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ONCOLYTIC VIRUS THERAPY THROUGH MATHEMATICAL MODELING: THE INFECTION-LYSIS TRADE-OFF IN CANCER DYNAMICS

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Abstract. One of the most fatal diseases globally is cancer. Its incidence continues to rise even though early detection methods and therapeutic approaches have been enhanced. So we necessitate ongoing research into its underlying causes and new treatment paradigms. In this paper, we study a mathematical model to treat cancer by oncolytic viruses (OVs), like adenovirus ONYX-15. The model incorporates three variables: the uninfected tumor cell density, the infected tumor cell density and the oxygen concentration. We prove that solutions exist, are non-negative and bounded, and we analyze equilibrium points along with their stability. We find that engineering an effective oncolytic virus requires a finely tuned interplay between two key properties: the virus's ability to infect tumor cells, and its oncolytic potency. If the virus is excessively cytotoxic to tumor cells but insufficiently infectious, infected cells will be destroyed faster than spreading the infection. This imbalance reduces the overall therapeutic efficacy, as the virus fails to propagate adequately through the tumor population.

Keywords: tumor treatment; oncolytic virotherapy; mathematical modeling; equilibrium points; stability.
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1. INTRODUCTION

As a novel anticancer strategy, oncolytic virotherapy exploits either genetically modified or naturally oncolytic viruses to infect and lyse malignant cells while sparing healthy tissue. This

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strategy is based on the capacity of OVs to first infect tumor cells and then replicate before lysing them. Thus, oncolytic virotherapy offers a more targeted and less toxic treatment [1], unlike other cancer treatments such as chemotherapy and radiotherapy, which can cause significant collateral damage to normal cells. The idea of using OVs against cancer began in the early 1900s when researchers noticed that some cancer patients experienced tumor shrinkage after contracting viral infections. This intriguing observation suggested that certain viruses might have the capability to target and destroy cancer cells. On the other hand, it is only in the last few decades, as a result of advances in virology, that oncolytic virotherapy has established itself as a viable cancer treatment. Modern oncolytic viruses (OVs) are engineered or chosen to improve their tumor-targeting ability, immune-boosting effects, and overall safety [2]. A major milestone in this field was the approval of T-VEC, a herpes simplex virus (HSV) engineered through genetic modification, by the FDA (Food and Drug Administration) in 2015, establishing it as the first OV authorized for treating advanced cancer. T-VEC illustrates the potential of OVs to enable anti-tumour immunity through the release of tumour-associated antigens and the promotion of immune cell recruitment [3]. Despite its promising potential, oncolytic virotherapy faces several significant challenges. These include overcoming the host immune system's antiviral defence mechanisms, ensuring optimal viral delivery to tumor sites, and maintaining uncompromised safety. Current research focuses on enhancing viral vectors, improving efficacy through combination therapies, and extending their use to a wider spectrum of cancers [4].

Many solid tumors are characterised by hypoxia (a state of low oxygen levels) which is a key driver of the tumor micro-environment. Harris, Wilson and Hay in [5, 6] have shown that hypoxia significantly affects the efficacy of oncolytic virus therapy. Firstly, hypoxia can interfere with viral replication. For example, replication of adenoviruses and herpes simplex virus (HSV)-based vectors is reduced under hypoxic conditions due to downregulation of viral gene expression and suppression of key cellular pathways required for viral propagation [7]. Secondly, hypoxia stabilizes hypoxia-inducible factors (HIFs), transcribs factors that regulate the expression profile of angiogenesis-related, metabolic and survival-promoting genes. HIF-1α, in particular, has been implicated in promoting resistance to OVT by enhancing the expression of anti-apoptotic proteins and reducing the sensitivity of cancer cells to virus-induced

cell death [8]. Furthermore, hypoxia is often associated with an environment characterized by the recruitment of regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), which can inhibit the anti-tumor immune response triggered by VOs, thus limiting their therapeutic efficacy [9, 10]. Despite these challenges, several strategies have been explored to overcome the limitations imposed by hypoxia. For example, engineering VOs to express genes under hypoxia-sensitive promoters or combining VOs with hypoxia-modulating agents, such as HIF-1α inhibitors or anti-angiogenic therapies, has shown promise for enhancing viral replication and immune activation in hypoxic tumors [11, 12].

Mathematical modeling plays a very important role in this field, providing a quantitative framework for describing and predicting VO dynamics in the tumor micro-environment. These models enable researchers to investigate the underlying mechanisms of viral replication, study the spread of viruses and the immune response caused by therapy, and -by integrating experimental data- they can also identify key parameters affecting the efficacy of virotherapy [13, 14]. For example, several models based on differential equations have been used to describe viral replication and its effect on tumor burden. These models have demonstrated the importance of viral diffusion rates within tumors, and the role of physical and immunological barriers in limiting therapeutic efficacy [15, 16]. In addition, mathematical modeling has a key role to play in assessing the impact of combination therapies, such as the combination of virotherapy with immunotherapy or radiotherapy [17, 18].

In this research, we investigate the impact of hypoxia on anti-tumor virotherapy using ordinary differential equation (ODE) models. As a general rule, viruses that infect cells more efficiently in oxygenated environments see their infection capacity diminish under hypoxic conditions [19], this especially holds true for adenoviruses like ONYX-015 [20]. Hypoxia negatively impacts the effectiveness of oncolytic viruses (OVs), along with any potential adjuvant radiotherapy that could be applied , it can limit the therapeutic effect of OVs, notably their capacity to infect cancer cells and induce cell death. To enable a systematic analysis of this phenomenon, we are investigating how oxygen concentration in the tumor micro-environment influences the

efficacy of oncolytic viruses (OVs), aiming to contribute a quantitative perspective to the oncology literature. In Section 2, we formalize the model's design, incorporating oxygen concentration in the tumor micro-environment. The dynamics are governed by a system of differential equations. Section 3 analyzes the dynamical system, addressing the existence, uniqueness, and boundedness of solutions, along with stability conditions.

2. MATHEMATICAL MODELING

This research focuses on analyzing the dynamics of oncolytic viruses (OVs) under hypoxic conditions and their impact on tumor progression. To this end, we examine a tumor composed of an initial population of proliferating tumor cells, into which an oncolytic virus is introduced via direct injection. We assume that the virus used is down-regulated under hypoxic conditions, similar to adenoviruses(The choice of adenovirus is justified by the influence of hypoxia on viral activity). The model incorporates three variables: $x(t)$ represents the uninfected tumor cell density, $y(t)$ represents the infected tumor cell density and $h(t)$ represents the oxygen concentration.

We emphasize that we focus on cell-to-cell infections, a recognised mechanism of infection in oncolytic viruses [21], which is a key element of our analysis. In our model, similar to earlier mathematical frameworks for Direct cell-to-cell transmission, we use rate-law dynamics to describe viral infection dynamics [22, 23, 24], but we incorporate the infection process using a Holling type II functional response function. This choice is made to take into account the saturation effect observed when cancer cells are already infected by the oncolytic virus (OV).

Hypoxia has been shown to significantly reduce the efficacy of oncolytic viruses. Studies such as [19, 20] demonstrate that hypoxic conditions impair viral replication and the ability of the virus to induce tumor cell lysis; for this we also consider that the infection rate and the mortality rate depend on the oxygen concentration. This leads to the following model:

$$\frac{dx}{dt} = rx\left(1-\frac{x+y}{K}\right) - \frac{\beta(h)xy}{1+\alpha y}, \tag{1}$$

$$\frac{dy}{dt} = \frac{\beta(h)xy}{1+\alpha y} - \delta(h)y, \tag{2}$$

$$\frac{dh}{dt} = \phi - \lambda h - \lambda_x hx - \lambda_y hy. \tag{3}$$

With initial conditions

$$x_0 \geq 0,\ y_0 \geq 0,\ h_0 \geq 0 \tag{4}$$

and

$$\delta'(h) \geq 0,\ \beta'(h) \geq 0,\ \text{for all } h \in [0,\infty[, \tag{5}$$

$$\delta(0) = \delta_0 \geq 0, \beta(0) = \beta_0 \geq 0, \tag{6}$$

$$\lim_{h\to\infty} \delta(h) = \delta_\infty > \delta_0,\ \lim_{h\to\infty} \beta(h) = \beta_\infty > \beta_0. \tag{7}$$

Each parameter is explained in detail below:

Parameter	Description
r	Growth rate of uninfected cells (x).
K	Carrying capacity (maximum cell density that the environment can support).
$\beta(h)$	Infection rate of uninfected cells by OVs, dependent on h.
α	Saturation parameter for the interaction between uninfected and infected cells.
$\delta(h)$	Mortality rate of infected cells (y), dependent on h.
ϕ	Production rate of oxygen (h).
λ	Natural degradation rate of oxygen (h).
λ_x	Oxygen consumption rate by uninfected cells (x).
λ_y	Oxygen consumption rate by infected cells (y).

TABLE 1. Parameters of the model: Description

3. MODEL ANALYSIS

Theorem 1. *If the initial conditions* (4) *are satisfied, then solutions of* $(1)-(3)$ *are positive and bounded.*

Proof: From the equation $(1)-(3)$, we have

$$x(t) = x_0 \exp\left(\int_0^t \left(r\left(1 - \frac{x(s)+y(s)}{K}\right) - \frac{\beta(h(s)y(s))}{1+\alpha y(s)}\right) ds\right),$$

$$y(t) = y_0 \exp\left(-\int_0^t \frac{\beta(h(s))x(s)}{1+\alpha y(s)} - \delta(h(s))\,ds\right)$$

and

$$h(t) = h_0 \exp\left(-\int_0^t \lambda + \lambda_x x(s) + \lambda_y y(s)\,ds\right) + \phi \int_0^t \exp\left(-\int_s^t \lambda + \lambda_x x(\mu) + \lambda_y y(\mu)\,d\mu\right) ds.$$

Therefore, if (4) are satisfied, we conclude that the solutions of problem $(1)-(3)$ are positive.

By utilizing a comparison argument: From (1) and (3), it follows that

$$\frac{dx}{dt} \leq rx\left(1-\frac{x}{K}\right), \quad \frac{dh}{dt} \leq \phi - \lambda h = \phi\left(1-\frac{\lambda}{\phi}h\right),$$

then

$$\limsup_{t\to\infty} x(t) \leq K, \ \limsup_{t\to\infty} h(t) \leq \frac{\phi}{\lambda}.$$

We also show from (2) that

$$\frac{dy}{dt} \leq \frac{\beta_\infty K}{\alpha}\left(1-\frac{\alpha\delta_0}{\beta_\infty K}y\right),$$

which implies that

$$\limsup_{t\to\infty} y(t) \leq \frac{\beta_\infty K}{\alpha\delta_0}.$$

Hence, the solutions are bounded.

Remark 1. *From* (1) *and* (2)*, we obtain* $\dfrac{d(x+y)}{dt} \leq rx\left(1-\dfrac{x+y}{K}\right)$*, so by the comparison principle we have* $\limsup_{t\to\infty}\left(x(t)+y(t)\right) \leq K$.

Let $(x(t),y(t),h(t))$ a solution of the problem $(1)-(3)$, by Theorem 1 we have $x(t) \geq 0$, $y(t) \geq 0$ and $h(t) \geq 0$, in addition if $x+y=K$ then from (1) and (2), we obtain

$$\frac{d(x+y)}{dt} = -\delta(h)y \leq 0,$$

similarly if $h = \dfrac{\phi}{\lambda}$ then from (3) we have

$$\frac{dh}{dt} = -(\lambda_x x + \lambda_y y)\frac{\phi}{\lambda} \leq 0.$$

We consider now

$$\Gamma = \{(x,y,h) \in \mathbb{R}^3 \mid x \geq 0, y \geq 0; x+y \leq K; 0 \leq h \leq \frac{\phi}{\lambda}\}.$$

Therefore, we deduce:

Lemma 1. *The region* Γ *is a positively invariant set for the problem* $(1)-(3)$.

Now, we determine the equilibrium points of model $(1)-(3)$ by finding the solutions to the system:

$$rx\left(1-\frac{x+y}{K}\right)-\frac{\beta(h)xy}{1+\alpha y}=0, \tag{8}$$

$$\frac{\beta(h)xy}{1+\alpha y}-\delta(h)y=0, \tag{9}$$

$$\phi-\lambda h-\lambda_x hx-\lambda_y hy=0. \tag{10}$$

It is easy to observe that $E_1(0,0,\frac{\phi}{\lambda})$ and $E_2(K,0,\frac{\phi}{\lambda_x K+\lambda})$ are solutions of system $(8)-(9)$. Concerning the interior equilibrium E^*, we state the following theorem:

Theorem 2. *Consider the system* $(1)-(3)$ *over the region* Γ.
1. If $\beta(h)\leq\frac{\delta(h)}{K}$*, then the only two positive equilibrium points of* $(1)-(3)$ *are* $E_1(0,0,\frac{\phi}{\lambda})$ *and* $E_2(K,0,\frac{\phi}{\lambda_x K+\lambda})$.
2. If $\beta(h)>\frac{\delta(h)}{K}$*, an additional equilibrium point* $E^*(x^*,y^*,h^*)$ *exist.*

Proof: First, note that if x ,y and h are strictly positive, then the system $(8)-(10)$ becomes as follows

$$r\left(1-\frac{x+y}{K}\right)-\frac{\beta(h)y}{1+\alpha y}=0,$$

$$\frac{\beta(h)x}{1+\alpha y}-\delta(h)=0,$$

$$\phi-\lambda h-\lambda_x hx-\lambda_y hy=0.$$

Which implies

$$F(x)=0,$$

$$y=g(x),$$

$$h=f(x,y).$$

with

$$F(x)=r(1+\alpha g(x))(K-x-g(x))-K\beta(h)g(x),$$

$$g(x) = \frac{\beta(h)}{\alpha\delta(h)}x - \frac{1}{\alpha},$$

$$f(x,y) = \frac{\phi}{\lambda + \lambda_x x + \lambda_y y}.$$

So to establish the existence of E^*, it is sufficient to show that $F(x) = 0$ has a solution in $[0,K]$, in fact:

From(5) and (6) $F(0) = \dfrac{K\beta(h)}{\alpha}$ is positive, on the other hand if $\beta(h) > \dfrac{\delta(h)}{K}$ then $F(K) = -Kg(K)\beta(h)\left(\dfrac{r}{\delta(h)} + 1\right)$ is negative, hence the existence of the solution is proven.

To show that the solution is unique, noting that:

$$F(x) = -r\frac{\beta(h)}{\delta(h)}\left(1 + \frac{\beta(h)}{\alpha\delta(h)}\right)x^2 + \left(r(K + \frac{1}{\alpha})\frac{\beta(h)}{\delta(h)} - \frac{K\beta^2(h)}{\alpha\delta(h)}\right)x + \frac{K\beta(h)}{\alpha},$$

so $F(x)$ is a concave parabola because its quadratic coefficient is negative then x^* is unique.

Since $F\left(\dfrac{\delta(h)}{\beta(h)}\right) = r\left(K - \dfrac{\delta(h)}{\beta(h)}\right) > 0$ if $\beta(h) > \dfrac{\delta(h)}{K}$, then $x^* > \dfrac{\delta(h)}{\beta(h)}$ which implies that y^* and h^* are positive.

Remark 2. *Equilibrium point* $E_2(K, 0, \dfrac{\phi}{\lambda_x K + \lambda})$ *represents the state where the infected cancer cells disappear and the uninfected cancer cells reach their maximum density (carrying capacity K), this scenario corresponds to a treatment failure. As a result, the cancer continues to grow, this finding highlights the importance of optimising the parameters of the oncolytic virus, such as infection rate and mortality rate, to prevent tumor regression and ensure successful treatment.*

To study local stability, we evaluate the Jacobian matrix at each equilibrium point, the Jacobian matrix is:

$$J = \begin{pmatrix} r\left(1 - \dfrac{2x+y}{K}\right) - \dfrac{\beta(h)y}{1+\alpha y} & -\dfrac{rx}{K} - \dfrac{\beta(h)x}{(1+\alpha y)^2} & -\dfrac{\beta'(h)xy}{1+\alpha y} \\ \dfrac{\beta(h)y}{(1+\alpha y)} & \dfrac{\beta(h)x}{(1+\alpha y)^2} - \delta(h) & \dfrac{\beta'(h)xy}{1+\alpha y} - \delta'(h)y \\ -\lambda_x h & -\lambda_y h & -\lambda - \lambda_x x - \lambda_y y \end{pmatrix}.$$

Linearizing system $(1)-(3)$ at $E_1(0,0,\frac{\phi}{\lambda})$ and $E_2(K,0,\frac{\phi}{\lambda_x K+\lambda})$ gives:

$$J(E_1)=\begin{pmatrix} r & 0 & 0 \\ 0 & -\delta(h_1) & 0 \\ -\lambda_x h_1 & -\lambda_y h_1 & -\lambda \end{pmatrix}, J(E_2)=\begin{pmatrix} -r & -r-K\beta(h_2) & 0 \\ 0 & K\beta(h_2)-\delta(h_2) & 0 \\ -\lambda_x h_2 & -\lambda_y h_2 & -\frac{\phi}{h_2} \end{pmatrix};$$

where

$$h_1=\frac{\phi}{\lambda},\ h_2=\frac{\phi}{K\lambda_x+\lambda}.$$

By examining $J(E_1)$ and $J(E_2)$, it's clear that $r>0$ is one eigenvalue of $J(E_1)$ and $\left\{-r, K\beta(h_2)-\delta(h_2), -\frac{\phi}{h_2}\right\}$ are the eigenvalues of $J(E_2)$. From these results, we obtain:

Theorem 3. *Consider the system* $(1)-(3)$ *over the region* Γ.

1. E_1 *is an unstable equilibrium point.*

2. If $\beta(h)<\frac{\delta(h)}{K}$*, then* E_2 *is locally asymptotically stable.*

At the equilibrium point E^* we have:

$$J(E^*)=\begin{pmatrix} -\frac{rx^*}{K} & -\frac{rx^*}{K}-\frac{\delta(h^*)}{1+\alpha y^*} & -\frac{\beta'(h^*)x^*y^*}{1+\alpha y^*} \\ \frac{\delta(h^*)y^*}{x^*} & -\frac{\alpha y^*\delta(h^*)}{1+\alpha y^*} & \frac{\beta'(h^*)x^*y^*}{1+\alpha y^*}-\delta'(h^*)y^* \\ -\lambda_x h^* & -\lambda_y h^* & -\frac{\phi}{h^*} \end{pmatrix}$$

with

$$h^*=\frac{\phi}{\lambda+\lambda_x x^*+\lambda_y y^*}.$$

We analyze the interior equilibrium E^* stability and state the following theorem:

Theorem 4. *Consider the system* $(1)-(3)$ *over the region* Γ.

E^* *is locally asymptotically stable, if*

$$tr(J(E^*))tr(cof(J(E^*)))<det(J(E^*))\ and\ det(J(E^*))<0.$$

Proof: The roots of the polynomial

$$P(X) = X^3 - tr(J(E^*))X^2 + tr(cof(J(E^*)))X - det(J(E^*)),$$

are The eigenvalues of $J(E^*)$, by using the Routh-Hurwitz criterion, all of the roots of $P(X)$ have negative real parts iff

$tr(J(E^*)) < 0$ (this condition holds for all parameter values in the model),

$$tr(J(E^*))tr(cof(J(E^*))) < det(J(E^*))$$

and $\quad det(J(E^*)) < 0.$

Remark 3. *The density of $y(t)$ (infected cancer cells) is determined by a equilibrium between infection rate $(\beta(h))$ and mortality rate $(\delta(h))$ (both are influenced by oxygen concentration (h)). The condition $\beta(h) > \frac{\delta(h)}{K}$ ensures the maintenance of an infected cell pool (existence of E*), while the bound $\limsup_{t\to\infty} y(t) \leq \frac{\beta_\infty K}{\alpha\delta_0}$ shows that hypoxia and the saturation effect of the infection rate (via α) limit the maximum infected tumor load.*

We now prove the theorem on the global stability of the equilibrium $E_2(K, 0, \frac{\phi}{\lambda_x K + \lambda})$, when $\lambda_x = 0$.

Theorem 5. *Consider the system $(1)-(3)$ over the region Γ.*
If $\lambda_x = 0$, $\lambda_y > 0$ and $\beta(h) < \frac{\delta(h)}{K}$ for all $h \in [0, \frac{\phi}{\lambda}]$, then E_2 is globally asymptotically stable on Γ.

Proof: If we consider $\lambda_x = 0$ the E_2 becomes $E_2(K, 0, \frac{\phi}{\lambda})$, noting that if $K\beta(h) < \delta(h)$, then there exists $\varepsilon \in (0,1)$ such that $K\beta(h) < \varepsilon\delta(h)$. We define the function V on $Int\,\Gamma \cup \{(K, 0, \frac{\phi}{\lambda})\}$ as follows:

$$V(x,y,h) = x - K\,ln\left(\frac{x}{K}\right) - K + y + \left(\frac{(1-\varepsilon)\delta_0}{2\lambda_y}\right)\left(h - \frac{\phi}{\lambda}\,ln\left(\frac{\lambda h}{\phi}\right) - \frac{\phi}{\lambda}\right).$$

It is easy to see that $V(K, 0, \frac{\phi}{\lambda}) = 0$, $V(x,y,h) > 0$ is strictly positive on $int\,\Gamma$ and we have:

$$\dot{V} = rx\left(1 - \frac{K}{x}\right)\left(1 - \frac{x+y}{K}\right) + \frac{K\beta(h)y}{1+\alpha y} - \delta(h)y + \left(\frac{(1-\varepsilon)\delta_0}{2\lambda_y}\right)\left(1 - \frac{\phi}{\lambda h}\right)(\phi - \lambda h - \lambda_y y)$$

$$= rx\left(1-\frac{K}{x}\right)\left(1-\frac{x+y}{K}\right)+\left(\frac{K\beta(h)}{1+\alpha y}-\varepsilon\delta(h)\right)y-(1-\varepsilon)\delta(h)y+$$
$$\left(\frac{(1-\varepsilon)\delta_0}{2\lambda_y}\right)\left(1-\frac{\phi}{\lambda h}\right)(\phi-\lambda h-\lambda_y y)$$
$$\leq rx\left(1-\frac{K}{x}\right)\left(1-\frac{x+y}{K}\right)+(K\beta(h)-\varepsilon\delta(h))\,y-(1-\varepsilon)\left(\frac{\delta_0}{2}-\delta(h)\right).$$

From Lemma 1 and since $\frac{\delta_0}{2} < \delta(h)$, It holds that $\dot{V} < 0$. By using LaSalle's invariance principle, it follows that E_2 is globally asymptotically stable.

4. CONCLUSIONS

In this paper, we study a mathematical model of cancer treatment using oncolytic viruses (OVs), incorporating the critical role of hypoxia in the tumor micro-environment. To conduct a thorough and systematic analysis of this phenomenon, we investigate OV efficacy and its dependence on oxygen concentration, aiming to contribute a quantitative perspective to the oncology literature. As a foundational step, we validate the biological plausibility of our model by establishing the existence, positivity, boundedness and stability of its solutions.

Finally, we can conclude that treatment fails and the density of uninfected tumor cells approaches the carrying capacity when the mortality rate induced by the virus is very high compared with the infection rate. This highlights the need for a precise equilibrium between the virus's infectivity and its cytotoxic effects. Thus, when developing an oncolytic virus, it is important to bear in mind that it is not recommended to have a virus that is too effective at killing and not effective enough at infecting. It is perhaps equally important to take hypoxia into account when modifying an oncolytic virus, as Efficacy of the OV also determined by hypoxia.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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