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DYNAMICS OF A MATHEMATICAL MODEL FOR CANCER THERAPY WITH ONCOLYTIC VIRUSES

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Abstract. Actually, cancer is considered one of the leading causes of death in the world. Various therapeutic strategies have been developed to combat this dangerous disease. This article investigates a promising therapeutic strategy by proposing a mathematical model that describes the dynamics of cancer treatment with oncolytic viruses. The proposed model integrates the time needed for infected tumor cells to produce new virions after viral entry, the probability of surviving during the latent period, and the saturation effect. We first prove the well-posedness of model and the existence of three equilibria that represent the desired outcome of therapy, the complete failure of therapy and the partial success of therapy. Furthermore, the stability analysis of equilibria and the existence of Hopf bifurcation are rigourously investigated.

Keywords: cancer therapy; oncolytic virus; time delay; stability; Hopf bifurcation.

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1. Introduction

Cancer is an abnormal growth of cells caused by multiple changes in gene expression leading to dysregulated balance of cell proliferation and cell death and ultimately evolving into a

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population of cells that can invade tissues and metastasize to distant sites, causing significant morbidity and, if untreated, death of the host [1]. From the World Health Organization (WHO) [2], it is a leading cause of death worldwide, accounting for an estimated 9.6 million deaths in 2018. Further, one in 5 men and one in 6 women worldwide develop cancer during their lifetime, and one in 8 men and one in 11 women die from the disease, according to the latest report from the International Agency for Research on Cancer (IARC) [3]. Worldwide, lung cancer remains the leading cause of cancer incidence and mortality, with 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018 [4].

Recently, a new therapeutic strategy has been proposed to fight against cancer. This strategy is based on oncolytic viruses that are usually modified from existing viruses in order to infect and kill cancer cells without causing damage to normal tissue. Therefore, many mathematical models have been proposed in order to understand the dynamics of tumor cells during this promising therapeutic strategy called oncolytic virotherapy. Based on the works [5, 6, 7, 8], Tian [9] proposed a basic model with burst size formulated by three ordinary differential equations (ODEs) in order to describe the interaction between tumor cells and oncolytic viruses. In 2013, Wang et al. [10], introduced a time discrete delay into [9] for to model the viral lytic cycle, which is a significant process in oncolytic virotherapy.

It is very important to note that all the models presented in [5, 6, 7, 9, 10] assumed that the infection process is bilinear and it follows the principle of mass action. However, as a nonlinear relationship between parasite dose and infection rate has been frequently observed in experiments in [11, 12]. Furthermore, the recent delayed model introduced in [10] does not consider the survival probability of infected cells during the latent period. Motivated by these biological reasons, in this paper, we will investigate the combined effects of saturation incidence, the time delay and the probability of surviving during the time delay interval on cancer-virus dynamics. To this end, we propose the following model:

$$\left\{\begin{array}{l} \frac{dx(t)}{dt} = rx(t)\big(1-\frac{x(t)+y(t)}{K}\big) - \frac{\beta x(t)v(t)}{1+\alpha v(t)}, \\ \frac{dy(t)}{dt} = \frac{\beta x(t-\tau)v(t-\tau)e^{-m\tau}}{1+\alpha v(t-\tau)} - \delta y(t), \\ \frac{dv(t)}{dt} = N\delta y(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)} - \mu v(t), \end{array}\right. \tag{1}$$

where $x(t)$, $y(t)$ and $v(t)$ are the concentrations of uninfected tumor cells, infected tumor cells and free virus particles at time t, respectively. The tumor follows logistic growth with r is the per capita tumor growth rate and K is the maximal tumor size. Uninfected tumor cells are infected by virus at a rate $\frac{\beta xv}{1+\alpha v}$, where β is a positive constant rate describing the infection process and α is a nonnegative constant that measures the saturation effect. The parameters δ and μ are, respectively, the death rates of infected tumor cells and free virus. The number N is the burst size of oncolytic viruses which represents the number of new viruses coming out from a lysis of an infected tumor cell. Finally, the delay τ denotes the time needed for infected tumor cells to produce new virus particles after viral entry and the factor $e^{-m\tau}$ accounts for the probability of surviving from time $t-\tau$ to time t, where m is the death rate for infected but not yet virus-producing cells.

The rest of this article is organized in the following manner. In section 2, we discuss the well-posedness of the model and we examine the conditions for the existence of equilibria. Section 3 deals with stability analysis and Hopf bifurcation. Lastly, section 4 is devoted to the discussion and conclusions.

2. Well-posedness and equilibria

For model (1) to be mathematically and biologically well-posed, it is necessary to prove the existence, nonnegativity and boundedness of solutions.

Let $C = C([-\tau,0],\mathbf{R}^3)$ be the Banach space of continuous functions mapping the interval $[-\tau,0]$ into $\mathbf{R}^3$ equipped with the sup-norm $\|\varphi\| = \sup_{-\tau\leq\theta\leq 0} |\varphi(\theta)|$ for $\varphi \in C$. It follows from the fundamental theory of functional differential equations [13] that there exists a unique solution $(x(t),y(t),v(t))$ of (1) with initial conditions $(x_0,y_0,v_0) \in C$. For virological reasons, we assume that these initial conditions satisfy:

$$x_0(\theta) \geq 0, \quad y_0(\theta) \geq 0, \quad v_0(\theta) \geq 0, \quad \theta \in [-\tau,0]. \tag{2}$$

Theorem 2.1. *Each solution of model (1) satisfying (2), remains non-negative and bounded for all $t \geq 0$.*

Proof. From the first equation of (1), we get

$$x(t) = x(0)e^{\int_0^t r\left(1-\frac{x(s)+y(s)}{K}\right)-\frac{\beta v(s)}{1+\alpha v(s)}ds},$$

which implies that that $x(t) \geq 0$ for all $t \geq 0$. From the second and third equations of (1), we obtain

$$\begin{aligned} y(t) &= y(0)e^{-\delta t} + e^{-m\tau-\delta t}\int_0^t \frac{\beta x(s-\tau)v(s-\tau)}{1+\alpha v(s-\tau)}e^{\delta s}ds, \\ v(t) &= [v(0)e^{-\int_0^t \frac{\beta x(s)}{1+\alpha v(s)}ds} + N\delta\int_0^t y(u)e^{\mu u-\int_u^t \frac{\beta x(s)}{1+\alpha v(s)}ds}du]e^{-\mu t}. \end{aligned}$$

It is not hard to show that $y(t) \geq 0$ and $v(t) \geq 0$ for $t \in [0,\tau]$. By repeating this procedure on the interval $[n\tau,(n+1)\tau]$ for all $n \in \mathbf{N}$, we obtain $y(t) \geq 0$ and $v(t) \geq 0$ for all $t \geq 0$. This proves the nonnegativity of solutions.

Now, we show the boundedness of the solutions. By the first equation of (1), we have $\frac{dx(t)}{dt} \leq rx(t)\left(1-\frac{x(t)}{K}\right)$ which implies by using comparison Principle that

$$\limsup_{t\to+\infty} x(t) \leq K.$$

Hence, $x(t)$ is bounded. Let $T(t) = x(t-\tau)e^{-m\tau} + y(t)$. Then

$$\begin{aligned} \frac{dT(t)}{dt} &= rx(t-\tau)\big(1-\frac{x(t-\tau)+y(t-\tau)}{K}\big)e^{-m\tau} - \delta y(t) \\ &\leq rK\big(1-\frac{x(t-\tau)}{K}\big)e^{-m\tau} - \delta y(t) \\ &\leq rKe^{-m\tau} - \rho T(t), \end{aligned}$$

where $\rho = \min\{r,\delta\}$. Then

$$\limsup_{t\to+\infty} T(t) \leq \frac{rKe^{-m\tau}}{\rho}.$$

Thus, $y(t)$ is bounded.

By the last equation of (1) and the boundedness of $y(t)$, we deduce that

$$\limsup_{t\to+\infty} v(t) \leq \frac{rKN\delta e^{-m\tau}}{\mu\rho},$$

which implies that $v(t)$ is bounded. This completes the proof.

Next, we study the existence of equilibria of model (1). Obviously, model (1) has two equilibria $E_0(0,0,0)$ and $E_1(K,0,0)$. Biologically, E_0 denotes the free equilibrium without cancer that

represents the desired outcome of therapy. However, E_1 represents the free equilibrium with cancer, it also called the failure therapy equilibrium. Hence, the basic reproduction number of (1) is given by

$$R_0 = \frac{NK\beta}{\beta K+\mu} e^{-m\tau}. \tag{3}$$

When $R_0 > 1$, model (1) has a third equilibrium $E^*(x^*, y^*, v^*)$, where

$$\begin{aligned} x^* &= \tfrac{\mu r+K\delta(N-e^{m\tau})(r\alpha-\beta)+\sqrt{\Delta}}{2r(N-e^{m\tau})(\beta e^{-m\tau}+\alpha\delta)}, \\ y^* &= \tfrac{rx^*(K-x^*)}{rx^*+K\delta e^{m\tau}}, \\ v^* &= \tfrac{\delta(N-e^{m\tau})}{\mu} y^*, \end{aligned} \tag{4}$$

with $\Delta = [K\delta(N-e^{m\tau})(\beta-r\alpha)-\mu r]^2 + 4\mu\delta Kre^{m\tau}(N-e^{m\tau})(\beta e^{-m\tau}+\delta\alpha)$.

Finally, we summarize the above discussions in the following result.

Theorem 2.2. *Let R_0 defined by (3).*

(i) If $R_0 \leq 1$, then model (1) has two equilibria $E_0(0,0,0)$ and $E_1(K,0,0)$.

(ii) If $R_0 > 1$, in addition to E_0 and E_1, model (1) has a unique positive equilibrium $E^*(x^*, y^*, v^*)$ that is defined by (4) and it represents the therapy partial success equilibrium.

3. Stability analysis and Hopf bifurcation

In this section, we investigate the local stability of the three equilibria. Let $E(x,y,v)$ be an arbitrary equilibrium of model (1). Then the characteristic equation at E is given by

$$\begin{vmatrix} r(1-\frac{2x+y}{K})-\frac{\beta v}{1+\alpha v}-\lambda & -\frac{rx}{K} & -\frac{\beta x}{(1+\alpha v)^2} \\ \frac{\beta v}{1+\alpha v}e^{-(m+\lambda)\tau} & -\delta-\lambda & \frac{\beta x}{(1+\alpha v)^2}e^{-(m+\lambda)\tau} \\ -\frac{\beta v}{1+\alpha v} & N\delta & -\frac{\beta x}{(1+\alpha v)^2}-\mu-\lambda \end{vmatrix} = 0. \tag{5}$$

Theorem 3.1. *The equilibrium $E_0(0,0,0)$ is always unstable.*

Proof. At $E_0(0,0,0)$, (5) reduces to

$$(r-\lambda)(\delta+\lambda)(\mu+\lambda) = 0,$$

where the roots are: $\lambda_1 = r$, $\lambda_2 = -\delta$ and $\lambda_2 = -\mu$. Since $\lambda_1 > 0$, it implies that E_0 is unstable.

Theorem 3.2. *The failure therapy equilibrium E_1 is locally asymptotically stable for any time delay $\tau \geq 0$ if $R_0 < 1$, and becomes unstable if $R_0 > 1$.*

Proof. At E_1, (5) reduces to

$$(r+\lambda)[\lambda^2 + (\beta K + \mu + \delta)\lambda + \delta(\beta K + \mu)(1 - R_0 e^{-\lambda\tau})] = 0. \tag{6}$$

Clearly, $\lambda = -r$ is a root of this equation. The remaining roots are given by the solutions of the following transcendental equation

$$\lambda^2 + (\beta K + \mu + \delta)\lambda + \delta(\beta K + \mu)(1 - R_0 e^{-\lambda\tau}) = 0. \tag{7}$$

For $\tau = 0$, we have $\beta K + \mu + \delta > 0$ and $\delta(\beta K + \mu)(1 - R_0) > 0$ if $R_0 < 1$. This implies that when $R_0 < 1$ all the roots of (6) have negative real parts for $\tau = 0$. Next, let $i\omega$ $(\omega > 0)$ be a root of (6). Then

$$\begin{cases} -\omega^2 + \delta(\beta K + \mu) = \delta(\beta K + \mu) R_0 \cos(\omega\tau), \\ (\beta K + \mu + \delta)\omega = -\delta(\beta K + \mu) R_0 \sin(\omega\tau), \end{cases} \tag{8}$$

which leads to

$$\omega^4 + [\delta^2 + (\beta K + \mu)^2]\omega^2 + \delta^2(\beta K + \mu)^2(1 - R_0^2) = 0. \tag{9}$$

Let $z = \omega^2$. Then the previous equation becomes

$$z^2 + [\delta^2 + (\beta K + \mu)^2]z + \delta^2(\beta K + \mu)^2(1 - R_0^2) = 0, \tag{10}$$

which has no positive solution when $R_0 < 1$. Thus, E_1 is locally asymptotically stable for $R_0 < 1$.

When $R_0 > 1$, we consider the following function

$$f(\lambda) = \lambda^2 + (\beta K + \mu + \delta)\lambda + \delta(\beta K + \mu)(1 - R_0 e^{-\lambda\tau}).$$

We have $f(0) = \delta(\beta K + \mu)(1 - R_0) < 0$ and $\lim_{\lambda \to +\infty} f(\lambda) = +\infty$. This shows that the equation $f(\lambda) = 0$ has at least one positive root. Consequently, the failure therapy equilibrium E_1 is unstable whenever $R_0 > 1$.

For the global asymptotic stability of E_1, we have the following result.

Theorem 3.3. *If $R_0 \leq 1$, then the failure therapy equilibrium E_1 is globally asymptotically stable for all $\tau \geq 0$.*

Proof. Let us define the following Lyapunov functional:

$$L(t) = e^{m\tau}y(t) + \frac{e^{m\tau}}{N}v(t) + \int_{t-\tau}^{t} \frac{\beta x(s)v(s)}{1+\alpha v(s)}ds.$$

Differentiating L with respect to t along the solutions of (1) one gets

$$\frac{dL}{dt}|_{(1)} = (1 - \frac{e^{m\tau}}{N})\frac{\beta xv}{1+\alpha v} - \frac{\mu e^{m\tau}}{N}v.$$

Since $\limsup_{t\to\infty} x(t) \leq K$, we have each ω-limit point satisfies $x(t) \leq K$. Thus, it is sufficient to consider solutions for which $x(t) \leq K$. By (3), we deduce that

$$\frac{dL}{dt}|_{(1)} \leq \frac{e^{m\tau}}{N}(\beta K + \mu)\big(R_0 - 1\big)v.$$

Consequently, $\frac{dL}{dt}|_{(1)} \leq 0$ for $R_0 \leq 1$. In addition, it is easy to show that the largest invariant subset of $\left\{(x,y,v)|\ \frac{dL}{dt} = 0\right\}$ is the singleton $\{E_1\}$. If follows from LaSalle's invariance principle [14] that E_1 is globally asymptotically stable when $R_0 \leq 1$.

It remains to study the stability of the therapy partial success equilibrium E^*. Then (5) reduces to

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 + (b_1\lambda + b_2)e^{-\lambda\tau} = 0, \tag{11}$$

where

$$\begin{aligned}
a_1 &= \mu + \delta + \frac{rx^*}{K} + \frac{\beta x^*}{(1+\alpha v^*)^2},\\
a_2 &= \delta\mu + (\mu+\delta)\frac{rx^*}{K} + \frac{\delta\beta x^*}{(1+\alpha v^*)^2} + \frac{r\beta(x^*)^2}{K(1+\alpha v^*)^2} - \frac{\beta^2 x^* v^*}{(1+\alpha v^*)^3},\\
a_3 &= \frac{r\mu\delta x^*}{K} + \frac{r\beta\delta(x^*)^2}{K(1+\alpha v^*)^2} - \frac{\beta^2\delta x^* v^*}{(1+\alpha v^*)^3},\\
b_1 &= \frac{\beta x^*}{1+\alpha v^*}\left(\frac{rv^*}{K} - \frac{N\delta}{1+\alpha v^*}\right)e^{-m\tau},\\
b_2 &= \frac{\beta x^*}{1+\alpha v^*}\left(\frac{r\mu v^*}{K} + \frac{N\beta\delta v^*}{(1+\alpha v^*)^2} - \frac{N\delta r x^*}{K(1+\alpha v^*)}\right)e^{-m\tau}.
\end{aligned}$$

When $\tau = 0$, the equation (11) reduces to

$$\lambda^3 + a_1\lambda^2 + (a_2 + b_1)\lambda + a_3 + b_2 = 0. \tag{12}$$

We have $a_1 > 0$ and $a_3 + b_2 = \dfrac{(N-1)\beta^2\delta x^* v^*}{(1+\alpha v^*)^3} + \dfrac{r\mu(\alpha\delta+\beta)x^* v^*}{K(1+\alpha v^*)} > 0$. By Routh-Hurwitz criterion, we easily deduce the following result.

Lemma 3.4. *Assume $R_0 > 1$ and $a_1(a_2+b_1) - (a_3+b_2) > 0$. Then E^* is locally asymptotically stable in the absence of time delay ($\tau = 0$).*

When $\tau > 0$, let $i\omega$ ($\omega > 0$) be a root of (11). Then

$$\begin{cases} a_1\omega^2 - a_3 = b_1\omega\sin(\omega\tau) + b_2\cos(\omega\tau), \\ -\omega^3 + a_2\omega = -b_1\omega\cos(\omega\tau) + b_2\sin(\omega\tau), \end{cases} \tag{13}$$

which implies that

$$\omega^6 + (a_1^2 - 2a_2)\omega^4 + (a_2^2 - 2a_1a_3 - b_1^2)\omega^2 + a_3^2 - b_2^2 = 0, \tag{14}$$

Let $z = \omega^2$. Then (14) becomes

$$g(z) := z^3 + p_2z^2 + p_1z + p_0 = 0, \tag{15}$$

where $p_2 = a_1^2 - 2a_2$, $p_1 = a_2^2 - 2a_1a_3 - b_1^2$ and $p_0 = a_3^2 - b_2^2$.

Obviously, the equation (15) has at least one positive root if $p_0 < 0$. Further, we have

$$g'(z) = 3z^2 + 2p_2z + p_1.$$

- If $p_0 \geq 0$ and $\Delta = p_2^2 - 3p_1 \leq 0$, then the equation (15) has no positive roots.
- If $p_0 \geq 0$ and $\Delta > 0$, then the equation $g'(z) = 0$ has a root defined by $z^* = \frac{\sqrt{\Delta} - p_2}{3}$. Moreover, the equation (15) has positive roots if and only if $z^* > 0$ and $g(z^*) \leq 0$.

Summary of the above discussions gives rise to the following Lemma.

Lemma 3.5.

(*i*) *If $p_0 < 0$, then the equation (15) has at least one positive root.*

(*ii*) *If $p_0 \geq 0$ and $\Delta \leq 0$, then the equation (15) has no positive roots.*

(*iii*) *If $p_0 \geq 0$ and $\Delta > 0$, then the equation (15) has positive root if and only if $z^* > 0$ and $g(z^*) \leq 0$.*

Based on Lemma 3.5, we consider the following conditions

(a) $p_0 \geq 0$ and $\Delta \leq 0$,

(b) $p_0 \geq 0$, $\Delta > 0$ and $z^* \leq 0$,

(c) $p_0 \geq 0$, $\Delta > 0$ and $g(z^*) > 0$.

Theorem 3.6. *Assume $R_0 > 1$ and $a_1(a_2+b_1)-(a_3+b_2) > 0$.*
If one of the conditions (a)–(c) is satisfied, then the therapy partial success equilibrium E^* is locally asymptotically stable for any time delay $\tau \geq 0$.

Proof. From Lemma 3.4, we deduce that E^* is locally asymptotically stable for $\tau = 0$. By Lemma 3.5, the equation (15) has no positive roots. Then (11) has no purely imaginary roots. Thus, the therapy partial success equilibrium E^* is locally asymptotically stable for all delay $\tau \geq 0$.

Remark 3.7. *Theorem 3.6 investigates the local stability of the therapy partial success equilibrium E^* for all delay $\tau \geq 0$. This result is not established by Wang et al.* [10].

Suppose that the equation (15) has positive roots. Without loss of generality, we assume that it has three positive roots, denoted by z_1, z_2 and z_3 with $z_1 < z_2 < z_3$. Then the equation (14) has three positive roots that are:

$$\omega_1 = \sqrt{z_1}, \ \ \omega_2 = \sqrt{z_2} \ \text{ and } \ \omega_3 = \sqrt{z_3}.$$

According to (13), we obtain

$$\tau_n^j = \frac{1}{\omega_j} \arccos\left(\frac{b_2(a_1\omega_j^2 - a_3) + b_1\omega_j^2(\omega_j^2 - a_2)}{b_2^2 + b_1^2\omega_j^2}\right) + \frac{2n\pi}{\omega_j}, \tag{16}$$

where $j = 1,2,3$ and $n \in \mathbf{N}$. Hence, $\pm i\omega_j$ is a pair of purely imaginary roots of (11) with $\tau = \tau_n^j$. Define

$$\tau_0 = \tau_0^{j_0} = \min_{j\in\{1,2,3\}}\{\tau_0^j\} \ \text{ and } \ \omega_0 = \omega_{j_0}.$$

Let $\lambda(\tau) = u(\tau) + i\omega(\tau)$ be the root of the equation (11) satisfying $u(\tau_n^j) = 0$ and $\omega(\tau_n^j) = \omega_j$. Differentiating both sides of (11) with respect to τ, we obtain

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{3\lambda^2 + 2a_1\lambda + a_2 + b_1e^{-\lambda\tau}}{\lambda(b_1\lambda + b_2)e^{-\lambda\tau}} - \frac{\tau}{\lambda}.$$

By a simple calculation, we get

$$\begin{aligned} Re\left(\frac{d\lambda}{d\tau}\right)^{-1}\Big|_{\tau=\tau_n^j} &= \frac{3\omega_j^4+2(a_1^2-2a_2)\omega_j^2+a_2^2-2a_1a_3-b_1^2}{b_1^2\omega_j^2+b_2^2}, \\ &= \frac{g'(\omega_j^2)}{b_1^2\omega_j^2+b_2^2}. \end{aligned}$$

It is not hard to check that $g'(\omega_1^2)>0$, $g'(\omega_2^2)<0$ and $g'(\omega_3^2)>0$. Hence, the transversality condition is verified. Therefore, we get the following result.

Theorem 3.8. *Assume $R_0>1$ and $a_1(a_2+b_1)-(a_3+b_2)>0$.*
If either $p_0<0$ or $p_0\geq 0$, $\Delta>0$, $z^*>0$ and $g(z^*)\leq 0$, then the therapy partial success equilibrium E^* is locally asymptotically stable for all $\tau\in[0,\tau_0)$ and becomes unstable when $\tau>\tau_0$. Further, model (1) undergoes a Hopf bifurcation at E^* when $\tau=\tau_n^j$, for $j=1,2,3$ and $n\in N$.

4. Conclusions

In this work, we have presented a mathematical model of cancer therapy with oncolytic viruses that incorporates the time needed for infected tumor cells to produce new virions after viral entry, the probability of surviving during the latent period, and the saturation effect. We firstly validated the plausibility of our model by proving the existence, nonnegativity and boundedness of the solutions. As in virology, the dynamics of our model depends on the basic reproduction number R_0 that represents the average number of new tumor infections produced by one infected cell during the period of infection when all tumor cells are uninfected. More precisely, when $R_0\leq 1$, the equilibrium $E_1(K,0,0)$ is globally asymptotically stable for any time delay. In this case, the tumor reaches its maximum size, and the therapy fails. When $R_0>1$, the virus persists in the host of tumor and the model has a unique positive equilibrium E^* which represents the therapy partial success equilibrium. Further, we have proved that the time delay could cause the equilibrium E^* to lose or gain its stability.

From the expression of the basic reproduction number R_0 given in (3), we can deduce that $R_0=R_0(\tau)$ is a decreasing function of time delay τ with $R_0(+\infty)=0$. For example, if the delay is sufficiently large, then the value of R_0 becomes less than one, the equilibrium E^* will

be lost and there are only two equilibria $E_0(0,0,0)$ and $E_1(K,0,0)$. Therefore, the oncolytic virotherapy totally fails. On the other hand, the models and results presented in [5, 6, 7, 9, 10] are improved and extended.

Conflict of Interests

The authors declare that there is no conflict of interests.

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