ON A MATHEMATICAL MODEL OF TUMOR-IMMUNE SYSTEM INTERACTIONS WITH AN ONCOLYTIC VIRUS THERAPY

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Abstract. We investigate a mathematical model of tumor–immune system interactions with oncolytic virus therapy (OVT). Susceptible tumor cells may become infected by viruses that are engineered specifically to kill cancer cells but not healthy cells. Once the infected cancer cells are destroyed by oncolysis, they release new infectious virus particles to help kill surrounding tumor cells. The immune system constructed includes innate and adaptive immunities while the adaptive immunity is further separated into anti-viral or anti-tumor immune cells. The model is first analyzed by studying boundary equilibria and their stability. Numerical bifurcation analysis is performed to investigate the outcomes of the oncolytic virus therapy. The model has a unique tumor remission equilibrium, which is unlikely to be stable based on the parameter values given in the literature. Multiple stable positive equilibria with tumor sizes close to the carrying capacity coexist in the system if the tumor is less antigenic. However, as the viral infection rate increases, the OVT becomes more effective in the sense that the tumor can be dormant for a longer period of time even when the tumor is weakly antigenic.

1. Introduction. Cancer immunotherapy is a promising new strategy to treat cancer and consists of activating and arming the immune system to fight cancers. There are many different approaches and oncolytic virus therapy (OVT) is one of the most encouraging immunotherapies [11, 14, 32]. The therapy takes advantage of the oncolytic nature of the viruses to replicate inside the infected cells and spread between tumor cells with the aim to drive the tumor cells to extinction without harming healthy cells [11, 14, 32].

A variety of oncolytic viruses have demonstrated anti-tumor efficacy, including adenoviruses, herpes simplex viruses, measles viruses, vesicular stomatitis virus and Newcastle disease virus [14, 32]. The most successful example of OVT is given by

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Talimogene Laherparepvec, known as T-Vec. This is a modified herpes simplex virus that has two viral gene deletions and is armed with the human GM-CSF gene. The T-Vec has been shown in a phase II study to increase the number of tumor-specific CD8\(^+\) T cells and to reduce the number of regulatory and suppressor T cells [11, 14, 32]. Encouraged from the good results obtained with T-Vec, a variety of OVs have been tested in clinical trials over the last few years [11, 14, 32]. Despite these intense studies, however, anti-tumor efficacy is still limited and as a result, new strategies are needed for further improvement of OVT [7, 16, 32].

The inhibition of the IFN pathway, the major anti-viral response of the cells, is frequently dysfunctional in cancer cells [14, 29, 32]. As a result, OVs can easily infect the transformed cells. On the other hand, host cells recognize the invasion of viruses and mount strong anti-viral responses through pattern-recognition receptors by the innate immune cells. Detection of viral components by innate immune cells then activates intracellular signaling cascades, leading to the secretion of type I IFNs, pro-inflammatory cytokines and chemokines, and increased expression of co-stimulatory molecules such as CD40, CD80 and CD86 [14, 29, 32]. These result in the activation of adaptive immunity that eventually kill viruses prematurely in addition to the killing by innate immune cells. Further, when OVs infect tumor cells, an inflammatory reaction is triggered due to the fact that viruses are able to induce immunogenic cell death (ICD) [14, 29, 32]. This process of ICD is a particular form of apoptosis, which triggers the endoplasmic reticulum with the consequent release of some dangerous metabolites. The APCs in the tumor microenvironment recognize these key metabolites and they are able to generate an immune response to induce an effective anti-tumor response via the recruitment and activation of dendritic cells and the consequent stimulation of specific T lymphocytes [14, 29, 32].

As a result, upon targeted tumor infection by the anti-tumor viruses, the immune system detects viral infection and both innate and adaptive immune responses are triggered and anti-viral response may dampen the effect of OVs by clearing virus prematurely before the benefit of its effect takes place. Consequently, the battle between anti-tumor and anti-viral immunity exists as triggering the immune system will clear virus along with its lytic effect of viral infection [11, 14, 32]. How to find a balance between anti-viral and anti-tumor immune responses to provide windows of opportunity to give oncolytic viruses the best way to clear off tumors is therefore very urgent.

Mathematical modeling has become an important tool for studying the dynamics of oncolytic virus. The first mathematical models of OVT were developed by Wodarz [46] who used ordinary differential equations to study the basic interactions between replicating viruses, tumor cells and immune responses. The models in [46] were the first models to separate the adaptive immunity into anti-viral and anti-tumor immunities. Subsequently, Wodarz and Komarova [47] and Komarova and Wodarz [23] extended the basic models to describe different scenarios and applied the model to specific tumor-virus systems. More recently, Eftimie et al. [9] proposed a complex system of tumor-virus-adaptive immune interaction to investigate the roles of oncolytic viruses and adaptive immune cells on the multi-stability and multi-instability which arose in the model dynamics. Eftimie and Eftimie [10] further explored the mechanism of polarization between M1 and M2 macrophages on the effectiveness of oncolytic virus therapy.

Okamoto et al. [34] developed a mathematical model for assessing whether oncolytic viruses with reduced tumor-specificity can eliminate tumors more effectively
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while keeping losses to normal cell populations low. Jenner et al. [19] derived a system of ordinary differential equations (ODEs) to model the interaction between oncolytic viruses and tumor cells by using the experimental data of Kim et al. [21]. They were able to optimize the parameters of the model and showed that the system of ODEs was sufficient to replicate the experimental results.

The majority of the mathematical models of OVT focused on either the innate or the adaptive immune response to OVT [38]. Recently, Storey et al. [38] built a model by incorporating both of these immune responses to explore the role of anti-tumor and anti-viral immunities on the treatment success of glioblastoma (GBM) with in vivo parameter values. In particular, an oncolytic herpes simplex virus (HSV) was considered and their model of ordinary differential equations consisted of seven state variables while the adaptive immune system was separated into anti-tumor and anti-viral immunities. They focused on the tradeoff between viral clearance by innate immune cells and the innate immune cell mediated recruitment of anti-viral and anti-tumor adaptive immune responses. Without the PD-1 inhibitors, Storey et al. [38] concluded that the innate immune cells’ ability to clear the virus quickly had a much larger effect on the treatment outcome than the adaptive immune cells’ anti-tumor activity. This conclusion remained true even for a highly antigenic tumor with a strong innate immune response. The faster recruitment of anti-tumor adaptive immune cells was not sufficient to offset the rapid viral clearance [38].

The goal of this work is to study the qualitative behavior and local bifurcations of the model proposed by Storey et al. [38]. We first present the mathematical model with a minor modification, namely the infected cell mediated proliferation rate of the innate immune cells is changed from the mass action law to a Michaelis-Menten function and we do not consider suppression of PD-1 molecules on adaptive immune cells. We study existence and stability of the boundary equilibria. Global asymptotic dynamics of the model in certain parameter regimes will be presented. Numerical bifurcation analysis using the plausible parameter values provided by [38] will be used to investigate treatment outcomes.

The remainder of this manuscript is organized as follows. The mathematical model is presented in the next section. Sections 3 and 4 study qualitative behavior of the model. Numerical bifurcation analysis is provided in Section 5 and the final section gives a brief summary and conclusions. Large size Jacobian matrices are relegated to the Appendix.

2. Mathematical model. In this section, we introduce the model proposed by Storey et al. [38] and convert the system into a dimensionless form. We then verify that solutions of the dimensionless model are bounded.

The tumor cells are classified into susceptible $T_S$ and infected $T_I$. The compartment of free viral particles is denoted by $V$, and $Z$ is the collection of activated innate immune cells where the innate immune cells including both macrophages and natural killer cells. The mathematical modeling of separation of adaptive immune cells into anti-viral and anti-tumor immunities was first proposed by Wodarz [46] in 2001 and was subsequently adopted by several researchers in the study of OVT [30, 38, 47, 49]. It is well known that adaptive immunity has an anti-tumor effect whereas its anti-viral effect may be less well known. The anti-viral immune defenses regulate the outcomes of viral infections wherein concerted actions of the innate and adaptive immunities restrict the replication and spread of the virus. The virus-induced signaling through pattern-recognition receptors drives an
inflammatory cascade encompassing type I and III interferons (IFNs) that inhibits virus replication and facilitates the presentation of viral epitopes by antigen-presenting cells (APCs) for priming of T and B cells [11, 14]. In particular, primed CD8+ T cells identify viral epitopes bound to major histocompatibility complex (MHC) class-I molecules of virus-infected cells and eliminating the virus replication niche in an antigen-specific manner [11, 14]. Further, using single-cell RNA sequencing to dissect the heterogeneity of CD4+ T cells response to tumor antigens, [29] revealed the molecular divergences between anti-tumor and anti-viral responses of these T cells. Motivated by these, the adaptive immunity is separated into anti-tumor and anti-viral immunities as in [30, 46]. Let $Y_T$ and $Y_V$ denote the tumor-specific and virus-specific adaptive immune cells, respectively. The unit of the cell populations is the number of cells while the unit of viral particles is given by pfu, the plaque-forming unit, and the time unit is an hour. A detailed description of the interacting terms is given in [38] and we briefly describe them below.

The susceptible tumor population grows logistically with intrinsic growth rate $r_T$ and carrying capacity $C_T$ for all tumor cells [30, 38, 46, 49]. The mass action kinetics with rate $\beta$ is used to describe viral infection of susceptible tumor cells [30, 38, 46, 49]. The susceptible tumor cells are killed by tumor-associated adaptive immune cells and this lysis is modeled by the Michaelis-Menten kinetics with the maximum killing rate $k_{TA}$ and half-saturation constant $h_T$ [30, 38]. The death rate of infected tumor cells is denoted by $\delta_T$ [30, 38]. The infected tumor cells are killed not only by both the innate and anti-viral adaptive immunities but also by the tumor-associated adaptive immune cells [30, 33, 38]. The Michaelis-Menten kinetics is used for each of these killings with the maximum killing rates given by $k_I$, $k_{TA}$, $k_{IA}$ for the innate, tumor-specific and viral-specific immune cells respectively [30, 38]. Each of the respective half saturation constant is the same and is given by $h_I$ [30, 38].

The addition of new viral population comes from the infected tumor cells’ lyses with viral burst size per infected tumor cell denoted by $b_T$ [31, 38, 46, 49]. The consumption of the virus by innate immune cells is modeled by the law of mass action with rate $k_{VZ}$ [38]. The viruses are also killed by the anti-viral adaptive immune cells with rate $k_{VA}$ and the natural death rate of the virus is denoted by $\omega$ [31, 38]. The first term in the expression of $Z$ equation denotes the activation of resting innate immune cells, where $s_{ZR}$ is the rate at which new resting innate immune cells arrive in the tumor site [35, 38]. These resting immune cells are also activated by the presence of virus at a rate $a_{ZV}$, and previously activated innate immune cells recruit more resting innate immune cells at the rate $a_{ZZ}$. Similar to Reynolds et al. [35], it is assumed in [38] that the activation of resting innate immune cells occurs quickly and hence a quasi-steady state analysis is used for the resting innate immune population.

Indeed, let $Z_R$ denote the resting innate immune cells. Then the interaction between the resting and activated innate immune cells is given by

$$\frac{dZ_R}{dt} = s_{ZR} - Z_R(a_{ZV}V + a_{ZZ}Z) - \delta_{ZR}Z_R$$

$$\frac{dZ}{dt} = Z_R(a_{ZV}V + a_{ZZ}Z).$$
where $\delta_{ZR}$ the death rate of resting innate immune cells. The middle term in the $Z_R$ equation is the rate for which innate immune cells are lost due to conversion to activated immune cells. Since the change of $Z_R$ occurs very rapidly, using the quasi-steady state approximation by setting $\frac{dZ_R}{dt} = 0$, we have $Z_R = \frac{s_{ZR}}{\delta_{ZR} + a_{ZZ}Z + a_{ZV}V}$. Therefore, $\frac{dZ}{dt} = \frac{s_{ZR}(a_{ZZ}Z + a_{ZV}V)}{\delta_{ZR} + a_{ZZ}Z + a_{ZV}V}$, which is the first term in the $Z$ equation given in the model of [38]. The quasi-steady state analysis has been used by many researchers [17, 27, 28, 37] in the area of mathematical biology to simplify equations. When one of the state variables changes very quickly compared to other slower state variables, the faster changing variable may be analyzed as if it were unchanging because it quickly reaches equilibrium [17, 37]. Therefore, the variable $Z_R$ may be regarded as a constant and hence $\frac{dZ_R}{dt} = 0$ can be used to simplify the equations.

The natural death rate of activated innate immune cells is given by $\delta_Z$ [38, 46]. The interaction with infected tumor cells can also increase proliferation of the innate immune cells and this recruitment rate is denoted by $a_Z$. In Storey et al. [38], a Holling type I functional response $a_ZT_I Z$ is adopted for this recruitment. However, the type I functional response assumes a linear increase with tumor cells. In a predator-prey model, this characterizes that the handling time (including chasing, catching, and eating a food item) is negligible [38]. A review of 814 functional responses from 235 studies shows that type I responses are not only exceptionally frequent among filter feeders but that they have only been reported from these consumers [20]. Thus, the type I functional response $a_ZT_I Z$ implies that the recruitment of innate immune cells to a tumor site should occur as soon as innate immune cells interact with infected cells. Nevertheless, it has been documented that the recruitment of NK cells to a tumor site may take tens of hours [31] whereas the time unit in [38] is an hour. Further, it has also been reported that immune recruitment terms are generally assumed to be of a Michaelis-Menten form [8]. Motivated by the above consideration, we replace the term $a_ZT_I Z$ by a Michaelis-Menten form. As the killing terms by the adaptive immune cells and the recruitment of the adaptive immune cells in [38] are of the same Michaelis-Menten forms and the killing term by the innate immune cells in [38] is modeled by $k_l T_I \frac{Z}{k_l + Z}$, we follow the assumption of innate killing in [38] as well as the assumption of the relationship between the killing and recruitment terms, and the recruitment of the innate immune cells therefore has the same Michaelis-Menten form, $a_ZT_I \frac{Z}{k_l + Z}$. This particular killing rate was used in [30] to incorporate tumor architecture that may hinder anti-tumor immune cell infiltration [13].

The last two equations of the model describe time-evolution of the adaptive immune cells. The tumor-specific adaptive immune cells are recruited by the innate immune cells with the recruitment rate $a_{TZ}$ [38]. In addition, antigens on both the susceptible and infected tumor cells stimulate proliferation of the anti-tumor adaptive immune cells with rate $a_{AT}$ and half saturation constant $h_T$ [30, 38]. Here, $a_{AT}$ is a measure of tumor antigenicity. The larger the $a_{AT}$, the more antigenic the tumor is [30, 38]. The parameter $\delta_{VT}$ is the natural death rate of anti-tumor adaptive immune cells [30, 38]. In [38], a fraction $F(P, L)$ representing suppression of $T$ cell activation by the complex of PD-1 and PD-L1 is incorporated, where $P$ is the PD-1 expression on adaptive immune cells and $L$ denotes the molar concentration of
PD-L1 within the tumor microenvironment. We omit this mechanism in this study since we do not consider treatment of immune checkpoint inhibitors. That is, we set $F(P, L) = 1$. Similarly, the anti-viral adaptive immune cells are also activated by the innate immune cells with rate $a_Z$ and are stimulated by the antigens on the infected tumor cells with rate $a_A$ and half saturation constant $h_I$ \[30, 38\]. The death rate of these cells is denoted by $\delta_Y$ \[30, 38, 46\]. The model of the tumor-virus-immune interaction takes the following form:

\[
\begin{align*}
T'_S &= r_T T_S \left(1 - \frac{T_S + T_I}{C_T}\right) - \beta T_S V - \frac{k_TA T_S Y_T}{h_T + T_S} \\
T'_I &= \beta T_S V - \delta_T T_I - \frac{k_I T_I Z}{h_I + Z} - \frac{k_TA T_I Y_T}{h_I + T_I} - \frac{k_IA T_I Y_V}{h_I + T_I} \\
V' &= b_T \delta_T T_I - k_{VZ} V Z - k_{VA} V Y_V - \omega V \\
Z' &= \frac{s_{ZR}(a_{ZZ} Z + a_{ZV} V)}{\delta_{ZR} + a_{ZZ} Z + a_{ZV} V} + \frac{a_Z T_I Z}{h_I + Z} - \delta_Z Z \\
Y'_T &= a_T Z Z + \frac{a_{AT}(T_S + T_I) Y_T}{h_T + T_S + T_I} - \delta_{YT} Y_T \\
Y'_V &= a_V Z Z + \frac{a_A T_I Y_V}{h_I + T_I} - \delta_{YV} Y_V.
\end{align*}
\]

Tables 2 and 3 of \[38\] provide baseline parameter values as well as plausible ranges of parameter values for sensitivity analysis. The global sensitivity analysis given in \[38\], Figure 3 shows that the susceptible tumor population is most sensitive to the viral infection rate $\beta$, tumor growth rate $r_T$ and tumor carrying capacity $C_T$. Figure 1 depicts a schematic diagram of the model (1).

There are 26 parameters in (1). To study (1), we first rescale the system by letting

\[
\begin{align*}
\hat{T}_S &= \frac{T_S}{C_T}, \quad \hat{T}_I = \frac{T_I}{C_T}, \quad \hat{V} = \frac{V}{r_T}, \quad \hat{Z} = \frac{Z}{C_T} \\
\hat{Y}_T &= \frac{k_{TA}}{r_T C_T} Y_T, \quad \hat{Y}_V = \frac{k_{IA}}{r_T C_T} Y_V
\end{align*}
\]

and

\[
\begin{align*}
\hat{t} &= r_T t, \quad \hat{h}_T = h_T / C_T, \quad \hat{\delta}_T = \delta_T / r_T, \\
\hat{k}_I &= k_I / r_T, \quad \hat{h}_I = h_I / C_T, \\
\hat{h}_T &= h_T / C_T, \quad \hat{\delta}_{ZR} = \delta_{ZR} / r_T, \quad \hat{b}_T = \beta b_T C_T / r_T, \\
\hat{k}_{VZ} &= k_{VZ} C_T / r_T, \quad \hat{k}_{VA} = k_{VA} C_T / k_{IA}, \quad \hat{\omega} = \omega / r_T, \\
\hat{\delta}_{YT} &= \delta_{YT} / r_T, \quad \hat{s}_{ZR} = s_{ZR} / (r_T C_T), \\
\hat{\alpha}_Z &= a_Z C_T / r_T, \quad \hat{\delta}_Z = \delta_Z / r_T, \\
\hat{\alpha}_{ZZ} &= a_{ZZ} C_T / r_T, \quad \hat{\alpha}_{ZV} = a_{ZV} / \beta, \\
\hat{\alpha}_{TZ} &= k_{TA} a_{TZ} / r_T^2, \quad \hat{\alpha}_{AT} = a_{AT} / r_T, \\
\hat{\alpha}_{VZ} &= k_{IA} a_{VZ} / r_T^2, \quad \hat{\alpha}_{AI} = a_{AI} / r_T, \quad \hat{\delta}_{YV} = \delta_{YV} / r_T.
\end{align*}
\]

Dropping off the hats, we obtain the following system with 20 parameters.
As in the analysis of many biological models of ordinary differential equations, we first prove that solutions of (4) exist for all future time, remain nonnegative and are bounded.

\[
T_S' = T_S (1 - (T_S + T_I)) - T_S V - \frac{T_S Y_T}{T_H + T_S}
\]
\[
T_I' = T_S V - \delta_T T_I - k_{II} T_I Z - \frac{T_I Y_T}{T_H + T_I} - \frac{T_I Y_V}{T_H + T_I}
\]
\[
V' = b_T \delta_T T_I - k_{VZ} V Z - k_{VA} V Y_V - \omega V
\]
\[
Z' = \frac{s_Z R (a_{ZZ} Z + a_{ZV} V)}{\delta_Z R + a_{ZZ} Z + a_{ZV} V} + a_Z T_I Z - \delta_Z Z
\]
\[
Y_T' = a_{TZ} Z + \frac{a_{AT} (T_S + T_I) Y_T}{h_T + T_S + T_I} - \delta_{Y_T} Y_T
\]
\[
Y_V' = a_{VZ} Z + \frac{a_{AV} T_I Y_V}{h_T + T_I} - \delta_{Y_V} Y_V
\]
\[
T_S(0) > 0, T_I(0) \geq 0, V(0) \geq 0, Z(0) \geq 0, T_s(0) \geq 0, T_I(0) \geq 0.
\]
Theorem 2.1. Solutions of (4) exist and remain nonnegative for \( t > 0 \). If \( h_T \geq h_I \), then solutions are bounded on \([0, \infty)\).

Proof. Let \( F(T_S, T_I, V, Z, Y_T, Y_V) \) denote the right hand side of (4). Since \( F \) is locally Lipschitz on \( \mathbb{R}^6_+ \), there exists a unique solution on \([0, t_0)\) for the initial value problem (4), where \( t_0 > 0 \) may depend on the initial condition. As \( T_S|_{T_S=0} = 0, T_I|_{T_I=0} \geq 0, V'|_{V=0} \geq 0, Z'|_{Z=0} \geq 0, Y_T'|_{Y_T=0} \geq 0 \) and \( Y_V'|_{Y_V=0} \geq 0 \), solutions of (4) are nonnegative on the interval of existence.

Let 
\[
X = T_S + T_I + V + \frac{k_I Z}{a_Z} + \frac{Y_T}{a_AT} + \frac{Y_V}{a_AI},
\]

Then 
\[
X' \leq T_S + b_T \delta_T T_I + \frac{k_I s_Z R}{a_Z} + \frac{a_T Z Z}{a_AT} + \frac{a_V Z Z}{a_AI} \leq a_0 X + \frac{k_I s_Z R}{a_Z},
\]

where \( a_0 = \max\{1, b_T \delta_T, \frac{a_T Z}{a_AT} + \frac{a_V Z}{a_AI} \} > 0 \). Consider the first-order linear equation 
\[
W' = a_0 W + \frac{k_I s_Z R}{a_Z} \quad \text{with} \quad W(0) = X(0).
\]

Since \( W(t) \) is defined on \([0, \infty)\) and \( X(t) \leq W(t) \) on \([0, t_0)\), \( X(t) \) can be extended to \( t = t_0 \). Consequently, solutions of (4) exist on \([0, \infty)\) and remain nonnegative.

Clearly, \( (T_S + T_I)' \leq T_S (1 - (T_S + T_I)) \) implies \( (T_S + T_I)'_{S+T_I \geq 0} \leq 0 \) and thus 
\[
\limsup_{t \to \infty} (T_S(t) + T_I(t)) \leq 1.
\]

As a result, for any \( \epsilon > 0 \) there exists \( t_0 > 0 \) such that 
\[
T_I(t) < 1 + \epsilon \quad \text{for} \quad t \geq t_0.
\]

It follows that for \( t \geq t_0 \), 
\[
V'(t) \leq b_T \delta_T (1 + \epsilon) - \omega V
\]

and hence 
\[
\limsup_{t \to \infty} V(t) \leq \frac{b_T \delta_T (1 + \epsilon)}{\omega}.
\]

Letting \( \epsilon \to 0 \), we have 
\[
\limsup_{t \to \infty} V(t) \leq \frac{b_T \delta_T}{\omega}.
\]

Further, 
\[
(T_I + \frac{k_I Z}{a_Z})' \leq T_S V - \delta_T T_I + \frac{s_Z h k_I}{a_Z} - \frac{k_I \delta Z}{a_Z} M - \frac{k_I Z}{a_Z} \quad \text{for} \quad M > 0
\]

and all \( t \) sufficiently large, where \( a_1 = \min\{\delta_T, \delta_Z\} > 0 \) and hence
\[
\limsup_{t \to \infty} (T_I + \frac{k_I Z}{a_Z}) \leq M/a_1.
\]

Therefore, 
\[
\limsup_{t \to \infty} Z(t) \leq M_Z \quad \text{for} \quad 0 < M_Z < \infty.
\]

Similarly, 
\[
(T_I + \frac{Y_V}{a_AI})' \leq T_S V - \frac{Y_V}{a_AI} - \frac{a_T Z Z}{a_AT} - \frac{a_V Z Z}{a_AI} \leq M_0 - a_2(T_I + \frac{Y_V}{a_AI}) \quad \text{for} \quad M_0 > 0
\]

and for all \( t \) sufficiently large, where \( a_2 = \min\{\delta_T, \delta_V\} > 0 \). Consequently, there exists \( 0 < M_YV < \infty \) such that 
\[
\limsup_{t \to \infty} Y_V(t) \leq M_YV.
\]

Assume \( h_T \geq h_I \) and let \( w = a_AT_T S + a_AT_T I + Y_T \). Then 
\[
w' \leq -a_AT_T S + a_AT_T (2 - (T_S + T_I)) + a_T Z Z - \delta_T a_AT_T I - \delta_T Y_T Y_T \leq M_1 - a_3(a_AT_T S + a_AT_T I + Y_T)
\]

for some \( M_1 > 0 \) and for all \( t \) sufficiently large, where \( a_3 = \min\{1, \delta_T, \delta_Y Y_T\} > 0 \). Hence 
\[
\limsup_{t \to \infty} Y_T(t) \leq M_Y T \quad \text{for} \quad 0 < M_Y T < \infty,
\]

and the proof is complete. \( \Box \)

3. Dynamics of the subsystems. We study asymptotic dynamics of the subsystems in this section with the \( T_S Y_T, Z Y_T Y_I \) and \( T_S Z Y_T Y_V \) subsystems given in sections 3.1, 3.2, and 3.3, respectively.
3.1. The $T_S Y_T$ subsystem. If initially there are no viruses and innate immune cells, i.e., $V(0) = 0 = Z(0)$, then $\lim_{t \to \infty} T_I(t) = \lim_{t \to \infty} Y_V(t) = 0$, and by [40], (4) is asymptotically autonomous to the following tumor-immune subsystem

$$
\begin{align*}
T_S' &= T_S(1 - T_S) - \frac{T_S Y_T}{h_T + T_S} \\
Y_T' &= \frac{a_{AT} T_S Y_T}{h_T + T_S} - \delta_Y Y_T.
\end{align*}
$$

(5)

System (5) is a classical predator-prey model and its dynamics are well known. Specifically, (5) has two boundary equilibria $E_{10} = (0, 0)$ and $E_{11} = (1, 0)$ where the tumor-free equilibrium $E_{10}$ is always a saddle point. The equilibrium $E_{11}$ for which the tumor is at its carrying capacity is globally asymptotically stable if $a_{AT} < \delta_Y (h_T + 1)$. If $a_{AT} > \delta_Y (h_T + 1)$, then (5) has a unique positive equilibrium $E_{12} = (\bar{T}_S, \bar{Y}_T)$, where

$$
\bar{T}_S = \frac{\delta_Y h_T}{a_{AT} - \delta_Y} \quad \text{and} \quad \bar{Y}_T = (1 - \bar{T}_S)(h_T + \bar{T}_S).
$$

(6)

The Jacobian matrix of (5) at the positive equilibrium $(\bar{T}_S, \bar{Y}_T)$ has the form

$$
J_1(E_{12}) = \begin{pmatrix}
1 - 2\bar{T}_S - h_T & -\bar{T}_S \\
\frac{a_{AT} h_T \bar{Y}_T}{(h_T + \bar{T}_S)^2} & 0
\end{pmatrix}.
$$

(7)

Therefore, $E_{12}$ is asymptotically stable if $1 - h_T - 2\bar{T}_S < 0$ and it is a repeller if $1 - h_T - 2\bar{T}_S > 0$. In particular, $E_{12}$ is asymptotically stable if $h_T \geq 1$.

Theorems 1 and 2 of [4] imply that $(\bar{T}_S, \bar{Y}_T)$ is globally asymptotically stable whenever it is locally asymptotically stable. The tumor-immune coexisting equilibrium undergoes a Hopf bifurcation [45] when it loses its stability, and the system has a unique positive limit cycle which is moreover globally asymptotically stable by [24, Theorem 4.2]. Without proofs, we summarize dynamics of (5) as follows. Notice that when $a_{AT} = \delta_Y (h_T + 1)$, the equilibrium $E_{11} = (1, 0)$ is non-hyperbolic. It is expected that a transcritical bifurcation occurs at this critical parameter regime and $E_{12}$ appears once the parameter values pass this bifurcation point.

**Proposition 3.1.** The following statements hold for system (5).

(a) The equilibrium $E_{11} = (1, 0)$ is globally asymptotically stable in $\{ (T_S, Y_T) \in \mathbb{R}_+^2 : T_S > 0 \}$ if $a_{AT} < \delta_Y (h_T + 1)$.

(b) Let $a_{AT} > \delta_Y (h_T + 1)$. Then (5) has a unique positive equilibrium $E_{12} = (\bar{T}_S, \bar{Y}_T)$. Moreover,

(i) $(\bar{T}_S, \bar{Y}_T)$ is globally asymptotically stable in the interior of $\mathbb{R}_+^2$ if $\bar{T}_S > (1 - h_T)/2$.

(ii) If $\bar{T}_S \leq (1 - h_T)/2$, then (5) has a unique positive limit cycle $L^*$ which is moreover globally asymptotically stable in the interior of $\mathbb{R}_+^2$.

Since the tumor-free equilibrium is always unstable, one would wish Proposition 3.1(a) does not occur since the tumor would attain at its maximum size. That is, a large tumor-specific adaptive immune proliferation rate $a_{AT}$ or a small immune cell death rate $\delta_Y$ would prevent the cancer growing to its maximum capacity. Under this circumstance, if in addition the tumor size in the coexisting equilibrium
is small, then there will be periods of time for which the tumor is dormant since trajectories converge to the positive periodic solution by Proposition 3.1(b)(ii). How long the dormant period last depends on the parameter values. Using the baseline parameter values of [38] and in dimensionless form, we obtain

\[ AT = 0.0833 > \delta_{YT}(h_T + 1) = 0.01953 \]  

and hence the equilibrium \((1,0)\) is unstable and \((\bar{T}_S, \bar{Y}_T)\) exists. Further, \(h_T = 5.236 \times 10^{-5} \) < 1 and \(\bar{T}_S = 0.003562 < (1 - h_T)/2 \approx 0.50\) so that in the absence of oncolytic virus therapy (OVT) the tumor and anti-tumor immune cells will be oscillating over time. Figure 2 plots the time evolution of the \(T_S Y_T\) subsystem (5) in hours, where the tumor is dormant for more than 300 days. However, the tumor reaches a large burden prior to dormancy and most likely the patient cannot survive before dormancy occurs.

**Figure 2.** The parameter values are \(h_T = 2.7 \times 10^4\), \(\delta_{YT} = 3.75 \times 10^{-4}\), \(r_T = 0.0192\), \(a_{AT} = 0.0016\) and \(k_{TA} = 1/24\) taken from the baseline values in [38] to illustrate oscillations of the \(T_S Y_T\) subsystem (5), where the time unit is an hour as given in [38].

### 3.2. The \(ZY_T Y_V\) subsystem.

If there is no susceptible tumor initially, then \(T_I(t)\) and \(V(t)\) will go extinct and the model (4) is then asymptotically autonomous to the following immune subsystem

\[
\begin{align*}
Z' &= \frac{s_{ZR} a_{ZZ} Z}{\delta_{ZT} + a_{ZZ} Z} - \delta_{Z} Z, \\
Y_T' &= a_{TZ} Z - \delta_{YT} Y_T, \\
Y_V' &= a_{VZ} Z - \delta_{YV} Y_V.
\end{align*}
\]  

(8)

Since the equation of innate immune cells is decoupled from the adaptive immune system, dynamics of (8) is very simple. In particular, if \(s_{ZR} a_{ZZ} > \delta_{ZT} \delta_{Z}\), then (8) has a unique interior equilibrium \((\hat{Z}, \hat{Y}_T, \hat{Y}_V)\) where

\[
\begin{align*}
\hat{Z} &= \frac{s_{ZR} a_{ZZ} - \delta_{ZT} \delta_{Z}}{a_{ZZ} \delta_{Z}}, \quad \hat{Y}_T = \frac{a_{TZ} \hat{Z}}{\delta_{YT}}, \quad \text{and} \quad \hat{Y}_V = \frac{a_{VZ} \hat{Z}}{\delta_{YV}}.
\end{align*}
\]  

(9)

The global dynamics of (8) is described below without proofs. Specifically, if the activation rate of the innate immune cell is smaller than its death rate, then both the innate and adaptive immune cells will eventually be cleared off. If the activation
rate of innate immunity is large, then the innate and adaptive immune cells will be stabilized at positive levels.

**Proposition 3.2.** The following statements hold for (8).

(a) If $s_{ZR} a_{ZZ} < \delta_{ZR} \delta_{Z}$, then equilibrium $E_{20} = (0, 0, 0)$ is globally asymptotically stable in $\mathbb{R}^3_+$.  

(b) If $s_{ZR} a_{ZZ} > \delta_{ZR} \delta_{Z}$, then equilibrium $E_{21} = (\hat{Z}, \hat{Y}_T, \hat{Y}_V)$ is globally asymptotically stable in $\{(Z, Y_T, Y_V) \in \mathbb{R}^3_+: Z > 0\}$.

The results in Proposition 3.2 can be interpreted as the homeostatic of the immune system in the absence of cancer. When $s_{ZR} a_{ZZ} = \delta_{ZR} \delta_{Z}$, then $(\hat{Z}, \hat{Y}_T, \hat{Y}_V)$ is non-hyperbolic and it can be easily shown that the equilibrium is globally attracting. Applying the baseline parameter values given in [38], we have $s_{ZR} a_{ZZ} = 2.1701 < \delta_{ZR} \delta_{Z} = 2.6042$. Therefore, the immune system is stabilized at the zero level, that is, negligible, in the absence of tumor. Consequently, in order to illustrate Proposition 3.2(b), variations of the baseline parameter values are needed. Here, $s_{ZR} = 0.5$, $a_{ZZ} = 0.001$, $\delta_{ZR} = 0.001$, $\delta_{Y_T} = 3.75 \times 10^{-2}$ and $\delta_{Y_V} = 5.54 \times 10^{-2}$ so that $s_{ZR} a_{ZZ} - \delta_{ZR} \delta_{Z} = 4.92 \times 10^{-4} > 0$. The cell populations are stabilized by the time $t = 1000$ hours as shown in Fig 3.

![Figure 3](image_url)

**Figure 3.** One solution of the immune $ZY_T Y_V$ subsystem (8) is plotted to illustrate stabilization of the model, Proposition 3.2(b). The parameter values are given in text.

### 3.3. The $T_S Z Y_T Y_V$ subsystem.

If there are no viruses initially, then (4) reduces to the following subsystem of tumor-immune interaction

$$
\begin{align*}
T'_S &= T_S \left(1 - T_S\right) - \frac{T_S Y_T}{h_T + T_S} \\
Z' &= \frac{s_{ZR} a_{ZZ} Z}{\delta_{ZR} + a_{ZZ} Z} - \delta_{Z} Z \\
Y'_T &= a_{TZ} Z + \frac{a_{AT} T_S Y_T}{h_T + T_S} - \delta_{Y_T} Y_T \\
Y'_V &= a_{YV} Z - \delta_{Y_V} Y_V.
\end{align*}
$$

Notice that the $Y_V$ variable in (10) comes from the model formulation in system (4). Both anti-tumor and anti-viral adaptive immune cells can be activated by the
innate immune cells whereas the innate immune cells are not only activated by virus but also by previously activated innate immune cells. Although there are no viruses present in the system, it is reasonable to assume that an individual’s immune system has small quantities of both anti-viral and anti-tumor adaptive immunities even in the absence of cancer. As noted in Section 1, some T cells play double roles of anti-viral and anti-viral in the immune system [12, 14, 29].

Clearly, (10) always has two equilibria \( E_{30} = (0, 0, 0, 0) \) and \( E_{31} = (1, 0, 0, 0) \). From the Jacobian matrix of (10) at these equilibria, we see that \( E_{30} \) is a saddle point while \( E_{31} \) is asymptotically stable if \( s_{ZRaZZ} < \delta_Z \delta_Z \) and \( a_{AT} < \delta_{YT}(h_T + 1) \). System (10) has an equilibrium of the form \( E_{32} = (\hat{T}_S, 0, \hat{Y}_T, 0) \) provided \( a_{AT} > \delta_{YT}(h_T + 1) \) by Proposition 3.1(b), where \( \hat{T}_s \) and \( \hat{Y}_T \) are defined by (6). The Jacobian matrix at \( E_{32} \) is given by (24) in the Appendix.

From (24), it is clear that \( s_{ZRaZZ} \delta_Z - \delta_Z \) and \( -\delta_{YV} \) are two eigenvalues. The other two eigenvalues are from the \( T_S \hat{Y}_T \)-subsystem (5) given in (7). Therefore, \( E_{32} \) is asymptotically stable if \( s_{ZRaZZ} < \delta_Z \delta_Z \) and \( \hat{T}_S > (1-h_T)/2 \). Further, equilibrium \( E_{33} = (0, \hat{Z}, \hat{Y}_T, \hat{V}) \) exists if \( s_{ZRaZZ} > \delta_Z \delta_Z \), where \( \hat{Z}, \hat{Y}_T, \) and \( \hat{V} \) are defined in (9). Its stability depends on the eigenvalues of the triangular matrix (25). Here,\[
\frac{s_{ZRaZZ} \delta_Z - \delta_Z}{(\delta_Z + a_{AT} \hat{Z})^2} = \frac{s_{ZRaZZ} (\delta_Z \delta_Z - s_{ZRaZZ})}{s_{ZRaZZ}} < 0 \text{ by the existence condition of } E_{33}.
\]

Therefore, \( E_{33} \) is asymptotically stable if \( \hat{Y}_T > h_T \), i.e., if \( a_{AT} \hat{Z} > \delta_{YT} h_T \).

For the existence of a positive equilibrium, it is necessary \( s_{ZRaZZ} > \delta_Z \delta_Z \). Since the \( Z \) equation can be decoupled in (10), the \( Z \) and \( Y_V \) components of a positive equilibrium are given by \( \hat{Z} \) and \( \hat{Y}_V \), respectively. The \( T_S \) and \( Y_T \) components are the positive intersections of the functions given by

\[
Y_T = -T_S^2 + (1 - h_T) T_S + h_T := f(T_S)
\]

and

\[
Y_T = \frac{a_{TZ} \hat{Z} (h_T + T_S)}{(\delta_{YT} - a_{AT}) T_S + h_T \delta_{YT}} := g(T_S),
\]

and they form the positive equilibria of the following system

\[
\begin{align*}
T'_S &= T_S (1 - T_S) - \frac{T_S Y_T}{h_T + T_S} \\
Y'_T &= a_{TZ} \hat{Z} + \frac{a_{AT} T_S Y_T}{h_T + T_S} - \delta_{YT} Y_T.
\end{align*}
\]

The graph of \( f \) is a concave parabola with vertex in the second quadrant if \( h_T > 1 \) and in the first quadrant if \( h_T < 1 \). Moreover, \( f(1) = 0 \) and

\[
f^\infty := \max_{{x \geq 0}} f(x) = \begin{cases} 
  h_T & \text{if } h_T \geq 1 \\
  \frac{(1 + h_T)^2}{4} & \text{if } h_T < 1.
\end{cases}
\]

If \( \delta_{YT} \geq a_{AT} \), then \( g'(x) > 0 \) and \( g''(x) \leq 0 \) for \( x \geq 0 \) with \( g(0) = \frac{a_{TZ} \hat{Z}}{\delta_{YT} - a_{AT}} = \hat{Y}_T \) and

\[
g(\infty) = \frac{a_{TZ} \hat{Z}}{\delta_{YT} - a_{AT}} \leq \infty. \text{ If } \delta_{YT} < a_{AT}, \text{ there exists a unique } T_{S_c} := \frac{h_T \delta_{YT}}{a_{AT} - \delta_{YT}} > 0 \text{ such that } g(T_{S_c}) = \infty \text{ and } g \text{ is increasing on the interval } (0, T_{S_c}).
\]
existence of interior equilibrium of (13), we separate the discussion into $h_T \geq 1$ and $h_T < 1$.

Let $h_T \geq 1$. Then it is clear from the above discussion that (13) has no positive equilibrium if $g(0) \geq f(0) = h_T$ and there is a unique positive equilibrium $(\tilde{T}_S, \tilde{Y}_T)$ if $g(0) < f(0)$. The case of $h_T < 1$ is more complicated. There exists a unique positive equilibrium $(\check{T}_S, \check{Y}_T)$ if $g(0) < f(0)$ and $\delta_{YT} < a_{AT}$. See Fig. 4(a). The number of positive equilibrium can be either 0, 1 or 2 if either (i) $g(0) < f(0)$ and $\delta_{YT} \geq a_{AT}$ or (ii) $g(0) \geq f(0)$ hold. Figure 4(b) provides the case of two positive intersections with $h_T = 0.1, \hat{Z} = 0.6, a_{AT} = 0.15, \delta_{YT} = 0.9$ and $a_{TZ} = 0.1$ so that $g(0) = 0.12 > f(0) = 0.1$ and $T_{Sc} < 0$. Observe that $E_{33} = (0, \hat{Z}, \hat{Y}_T, \hat{Y}_V)$ is asymptotically stable if $g(0) > f(0)$. Therefore, one would expect that the coexisting equilibrium near $E_{33}$ is always unstable while the other coexisting equilibrium may be stable when there are two coexisting equilibria and $g(0) > f(0)$.

The Jacobian matrix at a positive equilibrium $E_{34} = (\check{T}_S, \hat{Z}, \check{Y}_T, \hat{Y}_V)$ of (10) is given by (26). Eigenvalues of $J(E_{34})$ consist of $-\delta_{YV} < 0, \frac{s_{ZK}a_{ZZ} \delta_{ZR}}{(\delta_{ZR} + Z)^2} - \delta_{Z} < 0$, and the eigenvalues of

$$J = \begin{pmatrix}
1 - 2\check{T}_S - \frac{h_T \check{Y}_T}{(h_T + \check{T}_S)^2} & -\check{T}_S & \frac{h_T a_{AT} \check{Y}_T}{(h_T + \check{T}_S)^2} & a_{AT} \check{T}_S - \delta_{YT} \\
\frac{a_{AT} h_T \check{Y}_T}{(h_T + \check{T}_S)^2} & \frac{h_T + \check{T}_S}{h_T + \check{T}_S} & \frac{a_{AT} \check{T}_S}{h_T + \check{T}_S} & \frac{a_{AT} \check{T}_S}{h_T + \check{T}_S} - \delta_{YT}
\end{pmatrix}.$$

(15)
example, if either of the table is reversed, then the corresponding equilibrium becomes unstable. For it is straightforward to verify that
\[ \eta < 0 \]
We have
\[ E_{33} \]
\[ \eta > 0 \]
If one of the inequalities listed in the third column of the table is reversed, then the corresponding equilibrium becomes unstable. For example, if either \( s_{2R} a_{2Z} > \delta_2 \delta g \) or \( a_{AT} < \delta_Y (h_T + 1) \), then \( E_{31} \) is unstable, and if \( \eta > 0 \), then \( E_{34} \) is unstable.

### Table 1. Existence and stability of equilibria of \( T_S Z Y_T Y_V \) subsystem (10)

| Equilibrium | Existence | Asymptotic stability |
|-------------|-----------|----------------------|
| \( E_{30} \) | Always    | Unstable             |
| \( E_{31} \) | Always    |                      |
| \( E_{32} \) | \( a_{AT} > \delta_Y (h_T + 1) \) | \( s_{2R} a_{2Z} < \delta_2 \delta g \) \& \( a_{AT} < \delta_Y (h_T + 1) \) |
| \( E_{33} \) | \( s_{2R} a_{2Z} > \delta_2 \delta g \) | \( \hat{Y}_T > h_T \) \( \text{(i.e., } a_{TZ} \hat{Z} > \delta_Y h_T) \) |
| \( E_{34} \) | \( s_{2R} a_{2Z} > \delta_2 \delta g \), \( b_T \geq 1, \hat{Y}_T < h_T \) | \( \hat{Y}_T < h_T, a_{AT} > \delta_Y \eta < 0 \) |
| \( E_{34} \text{.} \) | \( s_{2R} a_{2Z} > \delta_2 \delta g \), \( b_T < 1, \hat{Y}_T < h_T \), \( a_{AT} > \delta_Y \) | \( \eta < 0 \) |

* This is a case for which the positive equilibrium is unique. System (10) may have more than one positive equilibrium.

### Table 2. Equilibria of \( T_S Z Y_T Y_V \) subsystem (10) and their biological interpretations

| Equilibrium | Interpretation |
|-------------|----------------|
| \( E_{30} = (0, 0, 0, 0) \) | Extinction of all cell populations |
| \( E_{31} = \left( \hat{T}_S, 0, \hat{Y}_T, \hat{Y}_V \right) \) | Susceptible tumor only |
| \( E_{32} = \left( \hat{T}_S, 0, \hat{Y}_T, 0 \right) \) | Coexistence of susceptible tumor and anti-tumor immune cells |
| \( E_{33} = \left( 0, \hat{Z}, \hat{Y}_T, \hat{Y}_V \right) \) | Immune cells only |
| \( E_{34} = \left( \hat{T}_S, Z, \hat{T}_V, \hat{Y}_V \right) \) | Coexistence of susceptible tumor and immune cells |

Notice \( J \) is also the Jacobian matrix of (13) evaluated at the equilibrium (\( \hat{T}_S, \hat{Y}_T \)). Using the relation
\[ \frac{a_{AT} \hat{T}_S}{h_T + \hat{T}_S} - \delta_Y = -\frac{a_{TZ} \hat{Z}}{\hat{Y}_T}, \]
the determinant of \( J \), \( det(J) \), becomes
\[ det(J) = \frac{\delta_Y h_T \hat{T}_S^2 + 2(a_{TZ} \hat{Z} - \delta_Y h_T) \hat{T}_S + \delta_Y h_T - a_{TZ} \hat{Z}}{\hat{Y}_T}. \] (16)
The numerator of \( det(J) \) is a convex quadratic function with discriminant equals
\[ \Delta := -4(\delta_Y h_T - a_{TZ} \hat{Z}) a_{TZ} \hat{Z}. \] (17)
Notice \( \Delta < 0 \) is equivalent to \( g(0) < f(0) \) and hence \( det(J) > 0 \) by (16) if \( g(0) < f(0) \), i.e., if \( \hat{Y}_T < h_T \). The trace of \( J \) is given by
\[ \eta := tr(J) = -\frac{2 \hat{T}_S^2 + (a_{AT} - \delta_Y + 1 - h_T) \hat{T}_S - \delta_Y h_T}{h_T + \hat{T}_S}. \] (18)
We have \( \eta < 0 \) if \( h_T \geq 1 \) and \( a_{AT} \leq \delta_Y \). On the other hand, if \( a_{AT} > \delta_Y \), then it is straightforward to verify that \( \eta < 0 \) if \( \hat{T}_S \geq \frac{a_{AT} - \delta_Y + 1 - h_T}{2} \).

The above discussion on the existence and stability of equilibria of (10) is summarized in Table 1 whereas Table 2 provides biological interpretations of these equilibria.

Notice Table 1 summarizes existence and local asymptotic stability of equilibria of the \( T_S Z Y_T Y_V \) subsystem (10). If one of the inequalities listed in the third column of the table is reversed, then the corresponding equilibrium becomes unstable. For example, if either \( s_{2R} a_{2Z} > \delta_2 \delta g \) or \( a_{AT} > \delta_Y (h_T + 1) \), then \( E_{31} \) is unstable, and if \( \eta > 0 \), then \( E_{34} \) is unstable.
The dynamics of the interaction between susceptible tumor cells and innate and adaptive immune cells are complicated. There are ten parameters involved with both positive and negative feedback in the interaction. If either the death rate $\delta Z$ of activated innate immune cells or the death rate $\delta Z R$ of resting innate immune cells is large and if the antigenicity $a_{AT}$ of the tumor is small, then the tumor cells cannot be controlled. In this scenario, only the susceptible tumor cells can persist and will reach to the carrying capacity. However, if the antigenicity $a_{AT}$ of the tumor is large, then the susceptible tumor and anti-tumor immune cells can coexist at an equilibrium where the tumor size is smaller than its carrying capacity. Further, if the innate immune cells have a large activation rate, $a_{TZ} \hat{Z} > \delta_{YT} h_T$, then the susceptible tumor will be eradicated. If, on the other hand, the innate immune cell has a small activation rate, $a_{TZ} Z \hat{Z} < \delta_{YT} h_T$, then the susceptible tumor and immune cells will coexist if $\eta > 0$, where $\eta$ depends on the tumor killing rate and the mortality rate of the anti-tumor immune cells among other mechanisms. It is suspected that the populations will be oscillating over time if $\eta > 0$.

We next study asymptotic dynamics of (10). The dynamics are easy to understand if $s_{ZR} \alpha_{ZZ} < \delta_{ZR} \delta Z$. Indeed, $s_{ZR} \alpha_{ZZ} < \delta_{ZR} \delta Z$ implies $\lim_{t \to \infty} \hat{Z}(t) = 0 = \lim_{t \to \infty} Y_T(t)$, and solutions of (10) are thus asymptotically autonomous to the subsystem system (5) by [40, Theorem 1.6]. In addition, if $a_{AT} < \delta_{YT}(h_T + 1)$, the only equilibria are $E_{30} = (0, 0, 0, 0)$ and $E_{31} = (1, 0, 0, 0)$ by Table 1, where $E_{31}$ is asymptotically stable. Further, Proposition 3.1(a) implies (1, 0) is globally asymptotically stable for (5) and hence $E_{31}$ is globally asymptotically stable for (10). On the other hand, if $a_{AT} > \delta_{YT}(h_T + 1)$, then $E_{31}$ is unstable and $E_{32} = (T_S, 0, Y_T, 0)$ exists. Since $(T_S, Y_T)$ is globally asymptotically stable for (5) if $T_S > (1 - h_T)/2$, $E_{32}$ is globally asymptotically stable for (10) if $T_S > (1 - h_T)/2$.

If $T_S \leq (1 - h_T)/2$, then (5) has a unique positive limit cycle $L^*(t)$ which is moreover globally asymptotically stable by Proposition 3.1(b)(ii). Consequently, the limit cycle is globally asymptotically stable for (10). These results are summarized as follows. For notational convenience, we let $\Gamma_T = \{(T_S, Z, Y_T, Y_T) \in \mathbb{R}_+^4 : T_S > 0\}$.

**Proposition 3.3.** Let $s_{ZR} \alpha_{ZZ} < \delta_{ZR} \delta Z$. The following statements hold for (10).

(a) The equilibrium $E_{31} = (1, 0, 0, 0)$ is globally asymptotically stable in $\Gamma_T$ if $a_{AT} < \delta_{YT}(h_T + 1)$.

(b) If $a_{AT} > \delta_{YT}(h_T + 1)$, then (10) has an equilibrium of the form $E_{32} = (T_S, 0, Y_T, 0)$. Moreover,

(i) $E_{32}$ is globally asymptotically stable in $\Gamma_T$ if $T_S > (1 - h_T)/2$,

(ii) (10) has a unique limit cycle on the positive $T_S Y_T$ coordinate plane which is moreover globally asymptotically stable in $\Gamma_T$ if $T_S \leq (1 - h_T)/2$.

When there are no viruses and the innate immune system’s activation rate is smaller than its death rate, the tumor will attain to its maximum size if the adaptive immune system is weak with $a_{AT} < \delta_{YT}(h_T + 1)$ as shown in Proposition 3.3(a). If the adaptive immune system is not weak, then the tumor will attain at a smaller level $T_S$ if $T_S$ is larger than $(1 - h_T)/2$. If $T_S$ is small, then the tumor will be dormant for some periods of time. See Proposition 3.3(b). The period of dormancy may depend on parameter values.

If the innate immune system’s activation rate is larger than its death rate, i.e., $s_{ZR} \alpha_{ZZ} > \delta_{ZR} \delta Z$, then since there are no viruses, we have $\lim_{t \to \infty} Z(t) = \hat{Z}$ and
\[
\lim_{t \to \infty} Y_V(t) = \hat{Y}_V \quad \text{if} \quad Z(0) > 0, \quad \text{where} \quad \hat{Z} \quad \text{and} \quad \hat{Y}_V \quad \text{are defined in (9).} \quad \text{As} \quad Z(0) = 0 \quad \text{would reduce (10) to the system (5) discussed in section 3.1, we assume} \quad Z(0) > 0. \quad \text{Consequently, system (10) is asymptotically autonomous to system (13). Notice that (13) can be viewed as a predator-prey model with a constant stocking} \quad a_T Z \quad \text{of the predator. There always exists a tumor-free equilibrium} \quad E_{33} = (0, \hat{Z}, \hat{Y}_T, \hat{Y}_V), \quad \text{where} \quad E_{33} \quad \text{is asymptotically stable if} \quad g(0) = \hat{Y}_T > h_T = f(0) \quad \text{by Table 1. Under some additional conditions, there is no positive equilibrium and it can be shown that} \quad E_{33} \quad \text{is globally asymptotically stable. Let} \quad \Gamma_Z = \{(T_S, Z, Y_T, Y_V) \in \mathbb{R}_+^4 : Z > 0\}.
\]

**Theorem 3.1.** Let \( s_Z r a_{ZZ} > \delta_Z r \). If either \( 1 \leq h_T < \hat{Y}_T \) or \((1 + h_T)^2/4 < \hat{Y}_T \) and \( h_T < 1 \), then the tumor-free equilibrium \( E_{33} = (0, \hat{Z}, \hat{Y}_T, \hat{Y}_V) \) is globally asymptotically stable for (10) in \( \Gamma_Z \).

**Proof.** Observe that \((1 + h_T)^2/4 > h_T \) when \( h_T < 1 \). By the assumptions, equilibria \( E_{3i} \), \( 0 \leq i \leq 2 \), are unstable and (10) has no positive equilibrium. Moreover, \( E_{33} \) is asymptotically stable since \( \hat{Y}_T > h_T \) holds. We prove that \( E_{33} \) is globally attracting in \( \Gamma_Z \). Let \((T_S(0), Z(0), Y_T(0), Y_V(0)) \) be given arbitrarily with \( Z(0) > 0 \). Then for any \( \epsilon > 0 \) there exists \( t_1 > 0 \) such that \( Z(t) > \hat{Z} - \epsilon \) for \( t \geq t_1 \). Therefore, \( Y_V'(t) \geq a_T Z (\hat{Z} - \epsilon) - \delta_Y T Y_T \) for \( t \geq t_1 \) implies \( \liminf_{t \to \infty} Y_V(t) \geq \hat{Y}_T = g(0) \). Thus, for any \( \epsilon > 0 \) there exists \( t_0 > t_1 \) such that \( Y_V(t) > \hat{Y}_T - \epsilon \) for \( t \geq t_0 \). Since \( f^\infty = h_T \) if \( h_T = 1 \) and \( f^\infty = (1 + h_T)^2/4 > h_T \) if \( h_T < 1 \), we choose \( \epsilon > 0 \) such that \( g(0) - \epsilon > f^\infty \) by the assumption. Then for all \( t \geq t_0 \) we have

\[
T_S'(t) \leq T_S(1 - T_S - \frac{\hat{Y}_T - \epsilon}{h_T + T_S}) \leq T_S \frac{f(T_S) - g(0) + \epsilon}{h_T + T_S} \leq T_S \frac{f^\infty - g(0) + \epsilon}{h_T + T_S},
\]

It follows that \( T_S'(t) < 0 \) for \( t \geq t_0 \) and hence \( \lim_{t \to \infty} T_S(t) = T^*_S \geq 0 \) exists. If \( T^*_S > 0 \), then as \( 0 = \lim_{t \to \infty} T_S(t) \leq T_S \frac{f(T_S) - (\hat{Y}_T - \epsilon)}{h_T + T_S} < 0 \), we obtain a contradiction. Thus \( T_S = 0 \), and it can be verified that \( \lim_{t \to \infty} Y_V(t) = \hat{Y}_V \). Therefore \( E_{33} \) is globally attracting in \( \Gamma_Z \).

Recall that \( \liminf_{t \to \infty} Y_V(t) \geq \hat{Y}_T \) if \( Z(0) > 0 \) and \( s_Z r a_{ZZ} > \delta_Z r \). Thus we may assume \( Y_V(t) \geq 0 \) for \( t \geq 0 \) for any solutions of (10) with \( Z(0) > 0 \) when \( s_Z r a_{ZZ} > \delta_Z r \). Since \( T_S^\infty \mid T_S \geq 1 < 0 \), without loss of generality, we may assume \( 0 < T_S(t) < 1 \) for \( t \geq 0 \). It follows that for any \( \epsilon > 0 \) there exists \( t_2 > 0 \) such that \( Y_V'(t) \leq a_T Z (\hat{Z} + \epsilon) - \delta_Y Y_T Y_T \) for \( t \geq t_2 \). In addition, let \( \hat{Y}_T < h_T \) and \( h_T \geq 1 \). Then (10) has a unique positive equilibrium \( E_{34} \) by Table 1. In the case of \( a_{AT} \leq \delta_Y T \), \( E_{34} \) is asymptotically stable since \( \Delta < 0 \) and \( \eta > 0 \), and moreover

\[
\limsup_{t \to \infty} Y_T(t) \leq \frac{a_T Z (h_T + 1)}{\delta_Y T (h_T + 1) - a_{AT}} := Y_T^\infty.
\]

Since \( E_{34} \) is asymptotically stable in this parameter regime, one would expect \( E_{34} \) to be globally asymptotically stable. In the following, we impose an extra condition to prove that \( E_{34} \) is globally asymptotically stable in \( \Gamma_{TZ} = \{(T_S, Z, Y_T, Y_V) \in \mathbb{R}_+^4 : T_S > 0, Z > 0\} \).
Theorem 3.2. Let $sZH_{AZZ} > \delta Z_{RZ}$, $\hat{Y}_T < h_T$, $h_T \geq 1$ and $a_{AT} \leq \delta_{YT}$. If either $Y_T^\infty \leq 1$ or $Y_T^\infty > 1$ and $\delta_{YT}(h_T + 1) - a_{AT} > \frac{h_T + 1}{2}(-1 + \sqrt{1 + 4a_{TZ}Z})$, then $E_{34} = (\hat{T}_S, Z, \hat{Y}_T, \hat{Y}_V)$ is globally asymptotically stable in $\Gamma_{TZ}$ for system (10).

Proof. By the assumptions, (10) has a unique positive equilibrium $E_{34}$ which is moreover asymptotically stable by Table 1. Let $(T_S(t), Z(t), Y_T(t), Y_V(t))$ be a solution of (10) with $T_S(0), Z(0) > 0$. Since $\lim_{t \to \infty} Z(t) = \hat{Z}$ and $\lim_{t \to \infty} Y_V(t) = \hat{Y}_V$, it is sufficient to prove that the equilibrium $(\hat{T}_S, \hat{Y}_T)$ is globally attracting for system (13). Using $\liminf_{t \to \infty} Y_T(t) \geq \hat{Y}_T$ and $0 < T_S(t) < 1$ for $t \geq 0$, we have $\frac{Y_T'}{Y_T} > a_{TZ}\hat{Z} - \delta_{YT}\hat{Y}_T = 0$. Similarly, $\frac{Y_T'}{\hat{Y}_T} \leq a_{TZ}\hat{Z} + a_{TZ}\frac{1 + Y_T^\infty}{h_T + 1} - \delta_{YT}Y_T^\infty = 0$.

Therefore we may assume $\hat{Y}_T \leq Y(t) \leq Y_T^\infty$ for $t \geq 0$.

Applying the Dulac criterion with $G(T_S, Y_T) = 1/(T_SZ_T)$ on the region $D = \{(T_S, Y_T) \in \mathbb{R}_+^2 : 0 < T_S < 1, \hat{Y}_T \leq Y_T \leq Y_T^\infty\}$, where every solution of (13) eventually enters in $D$ and remains there. Then as $h_T \geq 1$

$$
\Gamma^* := \frac{\partial(T_S^2G)}{\partial T_S} + \frac{\partial(Y_T^2G)}{\partial Y_T} = -\frac{1}{Y_T} + \frac{1}{(h_T + T_S)^2} - \frac{a_{TZ}}{T_SZ_T^2} \leq 1 - \frac{1}{Y_T^\infty} - \frac{a_{TZ}}{(Y_T^\infty)^2}. \quad (20)
$$

If $Y_T^\infty \leq 1$, then $\Gamma^* < 0$ on $D$. If $Y_T^\infty > 1$, then $\Gamma^* < 0$ on $D$ is equivalent to $(Y_T^\infty)^2 - Y_T^\infty - a_{TZ}\hat{Z} < 0$. Substituting the expression $Y_T^\infty$ by (19) and simplifying, $(Y_T^\infty)^2 - Y_T^\infty - a_{TZ}\hat{Z} < 0$ becomes

$$
-\left(\delta_{YT}(h_T + 1) - a_{AT}\right)^2 - (h_T + 1)\left(\delta_{YT}(h_T + 1) - a_{AT}\right) + a_{TZ}\hat{Z}(h_T + 1)^2 < 0.
$$

This latter inequality holds by the assumption $\delta_{YT}(h_T + 1) - a_{AT} > \frac{h_T + 1}{2}(-1 + \sqrt{1 + 4a_{TZ}Z})$. Therefore, (13) has no periodic solution in $D$. It follows from the Poincaré-Bendixson Theorem [3] that $(\hat{T}_S, \hat{Y}_T)$ is globally asymptotically stable for (13) and the proof is complete. \hfill \Box

The assumption $a_{AT} \leq \delta_{YT}$ given in Theorem 3.2 can be relaxed. Let $\delta_{YT} < a_{AT} < \delta_{YT}(h_T + 1)$ so that $Y_T^\infty > 0$ in (19) is well defined. Suppose $\hat{T}_S \geq (a_{AT} - \delta_{YT} + 1 - h_T)/2$. Then $\eta < 0$ and $E_{34}$ is asymptotically stable. Using a similar argument as in the proof of Theorem 3.2, we have the following corollary.

Corollary 3.1. Let $sZH_{AZZ} > \delta Z_{RZ}$, $\hat{Y}_T < h_T$, $h_T \geq 1$, $\delta_{YT} < a_{AT} < \delta_{YT}(h_T + 1)$, and $\hat{T}_S \geq (a_{AT} - \delta_{YT} + 1 - h_T)/2$. If either $Y_T^\infty \leq 1$ or $Y_T^\infty > 1$ and $\delta_{YT}(h_T + 1) - a_{AT} > \frac{h_T + 1}{2}(-1 + \sqrt{1 + 4a_{TZ}Z})$, then $E_{34} = (\hat{T}_S, Z, \hat{Y}_T, \hat{Y}_V)$ is globally asymptotically stable in $\Gamma_{TZ}$ for system (10).

Recall from sections 3.1 and 3.2 with the baseline parameter values given in [38], we have $sZH_{AZZ} < \delta Z_{RZ}$, $a_{AT} > \delta_{YT}(h_T + 1)$ and $\hat{T}_S > (1 - h_T)/2$. Therefore, equilibria $E_{3i}$, $0 \leq i \leq 2$, are unstable and there are no other equilibria. Solutions of (10) will converge to the positive periodic solution $L^*(t)$ of the $T_SZ_T$ subsystem and hence the adaptive immune system is able to drive the tumor into remission and relapse phenomenon.
4. Dynamics of the full model. Building on the dynamics of the model on the boundaries, in this section we discuss asymptotic dynamics of the full system (4). We first provide existence of boundary equilibria and their stability in section 4.1. Global dynamics of the model in certain parameter regimes are given in section 4.2.

4.1. Boundary equilibria and their stability. System (4) always has two equilibria \( E_0 = (0,0,0,0,0,0) \) and \( E_1 = (1,0,0,0,0,0) \). The Jacobian matrix at \( E_0 \) and \( E_1 \) are given in (27) and (28) respectively. From (27), we see that \( E_0 \) is always a saddle point, and by (28) \( E_1 \) is asymptotically stable if \( s_{ZRS} < \delta Z \), \( a_{AT} < \delta T (h_T + 1) \) and \( \omega > b_T \). Equilibrium \( E_2 = (\bar{T}_S,0,0,0,0,0) \) exists if \( a_{AT} > \delta T (h_T + 1) \) and its stability depends on the eigenvalues of \( J(E_2) \) given in (29), where \( \bar{j}_{11}, \bar{j}_{15}, \bar{j}_{51}, \bar{j}_{55} \) form the matrix \( J_1(E_{12}) \) defined in (7). The eigenvalues of \( J(E_2) \) are \( -\delta TV, \frac{s_{ZRS}}{\delta Z} - \delta Z \), and the eigenvalues of \( J_1(E_{12}) \) and

\[
\begin{pmatrix}
-\delta_T - \bar{Y}_T/h_I & \bar{T}_S \\
\delta_T & -\omega
\end{pmatrix}.
\]

Therefore, \( E_2 \) is asymptotically stable if \( s_{ZRS} < \delta Z \), \( \bar{T}_S > (1 - h_T)/2 \) and \( \omega(\delta_T + \bar{Y}_T/h_I) > b_T \). Equilibrium \( E_3 = (0,0,0,\bar{Z},\bar{Y}_T,\bar{Y}_V) \) exists if \( s_{ZRS} > \delta Z \). The Jacobian matrix of (4) evaluated at \( E_3 \) is given in (30). From (30), we see that \( E_3 \) is asymptotically stable if \( \bar{Y}_T > h_T \). Suppose a unique equilibrium of the form \( E_4 = (\bar{T}_S,0,0,\bar{Z},\bar{Y}_T,\bar{Y}_V) \) exists. Its stability depends on \( J(E_4) \), given in (31), where *s are unimportant terms, and \( \bar{j}_{11}, \bar{j}_{15}, \bar{j}_{51}, \bar{j}_{55} \) form the Jacobian matrix \( J \) given in (15). The eigenvalues of \( J(E_4) \) consist of \( -\delta TV < 0, \frac{s_{ZRS}}{(\delta Z + \delta Z \bar{Z})^2} - \delta Z < 0 \), the eigenvalues of \( J \) given in (15) and the eigenvalues of

\[
\begin{pmatrix}
\bar{j}_{22} & \bar{T}_S \\
\delta_T & \bar{j}_{33}
\end{pmatrix},
\]

where \( \bar{j}_{22} = -\delta_T - k_{1}\bar{Z}/(h_I + \bar{Z}) - \bar{Y}_T/h_I < 0 \) and \( \bar{j}_{33} = -k_{VZ}\bar{Z} - \omega < 0 \). We conclude that \( E_4 \) is asymptotically stable if \( \eta < 0 \) and

\[
\eta := (k_{VZ}\bar{Z} + \omega)(\delta_T + k_{1}\bar{Z}/(h_I + \bar{Z}) + \bar{Y}_T/h_T) - \delta_T \bar{T}_S
\]

is positive. The existence and stability of boundary equilibria of system (4) are summarized in Table 3 and Table 4 provides biological interpretations of these equilibria.
Proposition 4.1. If the infected tumor cells will be cleared off, which is shown in Proposition 4.1.

Some global asymptotic results.

4.2. Some global asymptotic results. It is expected that if the burst size $b_T$ of infected tumor cells is smaller than the viral clearance rate $\omega$, the viruses as well as the infected tumor cells will be cleared off, which is shown in Proposition 4.1.

**Proposition 4.1.** If $\omega > b_T$, then solutions of (4) satisfy $\lim_{t \to \infty} T_I(t) = 0 = \lim_{t \to \infty} V(t)$.

**Proof.** Since $\lim_{t \to \infty} T_S(t) \leq 1$, for any $\epsilon > 0$ there exists $t_0 > 0$ such that $T_S(t) < 1 + \epsilon$. We choose $\epsilon > 0$ sufficiently small such that $\omega > (1 + \epsilon)b_T$. Then $T'_I(t) < (1 + \epsilon)V - b_T T_I$ and $V'(t) < b_T b_T I - \omega V$ for $t \geq t_0$. Consider the linear system for $t \geq t_0$

| Equilibrium | Biological meaning |
|-------------|---------------------|
| $E_0 = (0,0,0,0)$ | Extinction of tumor, virus and immune cells |
| $E_1 = (1,0,0,0,0)$ | Susceptible tumor only |
| $E_2 = (\tilde{T}_S,0,0,\tilde{Y}_T,0)$ | Coexistence of susceptible tumor and anti-tumor immune cells |
| $E_3 = (0,0,\tilde{Z},\tilde{Y}_T,\tilde{Y}_V)$ | Immune cells only |
| $E_4 = (\tilde{T}_S,0,0,\tilde{Z},\tilde{Y}_T,\tilde{Y}_V)$ | Coexistence of susceptible tumor and immune cells |

**Table 4.** Biological interpretations of boundary equilibria of full system (4).
\[
\begin{align*}
x' &= -\delta_T x + (1 + \epsilon)y \\
y' &= b_T \delta_T x - \omega y \\
x(t_0) &= T_1(t_0), y(t_0) = V(t_0).
\end{align*}
\]

Notice the above linear system is two-dimensional and cooperative with all solutions convergent to \((0, 0)\) by \(\omega > (1 + \epsilon)b_T\). Since \(T_1(t) \leq x(t)\) and \(V(t) \leq y(t)\) for \(t \geq t_0\), \(\lim_{t \to \infty} T_1(t) = 0 = \lim_{t \to \infty} V(t)\) is shown. \(\square\)

Next, we provide sufficient conditions for which the susceptible tumor cells will be eradicated. In particular, when the innate immune system is strong and can recruit anti-tumor adaptive immune cells successfully while the susceptible tumor cells can be killed effectively, then the susceptible tumor cells will be driven to extinction eventually.

**Proposition 4.2.** Let \(s_{ZR}a_{ZZ} > \delta_Z \delta_{ZR}\). If either \(1 \leq h_T < \hat{Y}_T\) or \((1 + h_T)^2/4 < \hat{Y}_T\) and \(h_T > 1\), then solutions of (4) with \(Z(0) > 0\) satisfy \(\lim_{t \to \infty} T_S(t) = 0\).

**Proof.** The proof is similar to the proof of Theorem 3.1. Let \(Z(0) > 0\). The inequality \(s_{ZR}a_{ZZ} > \delta_Z \delta_{ZR}\) implies \(\hat{Z} > 0\) is well defined. Notice \(Z' > s_{ZR}a_{ZZ} \frac{Z}{\delta_{ZR} + a_{ZZ} \hat{Z}} - \delta_Z Z\) and hence \(\lim_{t \to \infty} Z(t) \geq \hat{Z}\). Therefore for any \(\epsilon > 0\) there exists \(t_0 > 0\) such that \(Z(t) > \hat{Z} - \epsilon\) for \(t \geq t_0\). Consequently, \(Y_T'(t) \geq a_{AT}(\hat{Z} - \epsilon) - \delta_Y T\) for \(t \geq t_0\) implies \(\lim_{t \to \infty} Y_T(t) \geq \hat{Y}\) and thus \(Y_T(t) > \hat{Y}\) for all \(t\) large. We choose \(\epsilon > 0\) such that \(\hat{Y} > \hat{Z} - \epsilon > f^\infty\). As a result, for all \(t\) large we have

\[
T_S' \leq T_S(1 - T_S) - \frac{T_S(\hat{Y}_T - \epsilon)}{h_T + T_S}
\]

\[
= \frac{T_S}{h_T + T_S}(f(T_S) - (\hat{Y}_T - \epsilon)) < \frac{T_S}{h_T + T_S}(f^\infty - (\hat{Y}_T - \epsilon)) < 0,
\]

where \(f^\infty\) is defined in (14). Consequently, \(\lim_{t \to \infty} T_S(t) = T_S^* \geq 0\) exists. If \(T_S^* > 0\), then \(0 = \lim_{t \to \infty} T_S'(t) < 0\), a contradiction occurs. Therefore, we conclude that \(\lim_{t \to \infty} T_S(t) = 0\). \(\square\)

The dynamics of the tumor-immune-virus interactions is easier to understand when the innate immune system is weak and the virus has a large death rate. If, in addition, the tumor is not antigenic then the anti-tumor adaptive immunity cannot control the tumor and the tumor will grow to its carrying capacity. Let \(R_T = \{(T_S, T_I, V, Z, Y_T, Y_V) \in \mathbb{R}_+^6 : T_S > 0\}\).

**Theorem 4.1.** Let \(s_{ZR}a_{ZZ} < \delta_Z \delta_{ZR}\), \(b_T < \omega\) and \(a_{AT} < \delta_{YT}(h_T + 1)\). Then \(E_1 = (1, 0, 0, 0, 0, 0)\) is globally asymptotically stable in \(R_T\).

**Proof.** By the assumptions \(E_1\) is asymptotically stable and \(E_i, 2 \leq i \leq 4\), do not exist. Proposition 4.1 implies \(\lim_{t \to \infty} T_I(t) = 0 = \lim_{t \to \infty} V(t)\). Thus for any \(\epsilon > 0\) there exists \(t_1 > 0\) such that \(a_Z T_1(t)/h_I + Z(t)) < \epsilon\) and \(V(t) < \epsilon/a_{ZV}\) for \(t \geq t_1\). It follows that \(Z' < s_{ZR}(a_Z \hat{Z} + \epsilon) - \delta_Z Z\) for \(t \geq t_1\). We choose \(\epsilon > 0\) so that \(s_{ZR}a_{ZZ} < \delta_Z(\delta_{ZR} + \epsilon)\). Consequently, \(\lim\sup_{t \to \infty} Z(t) \leq \frac{\epsilon \delta_{ZR}}{\delta_Z(\delta_{ZR} + \epsilon) - \delta_{ZR}a_{ZZ}}\). Letting \(\epsilon \to 0\), we have \(\lim_{t \to \infty} Z(t) = 0\). Therefore, (4) is asymptotically autonomous to
the $T_S Y_T$ system (5), and hence $E_1$ is globally asymptotically stable by Proposition 3.1(a).

If the tumor is more antigenic, then the anti-tumor adaptive immune cells can control the tumor in the sense that the tumor will be stabilized at a smaller size than its carrying capacity. Let $R_{TV} = \{(T_S, T_I, V, Z, Y_T, Y_V) \in \mathbb{R}^6_+ : T_S > 0, Y_T > 0\}$.

**Theorem 4.2.** Let $s_Z R a_{ZZ} < \delta_Z \delta_Z R$, $\omega > b_T$, $a_{AT} > \delta_Y (h_T + 1)$, and $T_S > (1 - h_T)/2$. Then $E_2 = (T_S, 0, 0, 0, Y_T, 0)$ is globally asymptotically stable in $R_{TV}$.

**Proof.** Clearly $E_2$ exists and $\omega > b_T$ implies $\omega \delta_T > b_T \delta_T > b_T \delta_T \bar{T}_S$. Hence $E_2$ is asymptotically stable and (4) only has equilibria $E_i$, $0 \leq i \leq 2$, where $E_0$ and $E_1$ are unstable. It follows from Proposition 4.1 that $\lim\limits_{t \to \infty} Y_T(t) = 0 = \lim\limits_{t \to \infty} V(t)$. Further, $\lim\limits_{t \to \infty} Z(t) = 0$ as $s_Z R a_{ZZ} < \delta_Z \delta_Z R$, which implies $\lim\limits_{t \to \infty} Y_V(t) = 0$. Therefore, system (4) is asymptotically autonomous to the $T_S Y_T$ subsystem (5) and the results follows by Proposition 3.1(b)(i).

We remark that if $s_Z R a_{ZZ} < \delta_Z \delta_Z R$, $\omega > b_T$, $a_{AT} > \delta_Y (h_T + 1)$ and $\bar{T}_S \leq (1 - h_T)/2$, then by Proposition 3.1(b)(ii) solutions of (4) converge to the limit cycle of the $T_S Y_T$ subsystem if $T_S(0) > 0$ and $Y_T(0) > 0$. In this circumstance, the tumor size will be oscillating over time and remissions of the cancer may be observed.

**Corollary 4.1.** Let $s_Z R a_{ZZ} < \delta_Z \delta_Z R$, $\omega > b_T$, $a_{AT} > \delta_Y (h_T + 1)$, and $\bar{T}_S \leq (1 - h_T)/2$. Then solutions of (4) with $T_S(0) > 0$ and $Y_T(0) > 0$ converge to $L^*(t)$ in the positive $T_S Y_T$-coordinate plane.

If resting innate immune cells can be activated successfully, then the tumor will be driven to extinction even when the tumor is not antigenic but the tumor-associated adaptive immunity is strong, as shown below. Let $R_Z = \{(T_S, T_I, V, Z, Y_T, Y_V) \in \mathbb{R}^6_+ : Z > 0\}$.

**Theorem 4.3.** Let $s_Z R a_{ZZ} > \delta_Z \delta_Z R$, $\omega > b_T$ and $a_{AT} < \delta_Y (h_T + 1)$. If either $1 \leq h_T < Y_T^b$ or $(1 + h_T)^2/4 < Y_T^b$ and $h_T < 1$, then $E_3 = (0, 0, 0, \bar{Z}, \bar{Y}_T, \bar{Y}_V)$ is globally asymptotically stable in $R_Z$.

**Proof.** From the given conditions, $E_2$ does not exist while $E_1$ is unstable and $E_3$ exists. Also the assumption on $Y_T^b$ implies no equilibrium of the form $(T_S, 0, 0, Z, Y_T, Y_V)$ exists. Moreover, $\lim\limits_{t \to \infty} Y_T(t) = 0 = \lim\limits_{t \to \infty} V(t)$ by Proposition 4.1 and $\lim\limits_{t \to \infty} T_S(t) = 0$ by Proposition 4.2. Therefore, (4) is asymptotically autonomous to (8) and the result follows.

When the activation of resting innate immune cells is strong but with a weak anti-tumor adaptive immunity, then the susceptible tumor will end up stabilize at a level that is smaller than its maximum size. Let $R_{TZ} = \{(T_S, T_I, V, Z, Y_T, Y_V) \in \mathbb{R}^6_+ : T_S > 0, Z > 0\}$.

**Theorem 4.4.** Let $s_Z R a_{ZZ} > \delta_Z \delta_Z R$, $\omega > b_T$, $a_{AT} < \delta_Y (h_T + 1)$ and $h_T \geq 1$. Then $E_4 = (\bar{T}_S, 0, 0, \bar{Z}, \bar{Y}_T, \bar{Y}_V)$ is globally asymptotically stable in $R_{TZ}$ if either (i) $Y_T^\infty \leq 1$ or (ii) $Y_T^\infty > 1$ and $\delta_Y (h_T + 1) - a_{AT} > (h_T + 1)/2(-1 + \sqrt{1 + 4 a_{AT} \bar{Z}})$.

**Proof.** Notice $\lim\limits_{t \to \infty} V(t) = 0 = \lim\limits_{t \to \infty} T_I(t)$ by Proposition 4.1 since $\omega > b_T$. Therefore, system (4) is asymptotically autonomous to the subsystem (10) and the result follows from Theorem 3.5.
A similar result parallel to Theorem 4.4 can be obtained if \( \delta_{YT} < a_{AT} < \delta_{YT}(h_T + 1) \) by applying Corollary 3.1.

**Corollary 4.2.** Let \( s_{ZR} a_{ZZ} > \delta_{ZR} \delta_Z, \hat{Y}_T < h_T, h_T \geq 1, \delta_{YT} < a_{AT} < \delta_{YT}(h_T + 1), \hat{T}_S \geq (a_{AT} - \delta_{YT} + 1 - h_T)/2, \) and \( \omega < b_T \). If either \( Y_T^\infty \leq 1 \) or \( Y_T^\infty > 1 \) and \( \delta_{YT}(h_T + 1) - a_{AT} > \frac{h_T + 1}{2}(-1 + \sqrt{1 + 4a_{TZ}Z}) \), then \( E_4 = (\hat{T}_S, 0, 0, \hat{Z}, \hat{Y}_T, \hat{Y}_V) \) is globally asymptotically stable in \( R_{TZ}^2 \) for system (4).

5. **Numerical bifurcation analysis.** Dynamics of the tumor-virus-immune interactions are complicated, where the innate immunity on one hand can eliminate viruses and stimulate the adaptive immune system on the other hand. The global dynamics given in the previous section shed some lights on the basic interactions. In order to understand the combined effects of different mechanisms, however, numerical explorations are inevitable. In this section, we provide numerical bifurcation analysis of the model. In sections 3 and 4, the mathematical analyses are performed on the dimensionless system (4). The dimensionless form of the equations are often more difficult to give biological interpretations of the parameters and variables since they have been rescaled in the nondimensionalization procedure. Therefore, the numerical study in this section will be carried out on the original system (1).

Bifurcation analysis usually begins with the identification of equilibria which often provide useful information about the dynamics of biological systems and can lead to predictions of their asymptotic behavior. A numerical method for locating bifurcations of equilibria has been developed by Wei [43] and successfully applied to several biological systems [18, 44]. However, the identification of equilibria of system (1) fails to converge to the positive equilibria when the tumor size of an equilibrium is almost as large as the carrying capacity \( C_T = 5.157 \times 10^8 \). Furthermore, the system may exhibit coexistence of three such equilibria. For example, system (1) has two stable positive equilibria \((515696698, 13, 481, 9.98, 1496, 45.3)\) and \((515695241, 356.6, 1313.7, 10, 1500, 53.4)\) and one unstable positive equilibrium \((515690832, 1408, 51448, 10, 1500, 102)\) when \( \beta = 3.26 \times 10^{-12}, a_{AT} = 2.08 \times 10^{-4} \) and all other parameter values are the same as in Table 1 of [38]. This fact together with the existence of the boundary equilibrium \( E_1 = (C_T, 0, 0, 0, 0) \) makes it difficult to identify all positive equilibria because the solution sometimes tends to converge to \( E_1 \). Other numerical methods for bifurcation analysis must be constructed to overcome the difficulty.

5.1. **Numerical methods for bifurcation analysis.** Sensitivity analysis is aimed at measuring the impacts of changes in parameter values on changes in model output. It can be used to select the bifurcation parameters which contribute most on output uncertainty. Storey et al. [38] have performed parameter sensitivity analysis for system (1) and have shown that the viral infection rate \( \beta \) has the most significant impact on the final tumor size. First, using \( \beta \) as a bifurcation parameter, we consider a positive equilibrium \( E_5 = (T_S, T_I, V, Z, Y_T, Y_V) \). Given \( T_I \), the state variables \( V, Z, Y_V \) are obtained by solving the following equations:

\[
0 = b_T \delta_T T_I - k_{VZ} VZ - k_{VA} VY_V - \omega V \\
0 = \frac{s_{ZR}(a_{ZZ} Z + a_{ZV} V)}{\delta_{ZR} + a_{ZZ} Z + a_{ZV} V} + \frac{a_Z T_I Z}{h_I + Z - \delta_Z Z}
\]
0 = a_{VZ}Z + \frac{a_{AT}T_1Y_V}{h_I + T_1} - \delta_{YV}Y_V.

Then, the state variables $T_S$ and $Y_T$ can be solved using the following equations:

\begin{align*}
0 &= r_T T_S \left(1 - \frac{T_S + T_I}{C_T}\right) - k_{TA} T_S Y_T \frac{h_T + T_S}{h_T + T_I} - \delta_T T_I - \frac{k_I T_I Z}{h_I + Z} \\
&\quad - k_{TA} T_I Y_T \frac{h_I + T_I}{h_I + T_I}, \\
0 &= a_{TZ} Z + \frac{a_{AT} (T_S + T_I) Y_T}{h_T + T_S + T_I} - \delta_{YT} Y_T.
\end{align*}

(22)

To construct a one-dimensional bifurcation diagram, a range $[0, T_{I_{max}}]$ for the state variable $T_I$ is considered where $T_{I_{max}} = \delta_{VY} \times h_I / (a_{AI} - \delta_{VY})$. Note that $T_I \leq T_{I_{max}}$ if $\bar{T}_I$ satisfies (21). We consider the $T_I$ values $0 < T_{I1} < T_{I2} < \cdots < T_{I_n} < T_{I_{max}}$. For each $T_{I_i}$, $1 \leq i \leq n$, the corresponding positive equilibrium $E_{Si} = (T_{Si}, T_{I_i}, V_i, Z_i, Y_{Ti}, Y_{Vi})$ is obtained by solving (21) and (22), and the corresponding $\beta_i$ value satisfies $\beta_i = [r_T (1 - (T_{Si} + T_{I_i}) / C_T) - k_{TA} Y_{Ti} / (h_T + T_{Si})] / V_i$. Then the stability for each of the positive equilibria is computed, the positive equilibria $E_{Si}$, $1 \leq i \leq n$, is sorted in ascending order using $T_{Si}$ values, and the parameter value at which the positive equilibrium point changes its stability is identified. For a two-dimensional bifurcation diagram, the second bifurcation parameter and a range of the parameter values are selected, a set of grid points over this range is constructed, and then the bifurcation points in $\beta$ for each grid point of the second bifurcation parameter are located using the above process. The grid points for the second parameter with their corresponding bifurcation points in $\beta$ give the bifurcation curves on the two-dimensional bifurcation domain.

5.2. Bifurcation analysis with baseline parameter values. Recall that the parameter values used in [38] are adopted as the baseline parameter values in this paper. An hour has been taken as the unit of time in [38]. However, many parameters such as those for cell doubling time and half-life are measured in days. Furthermore, bifurcation analysis studies the asymptotic dynamics of a system and cell population dynamics are often presented using one day as the unit of time. Therefore one day is used as the unit of time throughout this section, and the corresponding parameter values are given as follows:

\begin{align*}
\delta_T &= 4/3, \quad \delta_Z = 2.88, \quad \delta_Z = 0.192, \quad \delta_{YT} = 9 \times 10^{-3}, \\
\delta_{VY} &= 0.13296, \quad k_{TA} = 1, \quad k_{IA} = 1, \quad k_{VZ} = 0.12, \\
k_{VA} &= 2.4 \times 10^{-4}, \quad s_{ZR} = 1.92, \quad \omega = 0.6, \quad a_{ZZ} = 0.24, \\
a_{ZV} &= 2.4, \quad a_Z = 5.76 \times 10^{-5}, \quad a_{TZ} = 0.6, \quad a_{AT} = 0.0384, \\
a_{VZ} &= 0.6, \quad a_{AI} = 0.6, \quad r_T = 0.4608, \quad \beta = 6 \times 10^{-8}, \\
C_T &= 5.157 \times 10^8, \quad b_T = 50, \quad h_T = 2.7 \times 10^4, \quad h_I = 10^4.
\end{align*}

(23)

From Table 3, the boundary equilibria $E_0$, $E_1$, and $E_2$ exist and are unstable. The equilibria $E_3$ and $E_4$ do not exist. The population levels for susceptible tumor cells are $5.157 \times 10^8$, $8265$, and $0$ for $E_1$, $E_2$, and $E_0$, respectively. Figure 5(a) shows a one-dimensional bifurcation diagram using the viral infection rate $\beta$ as the bifurcation parameter. No positive equilibrium exists for the baseline parameter values, where $\beta = 6 \times 10^{-8}$. Although no stable equilibrium exists as shown in Figure 5(a), the system possesses a stable limit cycle as an attractor. The cell populations oscillate over time as shown in Fig. 5(b). A positive equilibrium, which
is unstable, bifurcates from $E_2$ at $\beta = 3.22 \times 10^{-6}$. The positive equilibrium does not change its stability as the viral infection rate increases.

Figure 5(b) also shows that the susceptible tumor cells start to become infected as the population level reaches a certain level. This stimulates the growth of the virus population and in turn triggers the infection of susceptible tumor cells. Marelli et al. [32] have reported that oncolytic viruses replicate inside infected tumor cells and kill them. The infected tumor cells release the viral particles as they burst. These viral particles freed from lysed tumor cells continue to infect other tumor cells. The whole population of susceptible tumor cells rapidly becomes infected and is killed by oncolytic viruses and immune cells $Z$, $Y_T$, and $Y_V$ in about two weeks. The immune cells are still active and able to control the disease after tumor cells have been eliminated. This phenomenon mimics tumor mass dormancy in which the tumor cells divide but the tumor is limited by size because of either limitations in blood supply or an active immune system [1]. This stage reflects a balance between cell division and cell death. However, these immune cell populations start to decrease in the absence of tumor cells leading to increases in risk of tumor recurrence.

The host remains tumor free and the immune system remains active for a short period of time after OVT treatment. The equilibrium $E_3 = (0, 0, 0, Z, Y_T, Y_V)$ can be considered as a remission equilibrium, and the cancer is cured if $E_3$ is stable. According to (1), the immune system is able to prevent the tumor from recurrence if the tumor-specific adaptive immune cell population $Y_T$ maintains over a level of $h_{TT}/k_{TA} = 1.24 \times 10^4$. The population level of $Y_T$ has a direct effect on tumor recurrence. Figure 5(b) shows that the cell population for $Y_T$ is far below this level causing tumor relapse. The fifth equation in (1) shows that in the absence of tumor cells, the stimulation of tumor-specific adaptive immune cells solely relies on the population level of innate immune cells $Z$. The population level $Y_T$ will eventually fall below $1.24 \times 10^4$ leading to tumor recurrence if $Z < 1.24 \times 10^4 \delta_{VT}/a_{TZ} = 186$. The innate immune cells may indirectly cause tumor recurrence.

Table 3 reveals that the activation rates $a_{ZZ}$ and $a_{TZ}$ of resting immune cells and tumor specific adaptive immune cells, respectively, the source rate $s_{ZR}$ of resting immune cells, and death rates $\delta_{VT}$, $\delta_{ZR}$, and $\delta_Z$ of these immune cells are the parameters that affect the existence and stability of $E_3$. The remission equilibrium $E_3$ exists and is stable if the activation rates $a_{ZZ}$, $a_{TZ}$, and $s_{ZR}$ are brought to the right endpoints and the death rates $\delta_{VT}$, $\delta_{ZR}$, and $\delta_Z$ are brought to the left endpoints of the plausible ranges of parameter values (Tables 2 and 3 of [38]). However, changes in only some of these parameter values cannot make $E_3$ a stable equilibrium indicating that a cure is almost impossible for an advanced cancer [26].

Figure 5(c) shows the cell dynamics for parameter values of $a_{TZ}$, $s_{ZR}$, $\delta_{ZR}$, and $a_{ZZ}$ taken to the extremes of the parameter ranges. The cell population for the tumor-specific adaptive immune cells $Y_T$ maintains at a level over $1.24 \times 10^4$ after the tumor cells are eliminated, and then it decreases with time. As the population level of $Y_T$ falls below this threshold level, the balance between tumor cell proliferation and T cell-mediated killing is broken and tumor relapse occurs. The tumor relapses about every 575 days which is a longer period than that shown in Fig. 5(b). Strengthen an immune system or enhance immune activity may prolong remission.

5.3. **Bifurcation analysis of the model with low antigenicity.** When a positive equilibrium exists, it satisfies the third equation in (21) and the second equation in (22). Using the baseline parameter values leads to $T_I < \delta_{VT} h_{TI} / (a_{AT} - \delta_{VT}) = 2847$ and $T_S + T_I < \delta_{VT} h_{TI} / (a_{AT} - \delta_{VT}) = 8265$, which represents a very small
Figure 5. (a) Bifurcation diagram using $\beta$ as the bifurcation parameter, where all other parameter values are the same as in (23). The dashed lines at $\log(T_S) = -1$ (blue), $\log(T_S) = 8.7124$ (green), and $\log(T_S) = 3.9172$ (cyan) represent the unstable equilibria $E_0$, $E_1$, and $E_2$, respectively. The black dashed line between $E_2$ and $E_0$ represents an unstable positive equilibrium. (b) and (c) are the time series of cell populations for $\beta = 6 \times 10^{-8}$. The other parameter values in (b) are same as those in (a) while $a_{TZ} = 2.4$, $s_{ZR} = 4.8$, $\delta_{ZR} = 1.658$, and $a_{ZZ} = 4.8$ in (c). The tick label -1 on the vertical axis represents a population level less than 0.1.

tumor. Section 5.2 shows that the system with baseline parameter values does not possess a stable positive equilibrium. In this subsection, $a_{AT}$ and $\beta$ are used as bifurcation parameters, and Fig. 6(a) presents a two-dimensional bifurcation diagram. The equilibria are shown in the regions where they are stable. Several bifurcations occur for the system with a tumor of low antigenicity.

From Theorem 4.1, $E_1$ is globally asymptotically stable in the region where it is locally stable. The system has a low viral infection rate and low antigenicity in this region. A part of this region has a viral infection rate $\beta$ below the plausible range suggested in [38]. Oncolytic viral therapy is ineffective due to low viral infection rates, and low antigenicity is known to allow the tumor to escape the
immune response and continue to grow [2]. Under this circumstance, any small tumor can grow and reach its carrying capacity. From Theorem 4.2 and Proposition 3.1(b)(ii), \( E_2 \) is globally asymptotically stable in the region bounded by \( a_{AT} = \delta_Y T (1 + h_T / C_T) = 9.00047 \times 10^{-3} \) (a transcritical bifurcation), \( \beta < \omega / b_T C_T \) (a transcritical bifurcation), and \( a_{AT} = \delta_Y (C_T + h_T) / (C_T - h_T) = 9.00094 \times 10^{-3} \) (a Hopf bifurcation). However, this region is too small to give any significant meaning of the changes in dynamics as parameter values vary over this region. No stable equilibrium exists for \( a_{AT} > 0.009 \) in the parameter domain, and the cell populations oscillate over time and the dynamics are similar to those shown in Section 5.2.

A positive equilibrium bifurcates from \( E_1 \) as the viral infection rate increases. Two stable positive equilibria, denoted by \( E_{51} \) and \( E_{52} \), may coexist. Two saddle-node bifurcations and one Hopf bifurcation occur in a very small range of \( \beta \) values (close to \( \beta = 8 \times 10^{-11} \)) as \( \beta \) increases. Fig. 6(b) shows a closer look at the region containing these bifurcations. Both \( E_{51} \) and \( E_{52} \) coexist in the region between the two saddle-node bifurcations when the second saddle-node bifurcation occurs before the Hopf bifurcation as \( \beta \) increases. Both \( E_{52} \) and a limit cycle coexist in the region in between the first saddle-node bifurcation and the Hopf bifurcation when the Hopf bifurcation occurs before the second saddle-node bifurcation.

Figure 6. (a) Bifurcation diagram using \( \beta \) and \( a_{AT} \) as the bifurcation parameters, where all other parameter values are the same as in (23). (b) A closer look at the bifurcation curves for \( \log(\beta) \in [-10.12, -9.97] \).

Figure 7(a) shows a bifurcation diagram using \( \beta \) as the bifurcation parameter with \( a_{AT} \) fixed at 0.005. Note that the parameter value presents a case of low tumor antigenicity. Stable equilibria exist with tumor population level close to its carrying capacity when the viral infection rate is small. The rectangle shown in Fig. 7(a) around \( \beta = 10^{-10} \) is magnified and shown in Fig. 7(b). A transcritical bifurcation occurs at \( \beta = 2.369 \times 10^{-11} \), two saddle-node bifurcations at \( \beta = 7.81 \times 10^{-11} \) and \( \beta = 7.83 \times 10^{-11} \), and one Hopf bifurcation at \( \beta = 8.12 \times 10^{-11} \). Positive equilibria, which have tumor sizes nearly equal to the carrying capacity, exist between the transcritical bifurcation and the saddle-node bifurcation. They also exist between
the saddle-node bifurcation and the Hopf bifurcation. In practice, these two positive equilibria can be considered the same as $E_1$.

A limit cycle (light blue curve) bifurcates from a stable equilibria via a Hopf bifurcation as shown in Fig. 7(b). The tumor size oscillates and remains large initially. The amplitude of the limit cycle increases as the viral infection rate increases. A fold bifurcation of limit cycles occurs giving birth to the other stable limit cycle (green curve) and an unstable limit cycle (not shown in the figure). Complete pictures near fold bifurcations of limit cycles have been carried out and studied in [5, 42]. It requires more complicated algorithms to compute the bifurcation as well as the amplitude and period of unstable limit cycles. The unstable limit cycles are not computed in this paper because they do not provide information about the asymptotic behavior of the system and it can be easily determined that the appearance and disappearance of limit cycles shown in Fig. 7(a) are via fold bifurcations of limit cycles. The other fold bifurcation of limit cycles occurs at $\beta = 9.5 \times 10^{-9}$ leading to the disappearance of the stable limit cycle (light blue curve). Both stable limit cycles coexist for $\beta \in (1.93 \times 10^{-9}, 9.5 \times 10^{-9})$.

Time series plots of stable limit cycles are provided in Figs. 8(a) and (b) for $\beta = 9.4 \times 10^{-9}$. Bistability exists for $\beta \in (1.93 \times 10^{-9}, 9.5 \times 10^{-9})$. Figure 8(a) shows an example of a short time regression. The tumor mass is reduced, and the tumor becomes microscopic but it grows back quickly. The tumor size oscillates with a short period of 28 days. The other limit cycle (Fig. 8(b)) shows a period of remission of 61 days, and the tumor size oscillates with a period of 113 days. Medical research studies have reported that the outcome of cancer treatment depends on the cancer type, size and extension of the tumor, and the strength of the patient’s immune response [36, 48]. Whether OVT is effective or not may depend on the initial state of a tumor when $\beta \in (1.93 \times 10^{-9}, 9.5 \times 10^{-9})$. 

Figure 7. (a) Bifurcation diagram using $a_{AT} = 0.005$ and $\beta$ as the bifurcation parameters, where all other parameter values are the same as in (23). The blue dashed curve represents unstable positive equilibria and the red curve represents stable equilibria. The light blue and green curves represent stable limit cycles. (b) A closer look at the rectangle shown in (a).
The limit cycle shown in Fig. 8(a) coincides with the unstable limit cycle at the fold bifurcation point where $\beta = 9.5 \times 10^{-9}$, and both stable and unstable limit cycles disappear. The limit cycle cannot persist and approaches the other limit cycle when $\beta = 9.5 \times 10^{-9}$ as shown in Fig. 8(c). The population dynamics in this case is similar to the population dynamics of the system with the baseline parameter values. A tumor with low antigenicity may be associated with poor outcome of OVT treatment when the infection rate $\beta$ is small. Oncolytic viral infection of tumor cells enhances antigenicity of the tumor [12]. As the infection rate $\beta$ increases, OVT can be effective in achieving tumor remission despite intrinsic low antigenicity of the tumor.

Figure 8. Time series of cell populations for $a_{AT} = 0.005$ and (a) $\beta = 9.4 \times 10^{-9}$, (b) $\beta = 9.4 \times 10^{-9}$, and (c) $\beta = 9.5 \times 10^{-9}$. The tick label -1 on the vertical axis represents a population level less than 0.1.

5.4. Bifurcation analysis with respect to burst size of infected cells and tumor growth rate. The previous examples suggest that the immune system is able to effectively and efficiently eliminate the infected cells. The viral burst size released from each infected cell can stimulate the growth of the virus population which in turn enhances viral infection. Figure 9(a) presents the bifurcation diagram
using burst size $b_T$ of infected cells and viral infection rate $\beta$ as bifurcation parameters. There are one transcritical bifurcation curve, one Hopf bifurcation curve, and four saddle-node bifurcation curves. Three branches of positive equilibria exist and are labeled as $E_{51}$, $E_{52}$, and $E_{53}$. Figure 9(b) shows the phase-parameter diagram using $\beta$ as the bifurcation parameter. Similar to the case shown in Fig. 6(b) the equilibrium $E_{51}$ has a tumor population level nearly equal to the carrying capacity. The equilibrium $E_{52}$ appears via a saddle-node bifurcation and coexists with $E_{51}$ until $E_{51}$ disappears via a saddle-node bifurcation. The equilibrium $E_{53}$ appears via a saddle-node bifurcation and coexists with $E_{52}$, and it loses its stability by giving birth to a stable limit cycle (green curve) via a Hopf bifurcation. The amplitude of the limit cycle increases rapidly, and the limit cycle become similar to that shown in Fig. 6(b). Figure 9(a) also shows that increases in either parameter values lead to the disappearance of $E_{51}$ and appearance of the limit cycle and promote the effectiveness of OVT treatment.

The bifurcations with respect to the tumor cell growth rate is also studied and shown in Fig. 9(c). Bifurcations occur only in a parameter domain with extremely small values in tumor cell growth rate $r_T$ and extremely large values in viral infection rate $\beta$. A positive equilibrium $E_5$ exists in the parameter domain. This equilibrium gains its stability as $\beta$ increases and then loses its stability as $\beta$ increases further. In fact the $\beta$ values shown in Fig. 9(c) are much larger than the largest value of the range of $\beta$ in [38]. The bifurcation in this case is not elaborated herein because the parameter domain is not meaningful and the bifurcation is not significant.

6. **Summary and conclusions.** Oncolytic virus therapy (OVT) is a cancer immunotherapy by injecting cancerous tissue with viruses that can infect and replicate in cancer cells and destroy these cells [11, 14, 32]. The therapy has a growing interest to cancer clinicians and researchers due to its selectivity for cancer cells over healthy cells [11, 14, 32]. Although OVT is an ideal anti-cancer therapy over various other treatment modalities, there is only limited success in cancer clinical studies. One major drawback of OVT is that the virus may be killed by the patient’s own immune system before it spreads throughout the tumor cell population [11, 14, 32]. Mathematical modeling therefore becomes an indispensable tool for understanding the various mechanisms among tumor, viruses, and the immune system interactions.

In this work, we present and study a mathematical model of ordinary differential equations developed by Storey et al. [38]. The system consists of tumor cells, oncolytic viruses, innate immune cells, and adaptive immune cells, where the adaptive immunity is separated into either anti-viral or anti-tumor immunity. In [38], the parameter values are obtained from various studies involving lethal brain tumor (GBM) and the authors perform global sensitivity analysis to reach their biological conclusions. Our goal here is to provide mathematical and numerical bifurcation analysis of the model.

We first verify that the resulting system is point dissipative and therefore the model is biologically sound. It is shown that the virus will be cleared off if the viral burst rate is smaller than its natural death rate. The susceptible tumor population will grow to its carrying capacity if the virus infection rate is small and the anti-tumor adaptive immunity’s proliferation rate is smaller than its death rate. In particular, if the tumor is less antigenic and has a small viral infection rate, then the tumor cannot be controlled even if it is small when detected. We derive sufficient conditions for which susceptible tumor cells can be eliminated for all sizes, provided
in Theorem 4.3. However, using the plausible parameter values given in [38] it is demonstrated numerically in section 5 that such a remission cannot be achieved.

The effect of the parameters on the outcome of OVT treatment as well as cell population dynamics is studied via bifurcation analysis. Numerical methods have been constructed to perform bifurcation analysis for the model. The parameter values used in [38] have been adopted as the baseline parameter values. No stable positive equilibrium exists for the model with the baseline parameter values. Oncolytic viruses are known to target cancer cells specifically, kill them directly, and simultaneously stimulate the immune system [32, 38]. Numerical computations illustrate that the tumor cells become infected as the tumor grows large and then

Figure 9. (a) Bifurcation diagram using $a_{AT} = 0.008$, $a_{AI} = 0.1$, and $\beta$ and $a_{AI}$ as the bifurcation parameters, where all other parameter values are the same as in (23). (b) Bifurcation diagram using $a_{AT} = 0.008$, $a_{AI} = 0.1$, $b_T = 50$, and $\beta$ as the bifurcation parameter. The blue dashed curve represents unstable positive equilibria and the red curve represents stable equilibria. The green curve represents stable limit cycles. (c) Bifurcation diagram using $\beta$ and $r_T$ as the bifurcation parameters, where all other parameter values are the same as in (23).
the OVs and immune cells can rapidly eliminate the infected cells leading to tumor remission. The OVT is effective, and the cancer can be cured if the remission equilibrium is stable. However, the stability of the remission equilibrium is almost impossible to attain for the parameter values in the plausible ranges. When the remission equilibrium is unstable, tumor relapse occurs within different time frames. Medical evidence also shows that it is difficult to achieve a complete cure for cancer [22, 26], and cancer recurrence after therapy is frequent [1]. The simulation also indicates that while the adaptive immune system may have a direct effect on tumor relapse, the innate immune system also play a role in the development of tumor relapse.

Other parameters are used as bifurcation parameters in the bifurcation analysis. Because immune cells eliminate infected tumor cells effectively, the viral infection rate becomes an important parameter for successful treatment. Multiple stable positive equilibria exist for a weakly antigenic tumor when the viral infection rate is small. Most of these positive equilibria represent tumors with sizes nearly equal to the carrying capacity. A small tumor population grows to its carrying capacity. As the viral infection rate increases, the OVT becomes effective despite an intrinsic low antigenicity of the tumor and the population dynamics are similar to those of the model with baseline parameter values. Fukuhara and Todo [12] have reported that infection of tumor cells by oncolytic viruses enhances tumor antigenicity. High burst size ($b_T$) of infected cells can enhance infection of tumor cells. A bifurcation diagram shows that $b_T$ in the plausible range is enough to produce sufficiently high viral infection of tumor cells.

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Appendix A. Jacobian matrices. In this appendix, we present some large size Jacobian matrices discussed in the main texts.

$$J(E_{32}) = \begin{pmatrix} 1 - 2\bar{T}_S - h_T & 0 & -\bar{T}_S \hline h_T + T_S & 0 \end{pmatrix}.$$ (24)

$$J(E_{33}) = \begin{pmatrix} 1 - \dot{Y}_T/h_T & 0 & 0 & 0 \hline 0 & \frac{szRaZZ}{\delta_Z} - \delta_Z & 0 & 0 \hline \frac{a_T T Y_T}{(h_T + T_S)^2} & a_T Z & 0 & 0 \hline 0 & a_V Z & 0 & -\delta_Y V \end{pmatrix},$$ (25)

where $*$ is an unimportant term.
For the full model (4) we have

\[
J(E_0) = \begin{pmatrix}
1 & 0 & 0 & 0 & 0 & 0 \\
0 - \delta_T & 0 & 0 & 0 & 0 \\
0 b_T \delta_T - \omega & 0 & 0 & 0 & 0 \\
0 & 0 & * s_{Z_R} a_{Z_0} - \delta_Z & 0 & 0 \\
0 & 0 & 0 & a_{T0} & -\delta_{Y_T} & 0 \\
0 & 0 & 0 & a_{VZ} & 0 & -\delta_{TV}
\end{pmatrix}
\]  
\tag{27}

and

\[
J(E_1) = \begin{pmatrix}
-1 & 0 & 0 & 0 & * & 0 \\
0 - \delta_T & 1 & 0 & 0 & 0 & 0 \\
0 b_T \delta_T - \omega & 0 & 0 & 0 & 0 \\
0 & 0 & * s_{Z_R} a_{Z_0} - \delta_Z & 0 & 0 & 0 \\
0 & 0 & 0 & a_{T0} & a_{AT} h_T + 1 - \delta_{Y_T} & 0 \\
0 & 0 & 0 & a_{VZ} & 0 & -\delta_{TV}
\end{pmatrix}
\]  
\tag{28}

where *s are unimportant terms.

In addition,

\[
J(E_2) = \begin{pmatrix}
\tilde{j}_{11} & -\tilde{T}_S & -\tilde{T}_S & 0 & \tilde{j}_{15} & 0 \\
0 - \delta_T - \tilde{Y}_T / h_T & 0 & 0 & 0 \\
0 b_T \delta_T - \omega & 0 & 0 & 0 \\
0 & 0 & * s_{Z_R} a_{Z_0} - \delta_Z & 0 & 0 \\
\tilde{j}_{51} & * & 0 & a_{T0} & 0 & 0 \\
0 & 0 & 0 & a_{VZ} & 0 & -\delta_{TV}
\end{pmatrix}
\]  
\tag{29}
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\[ J(E_3) = \begin{pmatrix} 1 - \hat{Y}_T/h_T & 0 & 0 & 0 & 0 \\ 0 & \hat{j}_{22} & 0 & 0 & 0 \\ 0 & b_T \delta_T \hat{j}_{33} & 0 & 0 & 0 \\ 0 & * & * & \hat{j}_{44} & 0 \\ * & * & 0 & a_{TZ} - \delta_Y T & 0 \\ 0 & * & 0 & a_{VZ} & 0 & -\delta_{TV} \end{pmatrix}, \]

where \( \hat{j}_{22} = -\delta_T = k_I \hat{Z}/(h_I + \hat{Z}) - \hat{Y}_T/h_I - \hat{Y}_V/h_I < 0 \), \( \hat{j}_{33} = -k_{VZ} \hat{Z} - k_{VA} \hat{Y}_V - \omega < 0 \) and \( \hat{j}_{44} = s_{ZR} a_{ZZ} / (\delta_{ZR} + a_{ZZ} \hat{Z})^2 - \delta_Z < 0 \). Finally,

\[ J(E_4) = \begin{pmatrix} \hat{j}_{11} - \hat{T}_S & -\hat{T}_S & 0 & \hat{j}_{15} & 0 \\ 0 & \hat{j}_{22} & \hat{T}_S & 0 & 0 \\ 0 & b_T \delta_T \hat{j}_{33} & 0 & 0 & 0 \\ \hat{j}_{42} & * & s_{ZR} a_{ZZ} \left( \delta_{ZR} + a_{ZZ} \hat{Z} \right)^2 - \delta_Z & 0 & 0 \\ \hat{j}_{51} & * & 0 & a_{TZ} \left( \hat{T}_S + h_T - \hat{Y}_T \right) / \left( h_T + \hat{T}_S \right) - \delta_Y T & 0 \\ 0 & 0 & 0 & a_{VZ} & 0 & -\delta_{TV} \end{pmatrix}, \]

where *s are unimportant entries.

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