a rate of s. The virus-specific CTL expands in response to the antigen at a rate of c_v and decays at a rate of b. The CTL kills the infected tumor cells at a rate of p_v.

The virus lytic cycle is one of the main factors in virotherapy is ignoring in most of the presented mathematical models. After injecting into the tumor, the virus undergoes a process called the viral lytic cycle. First, the virus must enter the cell through the plasma membrane. After attaching to a receptor on the cell membrane, the virus releases its genetic materials into the cell. These stages are called adsorption and penetration. The third stage is integration that the host cell gene expression is arrested, and viral materials are embedded into the host cell nucleus. The fourth stage is biosynthesis that the virus uses the cell machinery to make large amount of viral components, and at the meantime, destroys the host's DNA. Then, it enters the last two stages, maturation and lysis. When many copies of viral components are made, they are assembled into complete viruses. These stages direct the production of enzymes that break down the host cell membrane. The cell eventually bursts, and new viruses come out. The number of newly formed viruses is called the burst size of the virus which is an important factor in the dynamics of virotherapy [**17**]. During the lytic cycle, each stage is mediated by a diverse group of proteins and needs time to complete [**21**, **37**, **38**, **39**, **40**]. These stages can differ among individual viruses and influence their spread rate and oncolytic potential. So, it is necessary and realistic to incorporate the role of the lytic virus cycle into mathematical models. Several clinical studies have also confirmed the existence of such a delay between the virus injection and the tumor volume change. For example, Oyama et al. [**41**] studied oncolytic virotherapy for human prostate cancer by conditionally replicating herpes simplex virus 1 vector G207. For the

first 2 days after the injection of G207, no significant changes were observed in the diameter of the tumor. Hsieh et al. [**13**] researched on the antitumor effect of Ad5WS2 on subcutaneous and ascites ML-1 tumors and for the first twenty days after the injection, tumor volume did not have any meaningful change.

Using the Wodarz model and considering the role of the virus lytic cycle, we propose the following model:

$$\begin{cases} \dfrac{dx}{dt} = rx(1 - \dfrac{x+y}{K}) - dx - \beta xv \\ \dfrac{dy}{dt} = \beta xy + sy(1 - \dfrac{x+y}{K}) - pyz - ay(t-\tau) \\ \dfrac{dz}{dt} = qyz - ez. \end{cases}$$

When an oncolytic virus infects a cancer cell, it takes some time to complete the virus lytic cycle. Then the new viruses are born, and the cancer cell dies. So, the infected cells die with a delay after the infection. In the above model, the term $ay(t-\tau)$ stands for the time delay caused by the virus lytic cycle. By incorporating the role of the lytic cycle, we will have a more realistic model than the original one.

In the rest of this paper, in section 2, we will analyze the positivity of the solutions, equilibria, and their stability for the original model. In section 3, we will study the positivity of the solutions and investigate the existence of a Hopf bifurcation for the model. Section 4 is devoted to confirming the results by providing numerical simulations and analyzing biological aspects of the mathematical results.

2 - Preliminary results

In this section, we provide some mathematical analyses of the original model, which will be used in the next section for the delayed model. We determine the positivity of the solutions, stability of the equilibria, and the existence of the periodic solutions. First, we change the variable as below:

$$x = K\bar{x}, \quad y = K\bar{y}, \quad z = K\bar{z}, \quad \bar{\beta} = K\beta, \quad \bar{p} = Kp, \quad \bar{q} = Kq.$$

So, after dropping the overbar notation for simplifying, we have the following model:

$$\begin{cases} \dfrac{dx}{dt} = rx(1-x-y) - dx - \beta xy \\ \dfrac{dy}{dt} = \beta xy + sy(1-x-y) - pyz - ay(t-\tau) \\ \dfrac{dz}{dt} = qyz - ez. \end{cases} \tag{2.1}$$

In the absence of delay ($\tau = 0$),

$$\begin{cases} \dfrac{dx}{dt} = rx(1-x-y) - dx - \beta xy \\ \dfrac{dy}{dt} = \beta xy + sy(1-x-y) - pyz - ay \\ \dfrac{dz}{dt} = qyz - ez. \end{cases} \tag{2.2}$$

Define

$$\Omega^+ = \{(x,y,z) | x \geq 0, y \geq 0, z \geq 0, 0 \leq x+y \leq 1\} \subset R^3.$$

The following lemma shows that Ω^+ is a positively invariant domain for the system(2.2). It is also a biologically meaningful range for the variables.

L e m m a 2.1. *Suppose that* $(x(t), y(t), z(t))$ *be a solution of system* (2.2), *and* $x(0) > 0, y(0) > 0, z(0) > 0$. *Then* $x(t) > 0, y(t) > 0$ *and* $z(t) > 0$ *for all* $t \geq 0$. *Moreover if* $0 < x(0) + y(0) < 1$, *then* $0 \leq x(t) + y(t) \leq 1$.

P r o o f. It is clear that the coordinate planes $yz(x = 0)$, $xz(y = 0)$ and $xy(z = 0)$ are invariant sets, so they cannot be reached in a finite time starting outside them, thanks to the Existence and Uniqueness theorem for ODEs. This implies that if $x(0) > 0, y(0) > 0, z(0) > 0$, then the solution $(x(t), y(t), z(t))$ can not intersect the coordinate planes, so for all $t \geq 0$, $x(t) > 0, y(t) > 0$ and $z(t) > 0$.

Furthermore,

$$\begin{aligned} x'(t) + y'(t) &= rx(1-x-y) - dx - \beta xy + \beta xy + sy(1-x-y) - pyz - ay \\ &\leq (rx+sy)(1-(x+y) \leq M(x+y)(1-(x+y)) \end{aligned}$$

So, $x'(t) + y'(t) \leq M(x+y)(1-(x+y))$, where $M = \max\{s, r\}$. Since $0 < x(0) + y(0) < 1$, so by the comparison theorem, $0 \leq x(t) + y(t) \leq 1$ for all $t \geq 0$. □

2.1 - *Equilibria analysis*

The equilibria of the system (2.2) are

$$E_0 = (0,0,0), \quad E_1 = \big(\frac{r-d}{r}, 0, 0\big), \quad E_2 = \big(0, \frac{s-a}{s}, 0\big),$$

$$E_3 = (0, \widehat{y}, \widehat{z}) = \big(0, \frac{e}{q}, \frac{q(s-a)-se}{pq}\big),$$

$$\bar{E} = (\bar{x}, \bar{y}, 0) = \big(\frac{a(r+\beta)-s(d+\beta)}{\beta(r+\beta-s)}, \frac{r(\beta-a)+d(s-\beta)}{\beta(r+\beta-s)}, 0\big)$$

and

$$E^* = (x^*, y^*, z^*) =$$
$$\big(\frac{q(r-d)-e(r+\beta)}{qr}, \frac{e}{q}, \frac{-aqr+dq(s-\beta)+\beta(rq-e(r+\beta-s))}{pqr}\big).$$

One reasonable assumption in (2.2) is $d < r$ because $d \geq r$ means that the immune system can demolish tumor cells, so virotherapy will not be needed. Throughout this paper, we assume that $d < r$. Furthermore, we assume that the infection rate of the tumor is bigger than the rate of growth of infected cells, i. e $\beta > s$.

The equilibrium points are biologically valid if their components are non-negative and the sum of the first and second components is less than one. Since we assumed $d < r$, these conditions satisfy at E_0 and E_1. If $s > a$, then E_2 exists and is biologically valid. When

$$qs > qa + se \quad and \quad pq > q(s-a) + e(p-s),$$

the component of E_3 are positive and biologically meaningful. To have these conditions at $\bar{E}$, it is necessary and sufficient that

$$0 < a - d < \beta, \quad a(r+\beta) > s(d+\beta) \quad and \quad ds + r\beta > ar + d\beta.$$

Finally, if $x^* > 0$ and $y^* > 0$, we have $0 < x^* + y^* = \frac{qr-dq-e\beta}{qr} < 1$. So, the necessary and sufficient conditions to E^* be biologically valid is

$$(2.3) \quad qr > dq + e(\beta + r) \quad and \quad q(ds + \beta r) + \beta es > q(ar + d\beta) + \beta e(r - \beta).$$

Now we determine the stability of the equilibrium points by using the variational matrix of the system(2.2), which is given by

$$\begin{pmatrix} r - 2rx - ry - d - \beta y & -(\beta + r)x & 0 \\ (\beta - s)y & \beta x + s - sx - 2sy - pz - a & -py \\ 0 & qz & qy - e \end{pmatrix}.$$

Stability of E_0. The variational matrix at E_0 is $\begin{pmatrix} r & 0 & 0 \\ b & -e & 0 \\ 0 & 0 & -q \end{pmatrix}$. As $r > 0$, so E_0 is an unstable equilibrium point.

Stability of E_1. Since for E_1 we have $r - 2rx - ry - d - \beta y = -rx$, so the variational matrix at E_1 is

$$\begin{pmatrix} d-r & 0 & 0 \\ 0 & (\beta - s)(\frac{r-d}{r}) + s - a & 0 \\ 0 & 0 & -e \end{pmatrix}.$$

Because of $r > d$, so E_1 is asymptotically stable if $(\beta - s)(\frac{r-d}{r}) + (s - a) < 0$. Otherwise if $(\beta - s)(\frac{r-d}{r}) + (s - a) > 0$, E_1 is a saddle point.

Stability of E_2. When $s > a$, the equilibrium $E_2 = (0, \frac{s-a}{s}, 0)$ exists, and the variational matrix is given by

$$\begin{pmatrix} (r-d) - (\beta + r)(\frac{s-a}{s}) & 0 & 0 \\ (\beta - s)(\frac{s-a}{s}) & a - s & p(\frac{a-s}{s}) \\ 0 & 0 & q(\frac{s-a}{s}) - e \end{pmatrix}.$$

The eigenvalues are $\lambda_1 = a - s$, $\lambda_2 = q(\frac{s-a}{s}) - e$ and $\lambda_3 = (r-d) - (\beta + r)(\frac{s-a}{s})$. Since $\lambda_1 = a - s < 0$, so if $\frac{e}{q} > \frac{s-a}{s}$ and $r - d < (r+\beta)(\frac{s-a}{s})$, E_2 is asymptotically stable. If $\frac{e}{q} < \frac{s-a}{s}$ or $r - d > (r + \beta)(\frac{s-a}{s})$, E_2 is unstable.

Stability of E_3. It is clear that the variational matrix at E_3 is

$$\begin{pmatrix} r - d - (\beta + r)\widehat{y} & 0 & 0 \\ (\beta - s)\widehat{y} & -s\widehat{y} & -p\widehat{y} \\ 0 & q\widehat{z} & 0 \end{pmatrix},$$

with the characteristic polynomial $\widehat{f}(\lambda) = ((r-d) - (\beta+r)\widehat{y} - \lambda)(\lambda^2 + s\widehat{y}\lambda + pq\widehat{y}\widehat{z})$. The roots of $\lambda^2 + s\widehat{y}\lambda + pq\widehat{y}\widehat{z}$ have negative real parts, so the stability of E_3 is determined by the sign of $r - d - (\beta + r)\widehat{y}$. If $r - d < \frac{e(\beta+r)e}{q}$, E_3 is asymptotically stable, and otherwise if $r - d > \frac{e(\beta+r)e}{q}$, E_3 is a saddle equilibrium point.

Stability of $\bar{E}$. The variational matrix at $\bar{E}$ is

$$\begin{pmatrix} -r\bar{x} & -(r + \beta)\bar{x} & 0 \\ (\beta - s)\bar{y} & -s\bar{y} & -p\bar{y} \\ 0 & 0 & q\bar{y} - e \end{pmatrix}.$$

So, the characteristic polynomial is $\Delta(\lambda) = (q\bar{y} - e - \lambda)f(\lambda)$, where $f(\lambda) = \lambda^2 + (r\bar{x} + s\bar{y})\lambda + \beta(\beta - s + r)\bar{x}\bar{y}$. Since $r\bar{x} + s\bar{y} > 0 \quad$ and $\quad \beta(\beta - s + r)\bar{x}\bar{y} > 0$, so, all roots of $f(\lambda)$ have negative real parts and the stability of $\bar{E}$ is determined by the sign of $q\bar{y} - e$. Therefore, if $q\bar{y} - e < 0$, then $\bar{E}$ is asymptotically stable, and otherwise if $q\bar{y} - e > 0$ the equilibrium point $\bar{E}$ is unstable. In the next lemma, we investigate the stability of E^*.

L e m m a 2.2. *If the condition* (2.3) *holds, E^* is asymptotically stable.*

P r o o f. The variational matrix at E^* is

$$\begin{pmatrix} -rx^* & -(r+\beta)x^* & 0 \\ (\beta - s)y^* & -sy^* & -py^* \\ 0 & qz^* & 0 \end{pmatrix},$$

with the characteristic polynomial $f(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$, by

$$a_1 = rx^* + sy^*, \quad a_2 = rsx^*y^* + pqy^*z^* + (\beta + r)(\beta - s)x^*y^*, \quad a_3 = pqrx^*y^*z^*.$$

We know that if all roots of the characteristic polynomial have negative real parts, E^* is asymptotically stable. On the other hand, by the Routh-Hurwitz Criterion [**45**], all roots of $f(\lambda) = 0$ have negative real parts if and only if

$$\mathbf{H_1} = |a_1| > 0, \quad \mathbf{H_2} = \begin{vmatrix} a_1 & a_3 \\ 1 & a_2 \end{vmatrix} > 0, \quad \mathbf{H_3} = \begin{vmatrix} a_1 & a_3 & 0 \\ 1 & a_2 & 0 \\ 0 & a_1 & a_3 \end{vmatrix} = a_3H_2 > 0.$$

Since x^*, y^*, z^* and the parameters are positive, $a_1 > 0$ and $a_3 > 0$. Therefore, all roots of the characteristic equation have negative real parts if and only if $H_2 = a_1a_2 - a_3 > 0$. By a direct calculation (note that $\beta > s$.) we get

$$a_1a_2 - a_3 = \beta r(\beta - s + r)x^{*2} + (\beta - s + r)\beta sx^*y^* + pqsy^*z^* > 0.$$

So, $H_1, H_2, H_3 > 0$, which implies that E^* is asymptotically stable. □

From a biological point of view, the stability of E_0 corresponds to the tumor removal and the treatment success, but E_0 is inherently unstable, so virotherapy does not lead to complete tumor removal. Since the stability of E_1 is equivalent to the existence of uninfected tumor cells, it is undesirable. The existence of E_2 means that all of the tumor cells are infected, but still, tumor cells exist, so its stability is not desirable. The stability of E_3 means that the tumor population is approaching zero, but there are still virus-infected cancer cells, so the stability of this equilibrium point is not desirable. The existence of $\bar{E}$ means that there

are infected and disinfected tumor cells, and its stability leads to treatment failure. The most critical equilibrium point is E^* because the existence of E^* means that tumor cells, infected tumor cells, and CTLs exist, and these conditions are more consistent with the clinical observations. Furthermore, the stability of E^* means that the tumor size remains in a controlled size, so we have a chance to get treatment after the virotherapy, using other methods such as chemotherapy. As we saw in the previous lemma, E^* is asymptotically stable, so we expect the tumor size decrease, but as we will see, if we consider the role of the viral lytic cycle in the model, E^* can become unstable.

One of our main goals in this paper is to show the superiority of the delayed model over the original model. As we saw, the stability of E_0, E_1, E_2, E_3 and $\bar{E}$, depending on the parameter values, can be changed in the original model. Therefore, studying the stability of these equilibrium points in the delayed model will not lead to new results. On the other hand, we saw that E^* is always asymptotically stable, but incorporating the delay in the model leads to change the stability of E^* and achieve different results from the original model. Therefore, in the next section, we only study the stability of E^* in the delayed model.

3 - Stability and Hopf bifurcation in the delayed model

In this section, we analyze the delayed model (2.1) and focus specifically on the stability and Hopf bifurcation in equilibrium point E^*. By the transformation $u_1 = x - x^*, u_2 = y - y^*, u_3 = z - z^*$, the system (2.1) is changed to

$$\frac{dU}{dt} = M_1 U(t) + M_2 U(t-\tau) + f(u_1, u_2, u_3)$$

where $U = (u_1, u_2, u_3)^T$,

$$\mathbf{M_2} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & -a & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad \mathbf{M_1} = \begin{pmatrix} A & B & 0 \\ C & D & E \\ 0 & F & 0 \end{pmatrix},$$

$$\mathbf{f(u_1, u_2, u_3)} = \begin{pmatrix} -(\beta + r)u_1 u_2 - r u_1^2 \\ (\beta - s)u_1 u_2 - s u_2^2 - p u_2 u_3 \\ q u_2 u_3 \end{pmatrix}$$

and

$$A = -rx^*,\ B = -(\beta+r)x^*,\ C = (\beta-s)y^*,\ D = -sy^*+a,\ E = -py^*,\ F = qz^*.$$

The characteristic polynomial corresponding to the linearized system is

$$\Delta(\lambda) = \det(\lambda I - M_1 - M_2 e^{-\lambda\tau}).$$

So, the characteristic equation can be written as

$$\Delta(\lambda) = \lambda^3 + m_1\lambda^2 + m_2\lambda + m_3 + (n_1\lambda^2 + n_2\lambda)e^{-\lambda\tau} = 0, \tag{3.1}$$

where

$$m_1 = -(A+D) \quad m_2 = AD - BC - EF, \quad m_3 = AEF, \quad n_1 = a, \quad n_2 = -Aa.$$

Clearly, $i\omega(\omega > 0)$ is a root of $\Delta(\lambda) = 0$ if and only if

$$-i\omega^3 - m_1\omega^2 + im_2\omega + m_3 - n_1\omega^2\cos\omega\tau + in_1\omega^2\sin\omega\tau + in_2\omega\cos\omega\tau + n_2\omega\sin\omega\tau = 0.$$

Separating the real and imaginary parts, we get

$$\begin{cases} -\omega^3 + m_2\omega + n_1\omega^2\sin\omega\tau + n_2\omega\cos\omega\tau = 0 \\ -m_1\omega^2 + m_3 - n_1\omega^2\cos\omega\tau + n_2\omega\sin\omega\tau = 0. \end{cases}$$

By squaring and adding both equations together, we have

$$\omega^6 + (m_1^2 - 2m_2 - n_1^2)\omega^4 + (m_2^2 - 2m_1m_3 - n_2^2)\omega^2 + m_3^2 = 0. \tag{3.2}$$

Denote $z = \omega^2, P = m_1^2 - 2m_2 - n_1^2, Q = m_2^2 - 2m_1m_3 - n_2^2$ and $R = m_3^2$. So, the equation (3.2) can be written as

$$H(z) = z^3 + Pz^2 + Qz + R = 0. \tag{3.3}$$

Since $R = m_3^2 > 0$ and $\lim_{z\to-\infty} H(z) = -\infty$, so it is obvious that $H(z)$ has at least one negative root. Without loss of generality, we assume that the equation (3.3) has two positive roots, $0 < z_1 < z_0$. So, the equation (3.2) has two positive roots $\omega_0 = \sqrt{z_0}$, and $\omega_1 = \sqrt{z_1}$. For $k = 0, 1$ and $j = 0, 1, 2, 3, ...$, we define

$$\tau_k^j = \frac{1}{\omega_k}\arccos\Big[\frac{(-n_1\omega_k^2)(m_1\omega_k^2 - m_3) + n_2\omega_k(\omega_k^3 - m_2\omega_k)}{(-n_1\omega_k^2)^2 + n_2^2\omega_k^2}\Big] + \frac{2\pi j}{\omega_k}, \tag{3.4}$$

and we take $\tau_0 = \min\left\{\tau_k^j\right\}_{k=0,1}^{j\geq 0}$.

So, $\pm i\omega_k$ is a pair of purely imaginary roots of (3.1) with $\tau = \tau_k^j$. At $\tau = 0$, the equation (3.1) becomes

$$\lambda^3 + m_1\lambda^2 + m_2\lambda + m_3 + (n_1\lambda^2 + n_2\lambda) = 0.$$

We studied the roots of this equation in the previous section, and we saw that when in the system (2.2) $\beta > s$ and $r > d$, all roots have negative real parts and E^* is asymptotically stable. Since $R = m_3^2 > 0$, based on [**42**] we have the following lemma.

Lemma 3.1. *Suppose that in the system* (2.1) $r > d$ *and* $\beta > s$.

(i) *If* $\Delta = P^2 - 3Q < 0$, *then all roots of the Eq.* (3.1) *have negative real parts for all* $\tau \geq 0$.

(ii) *If* $\bar{z} = \frac{-P+\sqrt{\Delta}}{3} > 0$ *and* $H(\bar{z}) < 0$, *then all roots of Eq.* (3.1) *have negative real parts when* $\tau \in [0, \tau_0)$.

Now we investigate Hopf bifurcation of the model (2.1) at E^*. Suppose that $\bar{z} = \frac{-P+\sqrt{\Delta}}{3} > 0$ and $H(\bar{z}) < 0$. As $\bar{z}$ is local minimum of $H(z)$ and $r > 0$, so (3.3) has two positive roots $z_1 < z_0$ where $H'(z_1) < 0$ and $H'(z_0) > 0$.

Let $\omega_0 = \sqrt{z_0}$, $\tau_0 = \min_{j\geq 0}\left\{\tau_0^j\right\}$ (defined in(3.4)), and $\lambda(\tau) = \alpha(\tau) + i\omega(\tau)$ be the root of (3.1) satisfying

$$\alpha(\tau_0) = 0, \quad \omega(\tau_0) = \omega_0. \tag{3.5}$$

To arise Hopf bifurcation we need to

$$\Omega = \operatorname{sign}\left\{\frac{d(Re\lambda)}{d\tau}\right\}_{\tau=\tau_0} = \operatorname{sign}\left\{Re(\frac{d\lambda}{d\tau})^{-1}\right\}_{\tau=\tau_0} > 0.$$

By differentiating both sides of (3.1) with respect to τ, we have

$$\big[(3\lambda^2 + 2m_1\lambda + m_2) + e^{-\lambda\tau}(2n_1\lambda + n_2) - \tau e^{-\lambda\tau}(n_1\lambda^2 + n_2\lambda)\big](\frac{d\lambda}{d\tau}) = \lambda e^{-\lambda\tau}(n_1\lambda^2 + n_2\lambda),$$

which leads to

$$(\frac{d\lambda}{d\tau})^{-1} = \frac{2\lambda^3 + m_1\lambda^2 - m_3}{-\lambda^2(\lambda^3 + m_1\lambda^2 + m_2\lambda + m_3)} + \frac{n_1\lambda^2}{\lambda^2(n_1\lambda^2 + n_2\lambda)} - \frac{\tau}{\lambda}.$$

So,

$$\begin{aligned}\Omega &= \operatorname{sign}\left\{Re(\frac{d\lambda}{d\tau})^{-1}\right\}_{\tau=\tau_0} \\ &= \frac{1}{\omega_0^2}\operatorname{sign}\Big[Re\left\{\frac{(m_3 + m_1\omega_0^2) + i(2\omega_0^3)}{(m_1\omega_0^2 - m_3) + i(\omega_0^3 - m_2\omega_0)} + \frac{n_1\omega_0^2}{-n_1\omega_0^2 + in_2\omega_0}\right\}\Big] \\ &= \frac{1}{\omega_0^2}\operatorname{sign}\Big[\frac{2\omega_0^6 + (m_1^2 - 2m_2 - n_1^2)\omega_0^4 - m_3^2}{n_1^2\omega_0^4 + n_2^2\omega_0^2}\Big].\end{aligned}$$

We know that

$$2\omega_0^6 + (m_1^2 - 2m_2 - n_1^2)\omega_0^4 - m_3^2 = 2z_0^3 + Pz_0^2 - R > 0.$$

Because if $2z_0^3 + Pz_0^2 - R \leq 0$, then

$$\begin{aligned} H(z_0) &= z_0^3 + Pz_0^2 + Qz_0 + R \geq z_0^3 + Pz_0^2 + Qz_0 + 2z_0^3 + Pz_0^2 \\ &= 3z_0^3 + 2Pz_0^2 + Qz_0 = z_0 H'(z_0). \end{aligned}$$

This is contradiction since $H(z_0) = 0$, but $z_0 > 0, H'(z_0) > 0$. So,

$$\Omega = \operatorname{sign}\left\{ Re(\frac{d\lambda}{d\tau})^{-1} \right\}_{\tau=\tau_0} > 0.$$

Therefore, the transversality condition holds successfully, and the system undergoes Hopf bifurcation at E^* for bifurcation value $\tau = \tau_0$.

We state this argument in the next theorem.

Theorem 3.2. *Suppose that $r > d$ and $\beta > s$.*

(I) *If $\Delta = p^2 - 3q < 0$, then E^* is asymptotically stable for all $\tau \geq 0$.*

(II) *If $\bar{z} = \frac{-p+\sqrt{\Delta}}{3} > 0$ and $H(\bar{z}) < 0$, then there exist a value τ_0, such that all roots of the Eq. (3.1) have negative real parts for $\tau \in [0, \tau_0)$. When $\tau = \tau_0$, the system (2.1) undergoes Hopf bifurcation at E^*.*

4 - Numerical simulation and conclusion

In this section, to validate the mathematical analysis, we present a numerical example for parameters, and we determine the stability of the equilibrium point E^* in the system (2.1) and (2.2). Based on the lemma (2.2), when $r > d$ and $\beta > s$, E^* is asymptotically stable equilibrium point of system (2.2). We take a set of parameter values as below:

$$(4.1) \quad r = 2, \quad d = 0.5, \quad \beta = 1.5, \quad s = 1, \quad p = 1, \quad a = 0.1, \quad q = 1.5, \quad e = 0.1.$$

For these parameter values, the equilibrium point is $E^* \approx (0.633, 0.066, 1.15)$. Figure 1 shows the phase space of the system (2.2), which confirmes the stability of E^*.

On the other hand, with these parameter values, the delayed model (2.1) is transformed to:

$$(4.2) \quad \begin{cases} \dfrac{dx}{dt} = 2x(1 - x - y) - 0.5x - 1.5xy \\ \dfrac{dy}{dt} = 1.5xy + y(1 - x - y) - yz - 0.1y(t - \tau) \\ \dfrac{dz}{dt} = 1.5yz - 0.1z \end{cases}$$

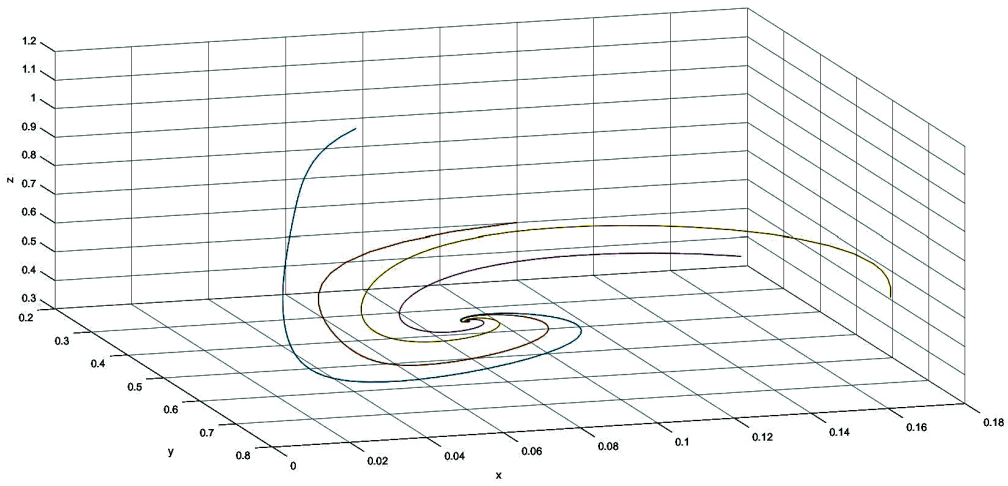

Fig. 1. E^* is asymptotically stable equilibrium point of system (2.2).

By a direct calculation, we get

$$P = 1.21778, \quad Q = -0.353844, \quad R = 0.0212188, \quad \bar{z} = \frac{-P + \sqrt{\Delta}}{3} = 0.125792$$

and

$$H(z) = z^3 + 1.21778z - 0.353844z + 0.0212188.$$

$H(z) = 0$ Has two positive roots $z_1 = 0.0896911$ and $z_0 = 0.161094$. So, $\omega_0 = \sqrt{z_0} = 0.401365$ and $\tau_0 \approx 4.40712$. For $\tau < 4.40712$, E^* is asymptotically stable, in $\tau = 4.40712$ system undergoes Hopf bifurcation and for $\tau > 4.40712$, E^* becomes unstable and system has a periodic solution. We simulate these changes in Figure 2. We have taken $(x_0, y_0, z_0) = (0.652, 0.066, 1.149)$. For $\tau = 1.40 < 4.40712$, E^* is asymptotically stable (Figure 2, A1 and B1). For $\tau = 4.40712$ system undergoes Hopf bifurcation (Figure 2, A2 and B2). Since it is not possible to obtain the periodic solution of the system, so Figure 2 (A2 and B2), shows a solution close to the periodic solution. When $\tau = 8.40 > 4.40712$, E^* becomes unstable, and the system has a stable periodic solution that attracts solutions around (Figure 2, A3 and B3). We have used dde23 by MATLAB, version R2017a.

As we saw in the mathematical analysis of the original model, E^* is always stable, which means that if we follow the treatment process based on the model

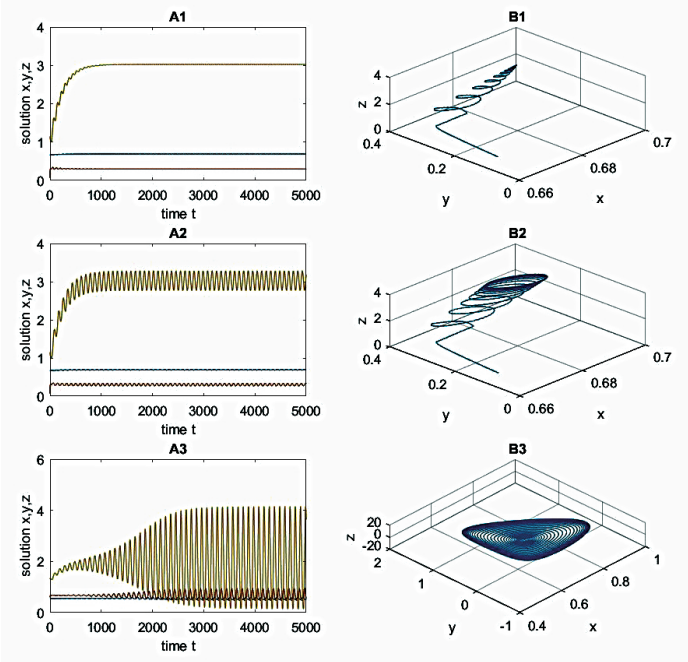

Fig. 2. Hopf bifurcation at E^*. (In the left panels , the orange, blue and red curves are z, x and y respectively).

(2.2), we hope to have a comparative treatment, but this can be misleading. By considering the role of the lytic cycle and simulating a delay in the model, we concluded that Hopf bifurcation could occur, and contrary to our expectations, E^* can become unstable. The presence of the Hopf cycle is not desirable, as it means oscillation in the size of the tumor. Being aware of the possibility of Hopf bifurcation leads to paying more attention to the patient's condition. As a clinical application, the oncolytic virus can genetically be modified in such a way that the time of the lytic cycle is not close to the bifurcation value to maintain the stability of E^*.

References

[**1**] D. Cervantes-García, R. Ortiz-López, N. Mayek-Pérez and A. Rojas-Martínez, *Oncolytic virotherapy*, Ann. Hepatol. **7** (2008), 34–45.

[**2**] D. H. Kirn and F. McCormick, *Replicating viruses as selective cancer therapeutics*, Mol. Med. Today **2** (1996), 519–527.

[**3**] M. S. Roberts, R. M. Lorence, W. S. Groene and M. K. Bamat, *Naturally oncolytic viruses*, Curr. Opin. Mol. Ther. **8** (2006), 314–321.

[**4**] J. M. Kaplan, *Adenovirus-based cancer gene therapy*, Curr. Gene Ther. **5** (2005), 595–605.

[**5**] E. Kelly and S. J. Russell, *History of oncolytic viruses: genesis and genetic engineering*, Mol. Ther. **15** (2007), 651–659.

[**6**] R. J. Huebner, W. P. Rowe, W. E. Schatten, R. R. Smith and L. B. Thomas, *Studies on the use of viruses in the treatment of carcinoma of the cervix*, Cancer **9** (1956), 1211–1218.

[**7**] C. M. Kunin, *Cellular susceptibility to enteroviruses*, Bacteriol. Rev. **28** (1964), 382–390.

[**8**] A. E. Moore, *The destructive effect of the virus of Russian far east encephalitis on the transplantable mouse sarcoma* 180, Cancer **2** (1949), 525–534.

[**9**] L. Pelner, G. A. Fowler and H. C. Nauts, *Effects of concurrent infections and their toxins on the course of leukemia*, Acta. Med. Scand. Suppl. **338** (1958), 1–47.

[**10**] A. R. Pond and E. E. Manuelidis, *Oncolytic effect of poliomyelitis virus on human epidermoid carcinoma (Hela tumor) heterologously transplanted to Guinea pigs*, Am. J. Pathol. **45** (1964), 233–249.

[**11**] S. Friberg and S. Mattson, *On the growth rates of human malignant tumors: implications for medical decision making*, J. Surg. Oncol. **65** (1997), 284–297.

[**12**] A.-M. Maatta, T. Liimatainen, T. Wahlfors, T. Wirth, M. Vaha-Koskela, L. Jansson, P. Valonen, K. Hakkinen, O. Rautsi, R. Pellinen, K. Makinen, J. Hakumaki, A. Hinkkanen and J. Wahlfors, *Evaluation of cancer virotherapy with attenuated replicative Semliki forest virus in different rodent tumor models*, Int. J. Cancer. **121** (2007), 863–870.

[**13**] J.-L. Hsieh, C.-H. Lee, M.-L. Teo, Y.-J. Lin, Y.-S. Huang, C.-L. Wu and A.-L. Shiau, *Transthyretin-driven oncolytic adenovirus suppresses tumor growth in orthotopic and ascites models of hepatocellular carcinoma*, Cancer Sci. **100** (2009), 537–545.

[**14**] H. Fukuhara, Y. Homma and T. Todo, *Oncolytic virus therapy for prostate cancer*, Int. J. Urol. **17** (2010), 20–30.

[**15**] S. F. Bonab and N. Khansari, *Virotherapy with Newcastle Disease Virus for Cancer Treatment and its Efficacy in Clinical Trials*, MOJ Immunol. **5** (2017), 00176, DOI: 10.15406/moji.2017.05.00176

[**16**] B. Xu, W. Zheng, D. Jin, D. Wang, X. Liu and X. Qin, *Treatment of pancreatic cancer using an oncolytic virus harboring the lipocalin-2 gene*, Cancer **118** (2012), 5217–5226.

[**17**] J. P. Tian, *The replicability of oncolytic virus: defining conditions in tumor virotherapy*, Math. Biosci. Eng. **8** (2011), 841–860.

[**18**] N. L. Komarova and D. Wodarz, *ODE models for oncolytic virus dynamics*, J. Theor. Biol. **263** (2010), 530–543.

[**19**] D. Wodarz and N. Komarova, *Towards predictive computational models of oncolytic virus therapy: basis for experimental validation and model selection*, PloS ONE **4** (2009), e4271.

[**20**] L. M. Wein, J. T. Wu and D. H. Kirn, *Validation and analysis of a mathematical model of a replication-competent oncolytic virus for cancer treatment: implications for virus design and delivery*, Cancer Res. **63** (2003), 1317–1324.

[**21**] J. P. Tian, Y. Kuang and H. Yang, *Intracellular viral life-cycle induced rich dynamics in tumor virotherapy*, Semantic Scholar, 2012, ID: 15696950.

[**22**] B. S. Choudhury and B. Nasipuri, *Efficient virotherapy of cancer in the presence of immune response*, Int. J. Dynam. Control **2** (2014), 314–325.

[**23**] J. T. Wu, H. M. Byrne, D. H. Kirn and L. M. Wein, *Modeling and analysis of a virus that replicates selectively in tumor cells*, Bull. Math. Biol. **63** (2001), 731–768.

[**24**] A. Friedman, J. P. Tian, G. Fulci, E. A Chiocca and J. Wang, *Glioma virotherapy: effects of innate immune suppression and increased viral replication capacity*, Cancer Res. **66** (2006), 2314–2319.

[**25**] A. Ashyani, O. Rabieimotlagh and H. M. Mohammadinejad, *A mathematical approach to effects of CTLs on cancer virotherapy in the second injection of virus*, J. Theor. Biol. **453** (2018), 78–87.

[**26**] Y. Guo, B. Niu and J. P. Tian, *Backward Hopf bifurcation in a mathematical model for oncolytic virotherapy with the infection delay and innate immune effects*, J. Biol. Dyn. **13** (2019), 733–748.

[**27**] S. Khajanchi and J. J. Nieto, *Mathematical modeling of tumor-immune competitive system, considering the role of time delay*, Appl. Math. Comput. **340** (2019), 180–205.

[**28**] H. M. Byrne, *The effect of time delays on the dynamics of avascular tumor growth*, Math. Biosci. **144** (1997), 83–117.

[**29**] M. Villasana and A. Radunskaya, *A delay differential equation model for tumor growth*, J. Math. Biol. **47** (2003), 270–294.

[**30**] D. Ghosh, S. Khajanchi, S. Mangiarotti, F. Denis, S. K. Dana and C. Letellier, *How tumor growth can be influenced by delayed interactions between cancer cells and the microenvironment?*, BioSystems **158** (2017), 17–30.

[**31**] N. Burić and D. Todorović, *Dynamics of delay-differential equations modelling immunology of tumor growth*, Chaos Solitons Fractals **13** (2002), 645–655.

[**32**] P. Bi, S. Ruan and X. Zhang, *Periodic and chaotic oscillations in a tumor and immune system interaction model with three delays*, Chaos **24** (2014), 023101, 16 pp.

[**33**] M. Galach, *Dynamics of the tumor-immune system competition-the effect of time delay*, Int. J. Appl. Math. Comput. Sci. **13** (2003), 395–406.

[**34**] A. D'ONOFRIO, F. GATTI, P. CERRAI and L. FRESCHI, *Delay-induced oscillatory dynamics of tumour-immune system interaction*, Math. Comput. Modelling **51** (2010), 572–591.

[**35**] D. WODARZ, *Viruses as antitumor weapons: defining conditions for tumor remission*, Cancer Res. **61** (2001), 3501–3507.

[**36**] D. WODARZ, *Computational approaches to study oncolytic virus therapy: insights and challenges*, Gene Ther. Mol. Biol. **8** (2004), 137–146.

[**37**] R. A. LAMB and G. D. PARKS, *Paramyxoviridae: the viruses and their replication*, in "Fields Virology", Vol. 1, B. N. Fields, D. M. Knipe and P. M. Howley, eds., Wolters Kluwer Health-Lippincott Williams and Wilkins, Philadelphia, PA, 2007, 1449–1496.

[**38**] M. MADIGAN and J. MARTINKO, eds., *Brock Biology of Microorganisms*, 11th ed., Prentice Hall, Upper Saddle River, 2006.

[**39**] P. PLATTET, L. ALVES, M. HERREN and H. C. AGUILAR, *Measles virus fusion protein: Structure, function and inhibition*, Viruses **8** (2016), 112.

[**40**] A. E. SMITH and A. HELENIUS, *How viruses enter animal cells*, Science **304** (2004), 237–242.

[**41**] M. OYAMA, T. OHIGASHI, M. HOSHI, M. MURAI, K. UYEMURA and T. YAZAKI, *Oncolytic viral therapy for human prostate cancer by conditionally replicating herpes simplex virus* 1 *vector G*207, Jpn. J. Cancer Res. **91** (2000), 1339–1344.

[**42**] S. RUAN and J. WEI, *On the zeros of third degree exponential polynomial with applications to a delayed model for the control of testosterone secretion*, IMA J. Math. Appl. Med. Biol. **18** (2001), 41–52.

[**43**] A. S. NOVOZHILOV, F. S. BEREZOVSKAYA, E. V. KOONIN and G. P. KAREV, *Mathematical modeling of tumor therapy with oncolytic viruses: regimes with complete tumor elimination within the framework of deterministic models*, Biol. Direct. **1** (2006), 1–6.

[**44**] A. D'ONOFRIO, *Metamodeling tumour-immune system interaction, tumour evasion and immunotherapy*, Math. Comput. Modelling 47 (2008), 614–637.

[**45**] B. A. FUCHS and V. I. LEVIN, *Functions of a complex variable and some of their applications*, Vol. II, Pergamon Press, London, 1961.

Hajimohammad Mohammadinejad
University of Birjand
Birjand, 0098, Iran
e-mail: hjmohammadin@gmail.com
hjmohammadin@birjand.ac.ir (Corresponding author)

Saeed Jani
University of Birjand
Birjand, 0098, Iran
e-mail: saeed.jani66@gmail.com

Omid RabieiMotlagh
University of Birjand
Birjand, 0098, Iran
e-mail: orabieimotlagh@birjand.ac.ir