

Analysis of the dynamics of a model using ONYX-015 adenoviruses in cancer therapy

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Abstract

Cancerous cells are a danger to the human organism. They can originate in any cell in the body. Although various cancer treatments exist, it has been shown that they are effective in some cases but less so in others. For this reason, drawing on the study by Yongmei Su and al, we propose a dynamic study that models the treatment of a tumor using adenoviruses. Despite the fact that the disease-free equilibrium point is unconditionally unstable, our study shows that the internal equilibrium point, under certain conditions, is locally asymptotically and globally stable.

Keywords: ONYX-015 adenovirus, cancer therapy, tumor cells, boundedness, permanence, Lyapunov function, equilibrium, local stability, global stability

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1 Introduction

Cancer represents an abnormality in the various stages of cellular regulation, namely cell lifespan, division, and/or differentiation. This dysfunction in the body triggers a set of mechanisms that the body employs to protect cancerous cells. This protection is modeled by a positive coefficient denoted by ε . In this article, we draw inspiration from the work of Yongmei Su et al. published in [1]. They focused on virotherapy as an innovative treatment approach. Specifically, the authors analytically studied the local stability of the disease-free equilibrium and the disease equilibrium. They then succeeded in controlling the inhibitor parameter u that renders the diseased equilibrium unstable. Their main findings are:

- Equilibrium without illness is inherently unstable.

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- The disease equilibrium is stable provided that there is no internal equilibrium.
- The disease equilibrium is unstable under the condition that internal equilibrium exists.

By examining the conditions for the existence of the internal equilibrium point, the authors determine the optimal value of the inhibitor parameter u that promotes the production of Coxsackie-Adenovirus Receptors (CAR) (see [7]), that is, the penetration strength of the viruses into the tumor necessary to destabilize the disease equilibrium point. Based on their study, it can be stated that the patient can neither be cured of the tumor nor live long-term with the disease. To address this shortcoming, we propose a formal and rigorous proof of the local and global stability of the internal equilibrium point through the construction of a Lyapunov function. Our approach allows us to control the disease by helping the patient live long-term with the disease. In this paper, we start from the model of [1], namely

$$\begin{cases} \frac{dw_1}{dt} = (1-u)\rho w_1 \left(1 - \frac{w_1 + w_2}{K}\right) - \frac{dw_1 w_3 w_4}{w_1 + w_2 + \varepsilon}, \\ \frac{dw_2}{dt} = \frac{dw_1 w_3 w_4}{w_1 + w_2 + \varepsilon} - (1-u)g w_2, \\ \frac{dw_3}{dt} = b(1-u)g w_2 - \frac{dw_1 w_3 w_4}{w_1 + w_2 + \varepsilon} - \gamma w_3, \\ \frac{dw_4}{dt} = au(m - w_4) - q w_4. \end{cases} \quad (1)$$

With $(\rho, d, \varepsilon, g, \gamma, a, q, b, m) \in (\mathbb{R}_+)^9$, $u \in]0;1[$ and $w_1 = w_1(t), w_2 = w_2(t), w_3 = w_3(t), w_4 = w_4(t) \in C^1(\mathbb{R}_+; \mathbb{R})$. Where

w_1 : density of cancerous cells not yet infected by the virus.

w_2 : density of cancerous cells infected with the virus.

w_3 : virus density expressed as cell density.

w_4 : total receptor density in the tumor.

ρ : the natural growth rate of the cancerous tumor.

K : cancer cell size.

u : the MEK inhibitor intensity parameter, which varies between 0 and 1.

d : the coefficient of infection of a tumor cell by the virus.

g : the mortality rate of virus-infected tumor cells.

b : the maximum size of new viruses resulting from the bursting of an infected tumor cell.

γ : the mortality rate of the virus.

a : the rate of CAR production by cells.

m : the number of receptors produced by tumor cells.

q : the rate of CAR loss from the cell surface.

ε : measures the protection afforded to cancerous cells by the dysfunction of the organism. It is expressed in cell numbers.

At the start of adenovirus therapy, at time $t_0 = 0$ we have the following densities: $w_1(0) > 0$, $w_3(0) > 0$, $w_4(0) > 0$ and $w_2(0) = 0$. In this paper, we establish the criteria under which the solutions are bounded and persistent. We then demonstrate the local stability of the internal equilibrium point. Finally, we present the conditions that determine the global stability of the internal equilibrium point.

Remark 1.1. The ONYX-015 adenovirus is a type of tumor-killing virus. It infects and replicates inside cancerous cells, causing cell lysis. The new viruses released from the bursting cells go on to infect other cancerous cells. In this article, given that cell lysis determines the dynamic process

of cancerous cell infection, we assume that in the third equation of system (1), the negative terms cannot outweigh the virus production term. Thus we have the following hypothesis:

(H1) : $w_3(t)$ is strictly increasing for all $t \geq 0$.

2 Boundedness and permanence of the Model

Let (w_1, w_2, w_3, w_4) be a non-extendable solution of system (1), defined on $[0, T)$, where $T \in (0, +\infty)$.

Let

$$\mathbb{R}_+^4 = \left\{ (w_1, w_2, w_3, w_4) \in \mathbb{R}^4 \mid w_1 \geq 0, w_2 \geq 0, w_3 \geq 0, w_4 \geq 0 \right\}$$

denote the positive cone (or positive quadrant) of $\mathbb{R}^4$. Its interior is

$$\text{int}(\mathbb{R}_+^4) = \left\{ (w_1, w_2, w_3, w_4) \in \mathbb{R}^4 \mid w_1 > 0, w_2 > 0, w_3 > 0, w_4 > 0 \right\},$$

and its boundary is denoted by $\partial\mathbb{R}_+^4$.

Lemma 2.1. *The positive cone of $\mathbb{R}^4$ is invariant to the system (1).*

Proof. In this section, we show that all state variables remain nonnegative for every $t \geq 0$. Let $w(t) = (w_1, w_2, w_3, w_4)^T$ and write system (1) in compact form

$$\frac{dw(t)}{dt} = f(w(t)),$$

where f is a C^1 vector field associated with system (1). It suffices to verify that, for $i \in \{1, 2, 3, 4\}$, $f_i(w) \geq 0$ when $w_i = 0$, $w_j \geq 0$ for all $j \neq i$, and $w \in \mathbb{R}_+^4$.

The following results can be obtained from system (1):

$$\text{If } w_1 = 0, w_2 \geq 0, w_3 \geq 0, \text{ and } w_4 \geq 0, \quad f_1(w) = 0, \quad (2)$$

$$\text{if } w_2 = 0, w_1 \geq 0, w_3 \geq 0, \text{ and } w_4 \geq 0, \quad f_2(w) = \frac{dw_1 w_3 w_4}{w_1 + \varepsilon} \geq 0, \quad (3)$$

$$\text{if } w_3 = 0, w_1 \geq 0, w_2 \geq 0, \text{ and } w_4 \geq 0, \quad f_3(w) = b(1-u)g w_2 \geq 0, \quad (4)$$

$$\text{if } w_4 = 0, w_1 \geq 0, w_2 \geq 0, \text{ and } w_3 \geq 0, \quad f_4(w) = aum \geq 0. \quad (5)$$

Based on (2)–(5) and given that $\mathbb{R}_+^4$ is a closed and convex set, by Nagumo's theorem, it is positively invariant under the action of the flux of system (1). Consequently, all solutions originating from $\mathbb{R}_+^4$ remain confined to the positive quadrant of $\mathbb{R}^4$ for all $t \geq 0$. $\square$

If we set

$$M_1 = K, \quad M_2 = \frac{dM_3 M_4}{(1-u)g}, \quad M_3 = \frac{b(1-u)gK}{\gamma},$$

$$M_4 = \max \left\{ w_4(0), \frac{aum}{au+q} \right\},$$

$$\underline{w}_1 = K \left(1 - \frac{M_2}{K} - \frac{dM_4 M_3}{(1-u)\rho\varepsilon} \right),$$

$$\underline{w}_2 = \frac{d \underline{w}_1 \underline{w}_3 \underline{w}_4}{(K+\varepsilon)(1-u)g}, \quad \underline{w}_3 = \frac{b(1-u)g \underline{w}_2}{dM_4 + \gamma},$$

$$\underline{w}_4 = \min \left\{ w_4(0), \frac{aum}{au+q} \right\}, \quad L_M = \frac{M_2}{K} + \frac{dM_4 M_3}{(1-u)\rho\varepsilon}.$$

Then we have the following theorem.

Theorem 2.2. *The model is permanent if $L_M < 1$.*

Proof. Throughout this proof, $t \in]0; +\infty[$.

We will show that there exist $M > 0$ and $m_{\underline{w}} > 0$ such that

$$\max \{ \limsup w_1(t), \limsup w_2(t), \limsup w_3(t), \limsup w_4(t) \} \leq M$$

and

$$\min \{ \liminf w_1(t), \liminf w_2(t), \liminf w_3(t), \liminf w_4(t) \} \geq m_{\underline{w}}.$$

From the CAR receiver equation, we have:

$$\text{if } w_4(0) < \frac{aum}{au+q}, \text{ then } w_4(0) \leq w(t) < \frac{aum}{au+q}.$$

If

$$\frac{aum}{au+q} < w_4(0),$$

then

$$\frac{aum}{au+q} < w_4(t) \leq w_4(0).$$

We have

$$\lim_{t \rightarrow +\infty} \sup w_4(t) \leq M_4.$$

In the same way,

$$\lim_{t \rightarrow +\infty} \inf w_4(t) \geq \underline{w}_4.$$

So w_4 is bounded and permanent in $]0; +\infty[$.

Based on the equations for cancerous cells w_1 and w_2 , for all $t > 0$,

$$\frac{dw_1(t)}{dt} + \frac{dw_2(t)}{dt} = (1-u)\rho w_1(t) \left(1 - \frac{w_1(t) + w_2(t)}{K} \right) - (1-u)gw_2(t).$$

Since positive invariance ensures that all variables remain positive, we have: for all $t > 0$, $w_1(t) \leq w_1(t) + w_2(t)$ and $-(1-u)gw_2(t) \leq 0$.

So, taking these two adjustments into account, we have

$$\frac{d(w_1(t) + w_2(t))}{dt} \leq (1-u)\rho \left(1 - \frac{w_1(t) + w_2(t)}{K} \right) (w_1(t) + w_2(t)).$$

Let $S(t) = w_1(t) + w_2(t)$, so

$$\frac{dS(t)}{dt} \leq (1-u)\rho \left(1 - \frac{S(t)}{K} \right) S(t).$$

Using a comparison argument for differential equations, we show that for all $t > 0$,

$$S(t) \leq \frac{(1-u)\rho C}{e^{-(1-u)\rho t} + \frac{(1-u)\rho C}{K}}, \quad C \in \mathbb{R}.$$

We have

$$\lim_{t \rightarrow +\infty} \sup S(t) \leq K,$$

which implies that

$$\lim_{t \rightarrow +\infty} \sup (w_1(t) + w_2(t)) \leq K.$$

We have from the cancerous cell equation w_1 and for all $t > 0$,

$$\frac{dw_1(t)}{dt} < \rho \left(1 - \frac{w_1(t)}{K} \right) w_1(t).$$

Using a comparison argument for differential equations, we show that for all $t > 0$,

$$w_1(t) < \frac{\rho C_1}{e^{-\rho t} + \frac{\rho C_1}{K}}, \quad C_1 \in \mathbb{R}.$$

We have

$$\lim_{t \rightarrow +\infty} \sup w_1(t) < K.$$

From the equation of the virus w_3 , we have for all $t > 0$,

$$\frac{dw_3(t)}{dt} < b(1-u)gK - \gamma w_3(t),$$

because $w_1(t) + w_2(t) \leq K$. Using the same reasoning as in the increase of w_1 , we show that for all $t > 0$,

$$w_3(t) < \frac{b(1-u)gK}{\gamma} + C_3 e^{-\gamma t}, \quad C_3 \in \mathbb{R}.$$

So

$$\lim_{t \rightarrow +\infty} \sup w_3(t) < M_3.$$

From the equation of infected cancerous cells, we have for all $t > 0$,

$$\frac{dw_2(t)}{dt} \leq dM_3M_4 - (1-u)gw_2(t).$$

Using the same reasoning as in the increase of w_1 , we have for all $t > 0$,

$$w_2(t) < \frac{dM_3M_4}{(1-u)g} + C_2 e^{-(1-u)gt}, \quad C_2 \in \mathbb{R}.$$

So

$$\lim_{t \rightarrow +\infty} \sup w_2(t) < M_2.$$

From the cancerous cell equation w_1 , and for $t > 0$,

$$\frac{dw_1}{dt} > (1-u)\rho w_1 \left(1 - \frac{M_2}{K} - \frac{dM_4M_3}{(1-u)\rho\epsilon} - \frac{w_1}{K} \right).$$

It follows that

$$\liminf_{t \rightarrow +\infty} w_1(t) \geq \underline{w}_1.$$

Based on **(H1)**, there exists a positive constant $\underline{w}_3$ such that $0 < \underline{w}_3 < M_3$ for all $t > 0$ and

$$\underline{w}_3 \leq \liminf_{t \rightarrow +\infty} w_3(t).$$

Considering the equation for infected cancerous cells, we have for all $t > 0$,

$$\frac{dw_2}{dt} > \frac{dw_1 w_3 w_4}{K + \varepsilon} - (1 - u)gw_2(t).$$

Using a comparison argument from differential equations, it follows that

$$\liminf_{t \rightarrow +\infty} w_2(t) \geq \underline{w}_2.$$

We have from the virus equation w_3 and for $t > 0$,

$$\frac{dw_3}{dt} > b(1 - u)g\underline{w}_2 - (dM_4 + \gamma)w_3(t).$$

Similarly, by using a comparison argument for differential equations,

$$\liminf_{t \rightarrow +\infty} w_3(t) \geq \underline{w}_3.$$

Designating $m_{\underline{w}} = \min(\underline{w}_1, \underline{w}_2, \underline{w}_3, \underline{w}_4) > 0$ and $M = \max(M_1, M_2, M_3, M_4)$, we have

$$\max\{\limsup w_1(t), \limsup w_2(t), \limsup w_3(t), \limsup w_4(t)\} \leq M$$

and

$$\min\{\liminf w_1(t), \liminf w_2(t), \liminf w_3(t), \liminf w_4(t)\} \geq m_{\underline{w}}.$$

□

Remark 2.3. The system is invariant in the strictly positive quadrant and is bounded for all $t > 0$. Therefore, the system is permanent.

3 Equilibrium points of the model

Building on the work of Yongmei Su et al. [1], we show that there are two trivial equilibrium points:

$$E_0^* = \left(0, 0, 0, \frac{aum}{au + q}\right)$$

and

$$E_1^* = \left(K, 0, 0, \frac{aum}{au + q}\right).$$

There is also an inner equilibrium point $E_2^* = (w_1^*, w_2^*, w_3^*, w_4^*)$ if

$$b > 1 + \gamma\Theta, \quad \Theta = \frac{(au + q)(K + \varepsilon)}{dKaum},$$

where

$$\begin{aligned} w_1^* &= \frac{\sigma + \sqrt{\sigma^2 + 4(b-1)K\gamma dw_4^* \rho g \varepsilon}}{2(b-1)dw_4^* \rho}, \\ w_2^* &= \left[\frac{(b-1)dw_4^*}{\gamma} - 1 \right] w_1^* - \varepsilon, \\ w_3^* &= \frac{(b-1)(1-u)g}{\gamma} w_2^*, \quad w_4^* = \frac{aum}{au + q}. \end{aligned}$$

Here,

$$\sigma = \rho\gamma(K + \varepsilon) - K(b-1)gdw_4^* + K\gamma g.$$

4 Analysis of the local stability of the internal equilibrium point

In this section, we study the local stability of the equilibrium point E_2^* of the model. We consider the Jacobian matrix of the linearized model in the vicinity of the equilibrium point E_2^* :

$$J(E_2^*) = \left(A_{mj}^{(2)} \right)_{1 \leq m, j \leq 4},$$

with

$$\begin{aligned} A_{m1}^{(2)} &= \frac{\partial h_m(E_2^*)}{\partial w_1}, & A_{m2}^{(2)} &= \frac{\partial h_m(E_2^*)}{\partial w_2}, \\ A_{m3}^{(2)} &= \frac{\partial h_m(E_2^*)}{\partial w_3}, & A_{m4}^{(2)} &= \frac{\partial h_m(E_2^*)}{\partial w_4}, \quad m = 1, 2, 3, 4, \end{aligned}$$

where

$$h_1(t) = (1-u)\rho w_1(t) \left(1 - \frac{w_1(t) + w_2(t)}{K} \right) - \frac{dw_1(t)w_3(t)w_4(t)}{w_1(t) + w_2(t) + \varepsilon}, \quad (6)$$

$$h_2(t) = \frac{dw_1(t)w_3(t)w_4(t)}{w_1(t) + w_2(t) + \varepsilon} - (1-u)gw_2(t), \quad (7)$$

$$h_3(t) = b(1-u)gw_2(t) - \frac{dw_1(t)w_3(t)w_4(t)}{w_1(t) + w_2(t) + \varepsilon} - \gamma w_3(t), \quad (8)$$

$$h_4(t) = au(m - w_4(t)) - qw_4(t). \quad (9)$$

The characteristic polynomial associated with the Jacobian matrix $J(E_2^*)$ of the linearized system near the equilibrium point E_2^* is

$$P_2(\lambda) = \det(J(E_2^*) - \lambda I_4),$$

where I_4 is the identity matrix of order 4. We obtain

$$\begin{aligned} A_{11}^{(2)} &= -\frac{1}{K}(1-u)\rho w_1^* + \frac{dw_1^*w_3^*w_4^*}{(w_1^* + w_2^* + \varepsilon)^2}, & A_{12}^{(2)} &= A_{11}^{(2)}, \\ A_{13}^{(2)} &= -\frac{(1-u)gw_2^*}{w_3^*} = -\frac{\gamma}{b-1}, & A_{14}^{(2)} &= -\frac{(1-u)(au+q)gw_2^*}{aum}, \\ A_{21}^{(2)} &= \frac{(1-u)gw_2^*}{w_1^*} - \frac{(1-u)gw_2^*}{w_1^* + w_2^* + \varepsilon}, \\ A_{22}^{(2)} &= -(1-u)g - \frac{(1-u)gw_2^*}{w_1^* + w_2^* + \varepsilon}, & A_{23}^{(2)} &= -A_{13}^{(2)}, & A_{24}^{(2)} &= -A_{14}^{(2)}, \\ A_{31}^{(2)} &= -A_{21}^{(2)}, & A_{32}^{(2)} &= b(1-u)g + \frac{(1-u)gw_2^*}{w_1^* + w_2^* + \varepsilon}, \\ A_{33}^{(2)} &= A_{13}^{(2)} - \gamma, & A_{34}^{(2)} &= A_{14}^{(2)}, \\ A_{41}^{(2)} &= 0, & A_{42}^{(2)} &= 0, & A_{43}^{(2)} &= 0, & A_{44}^{(2)} &= -au - q. \end{aligned}$$

The calculation of $P_2(\lambda)$ gives

$$\begin{aligned} P_2(\lambda) &= \left(A_{44}^{(2)} - \lambda \right) \left(-\lambda^3 + \left(A_{11}^{(2)} + A_{22}^{(2)} + A_{33}^{(2)} \right) \lambda^2 \right. \\ &\quad \left. + \left(A_{11}^{(2)} A_{21}^{(2)} - A_{11}^{(2)} A_{22}^{(2)} - A_{21}^{(2)} A_{13}^{(2)} - A_{11}^{(2)} A_{33}^{(2)} \right) \right) \end{aligned}$$

$$\begin{aligned}
& -A_{13}^{(2)}A_{32}^{(2)} - A_{22}^{(2)}A_{33}^{(2)})\lambda \\
& -A_{11}^{(2)}A_{21}^{(2)}A_{33}^{(2)} + A_{11}^{(2)}A_{21}^{(2)}A_{13}^{(2)} + A_{11}^{(2)}A_{13}^{(2)}A_{32}^{(2)} \\
& + A_{21}^{(2)}A_{13}^{(2)}A_{22}^{(2)} + A_{11}^{(2)}A_{22}^{(2)}A_{33}^{(2)} + A_{21}^{(2)}A_{13}^{(2)}A_{32}^{(2)}).
\end{aligned}$$

Let

$$Q(\lambda) = \lambda^3 + c_2\lambda^2 + c_1\lambda + c_0,$$

with

$$c_2 = -A_{11}^{(2)} - A_{22}^{(2)} - A_{33}^{(2)},$$

$$\begin{aligned}
c_1 = & -A_{11}^{(2)}A_{21}^{(2)} + A_{11}^{(2)}A_{22}^{(2)} + A_{21}^{(2)}A_{13}^{(2)} + A_{11}^{(2)}A_{33}^{(2)} \\
& + A_{13}^{(2)}A_{32}^{(2)} + A_{22}^{(2)}A_{33}^{(2)},
\end{aligned}$$

and

$$\begin{aligned}
c_0 = & A_{11}^{(2)}A_{21}^{(2)}A_{33}^{(2)} - A_{11}^{(2)}A_{21}^{(2)}A_{13}^{(2)} - A_{11}^{(2)}A_{13}^{(2)}A_{32}^{(2)} \\
& - A_{21}^{(2)}A_{13}^{(2)}A_{22}^{(2)} - A_{11}^{(2)}A_{22}^{(2)}A_{33}^{(2)} - A_{21}^{(2)}A_{13}^{(2)}A_{32}^{(2)}.
\end{aligned}$$

So,

$$P_2(\lambda) = (\lambda - A_{44}^{(2)})Q(\lambda).$$

Theorem 4.1. E_2^* is locally asymptotically stable if $b > 1 + \gamma\Theta$ and $0 < K < \nu w_1^*$, with

$$\nu = \frac{\rho}{g} \left(\frac{w_2^*}{w_1^*} \right)^{-1} > 1.$$

Proof. It is sufficient that the equation $Q(\lambda) = 0$ has solutions with a negative real part. According to the Routh–Hurwitz criterion, this equation admits solutions with a negative real part if and only if

$$c_2 > 0, \quad c_0 > 0, \quad c_2c_1 - c_0 > 0.$$

By replacing the coefficients of the Jacobian matrix of the linearized system in the vicinity of the equilibrium point E_2^* present in the expression of c_k , $k = 0, 1, 2$, by their values, we obtain:

$$\begin{aligned}
c_2 = & \frac{1}{K}(1-u)\rho w_1^* - \frac{dw_1^*w_3^*w_4^*}{(w_1^* + w_2^* + \varepsilon)^2} + (1-u)g + \frac{(1-u)gw_2^*}{w_1^* + w_2^* + \varepsilon} \\
& + \frac{\gamma}{b-1} + \gamma.
\end{aligned}$$

Taking into account the relationship

$$\frac{dw_1^*w_3^*w_4^*}{w_1^* + w_2^* + \varepsilon} - (1-u)gw_2^* = 0 \tag{10}$$

in determining the inner equilibrium point, we have

$$-\frac{dw_1^*w_3^*w_4^*}{(w_1^* + w_2^* + \varepsilon)^2} + \frac{(1-u)gw_2^*}{w_1^* + w_2^* + \varepsilon} = 0.$$

So,

$$c_2 = \frac{1}{K}(1-u)\rho w_1^* + (1-u)g + \frac{b}{b-1}\gamma.$$

Therefore, $c_2 > 0$ because all its components are so.

$$\begin{aligned} c_0 &= A_{11}^{(2)} A_{21}^{(2)} \left(A_{13}^{(2)} - \gamma - A_{13}^{(2)} \right) - A_{11}^{(2)} A_{13}^{(2)} A_{32}^{(2)} \\ &\quad - A_{11}^{(2)} A_{22}^{(2)} \left(A_{13}^{(2)} - \gamma \right) - A_{21}^{(2)} A_{13}^{(2)} \left(-(1-u)g + b(1-u)g \right), \\ c_0 &= \gamma A_{11}^{(2)} \left(-A_{21}^{(2)} + A_{22}^{(2)} \right) - A_{11}^{(2)} A_{13}^{(2)} \left(A_{32}^{(2)} + A_{22}^{(2)} \right) \\ &\quad - A_{21}^{(2)} A_{13}^{(2)} (b-1)(1-u)g, \\ c_0 &= \gamma A_{11}^{(2)} \left(-\frac{(1-u)gw_2^*}{w_1^*} - (1-u)g \right) \\ &\quad - A_{11}^{(2)} A_{13}^{(2)} (b(1-u)g - (1-u)g) - A_{21}^{(2)} A_{13}^{(2)} (b-1)(1-u)g, \\ c_0 &= \gamma A_{11}^{(2)} \left(-\frac{(1-u)gw_2^*}{w_1^*} - (1-u)g \right) \\ &\quad - A_{13}^{(2)} (b-1)(1-u)g \left(A_{11}^{(2)} + A_{21}^{(2)} \right). \end{aligned}$$

Therefore,

$$\begin{aligned} A_{11}^{(2)} + A_{21}^{(2)} &= -\frac{1}{K}(1-u)\rho w_1^* + \frac{dw_1^* w_3^* w_4^*}{(w_1^* + w_2^* + \varepsilon)^2} \\ &\quad + \frac{(1-u)gw_2^*}{w_1^*} - \frac{(1-u)gw_2^*}{w_1^* + w_2^* + \varepsilon}, \\ c_0 &= \gamma A_{11}^{(2)} \left(-\frac{(1-u)gw_2^*}{w_1^*} - (1-u)g \right) \\ &\quad - A_{13}^{(2)} (b-1)(1-u)g \left(-\frac{1}{K}(1-u)\rho w_1^* + \frac{(1-u)gw_2^*}{w_1^*} \right). \end{aligned}$$

Because taking into account (10), we have

$$\begin{aligned} c_0 &= \gamma \left(-\frac{1}{K}(1-u)\rho w_1^* + \frac{dw_1^* w_3^* w_4^*}{(w_1^* + w_2^* + \varepsilon)^2} \right) \left(-\frac{(1-u)gw_2^*}{w_1^*} - (1-u)g \right) \\ &\quad + \frac{\gamma}{b-1} (b-1)(1-u)g \left(-\frac{1}{K}(1-u)\rho w_1^* + \frac{(1-u)gw_2^*}{w_1^*} \right). \end{aligned}$$

Taking into account (10), we have

$$\begin{aligned} c_0 &= \frac{1}{K}(1-u)^2 \rho g \gamma w_2^* - \frac{(1-u)gw_2^*}{w_1^* + w_2^* + \varepsilon} \left(\frac{(1-u)g\gamma w_2^* + (1-u)g\gamma w_1^*}{w_1^*} \right) + \frac{(1-u)^2 g^2 \gamma w_2^*}{w_1^*}, \\ c_0 &= \frac{1}{K}(1-u)^2 \rho g \gamma w_2^* + \frac{(1-u)^2 g^2 \gamma w_2^*}{w_1^*} - \frac{(1-u)^2 g^2 \gamma w_2^*}{w_1^*} \left(\frac{w_1^* + w_2^*}{w_1^* + w_2^* + \varepsilon} \right), \\ c_0 &= \frac{1}{K}(1-u)^2 \rho g \gamma w_2^* + \frac{(1-u)^2 g^2 \gamma w_2^*}{w_1^*} \left(\frac{\varepsilon}{w_1^* + w_2^* + \varepsilon} \right). \end{aligned}$$

Thus, $c_0 > 0$ because all its components are so.

$$\begin{aligned}
c_1 &= A_{11}^{(2)} \left(-A_{21}^{(2)} + A_{22}^{(2)} + A_{33}^{(2)} \right) + A_{13}^{(2)} \left(A_{21}^{(2)} + A_{32}^{(2)} \right) + A_{22}^{(2)} \left(A_{13}^{(2)} - \gamma \right). \\
c_1 &= \left(-\frac{1}{K}(1-u)\rho w_1^* + \frac{dw_1^* w_3^* w_4^*}{(w_1^* + w_2^* + \varepsilon)^2} \right) \left(-\frac{(1-u)gw_2^*}{w_1^*} - (1-u)g \right) \\
&\quad - \frac{b\gamma}{b-1} \left(-\frac{1}{K}(1-u)\rho w_1^* - (1-u)g \right) \\
&\quad - \frac{\gamma}{b-1} \left(\frac{(1-u)gw_2^*}{w_1^*} + b(1-u)g \right).
\end{aligned}$$

Given (10), we have

$$\begin{aligned}
c_1 &= \frac{1}{K}(1-u)^2 \rho g (w_1^* + w_2^*) - \frac{(1-u)^2 g^2 w_2^*}{w_1^*} \left(\frac{w_1^* + w_2^*}{w_1^* + w_2^* + \varepsilon} \right) \\
&\quad + \frac{1}{K}(1-u)\rho w_1^* \frac{b\gamma}{b-1} - \frac{\gamma}{b-1} \frac{(1-u)gw_2^*}{w_1^*}. \\
c_2 c_1 - c_0 &= \frac{1}{K^2}(1-u)^3 \rho^2 g w_1^* (w_1^* + w_2^*) + \frac{1}{K^2}(1-u)^2 \rho^2 \frac{b}{b-1} \gamma (w_1^*)^2 \\
&\quad + \frac{1}{K}(1-u)^3 \rho g^2 (w_1^* + w_2^*) + \frac{1}{K}(1-u)^2 \rho g \frac{b}{b-1} \gamma w_1^* \\
&\quad + \frac{1}{K}(1-u)^2 \rho g (w_1^* + w_2^*) \frac{b}{b-1} \gamma + \frac{1}{K}(1-u)\rho w_1^* \frac{b^2}{(b-1)^2} \gamma^2 \\
&\quad - \frac{1}{K}(1-u)^3 \rho g^2 w_2^* \left(\frac{w_1^* + w_2^*}{w_1^* + w_2^* + \varepsilon} \right) - \frac{1}{K}(1-u)^2 \rho g w_2^* \frac{\gamma}{b-1} \\
&\quad - (1-u)^3 g^3 \frac{w_2^*}{w_1^*} \left(\frac{w_1^* + w_2^*}{w_1^* + w_2^* + \varepsilon} \right) \\
&\quad - (1-u)^2 g^2 \frac{w_2^*}{w_1^*} \left(\frac{w_1^* + w_2^*}{w_1^* + w_2^* + \varepsilon} \right) \frac{b}{b-1} \gamma \\
&\quad - (1-u)g \frac{w_2^*}{w_1^*} \frac{b}{(b-1)^2} \gamma^2 - \frac{1}{K}(1-u)^2 \rho g \gamma w_2^* \\
&\quad - (1-u)^2 g^2 \gamma \frac{w_2^*}{w_1^*} \left(\frac{\varepsilon}{w_1^* + w_2^* + \varepsilon} \right) - (1-u)^2 g^2 \frac{w_2^*}{w_1^*} \frac{\gamma}{b-1}. \\
c_2 c_1 - c_0 &> \frac{b}{(b-1)^2} \gamma^2 (1-u) \left(\frac{1}{K} \rho b w_1^* - g \frac{w_2^*}{w_1^*} \right) \\
&\quad + (1-u)^3 (w_1^* + w_2^*) g \left(\frac{1}{K^2} \rho^2 w_1^* + \frac{g}{w_1^* + w_2^* + \varepsilon} \left(\frac{1}{K} \rho (w_1^* + \varepsilon) - g \frac{w_2^*}{w_1^*} \right) \right) \\
&\quad + (1-u)^2 \gamma \frac{b}{b-1} \left(\left(\frac{1}{K} \rho w_1^* + 2g + g \frac{w_2^*}{w_1^*} \right) \left(\frac{1}{K} \rho w_1^* - g \frac{w_2^*}{w_1^*} \right) + g^2 \left(\frac{w_2^*}{w_1^*} \right)^2 \right).
\end{aligned}$$

To have $c_2 c_1 - c_0 > 0$, it suffices that

$$\frac{1}{K} \rho b w_1^* - g \frac{w_2^*}{w_1^*} > 0, \quad \frac{1}{K} \rho (w_1^* + \varepsilon) - g \frac{w_2^*}{w_1^*} > 0,$$

and

$$\frac{1}{K} \rho w_1^* - g \frac{w_2^*}{w_1^*} > 0.$$

So, $c_2c_1 - c_0 > 0$ if

$$K < \min \left\{ b \frac{\rho (w_1^*)^2}{g w_2^*}, \frac{\rho w_1^*(w_1^* + \varepsilon)}{g w_2^*}, \frac{\rho (w_1^*)^2}{g w_2^*} \right\}.$$

As $\varepsilon > 0$ and

$$b > 1 + \frac{\gamma(au + q)(K + \varepsilon)}{dKaum},$$

then

$$\min \left\{ b \frac{\rho (w_1^*)^2}{g w_2^*}, \frac{\rho w_1^*(w_1^* + \varepsilon)}{g w_2^*}, \frac{\rho (w_1^*)^2}{g w_2^*} \right\} = \frac{\rho (w_1^*)^2}{g w_2^*}.$$

Let

$$\nu = \frac{\rho}{\delta} \left(\frac{w_2^*}{w_1^*} \right)^{-1}.$$

Therefore, $c_2c_1 - c_0 > 0$ if $K < \nu w_1^*$.

According to the Routh–Hurwitz criterion, this equation admits only solutions with a negative real part. So, the roots of P_2 have negative real parts. This means that E_2^* is locally stable. $\square$

Interpretation 4.1. In this part, based on the analysis of the local stability of the equilibrium points E_k^* , $k = 0, 1, 2$, we find that:

- 1- The equilibrium point E_0^* is unconditionally unstable.
- 2- If $b < 1 + \gamma\Theta$, the equilibrium point E_1^* is stable and it is unstable when $b > 1 + \gamma\Theta$. The stability condition of E_1^* implies the absence of the equilibrium point E_2^* . On the other hand, the instability condition of E_1^* implies the existence of E_2^* . Thus, the condition of existence of E_2^* shows that all points located on the axes are unstable. They cannot therefore attract the other solutions of the system.
- 3- If $b > 1 + \gamma\Theta$ and

$$\nu = \frac{\rho}{g} \left(\frac{w_2^*}{w_1^*} \right)^{-1} > 1,$$

then E_2^* is stable.

This stability condition shows that:

- If

$$\frac{\rho}{g} > \frac{w_2^*}{w_1^*} > 1,$$

virus-infected tumor cells outnumber tumor cells. So, the ratio of the proliferation coefficient of uninfected tumor cells to the mortality rate of virus-infected tumor cells is higher than the infection ratio. The high number of infected tumour cells is due to the fact that the intensity of the inhibitor promotes high production of the CAR receptor, which in turn facilitates infection of tumour cells by the virus. On the other hand, infected cancerous cells burst more slowly than tumors grow. This is because the high intensity of the inhibitor promoting CAR expression can cause cell cycle arrest, which inhibits the adenovirus life cycle. This is because (S)-phase is the phase of the cell cycle during which DNA is replicated, and adenovirus needs to lock cells in order to reproduce and induce cell lysis.

- If

$$\left(\frac{w_2^*}{w_1^*} \right)^{-1} > \frac{g}{\rho} > 1,$$

then tumor cells outnumber infected tumor cells. So, the inverse of the infection rate is higher than the ratio of the mortality rate of virus-infected tumor cells to the proliferation rate of tumor cells. As a result, the bursting of infected faster than tumor cell proliferation. This is because the intensity of the inhibitor does not cause cell cycle arrest. In (S)-phase, the adenovirus locks the cells. On the other hand, the high number of cancerous cells is due to the fact that the high number of cancerous cells, however, is due to the fact that the inhibitor's intensity does not promote CAR production, which makes it harder for the virus to infect tumor cells.

- If

$$\frac{w_2^*}{w_1^*} < 1 \quad \text{and} \quad \frac{\rho}{g} > 1,$$

then tumor cells outnumber infected tumor cells, and the proliferation coefficient of tumor cells is higher than the mortality rate of virus-infected tumor cells. This is due to a low level of inhibitor intensity resulting from the aggressiveness of the tumor. This results in low CAR expression on the tumor cell surface.

The stability of E_2^* allows us to conclude that cancerous cells, infected cancerous cells, the virus and the CAR receptor can cohabit in the long term.

5 Global stability of the model's interior equilibrium point

In this section, the ideal was to study the global stability of the E_0^* equilibrium point (the disease-free equilibrium). But since the disease-free equilibrium is unconditionally unstable, we present sufficient conditions that guarantee the global stability of the interior equilibrium point E_2^* for $b > 1 + \gamma\Theta$. In other words, whatever the initial conditions $w_1(0)$, $w_2(0)$, $w_3(0)$, and $w_4(0)$, infected or uninfected cancerous cells, viruses and receptors can "cohabit" in the long term. The task will be to construct a Lyapunov function appropriate for the model.

Let

$$l_1 = \frac{d}{w_1 + w_2 + \varepsilon}, \quad l_2 = \frac{d}{w_2^*(M_1 + M_2 + \varepsilon)}, \quad l_3 = \frac{w_3^* w_4^*}{w_1^* + w_2^* + \varepsilon}.$$

$$\beta_{11} = \frac{2w_1^*}{w_2^* w_3^*} l_3 + \frac{w_1^* M_4}{w_2^* w_3^*} + \frac{w_1^*}{w_2^*} + \frac{w_4^*}{w_2^*} + \frac{w_1^*}{b w_3} l_3 + \frac{M_4}{b},$$

$$\beta_{12} = \frac{(1-u)\rho w_1^*}{K w_2^* w_3^* l_1},$$

$$\beta_{21} = \frac{w_4^*}{w_2^*} l_1 + \frac{w_1^*}{b w_3} l_1 l_3 + \frac{w_1^* (1-u)\rho}{w_2^* w_3^* K} + \frac{d w_4^*}{w_3^* w_2^*} + \frac{d M_3}{w_3^* w_2^*} + \frac{(1-u)g}{w_3},$$

$$\beta_{22} = \frac{w_1^*}{w_3^*} l_2 l_3 + \frac{w_1 w_3 w_4}{w_3^* M_2} l_2,$$

$$\beta_{31} = \frac{w_1^* M_4}{w_2^* w_3^*} l_1 + \frac{2w_1^*}{b w_3} l_1 l_3 + \frac{M_4}{b} l_1 + \frac{w_1^* w_3^*}{b w_3} l_1 + \frac{d w_4^*}{w_3^* w_2^*} + \frac{(1-u)g}{w_3},$$

$$\beta_{32} = \frac{\gamma}{b M_3} + \frac{w_1^* w_4 w_2^*}{b M_3} l_2,$$

$$\beta_{41} = \frac{w_1^*}{w_2^*} l_1 + \frac{d M_3}{w_3^* w_2^*} + \frac{w_1^* w_3^*}{b w_3} l_1, \quad \beta_{42} = \frac{w_4^*}{M_4}.$$

Theorem 5.1. *If $\beta_{11} < \beta_{12}$, $\beta_{21} < 2\beta_{22}$, $\beta_{31} < 2\beta_{32}$, and $\beta_{41} < 2\beta_{42}$, then the model's unique interior equilibrium point is globally and asymptotically stable.*

Proof. Assume that the model admits a single interior point

$$E_2^*(w_1^*, w_2^*, w_3^*, w_4^*).$$

Let us define the following functions:

$$U_1(w_1, w_2, w_3, w_4) = \left[w_1 - w_1^* - w_1^* \ln \left(\frac{w_1}{w_1^*} \right) \right],$$

$$U_2(w_1, w_2, w_3, w_4) = \left[w_2 - w_2^* - w_2^* \ln \left(\frac{w_2}{w_2^*} \right) \right],$$

$$U_3(w_1, w_2, w_3, w_4) = \left[w_3 - w_3^* - w_3^* \ln \left(\frac{w_3}{w_3^*} \right) \right],$$

$$U_4(w_1, w_2, w_3, w_4) = \left[w_4 - w_4^* - w_4^* \ln \left(\frac{w_4}{w_4^*} \right) \right].$$

The function $U : \mathbb{R}^4 \longrightarrow \mathbb{R}$ such that

$$\begin{aligned} U(w_1, w_2, w_3, w_4) = & \frac{w_1^*}{w_2^* w_3^*} U_1(w_1, w_2, w_3, w_4) + \frac{1}{w_3^*} U_2(w_1, w_2, w_3, w_4) \\ & + \frac{1}{b} U_3(w_1, w_2, w_3, w_4) + \frac{w_4^*}{au + q} U_4(w_1, w_2, w_3, w_4) \end{aligned}$$

admits zero for global minimum reached in $(w_1^*, w_2^*, w_3^*, w_4^*)$.

Let us show that the function U as defined is a Lyapunov function for the model:

(i) We have

$$U(w_1^*, w_2^*, w_3^*, w_4^*) = 0.$$

(ii) For any positive (w_1, w_2, w_3, w_4) solution of (1), $U(w_1, w_2, w_3, w_4)$ is positive.

(iii) Show that

$$\frac{dU}{dt} < 0.$$

We have

$$\begin{aligned} \frac{dU}{dt} = & \frac{w_1^*}{w_2^* w_3^*} \frac{dU_1}{dw_1} \frac{dw_1}{dt} + \frac{1}{w_3^*} \frac{dU_2}{dw_2} \frac{dw_2}{dt} \\ & + \frac{1}{b} \frac{dU_3}{dw_3} \frac{dw_3}{dt} + \frac{w_4^*}{au + q} \frac{dU_4}{dw_4} \frac{dw_4}{dt}, \\ \frac{dU}{dt} = & \frac{w_1^*}{w_2^* w_3^*} (w_1 - w_1^*) \frac{dw_1}{w_1 dt} + \frac{1}{w_3^*} (w_2 - w_2^*) \frac{dw_2}{w_2 dt} \\ & + \frac{1}{b} (w_3 - w_3^*) \frac{dw_3}{w_3 dt} + \frac{w_4^*}{au + q} (w_4 - w_4^*) \frac{dw_4}{w_4 dt}. \end{aligned}$$

We have

$$\begin{aligned}
 \frac{dw_1}{w_1 dt} &= \frac{dw_3^* w_4^* ((w_1 - w_1^*) + (w_2 - w_2^*))}{(w_1^* + w_2^* + \varepsilon)(w_1 + w_2 + \varepsilon)} + \frac{dw_3^* w_4^* - dw_3 w_4}{w_1 + w_2 + \varepsilon} \\
 &\quad + \frac{(1-u)\rho}{K} ((w_1^* - w_1) + (w_2^* - w_2)) \\
 &= \left(\frac{dw_3^* w_4^*}{(w_1^* + w_2^* + \varepsilon)(w_1 + w_2 + \varepsilon)} - \frac{(1-u)\rho}{K} \right) (w_1 - w_1^*) \\
 &\quad - \frac{dw_4}{w_1 + w_2 + \varepsilon} (w_3 - w_3^*) \\
 &\quad + \left(\frac{dw_3^* w_4^*}{(w_1^* + w_2^* + \varepsilon)(w_1 + w_2 + \varepsilon)} - \frac{(1-u)\rho}{K} \right) (w_2 - w_2^*) \\
 &\quad - \frac{dw_3}{w_1 + w_2 + \varepsilon} (w_4 - w_4^*), \\
 \frac{dw_2}{w_2 dt} &= \frac{dw_3^* w_4^*}{w_2^* (w_1 + w_2 + \varepsilon)} \left(1 - \frac{w_1^*}{w_1^* + w_2^* + \varepsilon} \right) (w_1 - w_1^*) \\
 &\quad + \frac{dw_1 w_4^*}{w_2^* (w_1 + w_2 + \varepsilon)} (w_3 - w_3^*) \\
 &\quad + \frac{d}{w_2^* (w_1 + w_2 + \varepsilon)} \left(-\frac{w_1^* w_3^* w_4^*}{w_1^* + w_2^* + \varepsilon} - \frac{w_1 w_3 w_4}{w_2} \right) (w_2 - w_2^*) \\
 &\quad + \frac{dw_1 w_3}{w_2^* (w_1 + w_2 + \varepsilon)} (w_4 - w_4^*), \\
 \frac{dw_3}{w_3 dt} &= \frac{1}{w_3} \left(\frac{dw_1^* w_3^* w_4^*}{(w_1 + w_2 + \varepsilon)(w_1^* + w_2^* + \varepsilon)} - \frac{dw_3 w_4}{w_1 + w_2 + \varepsilon} \right) (w_1 - w_1^*) \\
 &\quad + \frac{1}{w_3} \left(b(1-u)g + \frac{dw_1^* w_3^* w_4^*}{(w_1 + w_2 + \varepsilon)(w_1^* + w_2^* + \varepsilon)} \right) (w_2 - w_2^*) \\
 &\quad - \frac{1}{w_3} \left(\gamma + \frac{dw_1^* z}{w_1 + w_2 + \varepsilon} \right) (w_3 - w_3^*) \\
 &\quad - \frac{1}{w_3} \left(\frac{dw_1^* w_3^*}{w_1 + w_2 + \varepsilon} \right) (w_4 - w_4^*), \\
 \frac{dw_4}{w_4 dt} &= -\frac{1}{w_4} (au + q) (w_4 - w_4^*).
 \end{aligned}$$

Therefore, $\frac{dU}{dt}$ can be written as

$$\begin{aligned}
 \frac{dU}{dt} &= \left(\frac{dw_1^* w_4^*}{w_2^* (w_1^* + w_2^* + \varepsilon)(w_1 + w_2 + \varepsilon)} - \frac{(1-u)\rho w_1^*}{K w_2^* w_3^*} \right) (w_1 - w_1^*)^2 \\
 &\quad - \frac{(1-u)\rho w_1^*}{K w_2^* w_3^*} (w_1 - w_1^*) (w_2 - w_2^*) \\
 &\quad - \frac{dw_1^* w_4}{w_2^* w_3^* (w_1 + w_2 + \varepsilon)} (w_1 - w_1^*) (w_3 - w_3^*) \\
 &\quad - \frac{dw_1^*}{w_2^* (w_1 + w_2 + \varepsilon)} (w_1 - w_1^*) (w_4 - w_4^*) \\
 &\quad + \frac{dw_4^*}{w_2^* (w_1 + w_2 + \varepsilon)} (w_1 - w_1^*) (w_2 - w_2^*)
 \end{aligned}$$

$$\begin{aligned}
& + \frac{d}{w_3^* w_2^* (w_1 + w_2 + \varepsilon)} \left(-\frac{w_1^* w_3^* w_4^*}{w_1^* + w_2^* + \varepsilon} - \frac{w_1 w_3 w_4}{w_2} \right) (w_2 - w_2^*)^2 \\
& + \frac{dw_4^* w_1}{w_3^* w_2^* (w_1 + w_2 + \varepsilon)} (w_2 - w_2^*) (w_3 - w_3^*) \\
& + \frac{dw_1 w_3}{w_3^* w_2^* (w_1 + w_2 + \varepsilon)} (w_2 - w_2^*) (w_4 - w_4^*) \\
& + \frac{1}{b} \left(\frac{dw_1^* w_3^* w_4^*}{w_3 (w_1 + w_2 + \varepsilon) (w_1^* + w_2^* + \varepsilon)} - \frac{dw_4}{w_1 + w_2 + \varepsilon} \right) (w_1 - w_1^*) (w_3 - w_3^*) \\
& + \left(\frac{(1-u)g}{w_3} + \frac{dw_1^* w_3^* w_4^*}{bw_3 (w_1 + w_2 + \varepsilon) (w_1^* + w_2^* + \varepsilon)} \right) (w_2 - w_2^*) (w_3 - w_3^*) \\
& - \left(\frac{\gamma}{bw_3} + \frac{dw_1^* w_4}{bw_3 (w_1 + w_2 + \varepsilon)} \right) (w_3 - w_3^*)^2 \\
& - \frac{dw_1^* w_3^*}{bw_3 (w_1 + w_2 + \varepsilon)} (w_3 - w_3^*) (w_4 - w_4^*) \\
& - \frac{w_4^*}{w_4} (w_4 - w_4^*)^2.
\end{aligned}$$

$$\begin{aligned}
\frac{dU}{dt} \leq & \left(\frac{dw_1^* w_4^*}{w_2^* (w_1^* + w_2^* + \varepsilon) (w_1 + w_2 + \varepsilon)} - \frac{(1-u)\rho w_1^*}{K w_2^* w_3^*} \right) (w_1 - w_1^*)^2 \\
& + \frac{(1-u)\rho w_1^*}{K w_2^* w_3^*} \frac{(w_1 - w_1^*)^2 + (w_2 - w_2^*)^2}{2} \\
& + \frac{dw_1^* w_4}{w_2^* w_3^* (w_1 + w_2 + \varepsilon)} \frac{(w_1 - w_1^*)^2 + (w_3 - w_3^*)^2}{2} \\
& + \frac{dw_1^*}{w_2^* (w_1 + w_2 + \varepsilon)} \frac{(w_1 - w_1^*)^2 + (w_4 - w_4^*)^2}{2} \\
& + \frac{dw_4^*}{w_2^* (w_1 + w_2 + \varepsilon)} \frac{(w_1 - w_1^*)^2 + (w_2 - w_2^*)^2}{2} \\
& + \frac{d}{w_3^* w_2^* (w_1 + w_2 + \varepsilon)} \left(-\frac{w_1^* w_3^* w_4^*}{w_1^* + w_2^* + \varepsilon} - \frac{w_1 w_3 w_4}{w_2} \right) (w_2 - w_2^*)^2 \\
& + \frac{dw_4^*}{w_3^* w_2^*} \frac{(w_2 - w_2^*)^2 + (w_3 - w_3^*)^2}{2} \\
& + \frac{dw_3}{w_3^* w_2^*} \frac{(w_2 - w_2^*)^2 + (w_4 - w_4^*)^2}{2} \\
& + \frac{1}{b} \left(\frac{dw_1^* w_3^* w_4^*}{w_3 (w_1 + w_2 + \varepsilon) (w_1^* + w_2^* + \varepsilon)} + \frac{dw_4}{w_1 + w_2 + \varepsilon} \right) \frac{(w_1 - w_1^*)^2 + (w_3 - w_3^*)^2}{2} \\
& + \left(\frac{(1-u)g}{w_3} + \frac{dw_1^* w_3^* w_4^*}{bw_3 (w_1 + w_2 + \varepsilon) (w_1^* + w_2^* + \varepsilon)} \right) \frac{(w_2 - w_2^*)^2 + (w_3 - w_3^*)^2}{2} \\
& - \left(\frac{\gamma}{bw_3} + \frac{dw_1^* w_4}{bw_3 (w_1 + w_2 + \varepsilon)} \right) (w_3 - w_3^*)^2 \\
& + \frac{dw_1^* w_3^*}{bw_3 (w_1 + w_2 + \varepsilon)} \frac{(w_3 - w_3^*)^2 + (w_4 - w_4^*)^2}{2} - \frac{w_4^*}{w_4} (w_4 - w_4^*)^2.
\end{aligned}$$

$$\begin{aligned}
\frac{dU}{dt} \leq & \left[\frac{d}{\underline{w}_1 + \underline{w}_2 + \varepsilon} \left(\frac{w_1^* w_4^*}{w_2^* (w_1^* + w_2^* + \varepsilon)} + \frac{w_1^* M_4}{2w_2^* w_3^*} + \frac{w_1^*}{2w_2^*} + \frac{w_4^*}{2w_2^*} \right. \right. \\
& \left. \left. + \frac{w_1^* w_3^* w_4^*}{2bw_3(w_1^* + w_2^* + \varepsilon)} + \frac{M_4}{2b} \right) - \frac{(1-u)\rho w_1^*}{2Kw_2^* w_3^*} \right] (w_1 - w_1^*)^2 \\
& + \left[\frac{d}{\underline{w}_1 + \underline{w}_2 + \varepsilon} \left(\frac{w_4^*}{2w_2^*} + \frac{w_1^* w_3^* w_4^*}{2bw_3(w_1^* + w_2^* + \varepsilon)} \right) \right. \\
& \left. + \frac{(1-u)\rho w_1^*}{2Kw_2^* w_3^*} + \frac{dw_4^*}{2w_3^* w_2^*} + \frac{dM_3}{2w_3^* w_2^*} + \frac{(1-u)g}{2w_3} \right. \\
& \left. - \frac{d}{w_2^* (M_1 + M_2 + \varepsilon)} \left(\frac{w_1^* w_4^*}{w_1^* + w_2^* + \varepsilon} + \frac{w_1^* w_3^* w_4^*}{w_3^* M_2} \right) \right] (w_2 - w_2^*)^2 \\
& + \left[\frac{d}{\underline{w}_1 + \underline{w}_2 + \varepsilon} \left(\frac{w_1^* M_4}{2w_2^* w_3^*} + \frac{w_1^* w_3^* w_4^*}{bw_3(w_1^* + w_2^* + \varepsilon)} + \frac{M_4}{2b} + \frac{w_1^* w_3^*}{2bw_3} \right) \right. \\
& \left. + \frac{dw_4^*}{2w_3^* w_2^*} + \frac{(1-u)g}{2\alpha_3} - \frac{dw_1^* w_4^*}{bM_3(M_1 + M_2 + \varepsilon)} - \frac{\gamma}{bM_3} \right] (w_3 - w_3^*)^2 \\
& + \left[\frac{dw_1^*}{2w_2^* (\underline{w}_1 + \underline{w}_2 + \varepsilon)} + \frac{dM_3}{2w_3^* w_2^*} + \frac{dw_1^* w_3^*}{2bw_3(\underline{w}_1 + \underline{w}_2 + \varepsilon)} - \frac{w_4^*}{M_4} \right] (w_4 - w_4^*)^2.
\end{aligned}$$

Then

$$\begin{aligned}
\frac{dU}{dt} \leq & \frac{1}{2} \left(l_1 (\beta_{11} - \beta_{12}) (w_1 - w_1^*)^2 + (\beta_{21} - 2\beta_{22}) (w_2 - w_2^*)^2 \right. \\
& \left. + (\beta_{31} - 2\beta_{32}) (w_3 - w_3^*)^2 + (\beta_{41} - 2\beta_{42}) (w_4 - w_4^*)^2 \right),
\end{aligned}$$

with β_{ij} , $i = 1, 2, 3$, $j = 1, 2$, as defined above.

Taking into account the assumptions of the theorem, we have

$$\frac{dU}{dt} < 0.$$

We conclude that $E_2^*(w_1^*, w_2^*, w_3^*, w_4^*)$ is globally and asymptotically stable. $\square$

Remark 5.2. An analysis of global stability reveals that the stability established in the model holds up to a certain order. Beyond these values, a change in stability is observed.

6 Numerical simulation

We have chosen the control parameters such that

$$b > 1 + \gamma\Theta \quad \text{and} \quad K < \nu w_1^*.$$

To illustrate the local stability of the internal equilibrium point, we present, on the one hand, the trajectories of uninfected and infected cancer cells and, on the other hand, an orbit starting from the initial conditions

$$w_1(0) = 10^5, \quad w_2(0) = 0, \quad w_3(0) = 5 \times 10^2, \quad w_4(0) = 2 \times 10^{-2},$$

expressed in units of cells.

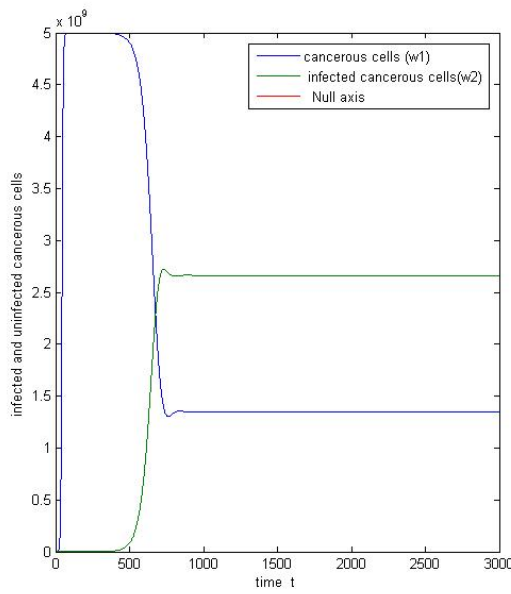
We choose a time step of $h = 10^{-2}$ and the number of iterations to be $N = 3 \times 10^5$. The control parameters are expressed in the same units as in [1].

We have

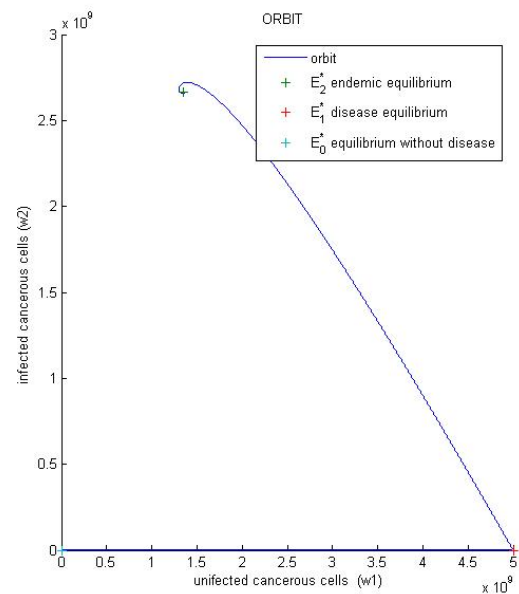
$$\begin{aligned} u &= 0,95, & \rho &= 5 \text{ cells day}^{-1}, & K &= 5 \times 10^9 \text{ cells}, & d &= 0,2 \text{ day}^{-1}, \\ \varepsilon &= 0,05 \text{ cells}, & g &= 0,5 \text{ day}^{-1}, & \gamma &= 0,5 \text{ day}^{-1}, & a &= 0,2 \text{ day}^{-1}, \\ m &= 9, & q &= 0,5 \text{ day}^{-1}, & b &= 4 \text{ cell}^{-1} \text{ day}^{-1}, & T &= 3000 \text{ day}. \end{aligned}$$

At equilibrium, we have the values of the unique internal equilibrium:

$$\begin{aligned} w_1^* &= 1,3494 \times 10^9, & w_2^* &= 2,6636 \times 10^9, \\ w_3^* &= 3,9954 \times 10^8, & w_4^* &= 2,4783. \end{aligned}$$



(a) Trajectories of Cancerous Cells



(b) Orbit

Figure 1: Numerical illustration of the local stability of the interior equilibrium point.

Interpretation 6.1. By choosing $b > 1 + \gamma\Theta$, the model has a unique interior point, and the disease equilibrium becomes unstable. During the process, the trajectory of uninfected cancerous cells grows rapidly at a certain time, until it reaches a certain value close to the maximum capacity K . This illustrates a slow infection of cancerous cells by the virus, as shown in Figure 1a. This slow rate of viral infection is due to the virus's search for receptors on the cell surface and the cell cycle process required for viral production within the body. After a certain period of time, we observe an increase in infected cancerous cells and a decrease in uninfected cells. This mechanism indicates that the adenovirus inhibits the progression of cancerous cells by infecting them. This fluctuating increase and decrease in cell numbers continues, and the cells eventually stabilize at a certain equilibrium level, as shown by the trajectories in Figure 1a. Thus, this stabilization of the trajectories leads to a long-term coexistence of cancerous cells, infected cancerous cells, the virus, and the receptor within the organism when the conditions for local stability of the endemic equilibrium E_2^* are met. As for the trajectory shown in Figure 1b, starting from the initial condition, it moves away from the disease-free equilibrium and heads toward the disease-free equilibrium. This indicates rapid growth of cancerous cells in the body. As the process progresses, at a certain point in time, the trajectory shifts from the diseased equilibrium toward the endemic equilibrium. This is due to the rapid growth of cancerous cells infected by the abundant presence of adenovirus in

the body, which leads to the regression of cancerous cells. At a certain point, the trajectory converges toward the endemic equilibrium E_2^* . Thus, E_2^* is stable, as illustrated in Figure 1b and demonstrated by the theoretical analysis. At this stage, at equilibrium, the cells cannot disappear nor can they evolve, but they can coexist within the body. This is therefore beneficial for the patient, who will be able to live with the disease long-term.

7 Conclusion

This article presents a mathematical model for treating tumors with oncolytic viruses. The study shows that when, $b > 1 + \gamma\Theta$, which is the condition for the existence of E_2^* we can maintain stability under certain conditions. This stability of E_2^* would mean that patients could live with the disease long-term. We conclude that the treatment reduces the number of cancerous cells in the body whatever the size of the tumor. This will allow us to slow the progression of the cancerous tumor and stabilize it at a certain rank.

Declarations

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Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

Not applicable.

Authors' Contributions

No datasets were generated or analyzed during the current study. Therefore, data sharing is not applicable to this article.

Availability Data and Materials

Not applicable.

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