Adv Syst Sci Appl 2024; **01**:69–81
Published online at https://ijassa.ipu.ru.

Combined Therapeutic Strategies for Cancer: Integrating Oncolytic Viruses and Inhibitors in a Mathematical Model

Majda El Younoussi[1*], Khalid Hattaf[1,2], Noura Yousfi[1]

[1] *Laboratory of Analysis, Modeling and Simulation (LAMS), Faculty of Sciences Ben M'Sick, Hassan II University of Casablanca, P.O Box 7955 Sidi Othman, Casablanca, Morocco*

[2] *Equipe de Recherche en Modélisation et Enseignement des Mathématiques (ERMEM), Centre Régional des Métiers de l'Education et de la Formation (CRMEF), 20340 Derb Ghalef, Casablanca, Morocco*

Abstract: The greatest cause of death worldwide continues to be cancer, a complicated set of diseases characterized by uncontrolled cell development. Although early identification and therapeutic approaches have improved, the incidence of the disease is still on the rise, demanding continued study into its underlying causes and cutting-edge treatment paradigms. For creative interventions and focused medicines, the variety of cancer kinds, which are influenced by genetics, way of life, and environmental variables, poses both difficulties and opportunities. In this paper, we present a mathematical model to treat cancer with combined therapies, oncolytic viruses and Mitogen-activated protein kinase inhibitors. We demonstrate that our model is both biologically and mathematically well-posed through the existence, the non-negativity and the boundedness of solutions. Furthermore, we study the equilibrium points as well as the stability of these equilibria. Finally, we use numerical simulations to illustrate the effect of this combined therapy on tumor cells.

Keywords: MAPK inhibitors, oncolytic viruses, mathematical modeling, stability, Hopf bifurcation.

1. INTRODUCTION

A type of biological therapy called oncolytic viruses is made to target and eliminate cancer cells while sparing normal cells. These viruses are produced naturally or genetically modified in a lab to target only cancer cells. The virus replicates inside the cancer cells after it has infected them, leading to the cells' bursting and dying. This process also releases new viral particles, which can infect nearby cancer cells and continue the cycle of destruction [2].

Certain oncolytic adenoviruses are notably dependent on the Coxsackie-adenovirus receptor (CAR), and variations in CAR expression levels within target cells could potentially impact the efficacy of viral infection and the resulting therapeutic advantages. CAR has been linked to numerous facets of cancer biology, including cell adhesion, signaling, and migration, in addition to its function in promoting viral entry, making it a viable therapeutic target [9].

Additionally, Mitogen-Activated Protein Kinase, also referred to as MAPK or MEK, is a family of serine/threonine protein kinases that are important for cellular functions like cell growth, differentiation, proliferation, and promoting CAR expression. MAPK has the potential to exploit the complex interplay between CAR and oncolytic viruses to enhance their cancer-killing capabilities and stimulate immune responses against tumor cells [1].

*Corresponding author: majda.elyounoussi-etu@etu.univh2c.ma

The development of our knowledge of cancer biology and treatment, on the other hand, has been greatly aided by mathematical modeling, particularly the use of ordinary differential equations (ODEs). The intricate dynamics and interactions between various cellular processes, signaling pathways, and therapeutic interventions in cancer can be better understood using ODE models. Researchers can predict how different treatment modalities will affect cancer cells and their microenvironment by creating and analyzing ODE-based models. They can also find potential targets for novel therapies. Further, ODE models can help integrate experimental and clinical data, allowing for the quantitative assessment of cancer progression and treatment outcomes.

In 2007, Zurakowski and Wodarz [11] used an ODE model to discuss the interactions between the populations of the average level of CAR expression on the surface of the cells, free virus populations, susceptible, uninfected and infected tumor cells. This model was generalized by Youshan and Qian in their work [10], the researchers constructed a mathematical model to simulate the impacts of both MEK inhibitors and viruses on tumor cells. This model is a free boundary problem, which means that it takes into account the growth and shrinkage of the tumor as the therapies are applied. The researchers used the model to explore how the combined therapies could reduce the tumor size. Recently, Nono et al. [7] recently expanded upon a prior model, applying it to brain cancer and introducing optimal control techniques to optimize the combination of oncolytic virotherapy and MEK inhibitors.

Incorporating delays in mathematical models for cancer treatment can play a crucial role in capturing the realistic behavior of biological systems and improving the accuracy of the model predictions. Motivated by all that, we propose in this paper an ODE model to study the dynamics of oncolytic viruses and their interaction with the coxsackie-adenovirus receptor and MAPK inhibitors in the context of cancer therapy, taking into account the duration required by tumor cells that have been infected to generate fresh viruses following the entry of the virus.

Our paper is organized into several key sections to present our research cohesively. We introduce our mathematical model in Section 2, and rigorously examine its well-posedness. Moving to Section 3, we delve into equilibrium points and their stability, including an exploration of the Hopf bifurcation, shedding light on the system's dynamic behavior. Section 4 presents the results of our numerical simulations, providing practical insights into the behavior of the model under various conditions. Finally, in Section 5, we offer a comprehensive conclusion, summarizing our findings, discussing their implications, and highlighting the broader significance of our research.

2. PRESENTATION AND WELL-POSEDNESS OF THE MODEL

Within this section, we present the subsequent ordinary differential equation (ODE) model:

$$\begin{cases} \frac{dS}{dt} = r(1-u)S(t)(1-\frac{S(t)+I(t)}{K}) - \frac{\beta W(t)S(t)V(t)}{1+\alpha V(t)} - dS(t), \\ \frac{dI}{dt} = \frac{\beta W(t-\tau)S(t-\tau)V(t-\tau)e^{-m\tau}}{1+\alpha V(t-\tau)} - \delta(1-u)I(t) - dI(t), \\ \frac{dV}{dt} = N\delta(1-u)I(t) - \frac{\beta W(t)S(t)V(t)}{1+\alpha V(t)} - \mu V(t), \\ \frac{dW}{dt} = \eta u(\gamma - W(t)) - hW(t), \end{cases} \tag{2.1}$$

where $S(t), I(t), V(t)$ and $W(t)$ are the concentration of uninfected tumor cells, infected tumor cells, free oncolytic virus particles and the average level of CAR molecules on cell surfaces at the time t, respectively. The factor r is the rate of tumor growth per individual in a population, slowed down by the value $(1-u)$, where u represents the intensity of MAPK inhibitor and varies between 0 and 1. If $u = 1$, the MAPK inhibitor has the maximum possible effect. If $u = 0$, every cell in the first phase continue to grow and the production of CAR

molecule is stopped. Moreover, for biological and mathematical reasons, we will suppose as in [11] that $d < r(1-u)$, where d is the rate of natural death of cells. The parameter K signifies the maximal tumor size. The term $\frac{\beta SVW}{1+\alpha V}$ models the rate of tumor cells infection by the virus in presence of CAR receptor and the interaction between them on the uninfected cell, where α measures the saturation effect, and β is the rate of infection process. The factor δ represents the virus induced death rate while the rate μ represents the decay of the virus. The parameter denoted as N represents the quantity of newly released viruses following the lysis of an infected tumor cell. Cells generate CAR molecules at a rate denoted as η and experience a loss of these molecules from their surface at a rate of h. The term $\gamma - w$ characterizes the saturation of CAR expression. Furthermore, τ represents the time required for the transition from tumor cell infection to new virus production, where m denotes the death rate for infected cells prior to virus production, and $e^{-m\tau}$ signifies the probability of survival during the time interval $[t-\tau, t]$.

To prove that the model is mathematically well-posed and biologically meaningful, it is important to demonstrate the existence, the boundedness and the non-negativity of solutions as time evolves.

Let $\mathcal{C}$ be the set of continuous functions from the interval $[-\tau, 0]$ to $\mathbb{R}^4$, with the supremum norm $||\phi||$ given by $\sup_{-\tau\leq\zeta\leq 0}|\phi(\zeta)|$, where $\phi \in \mathcal{C}$. Applying the fundamental theory of functional differential equations [4], we conclude that a single solution exists $(S(t), I(t), V(t), W(t))$, where the initial condition (S_0, I_0, V_0, W_0) are in $\mathcal{C}$ and we suppose that:

$$S_0(\zeta) \geq 0, I_0(\zeta) \geq 0, V_0(\zeta) \geq 0, W_0(\zeta) \geq 0, \zeta \in [-\tau, 0]. \tag{2.2}$$

Theorem 2.1:
Let's suppose that the initial conditions fulfill (2.2)*. Then each solution of model* (2.1) *stays non-negative for all* $t \geq 0$.

Proof
Using (2.2), we derive the following:

$$S(t) = S(0)e^{\int_0^t (1-u)(1-\frac{S(x)+I(x)}{K}) - \frac{\beta W(x)V(x)}{1+\alpha V(x)} - d\ dx},$$

then for all $t > 0$, we get $S(t) \geq 0$.
The second equation of model (2.1) gives

$$I(t) = I(0)e^{-\alpha t} + e^{-m\tau-\alpha t}\int_0^t \frac{\beta S(x-\tau)V(x-\tau)W(x-\tau)}{1+\alpha V(x-\tau)} e^{\alpha x} dx,$$

where $\alpha = \delta(1-u) + d$. Then $I(t) \geq 0$ for every $t \geq 0$.
From the third equation of model (2.1), we obtain

$$V(t) = (V(0)e^{-\int_0^t \frac{\beta S(x)}{1+\alpha V(x)} dx} + N\delta(1-u)\int_0^t I(y)e^{\mu y - \int_y^t \frac{\beta S(x)}{1+\alpha V(x)} dx} dy)e^{-\mu t}.$$

Thus, $V(t) \geq 0$ for every $t \geq 0$.
Utilizing the final equation from model (2.1), we acquire:

$$W(t) = W(0)e^{\int_0^t \frac{\eta u \gamma}{W(x)} - \eta u - h\ dx} \geq 0, \text{ for all } t \geq 0.$$

Hence, every solution of model (2.1) is non-negative for all $t \geq 0$. □

Theorem 2.2:
Each solution of the model (2.1)*, given non-negative initial conditions* (2.2)*, remains bounded for all* $t \geq 0$.

Proof
By the first equation of our model, we have

$$\frac{dS}{dt} \leq r(1-u)S(t)(1-\frac{S(t)-I(t)}{K}).$$

Using the comparison principal, we get

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

Therefore, $S(t)$ is bounded.
Let $Z(t) = S(t-\tau)e^{-m\tau} + I(t)$,
hence, we have

$$\begin{aligned}\frac{dZ}{dt} &= r(1-u)S(1-\frac{S+I}{K})e^{-m\tau} - dSe^{-m\tau} - \delta(1-u)I - dI\\ &\leq r(1-u)Ke^{-m\tau} - (r(1-u)+d)Se^{-m\tau} - (\delta(1-u)+d)I\\ &\leq r(1-u)Ke^{-m\tau} - cZ(t),\end{aligned}$$

where $c = c^{'}(1-u)+d$ and $c^{'} = \min\{r,\delta\}$. Then,

$$\limsup_{t\to+\infty} Z(t) \leq \frac{rK(1-u)e^{-m\tau}}{c},$$

and we get

$$\limsup_{t\to+\infty} I(t) \leq \frac{rK(1-u)e^{-m\tau}}{c}.$$

Hence, $I(t)$ is bounded.
From the third equation we deduce

$$\frac{dV}{dt} \leq N\delta(1-u)I - \mu V,$$

by $\limsup_{t\to+\infty} I(t) \leq \frac{rK(1-u)e^{-m\tau}}{c}$, we obtain

$$\limsup_{t\to+\infty} V(t) \leq \frac{N\delta(1-u)^2e^{-m\tau}}{\mu c}.$$

Thus, $V(t)$ is bounded.
By the fourth equation of (2.1) and $u \in [0,1]$, we get

$$\frac{dW}{dt} \leq \eta\gamma - (\eta+h)w,$$

then $\limsup_{t\to+\infty} W(t) \leq \frac{\eta\gamma}{\eta+h}$. Thus, $W(t)$ is bounded. □

3. EQUILIBRIA AND STABILITY ANALYSIS

Within this section, we explore the three equilibrium points of model (2.1) along with their stability characteristics.

3.1. Equilibrium Points of the Model

When there is no virus, the model (2.1) admits two infection-free equilibrium. The equilibrium point $E_0 = (0, 0, 0, W_0)$, which reflects the non-existence of cells and virus, and the equilibrium point $E_1 = (S_1, 0, 0, W_1)$ where $S_1 = K(1 - \frac{d}{r(1-u)})$ and $W_0 = W_1 = \frac{\eta u \gamma}{\eta u + h}$.
By $r(1-u) > d$, the equilibrium E_1 exists.
In the existence of the virus, there exists another equilibrium point called the endemic equilibrium $E^* = (S^*, I^*, V^*, W^*)$. We suppose that $I^* > 0$, $V^* > 0$ and we put

$$R_0 = \frac{\beta N \delta W_1 S_1 (1-u) e^{-m\tau}}{(\delta(1-u) + d)(\mu + \beta W_1 S_1)}.$$

R_0 is the reproduction number and represents the potential for the oncolytic virus to spread within the tumor cell population. By simple calculus, we show that the equilibrium E^* exists if $R_0 > 1$, this means that the virus can sustain its presence and spread within the tumor cells, leading to a persistent infection.
(S^*, I^*, V^*, W^*) are the solution of this system:

$$\begin{aligned}
r(1-u)S^*(1 - \frac{S^* + I^*}{K}) - \frac{\beta W^* S^* V^*}{1 + \alpha V^*} - dS^* &= 0, && (3.3)\\
\frac{\beta W^* S^* V^* e^{-m\tau}}{1 + \alpha V^*} - \delta(1-u)I^* - dI^* &= 0, && (3.4)\\
N\delta(1-u)I^* - \frac{\beta W^* S^* V^*}{1 + \alpha V^*} - \mu V^* &= 0, && (3.5)\\
\eta u(\gamma - W^*) - hW^* &= 0. && (3.6)
\end{aligned}$$

By equation (3.6), we get

$$W^* = \frac{\eta u \gamma}{\eta u + h}. \tag{3.7}$$

By adding the equation (3.4) to the equation (3.5), we get

$$V^* = \frac{\delta(1-u)(N - e^{m\tau}) - de^{m\tau}}{\mu} I^*. \tag{3.8}$$

By adding the equation (3.3) to the equation (3.4), we obtain

$$I^* = \frac{S^*(r(1-u)(K - S^*) - dK)}{r(1-u)S^* + Ke^{m\tau}(\delta(1-u) + d)}. \tag{3.9}$$

Obviously, by determining S^* we will determine V^* and I^*, for that we will use (3.7), (3.8) and (3.9) to find S^*. For simplification, we put:

$$P = \tfrac{\delta(1-u)(N-e^{m\tau}) - de^{m\tau}}{\mu} \text{ and } O = N\delta(1-u).$$

By equation (3.5), we get

$$(1 - \alpha V^*)OI^* - \beta W^* S^* V^* - \mu(1 + \alpha V^*)V^* = 0,$$

then,

$$O - \beta W^* S^* P - P\mu + (\alpha PO - \mu\alpha P^2)I^* = 0.$$

Using (3.9), we obtain

$$aS^2 + bS + c = 0,$$

where,

$$\begin{aligned} a &= -\beta W^* Pr(1-u) - \alpha OPr(1-u) + \alpha P^2 \mu r(1-u), \\ b &= Or(1-u) - P\mu r(1-u) - \beta W^* P^* K(1-u)e^{m\tau}(\delta + d) \\ &\quad + \alpha OPK(r(1-u) - d) - \alpha P^2 \mu r(1-u)K + \alpha P^2 \mu dK, \\ c &= (O\delta(1-u) - P\mu\delta(1-u) + Od - P\mu d)Ke^{m\tau}. \end{aligned}$$

Then

$$S^* = \frac{-b - \sqrt{\Delta}}{2a},$$

where $\Delta = b^2 - 4ac$.
Thus S^*, I^*, V^* and W^* are defined.

3.2. Stability Analysis

The characteristic equation at any equilibrium $E = (S, I, V, W)$ is given by

$$\begin{vmatrix} \frac{-r(1-u)S}{K} - \lambda & -\frac{r(1-u)S}{K} & -\frac{\beta WS}{(1+\alpha V)^2} & -\frac{\beta SV}{1+\alpha V} \\ \frac{\beta WVe^{-(m+\lambda)\tau}}{1+\alpha V} & -\delta(1-u) - d - \lambda & \frac{\beta WSe^{-(m+\lambda)\tau}}{(1+\alpha V)^2} & \frac{\beta VSe^{-(m+\lambda)\tau}}{1+\alpha V} \\ -\frac{\beta WV}{1+\alpha V} & N\delta(1-u) & -\frac{\beta WS}{(1+\alpha V)^2} - \mu - \lambda & -\frac{\beta SV}{1+\alpha V} \\ 0 & 0 & 0 & -\eta u - h - \lambda \end{vmatrix} = 0. \quad (3.10)$$

Theorem 3.1:
The equilibrium state $E_0 = (0, 0, 0, W_0)$ exhibits instability.

Proof
At $E_0 = (0, 0, 0, W_0)$ we get the following equation:

$$(r(1-u) - d - \lambda)(\delta(1-u) + d + \lambda)(\mu + \lambda)(\eta u + h + \lambda) = 0, \quad (3.11)$$

then the roots are $\lambda_1 = r(1-u) - d$, $\lambda_2 = -\delta(1-u) - d$, $\lambda_3 = -\mu$ and $\lambda_4 = -\eta u - h$.
Since we have $r(1-u) > d$, we get $\lambda_1 > 0$. Thus, E_0 is unstable. □

Theorem 3.2:
The equilibrium point $E_1 = (S_1, 0, 0, W_1)$ is locally asymptotically stable for every $\tau \geq 0$ if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof
At E_1, (3.10) becomes

$$\left(2r(1-u)\frac{S_1}{K} + d + \lambda\right)\left(\eta u + h + \lambda\right)\left(\lambda^2 + (\delta(1-u) + d + \beta W_1 S_1 + \mu)\lambda\right.$$

$$\left. + (\delta(1-u) + d)(\beta W_1 S_1 + \mu)(1 - R_0 e^{-\lambda\tau})\right) = 0. \quad (3.12)$$

Clearly, $\lambda_1 = -2r(1-u)\frac{S_1}{K} - d$ and $\lambda_2 = -\eta u - h$ represent two of the roots of the aforementioned equation, with the remaining roots arising from solutions to the subsequent

equation:

$$\lambda^2 + (\delta(1-u)+d+\beta W_1 S_1+\mu)\lambda + (\delta(1-u)+d)(\beta W_1 S_1+\mu)(1-R_0 e^{-\lambda\tau}) = 0. \tag{3.13}$$

If $R_0 > 1$, let

$$f(\lambda) = \lambda^2 + (\delta(1-u)+d+\beta W_1 S_1+\mu)\lambda + (\delta(1-u)+d)(\beta W_1 S_1+\mu)(1-R_0 e^{-\lambda\tau}).$$

We have $f(0) = (\delta(1-u)+d)(\beta W_1 S_1+\mu)(1-R_0) < 0$ and $\lim\limits_{\lambda\to+\infty} f(\lambda) = +\infty$.
In this case, the equation $f(\lambda) = 0$ possesses at least one positive root. Hence, if $R_0 > 1$ E_1 is unstable.

If $R_0 < 1$, we discuss two cases:
When $\tau = 0$, we get $\delta(1-u)+d+\beta W_1 S_1+\mu > 0$ and $(\delta(1-u)+d)(\beta W_1 S_1+\mu)(1-R_0) > 0$. Then all the roots of (3.12) have negative real parts for $\tau = 0$ and $R_0 < 1$.
When $\tau > 0$, let $i\omega$ be a purely imaginary root of (3.13) where $\omega > 0$. Then,

$$\begin{cases} -\omega^2 + (\delta(1-u)+d)(\beta W_1 S_1+\mu) &= (\delta(1-u)+d)(\beta W_1 S_1+\mu)R_0 cos(w\tau), \\ (\delta(1-u)+d+\beta W_1 S_1+\mu)\omega &= -(\delta(1-u)+d)(\beta W_1 S_1+\mu)R_0 sin(\omega\tau), \end{cases}$$

thus we get

$$\omega^4 + \Big((\delta(1-u)+d)^2 + (\beta W_1 S_1+\mu)^2\Big)\omega^2 + (\delta(1-u)+d)^2(\beta W_1 S_1+\mu)^2(1-R_0^2) = 0.$$

Let $x = \omega^2$, then we obtain

$$x^2 + \Big((\delta(1-u)+d)^2 + (\beta W_1 S_1+\mu)^2\Big)x + (\delta(1-u)+d)^2(\beta W_1 S_1+\mu)^2(1-R_0^2) = 0.$$

Hence if $R_0 < 1$, there is no positive solution.
Thus, E_1 is locally asymptotically stable for $R_0 < 1$. □

Theorem 3.3:
If $R_0 < 1$, the equilibrium E_1 is globally asymptotically stable.

Proof
Take into consideration the presented Lyapunov function:

$$L(t) = \delta(1-u)e^{m\tau} I(t) + \frac{\delta(1-u)+d}{N} e^{m\tau} V(t) + \delta(1-u)\int_{t-\tau}^{t} \frac{\beta W(\xi)S(\xi)V(\xi)}{1+\alpha V(\xi)} d\xi,$$

then, we obtain

$$\frac{dL}{dt} = \delta(1-u)\frac{\beta WSV}{1+\alpha V} - \frac{(\delta(1-u)+d)e^{m\tau}}{N}\left(\frac{\beta WSV}{1+\alpha V} + \mu V\right).$$

We have $\frac{V}{1+\alpha V} \le V$, $\limsup\limits_{t\to\infty} S(t) \le S_1$ and $\limsup\limits_{t\to\infty} W(t) \le W_1$. Then, we get

$$\frac{dL}{dt} \le \frac{(\delta(1-u)+d)(\beta W_1 S_1+\mu)(R_0-1)V}{N}.$$

Hence, if $R_0 < 1$ we obtain $\frac{dL}{dt} \le 0$. Clearly, $\frac{dL}{dt} = 0$ if and only if $S = S_0$, $I = 0$, $V = 0$ and $W = W_0$. Then the largest invariant set contained in $\{(S, I, V, W) | \frac{dL}{dt} = 0\}$ is the singleton $\{E_1\}$. By LaSalle's invariance principale [5], we deduce that E_1 is globally asymptotically stable when $R_0 < 1$. □

The characteristic equation at the equilibrium E^* can be expressed in the following manner:

$$(\eta u + h + \lambda)\left(\lambda^3 + p_1\lambda^2 + p_2\lambda + p_3 + (q_1\lambda + q_2)e^{-\lambda\tau}\right) = 0, \tag{3.14}$$

where,

$$\begin{aligned}
p_1 &= (1-u)\left(\frac{rS^*}{K} + \delta\right) + \frac{\beta W^* S^*}{(1+\alpha V^*)^2} + d + \mu,\\
p_2 &= (1-u)\left(\frac{\beta W^* S^*}{(1+\alpha V^*)^2} + \mu\right)\left(\frac{rS^*}{K} + \delta + \frac{d}{1-u}\right) - \frac{\beta^2 S^* V^* W^{*2}}{(1+\alpha V^*)^3}\\
&\quad + \frac{r(1-u)S^*}{K}\left(\delta(1-u) + d\right),\\
p_3 &= (\delta(1-u)+d)S^*\left(\frac{r(1-u)}{K}\left(\frac{\beta S^* W^*}{(1+\alpha V^*)^2} + \mu\right) - \frac{\beta^2 V^* W^{*2}}{(1+\alpha V^*)^3}\right),\\
q_1 &= \frac{(1-u)\beta S^* W^*}{1+\alpha V^*}\left(\frac{rV^*}{K} - \frac{\delta N}{1+\alpha V^*}\right)e^{-m\tau},\\
q_2 &= \frac{(1-u)\beta S^* W^*}{1+\alpha V^*}\left(\frac{\mu r V^*}{K} + \frac{N\delta}{1+\alpha V^*}\left(\frac{\beta V^* W^*}{1+\alpha V^*} - \frac{r(1-u)S^*}{K}\right)\right)e^{-m\tau}.
\end{aligned}$$

Since the root $\lambda_1 = -\eta u - h$ is negative, it remains to determine the roots of the following equation:

$$\lambda^3 + p_1\lambda^2 + p_2\lambda + p_3 + (q_1\lambda + q_2)e^{-\lambda\tau} = 0, \tag{3.15}$$

When $\tau = 0$, the equation (3.15) becomes

$$\lambda^3 + p_1\lambda^2 + (p_2 + q_1)\lambda + p_3 + q_2 = 0. \tag{3.16}$$

We have $p_1 > 0$, and by simple calculation we can find that $p_3 + q_2 > 0$. By Routh-Hurwitz criterion, we conclude the result bellow:

Lemma 3.4:
Suppose that $R_0 > 1$ and $p_1(p_2 + q_1) - (p_3 + q_2) > 0$. Then in the absence of delay ($\tau = 0$), all the roots of (3.15) have negative real parts. Hence, the equilibrium $E^* = (S^*, I^*, V^*, W^*)$ is locally asymptotically stable.

When $\tau > 0$, let $i\omega$ ($\omega > 0$) be a purely imaginary root of the equation (3.15). Thus,

$$\begin{cases} p_1\omega^2 - p_3 = q_1\omega\sin(\omega\tau) + q_2\cos(\omega\tau),\\ -\omega^3 + p_2\omega = -q_1\omega\cos(\omega\tau) + q_2\sin(\omega\tau), \end{cases} \tag{3.17}$$

then,

$$\omega^6 + \left(p_1^2 - 2p_2\right)\omega^4 + \left(p_2^2 - q_1^2 - 2p_1p_3\right)\omega^2 + p_3^2 - q_2^2 = 0. \tag{3.18}$$

For $x = \omega^2$, the equation (3.18) is reduced to

$$x^3 + (p_1^2 - 2p_2)x^2 + (p_2^2 - q_1^2 - 2p_1p_3)x + p_3^2 - q_2^2 = 0. \tag{3.19}$$

We consider the following function:

$$f(x) = x^3 + c_2x^2 + c_1x + c_0, \tag{3.20}$$

where $c_0 = p_3^2 - q_2^2$, $c_1 = p_2^2 - q_1^2 - 2p_1p_3$ and $c_2 = p_1^2 - 2p_2$.
Obviously $f'(x) = 3x^2 + 2c_2x + c_1$, and $\Delta' = 4(c_2^2 - 3c_1)$ its discriminant. Hence, we get the following result:

Lemma 3.5: *(i) If $c_0 < 0$, then the equation $f(x) = 0$ has at least one positive root.*
(ii) If $c_0 \geq 0$ and $\Delta' \leq 0$, then the equation $f(x) = 0$ has no positive roots.
(iii) If $c_0 \geq 0$ and $\Delta' > 0$, then the equation $f(x) = 0$ has a positive root if $x_1 > 0$ and $f(x_1) \leq 0$, where $x_1 = \frac{\sqrt{c_2^2 - 3c_1} - c_2}{3}$ is a root of $f'(x) = 0$.

By Lemma 3.4 and the previous Lemma we deduce the following theorem:

Theorem 3.6:
Assume that $R_0 > 1$, $c_0 \geq 0$ and $p_1(p_2 + q_1) - (p_3 + q_2) > 0$.
If any of the subsequent conditions are met,

- $\Delta' \leq 0$,
- $\Delta' > 0$ *and* $x_1 \leq 0$,
- $\Delta' > 0$ *and* $f(x_1) > 0$,

then the equilibrium point E^* is locally asymptotically stable for any non-negative time delay.

On the other hand, we study the Hopf bifurcation of model (2.1) at the equilibrium point E^*.
The stability of the equilibrium point E^* changes when the equation (3.15) has purely imaginary roots. So, we assume that ω_1, ω_2 and ω_3 are these positive roots. Moreover, we consider τ as a parameter of bifurcation. Substituting $\omega = \omega_\epsilon$ and $\tau = \tau^\epsilon$ in (3.17) where $\epsilon = 1, 2, 3$, we get

$$q_2(p_1\omega_\epsilon^2 - p_3) - q_1\omega_\epsilon(-\omega_\epsilon^3 + p_2\omega_\epsilon) = q_2^2 cos(\omega_\epsilon\tau^\epsilon) + q_1^2{\omega_\epsilon}^2 cos(\omega_\epsilon\tau^\epsilon),$$

thus, we obtain

$$\tau_n^\epsilon = \frac{1}{\omega_\epsilon}\left(arccos\left(\frac{q_2(p_1\omega_\epsilon^2 - p_3) + q_1\omega_\epsilon^2(\omega_\epsilon^2 - p_2)}{q_2^2 + q_1^2\omega_\epsilon^2}\right) + 2\pi n\right), \tag{3.21}$$

where $n \in \mathbb{N}$. Obviously, $\pm i\omega_\epsilon$ are purely imaginary roots of (3.15) with $\tau = \tau_n^\epsilon$. Let $\tau_0 = \min_{\epsilon\in\{1,2,3\}} \{\tau_0^\epsilon\}$ and $\lambda(\tau) = \psi(\tau) + i\omega(\tau)$ be the root of the equation (3.15) where $\psi(\tau_n^\epsilon) = 0$ and $\omega(\tau_n^\epsilon) = \omega_\epsilon$. Differentiating equation (3.15) with respect to τ, we get

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{3\lambda^2 + 2p_1\lambda + p_2 + q_1e^{-\lambda\tau}}{\lambda(q_1\lambda + q_2)e^{-\lambda\tau}} - \frac{\tau}{\lambda}.$$

Therefore, it is straightforward to deduce

$$\begin{aligned}\mathrm{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\Bigg|_{\tau=\tau_n^\epsilon} &= \frac{3\omega_\epsilon^4 + 2(p_1^2 - 2p_2)\omega_\epsilon^2 + p_2^2 - q_1^2 - 2p_1p_3}{q_1^2\omega_\epsilon^2 + q_2^2} \\ &= \frac{f'(\omega_\epsilon^2)}{q_1^2\omega_\epsilon^2 + q_2^2}.\end{aligned}$$

By $f'(\omega_1^2) > 0$, $f'(\omega_2^2) < 0$ and $f'(\omega_3^2) > 0$, the transversality condition is verified, and we suppose these conditions:
(a) $c_0 < 0$,
(b) $c_0 \geq 0, \Delta' > 0, x_1 > 0$ and $f(x_1) \leq 0$,
and we get the following result:

Theorem 3.7:
Suppose $R_0 > 1$ and $p_1(p_2 + q_1) - (p_3 + q_2) > 0$. If one of conditions (a)-(b) is satisfied, the equilibrium point E^* is locally asymptotically stable for all time delays $\tau \in [0, \tau_0)$. Furthermore, E^* becomes unstable when $\tau > \tau_0$. In addition, when $\tau = \tau_n^\epsilon$ model (2.1) undergoes a Hopf bifurcation at E^* where $\epsilon = 1, 2, 3$ and $n \in \mathbb{N}$.

4. NUMERICAL SIMULATIONS

This section presents numerical simulations of our system to demonstrate its dynamics and behavior. The system is evaluated with various initial conditions satisfying $S_0, I_0, V_0, W_0 > 0$, and the time interval is set from $t = 0$ to $t = 2000$. The following set of parameters, selected based on previous works [3, 6, 8, 11], are used: $r = 0.5$, $u = 0.5$, $d = 0.1$, $K = 2 \times 10^9$, $\alpha = 1.95 \times 10^{-10}$, $\beta = 1.2 \times 10^{-10}$, $\delta = 0.5$, $N = 1000$, $\mu = 20$, $\eta = 0.17$, $h = 0.07$, $\gamma = 7$, $\tau = 2$, $m = 1$. Using these values, we obtain $R_0 = 3.8481 > 1$, $p_1(p_2 + q_1) - (p_3 + q_2) = 11.2223 > 0$, $c_0 = 0.1873 > 0$, $\Delta' = 6.7108 \times 10^5 > 0$ and $f(x_1) = 0.1224 > 0$. According to Theorem 3.6, the equilibrium point E^* is locally asymptotically stable for any $\tau \geq 0$. This is illustrated and validated in Figure 4.1.

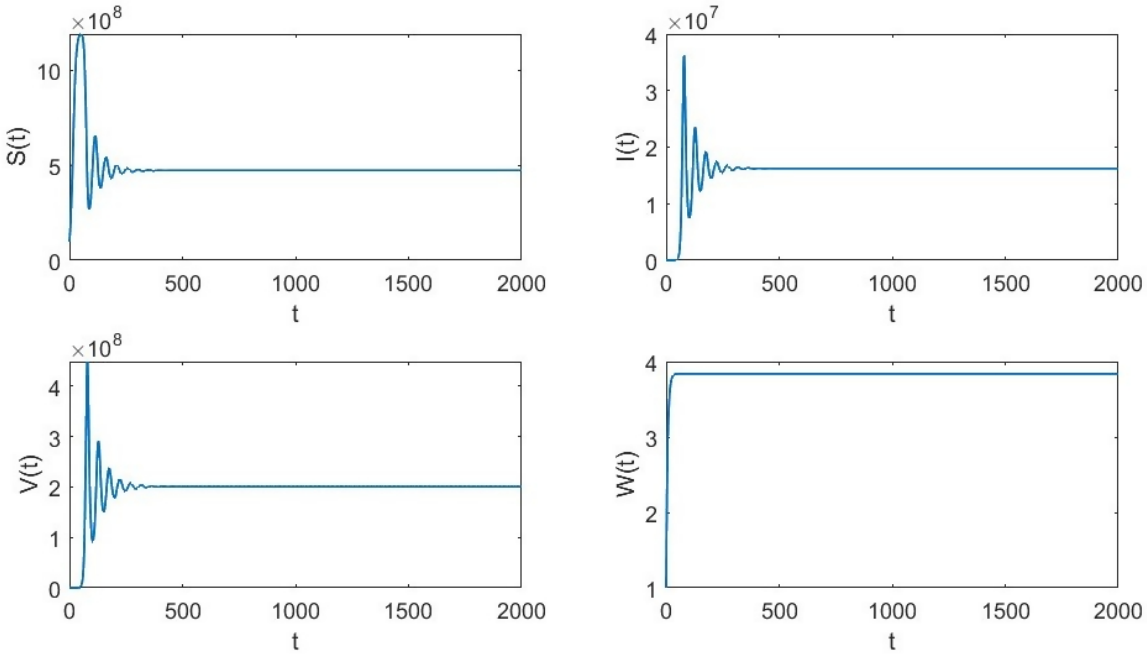

Fig. 4.1. Dynamical behavior of system (2.1) around the equilibrium point E^* when $\tau = 2$, $\mu = 20$ and $\gamma = 7$.

We then consider the same parameter values, except that γ is changed to 2 and μ to 0.65. In this case, we obtain $c_0 = -9.7104 \times 10^{-4} < 0$, which means that the condition of Theorem 3.6 is not satisfied. Therefore, the equilibrium E^* is unstable, as shown in Figure 4.2.

When $m = 0$ and $N = 100$, we obtain $R_0 = 19.0795 > 1$, $p_1(p_2 + q_1) - (p_3 + q_2) = 0.0054 > 0$, and $c_0 = -9.0776 \times 10^-4 < 0$. Therefore, the conditions for Theorem 3.7 are satisfied. Using equation (3.19) and (3.21), we obtain $\omega = 0.4186$ and $\tau_0 = 0.8567$. In Figure 4.3, when $\tau = 0.7 < \tau_0$, the equilibrium point E^* is locally asymptotically stable. However, when $\tau = \tau_0 = 0.8567$, model (2.1) undergoes a Hopf bifurcation at the equilibrium E^*. Furthermore, when the parameter τ exceeds the critical threshold τ_0 associated with the Hopf bifurcation, the equilibrium at the point E^* transitions from stable steady state to stable limit cycle oscillation, as illustrated in Figure 4.4. Moreover, all these results confirm our theoretical results stated in Theorem 3.7

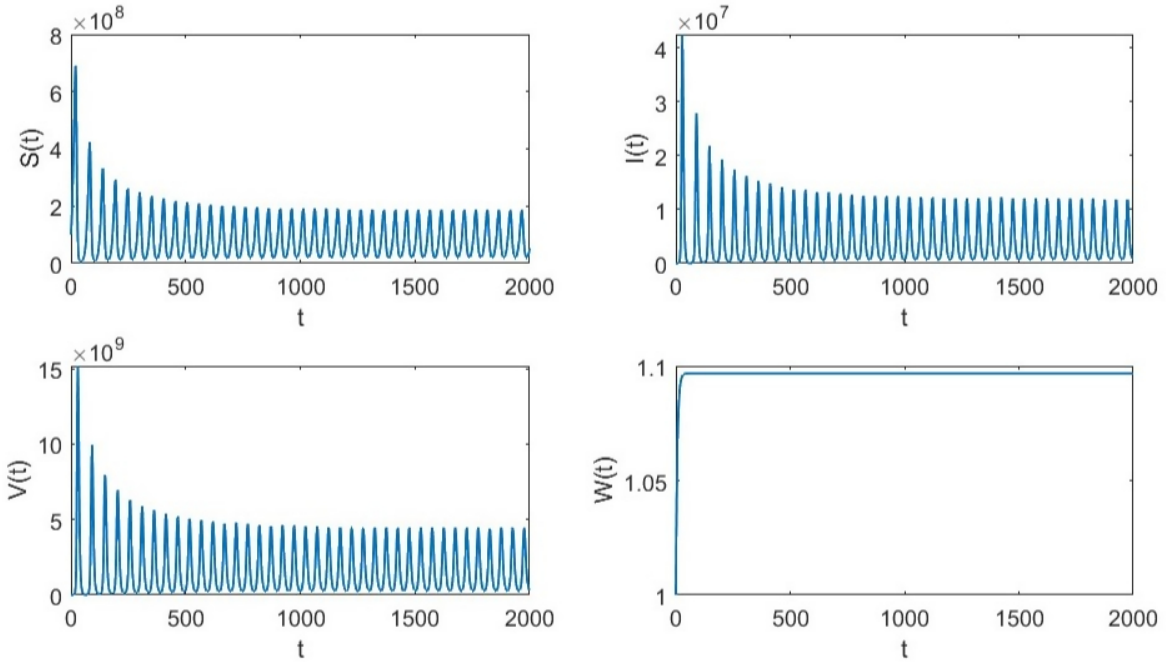

Fig. 4.2. Dynamical behavior of system (2.1) around the equilibrium point E^* when $\tau = 2$, $\mu = 0.65$ and $\gamma = 2$.

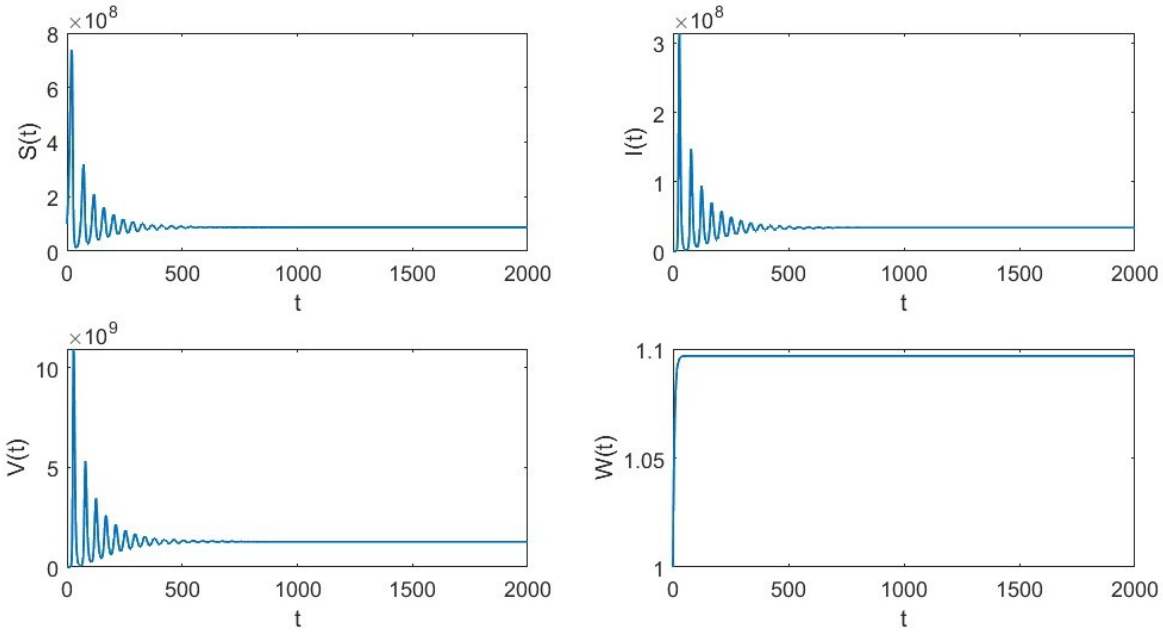

Fig. 4.3. The stability of the equilibrium point E^* when $\tau = 0.7 < \tau_0$.

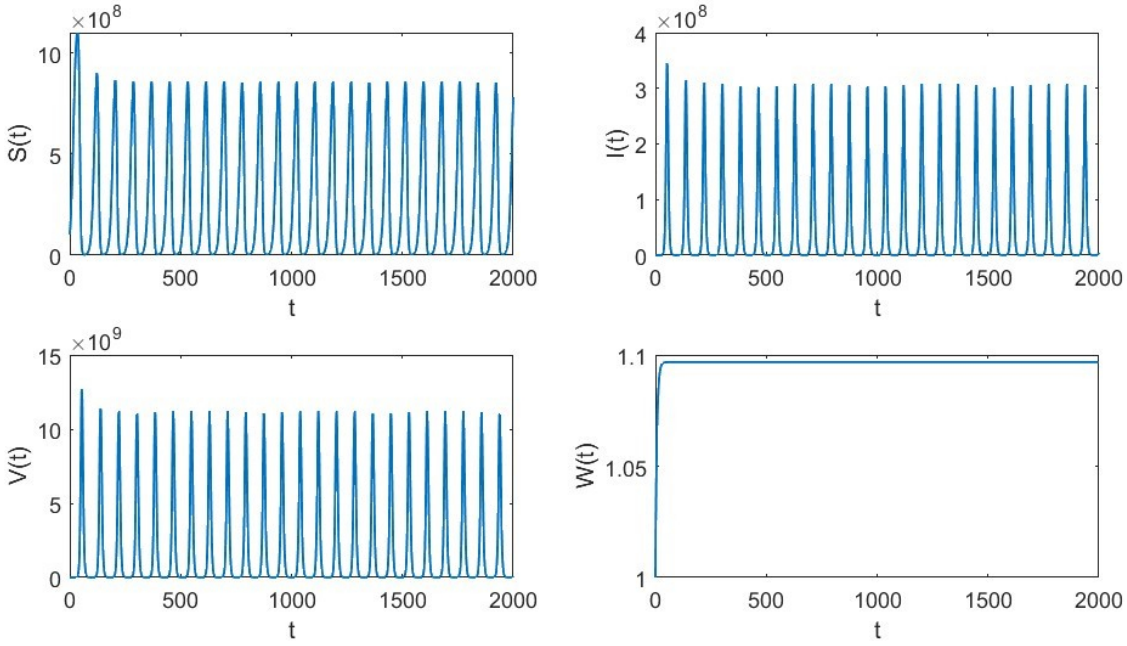

Fig. 4.4. The instability of the equilibrium point E^* when $\tau = 5 > \tau_0$.

5. CONCLUSION

This paper has presented a novel contribution by introducing an ordinary differential equation model with delay designed to comprehensively capture and analyze the intricate dynamics of tumor cells following the administration of oncolytic viruses. Our model has carefully considered the role of the Coxsackie adenovirus receptor (CAR), as well as the influence of mitogen-activated protein kinase inhibitors, factors that have played pivotal roles in the interaction between the virus and the tumor microenvironment. By incorporating these crucial elements, our research seeks to provide a deeper understanding of the underlying mechanisms governing the response of tumor cells to oncolytic virus treatment. Through this innovative model, our aim has been to provide valuable information that can inform the development of more effective therapeutic strategies to combat cancer. For that, we have proven that our proposed model is mathematically and biologically meaningful through its existence, non-negativity, and boundedness of solution. We have explored the equilibrium points of the model and have identified three possible steady states. The first, E_0, represents a state where there are no cells (uninfected or infected) and no virus particles. This equilibrium may not have biological relevance, as it reflects the non-existence of tumor cells and virus particles. The second, E_1, describes where there are uninfected tumor cells at a constant concentration S_1, but no infected tumor cells or virus particles, and the average level of CAR molecules on the surface of the cells is at W_1. This equilibrium could represent a state where the virus fails to infect and spread in the tumor. The third, E^*, was an endemic equilibrium in which uninfected tumor cells, infected tumor cells, virus particles, and CAR molecules on the surface of the cells reached constant concentrations over time: S^*, I^*, V^*, and W^*, respectively. This equilibrium could represent a coexistence between the tumor cells, infected cells, and the virus. Furthermore, an examination of the local stability of these three equilibrium points has been carried out employing the characteristic equation. Moreover, the global stability of the equilibrium point E_1 has been established by employing

an appropriate Lyapunov function. In addition to the stability analysis of the equilibria, we have also investigated the effects of time delay on the dynamics of the system. Our analysis has revealed that the introduction of a time delay parameter can lead to a Hopf bifurcation at the equilibrium point E^*, inducing a shift in equilibrium from a stable steady state to a stable limit cycle oscillation. Our numerical experiments additionally have validated the theoretical findings, demonstrating the impact of time delay on the system's behavior and the emergence of the Hopf bifurcation. Overall, our study has highlighted the importance of considering the time delay in modeling the dynamics of oncolytic virus therapy and has provided valuable information on the long-term behavior of the system.

ACKNOWLEDGEMENTS

We would like to extend our appreciation to everyone who contributed their knowledge and ideas to this research, regardless of how small a way. The editors and anonymous referees are thanked by the authors for their insightful criticism and recommendations, which significantly increased the caliber of this work.

REFERENCES

1. Cuschieri, J. & Maier, R. V. (2005) Mitogen-activated protein kinase (MAPK), *Critical care medicine*, **33**, S417–S419.
2. Everts, B. & van der Poel, H. G. (2005) Replication-selective oncolytic viruses in the treatment of cancer, *Cancer gene therapy*, **12**, 141–161.
3. Friedman, A., Tian, J. P., Fulci, G., Chiocca, E. A. & Wang, J. (2006) Glioma virotherapy: The effects of innate immune suppression and increased viral replication capacity, *Cancer Research*, **66**, 2314–2319.
4. Hale, J. & Verduyn Lunel, S.M. (1993) *Introduction to Functional Differential Equations*. New York, NY: Springer.
5. Huo, H., Zhao, H. & Zhu, L. (2015) The effect of vaccines on backward bifurcation in a fractional order HIV model, *Nonlinear Anal., Real World Appl.*, **26**, 289–305.
6. Linsenmann, T., Jawork, A., Westermaier, T., Homola, G., Monoranu, C. M. & Vince, G. H. (2019) Tumor growth under rhGM-CSF application in an orthotopic rodent glioma model, *Oncolytic Letter*, **17**(6), 4843–4850.
7. Nono, M. K. & Ngouonkadi, E. M. (2020) Synergistic effects of oncolytic adenovirus and MEK inhibitors on glioma treatment dynamics: Analysis and optimal control, *Applied Mathematical Sciences*, **14**(16), 781–800.
8. Okamoto, K. W., Priyanga, A. I. & Petty, T. D. (2014) Modeling oncolytic virotherapy: Is complete tumor-tropism too much of a good thing?, *Journal of Theoretical Biology*, **358**, 166–178.
9. Wunder, T., Schmid, K., Wicklein, D., Groitl, P., Dobner, T., Lange, T., Anders, M. & Schumacher, U. (2013) Expression of the coxsackie adenovirus receptor in neuroendocrine lung cancers and its implications for oncolytic adenoviral infection, *Cancer gene therapy*, **20**, 25–32.
10. YouShan, T. & Guo, Q. (2008) A mathematical model of combined therapies against cancer using viruses and inhibitors, *Science in China Series A: Mathematics*, **51**(12), 2315–2329.
11. Zurakowski, R. & Wodarz, D. (2007) Model-driven approaches for in vitro combination therapy using ONYX-015 replicating oncolytic adenovirus, *J Theoret Biol*, **245**, 1–8.

