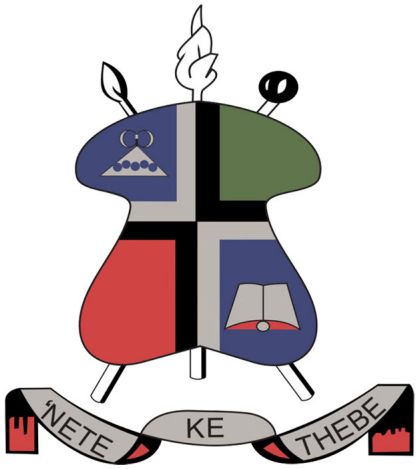

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Disrupting tumor vasculature with oncolytic viruses: A mathematical model

by

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Declaration

I hereby certify that this dissertation is my own research work and has not been submitted in part or in full, for any assessment in any other university.

----  -- Phallang Albert Motlomelo Date: April 2022.

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Dedication

This dissertation is dedicated to my beloved son Relebohile Gerard Motlomelo.

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Abstract

Cancer is a disease caused by accumulation of phenotype-altering genetic mutations in somatic cells, which results in abnormal growth of affected cells. Among many cancer therapies that are currently under clinical investigation, virotherapy, which uses viruses called oncolytic viruses (OVs) that specifically replicate in cancerous cells while sparing normal cells, has recently become one of the promising therapeutic approaches that aim to destroy cancer cells. The aim of this study is to understand the dynamics of disrupting tumor vasculature and tumor endothelium with OVs. The model is developed based on the modeling techniques that lead to a system of ordinary differential equations (ODEs). Qualitative analysis, non-dimensionalization and stability of ODEs are performed. We also derive the steady states of the model and investigate their stability. Interestingly, our results show that there are two stable points and one non-stable point from which we found that the treatment is successful if the viral clearance rate is larger than the lysis rate.

The simulations further show that oncolytic virotherapy is successful when both burst size and lysis rate are large, and fails whenever both are small.

Key words: Tumor cells, oncolytic viruses, mathematical model, burst size.

Chapter 1

Introduction

Oncolytic viruses (OVs) are a promising modern targeted cancer agents that target, infect and replicate within tumor cells or tumor-associated cells while having little or no harm on normal cells. As opposed to intratumoral injection, the systemic administration of OVs has many obstacles which limit the therapeutic benefits of this treatment mode. Such obstacles include neutralizing of OVs by circulating antibodies, inactivation of OVs by complement proteins and immune clearance [1, 2]. Despite advances in systemic delivery of OVs, the number of OVs that ultimately reach the tumor sites is often greatly reduced by pre-existing virus-specific neutralizing antibodies within blood [3–6]. Another major hurdle that limits an efficient systemic delivery of oncolytic viruses is tumor-associated endothelium [7], which often reduces entry of viral particles into the tumor-host tissue. If OVs only target tumor cells, then only a small fraction of tumor cells would be infected because not all OVs are able to reach the targeted tumor site(s) successfully. Thus, in addition to infecting and replicating within tumor cells, it is also equally important to consider OVs which are capable of infecting and replicating within tumor endothelial cells.

Some oncolytic viruses, such as vaccinia virus (VV) [8, 9] and herpes simplex virus (HSV) [10], are known to disrupt tumor-associated vasculature by infecting tumor endothelial cells (TECs) while sparing those in normal blood vessels [11]. It is important to note that tumor endothelium is structurally and functionally distinct from that of non-cancerous normal endothelium. In contrast to normal endothelium which consists of tightly and properly connected endothelial cells, tumor endothelium consists of distorted endothelial cells which lack pericytes form piles in various places and or have aberrant sprouts [7, 12, 13]. In an attempt to disrupt tumor vasculatur, in [14], it was

shown that the oncolytic viruses infected and replicated within the outgrowth endothelial cells and the newly produced oncolytic viruses further infected the surrounding tumor cells.

To sustain growth, accumulating evidence shows that solid tumors predominantly rely on a supply of blood from the nearby circulating blood vessels [12, 15, 16]. Facilitating tumor-associated vascular collapse may be a valuable treatment approach since tumor endothelial cells are vulnerable to oncolytic viruses infection [14, 17–19]. Most importantly, the destruction of tumor endothelium by oncolytic virus infection may provide another invaluable anti-angiogenesis pathway. In the present work, we devise a new mathematical model that describes tumor vasculature collapse by OVs.

1.1 Objectives of the Study

1.1.1 General Objective

The main objective of this study is to investigate the dynamics in disrupting tumor vasculature with virotherapy treatment.

1.1.2 Specific Objective

The specific objectives of this study are to:

- identify the dynamics of cancer growth,
- develop and analyse a mathematical model to investigate the dynamics of the interactions between tumor cells, endothelial cells and oncolytic viruses.

1.2 Outline

Chapter 1

Chapter 1 is the introduction that briefly reviewed tumor cells infection by the oncolytic viruses and gave motivation and objectives of the study.

Chapter 2

Angiogenesis and oncolytic viruses models, which investigate the interaction between the tumor cells and oncolytic viruses with and without immune response are presented in Chapter 2.

Chapter 3

Here we explore a mathematical model on the interactions between tumor cells and oncolytic viruses. We investigate the stability of the equilibrium points of the model equations.

Chapter 4

We perform the numerical results of the model and give biological interpretations.

Chapter 5

Discussion of the findings and conclusions of the present study is provided in this last Chapter.

Chapter 2

Literature Review

2.1 Introduction

Cancer refers to a group of diseases whereby cells divide more than they should or overgrow more than normal cells and may spread to other parts of the body. According to National Cancer Registry cancer kills more people than the combination of TB, AIDs and Malaria, and it is claimed that deaths related to cancer amounted to approximately 8.2 million in 2010, and the mortality rate is expected to rise with estimated 13 million deaths by 2030 [20–22].

Despite its common genetic themes, every cancer is different and develops very slowly over time(many years). The likelihood is thirty percent that an individual will get cancer in their lifetime, hence many describe it as the disease of old age. Cancer emerges when normal control systems (a system that promotes cell growth and a system that protect against irregular growth) within a single cell are disabled. More systems must be corrupted within a cell so that a cancer cell forms a mass of any size and starts producing Vascular Endothelial Growth Factor(VEGF) in order to promote the growth of new blood vessels(angiogenesis) [21, 22].

2.2 Angiogenesis

Angiogenesis is the formation of new blood vessels from pre-existing ones. It occurs in several stages of bodily life; however we are going to concentrate more on sprouting angiogenesis [23]. There are

three stages of angiogenesis: the first one is the proliferation of angiogenesis factors or regulators; the second is the growth of epithelial towards the tumor cell called migration and lastly, the adaptation to the new environment called mutation.

There are several angiogenic factors that stimulate the endothelial cells on existing blood vessels which then present the required receptors. The stimulated endothelial cells produce and release protease so to degrade the basement of the membrane. This degradation is influenced by tumor angiogenesis factors(TAFs) such as matric metalloproteinase(MMP) and Angiopoietin 2(ANG-2). The function of MMP is to degrade extracellular matrix(ECM) proteins and keep vessel walls solid, and that of ANG-2 is to destabilize the blood vessels. After the destabilization of the blood vessel, the endothelial cells can migrate out of them and proliferate. Several angiogenesis factors such as VEGF, fibroblast growth factors(FGFs) and others are involved in that process. The VEGF sticks to the kinase receptors on the surfaces of the endothelial cells, increasing proliferation and stimulating tubular walls of capillaries. The new vascular tube grows, targeting those areas with the highest concentration of angiogenic factors through the existing tissue layers. The VEGF and FGFs will encourage tube formation and remodeling being stabilized by ANG-2 involvement. Up to this far, the endothelial tubes do not have a stable structure to withstand blood pressure strength, so the angiogenic factors like TGF_{β} will engage pericytes and other substances to maintain the outer walls of the new vessels, hence the construction is completed.

However, the effects of angiogenesis are that the tumor will grow in size due to it being able to enter through thin layers of the vessels and into the circulatory system. After this then, it might not be removed easily. [24].

Among those highly valued therapies, [23] stated that inhibitors might be used to stop the production of angiogenic factors as well as the growth of new vessels. He also states that VEGF is responsible for stimulating endothelial cells proliferation and TGF_{β} for cell proliferation, differentiation and development.

According to [21], cancer growth goes through many processes; there is a certain primary amount of cancer cells(the model does not deal with the origin of cancer cells) appearing in an entirely healthy organ. Second, these cells influence the formation of pre-vascular cells from the existing vasculature and third, after some time, the formation of new blood vessels is started under which both normal and cancer cells compete for nutrients and oxygen for survival.

2.2.1 Angiogenesis Models

Yang (2012)

Considering the third equation in his model, we have

$$\frac{dT}{dt} = \alpha_3 AT(1 - \frac{T}{k_3}) - \beta_2 CT - \mu_3 T.$$

The cancer cells(T) are limited by the carrying capacity k_3 and the surrounding new blood vessels originated by angiogenesis (A).

Another equation is

$$\frac{dA}{dt} = \delta P + \varepsilon TA(1 - \frac{A}{k_4}) - \mu_5,$$

from which the angiogenesis cells growth, depends on tumor cells subject to space k_4. The endothelial cells(E) and the angiogenesis cells are compelled by the physical limitations and not subjected to nutrients and oxygen. However, the assumption is based on an early stage of angiogenesis (pre - angiogenesis) governed by

$$\frac{dP}{dt} = \gamma ET - \delta P - \mu_4 P.$$

From this equation, the stage corresponds to the release of VEGF by tumor cells of nearby blood vessels. Endothelial cells eventually respond to the VEGF by forming sprouts, from which migration and proliferation occur towards the tumor. The new blood vessels are called angiogenesis (endothelial cells A).

From this, it was found that the higher the capacity of building up new vascularization, ε, the less the amount of sprouts that came from the existing blood vessels needed for angiogenesis.

Villa (2018)

Three models of different dimensions were considered. The one dimensional model briefly explains the process or stages of migration and migration by endothelial in the formation of new sprouts. The main focus on this is that as tumor angiogenic factor is produced by the tumor and enters the tissue by diffusion until its contact with the nearby ECs, the enzymes are released to degrade the membrane basement under the influence of TAF. After that the migration towards the tumor and proliferation can take place. Upon analysis, C. Villa found that this model allows straight tackling

of ECs development towards the tumor and its retreat when the tumor is eliminated. Regardless of these improvements, the model could be extended to include other factors like sprout tip density or ECM function in the process.

2.3 Oncolytic Viruses

The Oncolytic Viruses(OVs) are viruses that can target, selectively infect and replicate within tumor cells. There are OVs that occur naturally and those genetically engineered in laboratories. Many treatments like chemotherapy, radiotherapy, physiotherapy and others have become more popular from which there has been many side effects reported by cancer patients. In order to address that, virotherapy has been a recent ongoing research. The advantage of this therapy is that the viruses can target tumor cells while sparing normal cells. Another advantage is that while infecting tumor cells, they can also produce or improve immunity in the form of antigens. Furthermore, OVs can be genetically modified so to incorporate or include the gene of interest at high levels in the process of infection and replication. Many genes can either be deleted to produce a safe virus or be inverted into a genome to increase efficacy. Different OVs infect cells in many ways. Such viruses like Vaccinia virus (VV) and Newcastle Disease Virus (NDC) enter cells through endocytosis while other viruses like HSV use nectic; Measles uses CD46 [25].

However, as we have indicated, the challenges of OVs are that only a small fraction will reach the tumor since the immune cells will demolish them before infecting other tumor cells [25, 26]. Another challenge that is when administering the OVs, care must be taken since they can also target and destroy healthy cells. In order to prevent that, there are procedures that can be used to control specific genes. One such is to use MicroRNA, which has low expression levels in a tumor cell. Another one is to increase specificity through modification of viral coat to tumor cells.

2.3.1 Oncolytic Viruses Models

Phan and Tian (2017)

Phan and Tian modified the model that was earlier studied by J.P. Tian without including immunity and now they include immune response, and the model is as follows:

$$\frac{dx}{dt} = \lambda x(1 - \frac{x+y}{C}) - \beta xv$$
$$\frac{dy}{dt} = \beta xv - \mu yz - \delta y$$
$$\frac{dv}{dt} = b\delta y - \beta xv - kvz - \gamma v,$$
$$\frac{dz}{dt} = syz - \rho z,$$

where

x stands for uninfected tumor cells,y infected tumor cells,v free viruses and z the innate immune cell population. λ is the tumor growth rate; C is the carrying capacity of tumor cells; β is the infection rate of the virus; μ is the immune killing rate of infected tumor cells; δ is death rate of the infected tumor cells; b is the burst size of OVs or the number of new viruses coming out from lysis of infected cells; k is the immune cells killing rate of viruses; γ is the clearance rate of viruses; s is the stimulation rate of the innate immune system and ρ is the immune clearance rate.

Their aim was to investigate the role played by innate immunity on infected tumor cells and virus populations. It was discovered that the model depends entirely on the viral burst size b and parameters corresponding to the natural immune response in the sense that when the burst size is large, the dynamics of the model is similar to the model without innate immunity; and for small values of burst size, the dynamics with immunity produce more equilibrium solutions and complicate the therapy. They further conclude that innate immunity reduces efficacy of oncolytic viruses by reducing new replications and blocking the spreading of infection. Further, they suggest considering adaptive immunity to improve the efficacy of oncolytic virotherapy as it tends to reduce tumor cells.

Salma M. AI-Tuwairqi et al. (2020)

Here Salma M. AI-Tuwairqi et al improved Phan and Tian's model by investigating the interaction between the innate immune system and uninfected tumor cells because both tumor and virus-infected cells are recognized by natural killer cells that are part of the innate immune system.They also investigated the role of immunity and its impact on both uninfected and infected cancer cells and free viruses and modified the model as follows

$$\frac{dx}{dt} = \lambda x(1 - \frac{x+y}{C}) - \beta xv - \alpha xz - dx,$$
$$\frac{dz}{dt} = s_1 yz + s_2 xz - \rho z,$$

and the other equations remain the same.

The assumption is that immune cells kill both types of cancer cells at the rates α and μ, respectively. Again both uninfected and infected cells stimulate the immune response at the rates s_2 and s_1 respectively; d is the death rate of uninfected cancer cells, and as usual, all the parameters are non-negative.

In this model, five equilibrium points were obtained and analysed, and there is one point different from Tuan and Phan and its significance is that immune cells kill both infected cells and the viruses. Further, the analysis was done based on two cases: low and high infection rates. It was found that when the infection is high and the stimulation rate of immune response is low, the virus is powerful, and when immunity is high, the immune response is dominant. Nevertheless, in both cases the size of the initial tumor decreases to a constant value.

2.4 Methodology

In this study we introduce a mathematical model that describes the interactions between the uninfected and infected tumor cells, unifected and infected endothelial cells and the oncolytic viruses. We analyse the model for positivity, boundedness, existence and invariance. We are also going to study the stability of the equilibrium points. Further, we explore the analytical and numerical solutions of the non-linear ODEs using MATLAB.

Chapter 3

A Mathematical Model

3.1 Introduction

In this chapter, we are going to develop a system of ordinary differential equations(ODEs) model that describes the local interactions between the tumor cells and oncolytic viruses. In particular, the model focuses on the attack of a solid tumor with oncolytic viruses.

3.2 Model Formulation

We develop a novel compartmental mathematical model that describes the dynamics of the interactions between the respective cell populations of tumor cells, tumor endothelial cells. The model also considers the population of oncolytic virus particles and their potential effects on cell populations. To account for the effects of oncolytic virus infection on tumor cells, tumor comprises the uninfected and infected cells, as its primary cell constituents. Similar to the tumor cell population, tumor endothelial cells are also segregated into uninfected and infected cell populations.

In this study, the OVs are systemically administered in the vicinity of the tumor microenvironment and are assumed to freely circulate with blood to reach tumor or tumor endothelial cells. Once the tumor or tumor endothelial cells are infected, the OVs replicate within the infected cell, leading to infected cell lysis. The newly produced OVs may further infect and lyse other uninfected tumor

cells or tumor endothelial cells [17]. Consequently, this may result in a collapse of tumor vasculature and tumor cell death. Note that in the present study we also investigate the possibility of using tumor endothelial cells as virus-producing cell "factories" (see an experimental study done in [14]) to increase the number of infectious oncolytic virions within tumor microenvironment.

In this model, we assume that tumor promotes its growth through the secretion of various cytokines such as vascular endothelial growth factor (VEGF) and tumor growth factor β (TGFβ), which promotes the activity and growth of tumorous cells. Hence, we represent the tumor growth rate as an algebraic sum of the intrinsic growth rate, a_T, and the enhanced proliferation by tumor, $\mu_\beta T_u$. To account for the difference in scales between the state variables, we use the well-established conversion rule, 1 $mm^3 \simeq 10^6$ cells for proportionality between volume and number of cells [26].

We present a full system of ordinary differential equations (ODEs) with a detailed description of how each equation of the state variable is derived in this study. The model parameter description is provided in Table 4.1.

Table 3.1: Model Variables

Variable	Description
$T_u(t)$	the total number of uninfected tumor cell population
$T_i(t)$	the total number of infected tumor cell population
$E_u(t)$	the total number of uninfected tumor endothelial cell population
$E_i(t)$	the total number of infected tumor endothelial cell population
$V(t)$	the total number of virions within tumor microenvironment
$I_\beta(t)$	the concentration of TGFβ within tumor microenvironment

The ODE system describing our model is given by the following equations:

$$\frac{dT_u}{dt} = \underbrace{(a_T + \mu_T E_u)\, T_u \left(1 - \frac{T_u + T_i}{K_T}\right)}_{\text{proliferation}} - \underbrace{\beta_T V T_u}_{\text{infection}} \tag{3.1}$$

$$\frac{dT_i}{dt} = \underbrace{\beta_T V T_u}_{\text{infection}} - \underbrace{l_v T_i}_{\text{death by lysis}} \tag{3.2}$$

$$\frac{dE_u}{dt} = \underbrace{\left(a_E + \mu_\beta \frac{I_\beta}{h_E + I_\beta}\right) E_u \left(1 - \frac{E_u + E_i}{K_E}\right)}_{\text{proliferation}} - \underbrace{\beta_E E_u V}_{\text{infection}} \tag{3.3}$$

$$\frac{dE_i}{dt} = \underbrace{\beta_E E_u V}_{\text{infection}} - \underbrace{l_v E_i}_{\text{death by lysis}} \tag{3.4}$$

$$\frac{dV}{dt} = \underbrace{\mu_v(t)}_{\text{virus injection}} + \underbrace{l_v b_T T_i}_{\text{lysis}} + \underbrace{l_v b_E E_i}_{\text{lysis}} - \underbrace{\omega V}_{\text{clearance}} \tag{3.5}$$

$$\frac{dI_\beta}{dt} = \underbrace{k_\beta T_u}_{\text{production by } T_u} - \underbrace{\lambda_\beta I_\beta}_{\text{decay}} \tag{3.6}$$

The initial conditions to the above system of equations are:

$$\begin{aligned} T_u(0) &= T_{u0} \text{ cells},\ T_i(0) = 0 \text{ cells},\ E_u(0) = E_{u0} \text{ cells},\ E_i(0) = 0 \text{ cells}, \\ V(0) &= V_0 \text{ plaque-forming units (PFU)},\ I_\beta(0) = I_{\beta 0}\ pg \end{aligned} \tag{3.7}$$

As in previous models [26, 27], OV injection into the system is modeled using a delta function $\mu_v(t) = \mu_v(0)\Delta(t - \tau)$, which accounts for an amount $\mu_v(0)$ of virus particles injected on a specified day (τ), and Δ is the Dirac delta function [26]. Here we follow the experiments in [28], where $\mu_v(0) = 5 \times 10^6$ virus particles is injected into the system on day $\tau (e.g., \tau = 19)$.

In equation 3.1, the term, $a_T T_u \left(1 - \frac{T_u + T_i}{K_T}\right)$, denotes an intrinsic growth of uninfected tumor cells in the absence of endothelial cells in which the tumor cells proliferate logistically at the rate a_T up to the carrying capacity K_T. The term $\mu_T E_u T_u \left(1 - \frac{T_u + T_i}{K_T}\right)$ indicates the endothelial cell-induced tumor growth, at the rate μ_T. In the absence of oncolytic virus infection, vascular tumor depends on the tumor vascularization (i.e., the flow of blood from the new vessels formed via angiogenesis (the formation of new blood vessels from pre-existing bloodstream) process) [11, 29–31]. For simplicity, we do not consider the complex subcellular events leading to tumor angiogenesis, such as sprouts formation and migration towards tumor. Instead, we consider the tumor as being in well-vascularized state. The second term, $-V\beta_T T_u$, denotes the infection of tumor cells by the oncolytic virions re-

leased within tumor microenvironment, V, with the infection rate, β_T.

In equation 3.2, the instantaneous transfer of a subpopulation of the uninfected tumor cells to the infected cell subpopulation following the oncolytic virus infection is represented by the first term, $V\beta_T T_u$. The death of the infected tumor cells, at the lysis rate l_v, is denoted by the last term, $-l_v T_i$. Here we assume that the death of the infected cell occurs very rapidly following the virus infection, hence the intrinsic growth of the infected cell is neglected.

In equation 3.3, the intrinsic proliferation of tumor endothelial cells is denoted by the term, $a_E E_u \left(1 - \frac{E_u+E_i}{K_E}\right)$ in the absence of TGFβ. The term $\mu_\beta \frac{I_\beta}{h_E+I_\beta} E_u \left(1 - \frac{E_u+E_i}{K_E}\right)$ denotes the TGFβ induced growth rate of endothelial cells. Since the tumor cells have a limit in secreting the TGFβ, the term $\mu_\beta \frac{I_\beta}{h_E+I_\beta}$ is used to account for the saturation effect of TGFβ on endothelial cell growth. The parameters, a_E and K_E, respectively define the intrinsic growth rate and the carrying capacity of the tumor endothelial cells while the parameters μ_β and h_E represent the TGFβ induced growth rate and the half-saturation constant for TGFβ secreted by tumor cells, respectively. In this study, we assume that tumor endothelial cells grow logistically in the absence of treatment, as has been done in [21]. Upon infection with the oncolytic virus particles, the instantaneous shift of the subpopulation of the uninfected tumor endothelial cells to the infected cell subpopulation is denoted by the term, $-\beta_E E_u V$. The infection rate of the tumor endothelial cells by the oncolytic virions are defined by β_E. Here we model the oncolytic virus infection with a mass action term, as done in [32]. Under this scenario, the infection rate is dependent on the number of uninfected tumor endothelial cells and the amount of oncolytic virions. We consider the mass action kinetics because the infection of the tumor endothelial cells depends on the amount of free oncolytic virus particles released from lysed carrier cells in the tumor vasculature, not on the carrier cell infiltrates. Note that tumor endothelium is prohibitive to the entry of tumor-specific lymphocytes [31]. Hence, we assume that the circulating carrier cells would ultimately be destroyed by the loaded virus. After lysis, there would be free virus particles circulating in the tumor vasculature that could infect the tumor endothelial cells.

In equation 3.4, the instantaneous transfer of uninfected tumor endothelial cells to the infected subpopulation is represented by the first term, $\beta_E E_u V$. The lysis of the infected tumor endothelial cells is defined by the last term, $-l_v E_i$, with lysis rate l_v.

In equation 3.5, once the infected carrier cells within tumor are lysed by the replication-competent virus, a new progeny of oncolytic virus particles would then infect neighboring tumor cells and, or tumor endothelial cells. After successful virus replication within infected cells, T_i and E_i, new virus particles are released and further infect the neighboring uninfected cells. Thus, the first term $\mu_v(t)$, accounts for an amount of virus particles injected on a specified day. The second term $l_v b_T T_i$, represents the production of new virions from the lysed infected tumor cells at a rate $l_v b_T$ that is proportional to their lysis. Similarly, the third term, $l_v b_E E_i$, denotes the increase in the concentration of virus particles within tumor as a result of the virions released from the lysed tumor endothelial cells, E_i, at a rate $l_v b_E$ that is proportional to their lysis. Similar to viral dynamics within tumor compartment, here b_T denotes the number of virions released from an infected tumor endothelial cell capable of forming viral plaques. An immune induced [33] or non-immune induced [34] virus inactivation and elimination is represented by the last term, ωV, where ω is the clearance rate within tumor microenvironment. Note that in the tumor microenvironment free viruses are susceptible to neutralization by circulating antibodies or other anti-virus immune cells. For simplicity, we assume that the virus clearance rate within tumor microenvironment (ω) embodies the immune-induced clearance or potential inactivation by an innate immune response. Note that there are no free virus particles within tumor because the moment a virus enters a tumor cell, it becomes retained within the cell it entered only; hence, it cannot infect other cells. Thus, it cannot constitute the free virus population as in the tumor microenvironment. This assumption is consistent with models in [35–38]. **In equation 3.6** the first term, $k_\beta T_u$ TGFβ is secreted by tumor cells at the rate k_β, and the last term, $\lambda_\beta I_\beta$, represents the decay of TGFβ at the rate λ_β.

3.3 Non-dimensionalization

In order to explore the qualitative behavior of our system, and investigate which parameters have the greatest influence on the model, we first simplify the relationship between state variables by **non-dimensionalization**. The significance of this procedure is not only to determine which parameters have a dominant effect on our system, but also to reduce the total number of parameters that can be altered.

To non-dimensionalise the system of equations (3.1–3.6), let $\hat{T}_u$ represent the non-dimensionalized

version of T_u, and $T^\star_{u0}$ be an order of magnitude of uninfected tumor cell population scale. We similarly rescale the values for other state variables as follows:

$$T_u = T^\star_{u0}\hat{T}_u, \quad T_i = T^\star_{i0}\hat{T}_i, \quad E_u = E^\star_{u0}\hat{E}_u, \quad E_i = E^\star_{i0}\hat{E}_i, \quad V = V^\star_0\hat{V}, \quad I_\beta = I^\star_{\beta 0}\hat{I}_\beta$$

and $t = t^\star_0\hat{t}$.

Next, considering Equation (3.1), this non-dimensionalization transforms leads to

$$\begin{aligned}
\frac{d\hat{T}_u}{d\hat{t}} &= \frac{t^\star_0}{T^\star_{u0}}\left[\left(a_T + (\mu_T E^\star_{u0})\hat{E}_u\right) T^\star_{u0}T_u\left(1 - \frac{T^\star_{u0}T_u + T^\star_{i0}T_i}{K_T}\right) - (\beta_T V^\star_0 T^\star_{u0})\hat{V}\hat{T}_u\right] \\
&= \left(t^\star_0 a_T + (t^\star_0\mu_T E^\star_{u0})\hat{E}_u\right) T_u\left(1 - \frac{T^\star_{u0}T_u + T^\star_{i0}T_i}{K_T}\right) - (t^\star_0\beta_T V^\star_0)\hat{V}\hat{T}_u \\
&= \left(1 + \left(\frac{K_E}{a_T}\mu_T\right)\hat{E}_u\right) T_u\left(1 - (\hat{T}_u + \hat{T}_i)\right) - \left(\frac{\beta_T}{l_v}\right)\hat{V}\hat{T}_u \\
&= \left(1 + \chi\hat{E}_u\right) T_u\left(1 - (\hat{T}_u + \hat{T}_i)\right) - \delta\hat{V}\hat{T}_u. \qquad (3.8)
\end{aligned}$$

Considering Equation (3.2), we have that

$$\begin{aligned}
\frac{d\hat{T}_i}{d\hat{t}} &= \frac{t^\star_0}{T^\star_{i0}}\left[(\beta_T V^\star_0 T^\star_{u0})\hat{V}\hat{T}_u - l_v T^\star_{u0}\hat{T}_i\right] \\
&= \left(\frac{\beta_T}{l_v}\right)\hat{V}\hat{T}_u - \left(\frac{l_v}{a_T}\right)\hat{T}_i \\
&= \delta\hat{V}\hat{T}_u - \sigma T_i. \qquad (3.9)
\end{aligned}$$

Next, we non-dimensionalize Equation (3.3) as follows:

$$\begin{aligned}
\frac{d\hat{E}_u}{d\hat{t}} &= \frac{t^\star_0}{E^\star_{u0}}\left[\left(a_E + \mu_\beta\frac{I^\star_{\beta 0}\hat{I}_\beta}{h_E + I^\star_{\beta 0}\hat{I}_\beta}\right) E^\star_{u0}E_u\left(1 - \frac{E^\star_{u0}E_u + E^\star_{i0}E_i}{K_E}\right) - (\beta_E V^\star_0 E^\star_{u0})\hat{V}\hat{E}_u\right] \\
&= \left(t^\star_0 a_E + \frac{\mu_\beta t^\star_0\hat{I}_\beta}{\frac{h_E}{I^\star_{\beta 0}} + \hat{I}_\beta}\right) E_u\left(1 - \frac{E^\star_{u0}E_u + E^\star_{i0}E_i}{K_E}\right) - (t^\star_0\beta_E V^\star_0)\hat{V}\hat{E}_u \\
&= \left(g + \tau\frac{\hat{I}_\beta}{\eta + \hat{I}_\beta}\right) E_u\left(1 - (\hat{E}_u + \hat{E}_i)\right) - \rho\hat{V}\hat{E}_u. \qquad (3.10)
\end{aligned}$$

Similarly, the equation for the infected tumor endothelial cells, Equation (3.4), is transformed as follows:

$$\begin{aligned}
\frac{d\hat{E}_i}{d\hat{t}} &= \frac{t^\star_0}{E^\star_{i0}}\left[(\beta_E V^\star_0 E^\star_{u0})\hat{V}\hat{E}_u - l_v E^\star_{u0}\hat{E}_i\right] \\
&= \left((t^\star_0\beta_E V^\star_0)\frac{E^\star_{u0}}{E^\star_{i0}}\right)\hat{V}\hat{E}_u - (t^\star_0 l_v)\,\hat{E}_i \\
&= \rho\hat{V}\hat{E}_u - \sigma E_i. \qquad (3.11)
\end{aligned}$$

Now, considering Equation (3.5), we have

$$\begin{aligned}\frac{d\hat{V}}{d\hat{t}} &= \frac{t_0^\star}{V_0^\star}\left[l_v b_T T_{i0}^\star \hat{T}_i + l_v b_E E_{i0}^\star \hat{E}_i - \omega V_0^\star \hat{V}\right] \\ &= \left(t_0^\star l_v b_T \frac{T_{i0}^\star}{V_0^\star}\right)\hat{T}_i + \left(t_0^\star l_v b_E \frac{E_{i0}^\star}{V_0^\star}\right)\hat{E}_i - (t_0^\star \omega)\hat{V} \\ &= (b_T K_T)\,\hat{T}_i + (b_E K_E)\,\hat{E}_i - \left(\frac{\omega}{a_T}\right)\hat{V} \\ &= b_1 \hat{T}_i + b_2 \hat{E}_i - \xi \hat{V}. \end{aligned} \tag{3.12}$$

Finally, the Equation (3.5) is transformed as follows:

$$\begin{aligned}\frac{d\hat{I}_\beta}{d\hat{t}} &= \frac{t_0^\star}{I_{\beta 0}^\star}\left[k_\beta T_{u0}^\star \hat{T}_u - \lambda_\beta I_{\beta 0}^\star \hat{I}_\beta\right] \\ &= \left(t_0^\star k_\beta \frac{T_{u0}^\star}{I_{\beta 0}^\star}\right)\hat{T}_u - (t_0^\star \lambda_\beta)\hat{I}_\beta \\ &= \left(\frac{k_{\beta K_T}}{a_T I_{\beta 0}^\star}\right)\hat{T}_u - \left(\frac{\lambda_\beta}{a_T}\right)\hat{I}_\beta \\ &= \hat{T}_u - \gamma \hat{I}_\beta. \end{aligned} \tag{3.13}$$

Our new system, Equations (3.8–3.13), was simplified by choosing $T_{u0}^\star$ and other new constants as:

$$t_0^\star = \frac{1}{a_T},\quad T_{u0}^\star = T_{i0}^\star = K_T,\quad E_{u0}^\star = E_{i0}^\star = K_E,\quad V_0^\star = \frac{a_T}{l_v},\quad I_{\beta 0}^\star = \frac{k_\beta K_T}{a_T},$$

and the new non-dimensionalized constants as:

$$\chi = \frac{K_E \mu_T}{a_T},\quad \delta = \frac{\beta_T}{l_v},\quad \sigma = \frac{l_v}{a_T},\quad \tau = \frac{\mu_\beta}{a_T},\quad \eta = \frac{h_E a_T}{k_\beta K_T},\quad \xi = \frac{\omega}{a_T},\quad b_1 = b_T K_T,$$
$$b_2 = b_E K_E,\quad \gamma = \frac{\lambda_\beta}{a_T},\quad g = \frac{a_E}{a_T},\quad \rho = \frac{\beta_E}{l_v}.$$

Dropping the *hats* for convenience, the final non-dimensionalized system of equations (3.8–3.13), identical to the original system in structure, is given by:

$$\frac{dT_u}{dt} = (1 + \chi E_u)\,T_u\,(1 - (T_u + T_i)) - \delta V T_u. \tag{3.14}$$
$$\frac{dT_i}{dt} = \delta V T_u - \sigma T_i. \tag{3.15}$$
$$\frac{dE_u}{dt} = \left(g + \tau \frac{I_\beta}{\eta + I_\beta}\right) E_u\,(1 - (E_u + E_i)) - \rho V E_u \tag{3.16}$$
$$\frac{dE_i}{dt} = \rho V E_u - \sigma E_i. \tag{3.17}$$
$$\frac{dV}{dt} = b_1 T_i + b_2 E_i - \xi V. \tag{3.18}$$
$$\frac{dI_\beta}{dt} = T_u - \gamma I_\beta. \tag{3.19}$$

The initial conditions for the non-dimensionalised system are defined as

$$T_u(0) = T^{\star}_{u0}, \quad T_i(0) = 0, \quad E_u(0) = E^{\star}_{u0}, \quad E_i(0) = 0, \quad V(0) = 0, \quad I_\beta(0) = I^{\star}_{\beta 0}. \tag{3.20}$$

This new non-dimensionalized system of our model is important for performing qualitative analysis in the next two sections. More specifically, we use it to examine the model equilibria, perform numerical analysis and investigate the best treatment regimes in the subsequent chapter.

3.4 Mathematical Analysis

3.4.1 Model Basic Properties

At this point, we first investigate and derive the inherent mathematical properties of the model system (3.1–3.6) along with the initial conditions described in Equation 3.7.

3.4.2 Positivity of Solutions

We first illustrate that our system obeys the positivity of solutions property. That means, given the non-negative initial conditions $(T_{u0}, T_{i0}, E_{u0}, E_{i0}, V_0, I_{\beta 0})$, then the solutions/trajectories of the system will also remain non-negative for all $t \in [0, \infty)$. This is an important property to establish since the system of equations (3.1–3.6) models the cells and virus populations, and the cytokine concentration within tumor microenvironment. Hence, we cannot have negative populations or concentrations. We thus have the following theorem:

Theorem 3.4.1. *Given that the initial conditions*

$$(T_{u0} > 0, T_{i0} > 0, E_{u0} > 0, E_{i0} > 0, V_0 > 0, I_{\beta 0} > 0)$$

of the system (3.1-3.6), the resulting solutions

$$(T_u(t), T_i(t), E_u(t), E_i(t), V(t), I_\beta(t))$$

are also non-negative for all $t \in [0, \infty)$.

Proof. Considering Equation 3.1, we have

$$\frac{dT_u}{dt} = T_u + \chi E_u T_u - [T_u^2 + T_u T_i + \chi E_u T_u T_i + \delta V T_u]$$
$$\geq T_u$$
$$=> \frac{dT_u}{dt} - T_u \geq 0,$$

which is a first order linear equation, and the integrationg factor is e^{-t}. We mutliply on both sides and integrate with respect to t to obtain

$$T_u = c_1 e^t.$$

Applying the initial conditons we have $T_u(0) = c_1 = T_{u0}$, and due to the fact that the exponential function is always positive, we have

$$T_u \geq T_{u0} e^t \geq 0.$$

From 3.2 we have

$$\frac{dT_i}{dt} = \delta V T_u - \sigma T_i,$$
$$\geq -\sigma T_i.$$

Using the integrating factor $e^{-\sigma t}$, the above equation becomes

$$T_i \geq c_2 e^{-\sigma t},$$
$$=> T_i \geq T_i(0) e^{-\sigma t} \geq 0.$$

Using the same procedure as above from equation 3.3, we have

$$\frac{dE_u}{dt} = \left(g + \tau \frac{I_\beta}{\eta + I_\beta}\right) T_u E_u \left(1 - (E_u + E_i)\right) - \rho V E_u$$
$$\geq -\rho E_u,$$
$$=> E_u \geq c_3 e^{-\rho t},$$
$$=> E_u \geq E_{u0} e^{-\rho t} \geq 0.$$

In the same token, we obtain the following:

From equation 3.4 we have

$$\frac{dE_i}{dt} = \rho V E_u - \delta E_i,$$
$$\geq -\delta E_i,$$
$$=> E_i \geq c_4 e^{-\delta t},$$

$$=> E_i \geq E_i(0)e^{-\sigma t} \geq 0.$$

From equation 3.5 we have

$$\frac{dV}{dt} = b_1 T_i + b_2 E_i - \xi V,$$
$$\geq -\xi V,$$
$$=> V \geq c_5 e^{-xit},$$
$$=> V \geq V(0)e^{-\xi t} \geq 0.$$

The last equation 3.6 becomes

$$\frac{dI_\beta}{dt} = T_u - \gamma I_\beta,$$
$$\geq -\gamma I_\beta,$$
$$=> I_\beta \geq c_6 e^{-\gamma t},$$
$$=> I_\beta \geq I_{\beta 0} e^{-\gamma t} \geq 0.$$

Hence Theorem 3.4.1 is proven. □

3.4.3 Boundedness of Solutions and Invariant Region

Proof. From 3.1 we have

$$\frac{dT_u}{dt} = T_u - T_u^2 - [\chi E_u(T_u^2 - T_u) + T_u T_i + \chi E_u T_u T_i + \delta V T_u]$$
$$\leq T_u - T_u^2$$

The above equation is a Bernoulli equation and the soluion is

$$T_u = \frac{T_u 0}{(T_u 0 + (1 - T_u 0)e^{-t})}$$

$$\lim_{t->\infty} sup T_u \leq \limsup \frac{T_u 0}{(T_u 0 + (1 - T_u 0)e^{-t})} \leq 1$$

Again from 3.1and 3.2 we have

$$\frac{dT_u}{dt} + \frac{dT_i}{dt} = T_u - T_u^2 - [\chi E_u(T_u^2 - T_u) + T_u T_i + \chi E_u T_u T_i + \delta V T_u] + \delta V T_u - \sigma T_i \leq T_u[1 - (T_u + T_i)];$$

therefore $\lim_{t->\infty} \sup(T_u + T_i) \leq 1$

From 3.3 we have

$$\frac{dE_u}{dt} = g(T_u E_u - T_u E_u^2 - T_u E_u E_i) - \tau \frac{I_\beta}{\eta + I_\beta}(T_u E_u^2 + T_u E_u E_i - T_u E_u) - \rho V E_u,$$

$$\leq g T_u (E_u - E_u^2) \leq g(E_u - E_u^2),$$

$$=> E_u = \frac{E_{u0}}{(E_u 0 + (1 - E_u 0)e^{-gt})}.$$

From here we have

$$\limsup E_u \leq \limsup \frac{E_{u0}}{(E_u 0 + (1 - E_u 0)e^{-gt})} \leq 1.$$

From 3.3 and 3.4 we have

$$\frac{dE_u}{dt} + \frac{dE_i}{dt} = g(T_u E_u - T_u E_u^2 - T_u E_u E_i) - \tau \frac{I_\beta}{(\eta + I_\beta)}(T_u E_u^2 + T_u E_u E_i - T_u E_u) - \rho V E_u + \rho V E_u - \delta E_i,$$

$$\leq g T_u E_u (1 - (E_u + E_i)),$$

$$\leq (1 - (E_u + E_i));$$

therefore,

$$\limsup(E_u + E_i) \leq 1.$$

From 3.5 we have

$$V = \frac{b_1 T_i + b_2 E_i}{\xi}(1 - e^{-\xi t}).$$

Now $\limsup V \leq \limsup \frac{b_1 T_i + b_2 E_i}{\xi}(1 - e^{-\xi t}) \leq \frac{b_1 + b_2}{\xi}$.

From 3.6 we have

$$I_\beta = \frac{T_u}{\gamma} + \frac{I_\beta 0 - T_u}{\gamma} e^{-\gamma t},$$

therefore

$$\limsup I_\beta \leq \limsup \frac{T_u}{\gamma} + \frac{I_\beta 0 - T_u}{\gamma} e^{-\gamma t} \leq \frac{1}{\gamma}.$$

Hence all the solutions in the model are bounded. □

3.4.4 Existence and Uniqueness of Solutions

Theorem 3.4.2. *For any non-negative initial values of the model state variables, a solution to the model described by the system (3.1–3.6) exists, and is unique in* $\mathbf{B_N}$*, for all time* $t > 0$*.*

Proof. Since the right-hand side of system (3.1–3.6) is $\mathbf{C}^1$ (class of continuously differentiable functions) satisfies the properties of locally Lipschitz functions, then the existence and uniqueness of solution to system (3.1–3.6) is ascertained according to the Cauchy-Lipschitz theorem [39, 40]. □

3.4.5 Steady States of the Base Model without Endothelial-induced Growth.

Steady states are

$$E_0 = \{T_u : 0, T_i : 0, I_b : 0, V : 0\},$$
$$E_1 = \left\{T_u : 1, T_i : 0, I_b : \tfrac{1}{\gamma}, V : 0\right\},$$
$$E_2 = \left\{T_u : \tfrac{\sigma\xi}{b_1\delta}, T_i : \tfrac{b_1\delta\xi - \sigma\xi^2}{b_1^2\delta^2 + b_1\delta\xi}, I_b : \tfrac{\sigma\xi}{b_1\delta\gamma}, V : \tfrac{b_1\delta - \sigma\xi}{b_1\delta^2 + \delta\xi}\right\}.$$

The Jacobian matrix is

$$J = \begin{pmatrix} -V\delta - T_i - 2\,T_u + 1 & -T_u & -T_u\delta & 0 \\ V\delta & -\sigma & T_u\delta & 0 \\ 0 & b_1 & -\xi & 0 \\ 1 & 0 & 0 & -\gamma \end{pmatrix}$$

We now evaluate the above Jacobian matrix and analyse the steady states of our system given above. The Jacobian matrix evaluated at the first steady state, E_0 is

$$J(E_0) = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & -\sigma & 0 & 0 \\ 0 & b_1 & -\xi & 0 \\ 1 & 0 & 0 & -\gamma \end{pmatrix}$$

The above matrix is lower triangular, so the eigenvalues are those elements on the main diagnonal;

$\lambda_1 = 1,$

$\lambda_2 = -\sigma,$

$\lambda_3 = -\xi,$

$\lambda_4 = -\phi.$

And from this we realize that the steady state E_0 is unstable because one eigenvalue ;λ_1 is positive.

The Jacobian matrix evaluated at the second steady state,E_1, is

$$J(E_1) = \begin{pmatrix} -1 & -1 & -\delta & 0 \\ 0 & -\sigma & \delta & 0 \\ 0 & b_1 & -\xi & 0 \\ 1 & 0 & 0 & -\gamma \end{pmatrix}$$

Considering the characteristic polynomial resulting from $det(J - \lambda I) = 0$ at E_1, we find that we have the following coefficients for the polynomial:

$a_0 = 1,$

$a_1 = \phi + \sigma + \xi + 1$

$$a_2 = \gamma\sigma + \gamma\xi + \sigma\xi + \sigma + \xi + \gamma - b_1\delta$$

$$a_3 = \gamma\sigma\xi + \gamma\sigma + \gamma\xi + \sigma\xi - b_1\delta(\gamma + 1)$$

$$a_4 = \gamma\sigma\xi - b_1\delta\gamma.$$

So by Routh-Hurwitz criteria the characteristic polynomial has negative roots if $a_1 > 0$, $a_2 > 0$, $a_3 > 0$, $a_4 > 0$. Definitely a_1, a_2, a_3 are positve while $a_4 > 0$ if $\sigma\xi > b_1\delta$.

The eigenvalues of the above matrix are:

$\lambda_1 = -1,$

$\lambda_2 = -\gamma,$

$\lambda_3 = -(\frac{(\sigma+\xi)}{2} + \frac{\sqrt{\sigma^2 - 2\sigma\xi + \xi^2 + 4b_1\delta}}{2}),$

$\lambda_4 = -\frac{(\sigma+\xi)}{2} + \frac{\sqrt{\sigma^2 - 2\sigma\xi + \xi^2 + 4b_1\delta}}{2}.$

We realize that the steady state E_1 is locally asymptotically stable whenever $\xi > b_1$.

The Jacobian matrix evaluated at the third steady state E_2 is

$$J(E_2) = \begin{pmatrix} -\frac{(b_1\delta - \sigma\xi)}{b_1\delta + \xi} - \frac{b_1\delta\xi - \sigma\xi^2}{b_1^2\delta^2 + b_1\delta\xi} - \frac{2\,\sigma\xi}{b_1\delta} + 1 & -\frac{\sigma\xi}{b_1\delta} & -\frac{\sigma\xi}{b_1} & 0 \\ \frac{(b_1\delta - \sigma\xi)}{b_1\delta + \xi} & -\sigma & \frac{\sigma\xi}{b_1} & 0 \\ 0 & b_1 & -\xi & 0 \\ 1 & 0 & 0 & -\gamma \end{pmatrix}$$

Without loss of generality, the third steady state seems a bit complex but we can say it is conditionally stable whenever

$$\frac{(b_1\delta - \sigma\xi)}{b_1\delta + \xi} + \frac{b_1\delta\xi - \sigma\xi^2}{b_1^2\delta^2 + b_1\delta\xi} + \frac{2\,\sigma\xi}{b_1\delta} > 1.$$

Chapter 4

Numerical Simulations and Results

4.1 Introduction

We now confer the results of the numerical simulations for our model in 3.1–3.6 . The simulations were carried out using MatLab solver for ODEs called ode23. The initial conditions are listed and the parameter values are taken from Table 4.1 below. The numerical simulations are demonstrated for the dimensional model. Free parameters were varied, especially those which have more significance in our model as we investigate stability.

4.2 Initial Conditions

The initial conditions are: $(T_u, T_i, E_u, E_i, V, I_\beta) = (1 \times 10^6, 0, 1 \times 10^6, 0, 10, 0)$.

4.2.1 Model Parameters and Initial Conditions

Table 4.1: Parameter Values Used in the Model Simulations

Parameter	Description	Value	Source
a_T	the intrinsic tumor growth rate	0.5822 day^{-1}	[41, 42]
K_T	the carrying capacity of tumor cells	2.33×10^8 cells	[41, 42]
l_v	the rate of death by lysis		free
β_T	the infection rate of tumor cells	8.9×10^{-4} virion^{-1} day^{-1}	[43]
a_E	the growth rate of tumor		
	endothelial cells	5.83×10^{-1} day^{-1}	[44]
k_β	the production rate of I_β by tumor cells	5.5×10^{-6} pg cell^{-1} day^{-1}	[44]
λ_β	the decay rate of I_β	0.693 day^{-1}	[44]
K_E	the carrying capacity of tumor		
	endothelial cells	7.5×10^6 cell $/cm^3$	[44]
β_E	the infection rate of tumor		
	endothelial cells		free
b_E	the number of virions released from		free
	an infected tumor endothelial cell	10	free
ω	virus clearance rate	8.9×10^{-5}	free
b_T	the number of virions released from		
	an infected tumor cell	100	[26]
μ_T	endothelial cell-induced growth rate	0.0	free
μ_β	TGF induced growth rate of endothelial	0.05	
	cells		free
h_E	half saturation constant	40	free

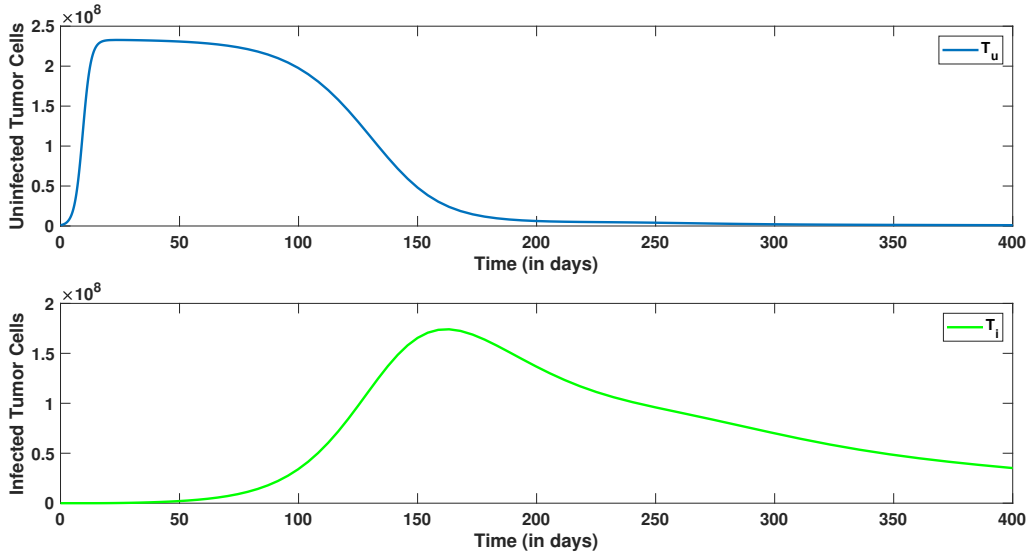

Figure 4.1: Tumor Cells, when lysis rate is 0.02, $\mu_\beta = 0$ and $\mu_T = 0.05$

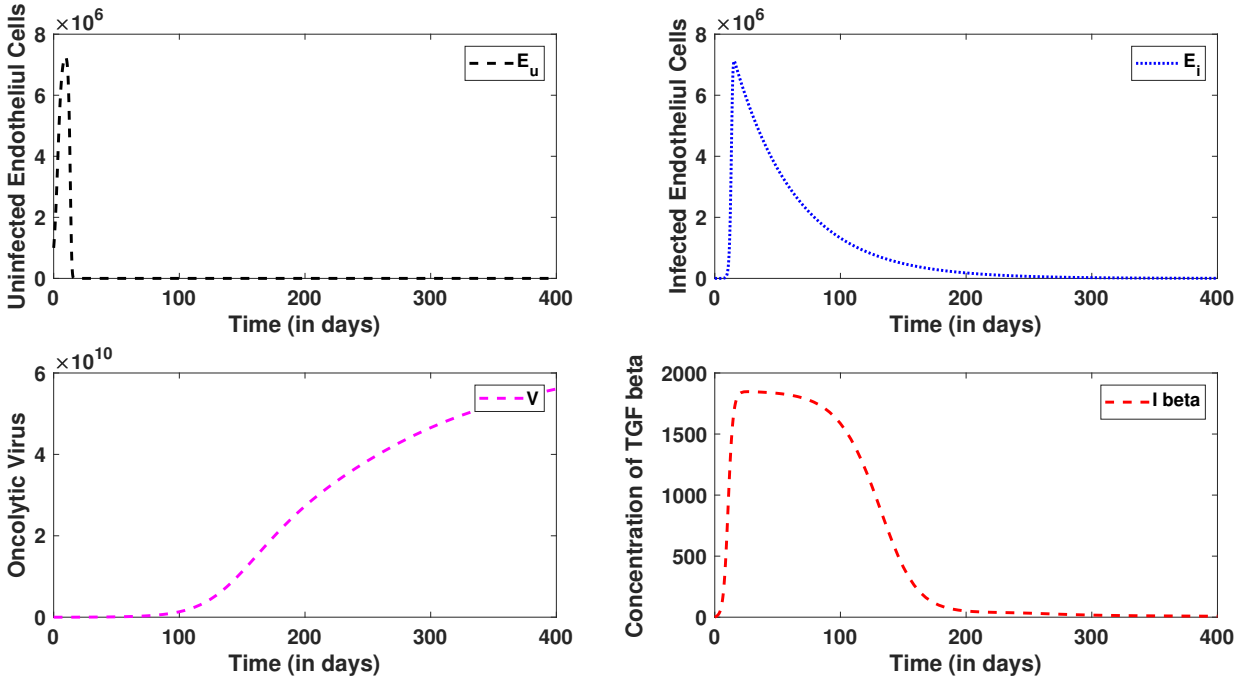

Figure 4.2: Endothelial Cells,Oncolytic Viruses, TGF_β, when lysis rate is 0.02, $\mu_\beta = 0$ and $\mu_T = 0.05$

The graphs in Figures 4.1 and 4.2 show that the uninfected tumor cells will grow logistically and decrease after some time due to more tumor cells getting infected. Also, we have the uninfected endothelial cells growing very fast from the beginning and eventually dropping quickly while on the other side the infected endothelial grow logistically and quickly grow faster and thereafter drop down with time. The OVs will grow with time, and as for the TGF_β the graph will decrease due to more

tumor cells being infected.

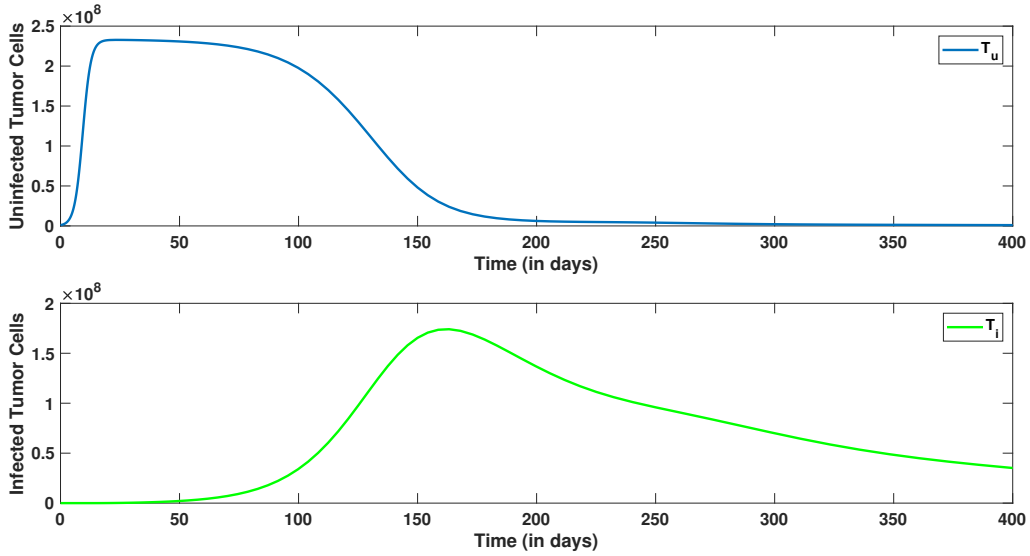

Figure 4.3: Tumor Cells, when lysis rate is 0.002, $\mu_\beta = \mu_T = 100$

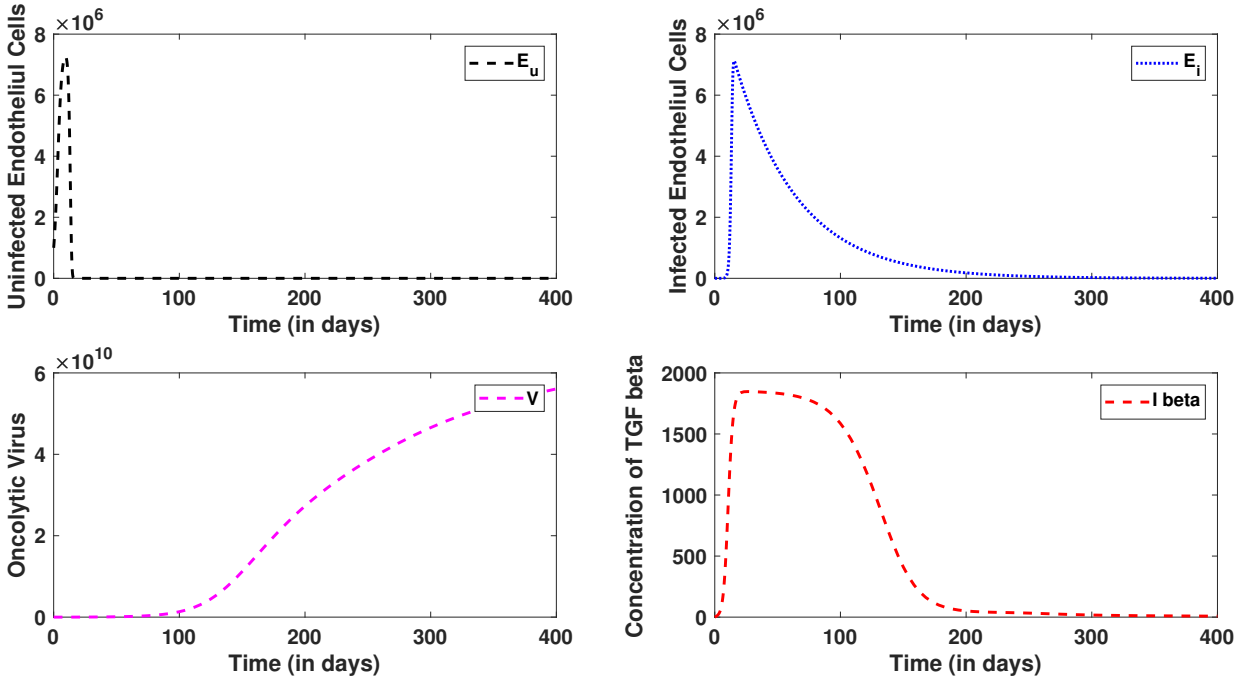

Figure 4.4: Endothelial Cells, Oncolytic Viruses, TGF_β, when lysis rate is 0.002, $\mu_\beta = \mu_T = 100$

In Figures 4.3 and 4.4 we have a lysis rate smaller than before and the burst size large. We realize that it will take some time for the tumor to get infected and after that the infected cells will take even a longer time to decrease, or there is a possibility that it might not be eliminated by the viruses.

Again, we can see that the longer it takes for the tumor to be infected, the longer the virus will take to replicate.

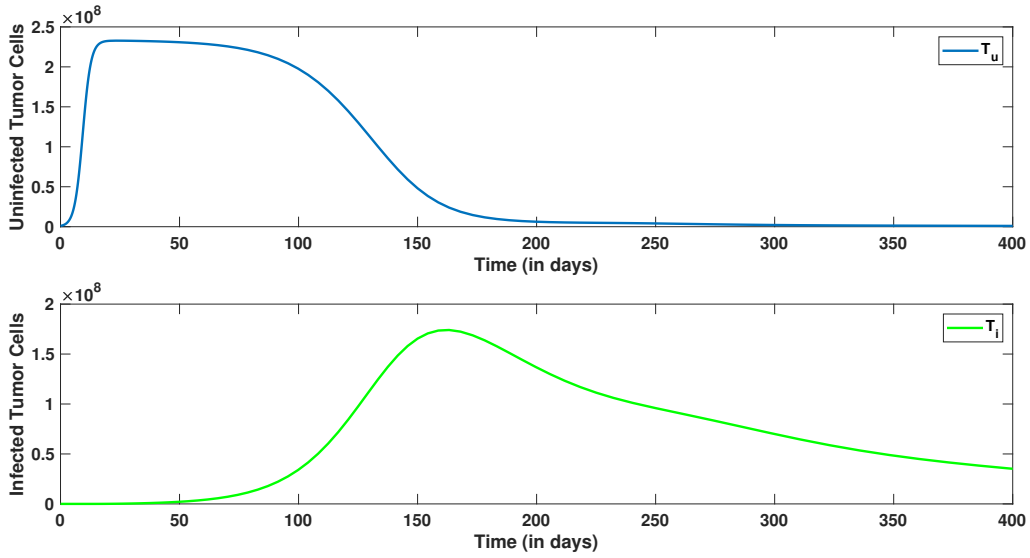

Figure 4.5: Tumor Cells, when burst sizes, $b_T = b_E = 1000$ viruses $V = 1000$

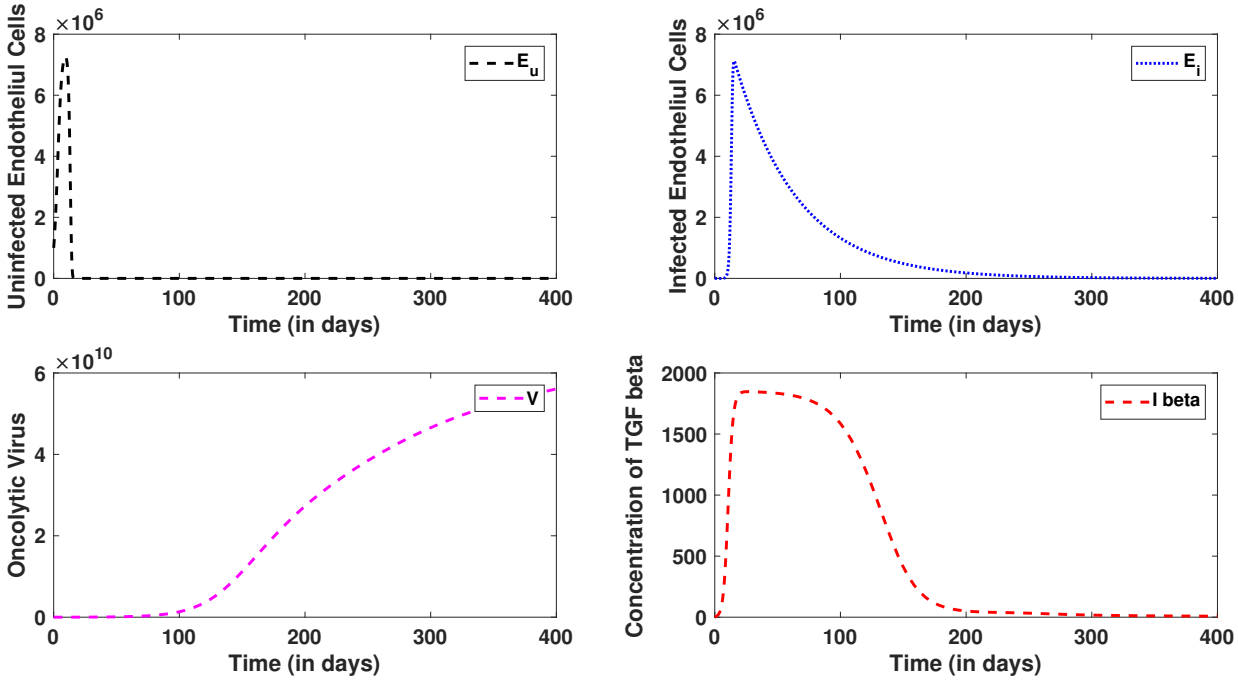

Figure 4.6: Endothelial Cells, Oncolytic Viruses, TGF_β, when burst sizes, $b_T = b_E = 1000$, viruses $V = 1000$

In Figures 4.5 and 4.6, if we start with the viruses already being administered at the highest concentration, and the burst sizes for both tumor and ECs are more prominent, both cells will be infected

quickly and the tumor will be eliminated within a short time, hence success in our treatment. The viruses will continue to grow up to a specific limit and with time be cleared of the body and the TGF_{β} will just be wiped off.

Chapter 5

Discussion and Conclusion

Cancer is now an emerging and invading disease that has recently claimed many lives, and in order to address such, cancer therapy has been an ongoing modern research. While many therapies have been claimed to have low efficacy with side effects on patients, virotherapy has been a better hope to address this problem jointly or on its own due to the discussion we had from Chapter 1 [45]. The main advantage of this therapy is that OVs can selectively infect and replicate within cancer cells to eliminate them. Another advantage is, while tackling cancer cells, the viruses also stimulate the immune system in the body. Some OVs can be engineered in laboratories and there are genes of interest which can be included or deleted in a particular OV to increase specifity [25].

In Chapter 2, we looked at OVs models on tumor cells, both uninfected and infected, and their interaction with the OVs. One model incorporated the role of innate immunity and the other did not; however, at the end both models results depended on the burst size. The conclusion is that they behave more or less the same depending on whether the burst size is large or small.

In this paper, we also investigated the dynamics between oncolytic viruses, tumor and endothelial cells, both uninfected and infected. Qualitative analysis was performed using stability theory of nonlinear systems having left out the endothelial cells. We found three equilibrium points, E_0, E_1, and E_2, out of which E_0 was unstable, and this behavior is similar in both Salma's model and the model he modified. Again, E_1 was found to be stable whenever burst size is less prominent than clearance rate, hence success in treatment. As fo E_2, we found that it is stable depending on some conditions.

Furthermore, numerical simulations were performed as indicated in Chapter 4. We found that when

the lysis rate is large the tumor will be eliminated within a reasonable time, whereas when the lysis is small it might take too long or may not even be eliminated. Considering large burst size and large lysis rate, we have found that the tumor will be eliminated within a very short time hence success in our treatment [22, 45, 46].

We can now conclude that, as we cut the supply through ECs, it looks that the tumor will shrink or we cannot really say it will die(maybe we can now have avascular stage as it may survive through other means such as diffussion) whenever lysis rate is small. Whereas when lysis rate is large the tumor will be eradicated very quickly. As we mentioned earlier that it is not easy for the viruses to reach the tumor side smoothly, we can conclude that indeed infecting the ECs is very significant in this study and it produces positive results.

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