COMBINED THERAPY FOR TREATING SOLID TUMORS WITH CHEMOTHERAPY AND ANGIogenic INHIBITORS

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(Communicated by Christina Surulescu)

Abstract. Anti-angiogenesis therapy has been an emerging cancer treatment which may be further combined with chemotherapy to enhance overall survival of cancer patients. In this paper, we investigate a system of nonlinear ordinary differential equations describing a microenvironment consisting of host cells, tumor cells, immune cells and endothelial cells while incorporating treatment combination with chemotherapy and anti-angiogenesis therapy. We perform a dynamical systems analysis demonstrating that our model is able to capture the three phases of cancer immunoediting: elimination, equilibrium, and escape. In addition, we present transcritical bifurcations for relevant parameter values that correspond to the progression from the elimination phase to the equilibrium phase. A range of medically useful tumor doubling times were simulated to determine how combined therapy affects the tumor microenvironment over the course of a 250 day treatment. This analysis found two additional bifurcation parameters that move the system of equations from the equilibrium phase to the elimination phase. We determine that the most important aspect of an effective therapy is the activation of the anti-tumor immune response.

1. Introduction. Cancer is one of the major causes of death in developed countries that continues to cause great hardship for humankind. The complex processes underlying its development continue to attract much attention from scientists across a variety of disciplines, and as such, research dedicated to understanding and combating cancer is one of the most active areas in biomedicine. The National Cancer Institute, an affiliate of the National Institutes of Health, estimates that 1.8 million Americans will be diagnosed with cancer in 2020 of which 606,520 will die [1].

Cancer is defined as a cluster of cells characterized by abnormal cell growth and division. Contrary to the ordinary cell cycle in which growth and division are regulated by a “crowding effect”, cancer cells can exhibit uncontrolled proliferation, a process initiated by gene mutations. Certain genes can convert a normal cell into a cancer cell by one of the following two ways [58]: A stimulating proto-onco
gene can become upregulated, or an inhibitory p53 gene can become downregulated. These gene mutations result in local proliferation of abnormal cells which form into a tumor that can invade the surrounding microenvironment.

During the initial avascular stage, a tumor relies on diffusion from nearby blood vessels to supply oxygen and nutrients for growth. This stage persists until the tumor grows to 1-3 mm\(^3\) after which oxygen can no longer reach certain regions, creating hypoxic areas within the tumor [7]. For further growth and progression, the tumor must begin the vascular stage, a multi-step process predominantly governed by tumor angiogenesis. During angiogenesis, various Tumor Angiogenic Factors (TAFs) are secreted to draw its own blood supply. The primary TAF is vascular endothelial growth factor (VEGF), which diffuses to nearby blood vessels and activates endothelial cells lining the blood vessel walls, stimulating their proliferation and migration towards the tumor and resulting in the creation of a new vascular network that extends from the surrounding macroenvironment into the tumor microenvironment. This new network provides the necessary oxygen and nutrients for continued tumor growth but also exacerbates the hypoxia within the tumor because of a poorly functioning vasculature [44].

The rapid division of tumor cells and the poor functioning of the vasculature lead tumors to have heterogeneous hierarchical divisions within the microenvironment. This leads to the tumor microenvironment being described as a “Russian doll” [33]. Different types of cancers have different hierarchical divisions and some examples of these divisions are hypoxic cores, proximal tumor microenvironment, and peripheral tumor environment [33]. The layers of the tumor themselves are also highly heterogeneous. Therefore, tumors can not be characterized by the growth rate of its individual cells since its macroscopic growth rate can change vastly over the course of its growth and development.

In addition to normal tissue and cancer cells, the tumor microenvironment includes immune cells, fibroblasts — both normal and carcinoma-associated, endothelial cells, chemokines, cytokines, various growth factors, and the extracellular matrix [38]. The interactions between cancer cells and these various components are complex, and thus, it is reasonable to consider the tumor microenvironment as an ecosystem in which cells are mainly competing for oxygen and nutrients. In particular malignant cancer cells are known to exploit the tumor microenvironment by modifying the metabolism of resident cells of the stroma, rendering it permissive rather than defensive, thus providing the opportunity for the tumor to invade nearby tissue [9].

While it has been well-established that the immune response can assist as well as hinder the development of a tumor [18], a complete understanding of the mechanisms governing this complex interplay is required in order to further develop cancer therapies. Cancer immunoediting is a concept developed within the last two decades that attempts to describe tumor immune interaction as a succession of three distinct phases [19], [30]. The first phase is elimination in which the tumor cells are eradicated by various cells from the innate and adaptive immune response. In the equilibrium phase, tumor cells develop a resistant population that enables the tumor to evade complete eradication and persist for several years. In the final phase referred to as escape, the tumor evades immune detection by a down-regulation or loss of the expression of tumor antigens; by an up-regulation of resistance against tumor cells and/or an increased expression of pro-survival genes; and by the development of an immunosuppressive tumor microenvironment [55].
Chemotherapy is a well-known and commonly used method of cancer treatment that involves cytotoxic agents preferentially targeting and killing cancerous cells, preventing them from undergoing further cell division and from metastasizing to other parts of the body. However, these agents are not perfectly targeting, and thus, attack not only the tumor cells but also the normal cells, leading to damaged tissues. Both theoretical and experimental research on chemotherapy have been carried out to determine an optimal dosing strategy that reduces the size of the tumor as much as possible while minimizing side effects due to the poor targeting.

Our understanding of the molecular mechanisms of angiogenesis has increased dramatically during the last few decades, leading to the development of anti-angiogenic therapy (AAT) that relies on blocking new blood vessel formation in tumors by targeting VEGF receptors. These agents typically contain a chemical structure which mimics the active sites of VEGF in an attempt to preferentially bind to receptor sites on endothelial cells, blocking VEGF from binding to these sites. However, as a monotherapy, AAT has produced modest benefit to the patient in preclinical and clinical trials [56], and thus, approval of its use must be in combination with chemotherapy.

One cancer that is currently being treated with combined chemotherapy and AAT is mesothelioma [29], an aggressive cancer caused primarily by occupational or environmental exposure to asbestos. Mesothelioma usually forms in the mesothelial lining of the pleural or peritoneal cavities and is known for having a very poor prognosis with less than 5% 5 year survival rate [43] and a median overall survival of only 9.5 months [5]. Although most Western nations have banned the use of asbestos, mesothelioma incidence is expected to increase in many countries in which it has not been banned yet [43]. In addition the development of rural areas has increased our exposure to carcinogenic fibers that are naturally present in the environment [13].

Mesothelioma is aggressive due to its ability to evade and inactivate the immune system [14]. Despite the infiltration of immune cells into the tumor microenvironment to compete for oxygen and key nutrients, mesothelioma cells can substantially affect T-cell function by releasing Glucose Transporter 1 to more efficiently access glucose. Similarly, mesothelioma cells can reduce the tryptophan levels in the microenvironment, which inhibits T-cell glycolysis and function by releasing L-type Amino acid Transporter 1 or Indoleamine-pyrrole 2,3-dioxygenase. Chu et. al [14] describe many additional pathways in which mesothelioma can successfully hinder the immune response, providing a rationale for the general ineffectiveness of immunotherapy in its treatment [43]. On the other hand, addition of bevacizumab to pemetrexed plus cisplatin significantly improved overall survival in mesothelioma with tolerable toxicity [62] and is now the standard treatment for the disease [23].

Mathematical models have been developed and analyzed in order to describe different aspects of solid tumor growth providing scientists with valuable insight into the mechanisms that control the development of solid tumors. Mathematical models have also provided answers to various questions that would otherwise be too costly to investigate experimentally [4], [11] [3]. A variety of mechanistic mathematical models involving ordinary differential equations (ODEs) have been developed to describe the evolution of tumor growth in its microenvironment, many of which consider the interaction of tumor and immune cells as a predator-prey system [54], [42], [32], [31]. Recent models incorporated other important effects on the tumor microenvironment such as interaction with healthy cells, administration of
various types of therapy, subdivision of the immune cells into multiple subpopulations, etc. [16], [45], [17], [40].

Other mathematical models proposed by researchers have described the dynamics of angiogenic signaling, the trigger that initiates tumor angiogenesis. Hahnfeldt et al. [26] developed and biologically validated a system of ODEs for the interactions between the primary tumor volume and the carrying capacity of the vasculature by conducting a series of experiments on mice with Lewis lung carcinoma. The carrying capacity of the vasculature in this model is defined to be the maximum tumor volume sustainable by the vascular network — a varying quantity predominantly determined by the volume of endothelial cells. Ledzewicz and Schattler [35], [36], [21], [34], [51], Benzekry et al. [6], and Glick and Mastroberardino [25] provided studies of the Hahnfeldt model or its variations [22], [20] in order to determine optimal drug and dosing protocols.

More recent models of the tumor microenvironment involving ODEs have combined tumor immune interactions and the idea that tumor growth depends upon the surrounding vasculature. Viger et al. [57] described the dynamics of angiogenic signaling by modifying the model in [16] to include a compartment for endothelial cells as a representative for the vasculature, an alternative to the time-dependent carrying capacity present in the Hahnfeldt model. Letellier et al. [37] extended the model in [57] by investigating the effects of combining chemotherapy and AAT. Pinho et al. [48] incorporated a combined therapy to explore how antiangiogenic agents may provide assistance to chemotherapy agents in reducing the volume of drug-resistant tumors. Their study, which included pharmacokinetics of the combined therapy, determined that the co-administration of antiangiogenic and chemotherapy agents can reduce tumor size more effectively compared to chemotherapy alone.

In this paper, we propose a new algebraically simple mathematical model that combines immune, tumor, endothelial, and host cell interactions. A dynamical systems analysis reveals three types of relevant solutions that correspond to the three distinct phases of cancer immunoediting. In addition, our model captures transcritical bifurcations of critical parameter values related to the tumor growth rate and its immunosuppressive capabilities. We use real cellular data from the literature in order to determine some of the parameter values, an important consideration as the use of mathematical modeling becomes more prevalent in the fight against cancer. The therapeutic approach we propose also uses biological data to determine the values for these effects. We believe this new mathematical model aids the field of cancer research by providing a critical step forward in establishing a closer relationship between mathematical modeling and clinical data.

2. Mathematical formulation. We formulate a new mathematical model describing the growth of a solid tumor under the effect of both angiogenesis therapy and chemotherapy treatments. In particular we develop a four dimensional system of nonlinear ordinary differential equations to describe the interactions between host, immune, tumor and endothelial cells that comprise the microenvironment surrounding a tumor. A description of each variable in the system is given below:

- $H(t)$: Host cell population in units of numbers of cells
- $I(t)$: Immune cell population in units of numbers of cells
- $T(t)$: Tumor cell population in units of numbers of cells
- $E(t)$: Endothelial cell population in units of numbers of cells
We believe it’s important to include host cells in any mathematical model that considers the tumor microenvironment to be an ecosystem because signaling interactions between tumor cells and resident cells play an important role in the evolution of the tumor [24], [28], [8]. All healthy cells in the tumor microenvironment that are not part of either the immune response or the vasculature comprise the host cell population. Based on general scientific knowledge of cancer and its development, we use assumptions described below in constructing the mathematical models with and without therapy.

2.1. Mathematical model without therapy.

1. Host Cell Dynamics: The host cells grow logistically with growth rate $r_h$ and carrying capacity $1/b_h$. Tumor cells compete with host cells for nutrients and oxygen via a mass action term with competition rate of $\alpha_{ht}$. This happens due to a tumor’s ability to grow new vasculature, rerouting nutrients such as glucose away from the host cells.

2. Immune Cell Dynamics: The response of the immune system is represented by a single “effector” cell population as done in [40]. We assume a healthy immune system in which a constant influx of T-cells given by $\sigma_i$ enters the microenvironment even in the absence of tumor cells. When tumor cells are present, immune cells are activated outside of the tumor microenvironment by the lymphatic system, and therefore, do not compete for nutrients with the other cells. The presence of the tumor both inhibits and stimulates the recruitment of immune cells, and we use the form $If(T)$ to model these effects where $f(T)$ is a quadratic function [54] in which the linear term represents stimulation using mass-action kinetics and the quadratic term represents inhibition where the inverse of the parameter $\beta_{it}$ represents a turning point from stimulatory to inhibitory in regard to the immune tumor interactions. Finally, the immune cells are assumed to be perfectly targeting and have a finite lifespan dying off at a constant rate of $\delta_i$.

3. Tumor Cell Dynamics: The tumor cells grow logistically where the growth rate $r_t$ is inversely proportional to tumor doubling time $\tau_t$ given in days according to

$$r_t = \frac{\ln 2}{\tau_t}.$$ 

The carrying capacity depends on endothelial cells [48] in the form of a linear function given by

$$\kappa(E) = K_{te} + \gamma_{te}E$$

where $K_{te}$ represents the maximum number of cells before the process of tumor angiogenesis begins. After angiogenesis occurs and vasculature has reached the tumor, the carrying capacity of the cancerous cells increases linearly as a function of the endothelial cell count. To account for leakiness of the vasculature that supplies nutrients to the tumor cells as well as the hypoxic regions and heterogeneity across the tumor microenvironment, we assume

$$\gamma_{te} < 1.$$ 

The immune response is effective at killing tumor cells upon interacting with each other with a killing rate of $\alpha_{ti}$.

4. Endothelial Cell Dynamics: The endothelial cells grow logistically with growth rate $r_e$ and carrying capacity $1/b_e$. Through angiogenesis the tumor increases the growth of endothelial cells by secreting VEGF, and thus, we include a
term proportional to the tumor cell count that contains an effective growth rate of $\rho_{et}$.

**Table 1. Values of all relevant parameters without therapy.**

| Parameter | Description | Value | Units | Source |
|-----------|-------------|-------|-------|--------|
| $r_h$     | Host cell growth parameter | $1.8 \cdot 10^{-1}$ | day$^{-1}$ | [40] |
| $r_t$     | Tumor growth parameter | $\frac{\ln(2)}{\tau_t}$ | day$^{-1}$ | estimated |
| $\tau_t$  | Tumor doubling time | $2 - 10$ | day | estimated |
| $r_e$     | Endothelial cell growth parameter | $2.15 \cdot 10^{-1}$ | day$^{-1}$ | [60] |
| $\rho_{et}$ | Tumor (VEGF) recruitment of endothelial cells | $9.22 \cdot 10^{2}$ | day$^{-1}$ | [25] |
| $\sigma_i$ | Influx of immune cells | $1.0 \cdot 10^4$ | cell day$^{-1}$ | [32] |
| $\delta_i$ | Immune cell natural death rate | $7.0 \cdot 10^{-3}$ | day$^{-1}$ | [50] |
| $b_h$     | Inverse of host cell carrying capacity | $1.0 \cdot 10^{-9}$ | cell$^{-1}$ | [40] |
| $\gamma_{te}$ | Tumor carrying capacity dependence parameter | $0.8$ | no units | estimated |
| $K_{te}$  | Tumor cell carrying capacity | $1.0 \cdot 10^6$ | cells | [25] |
| $b_e$     | Inverse of endothelial cell carrying capacity | $1.0 \cdot 10^{-7}$ | cell$^{-1}$ | [25] |
| $\alpha_{ht}$ | Host cell killing rate by tumor cells | $4.8 \cdot 10^{-10}$ | cell$^{-1}$ day$^{-1}$ | [40] |
| $\alpha_{it}$ | Immune cell response to tumor cell presence | $1.101 \cdot 10^{-7}$ | cell$^{-1}$ day$^{-1}$ | [40] |
| $\alpha_{it}$ | Linear immune cell inactivation rate by tumor cells | $2.8 \cdot 10^{-9}$ | cell$^{-1}$ day$^{-1}$ | [40] |
| $\beta_{it}$ | Quadratic immune cell inactivation rate by tumor cells | $3.2 \cdot 10^{-8}$ | cell$^{-1}$ day$^{-1}$ | [40] |

These assumptions lead to a system of differential equations given by

\[ \dot{H} = r_h H (1 - b_h H) - \alpha_{ht} HT \]  
\[ \dot{I} = \sigma_i + \alpha_{it} IT (1 - \beta_{it} T) - \delta_i I \]  
\[ \dot{T} = r_t T (1 - \frac{T}{K_{te} + \gamma_{te} E}) - \alpha_{ti} TI \]  
\[ \dot{E} = r_e E (1 - b_e E) + \rho_{et} T \]

The parameters of this system are presented in Table 1. We allow for the growth rate of the tumor cells to vary as a function of doubling time, which can vary drastically depending upon stage and type of cancer. The growth rate for endothelial cells $r_e$ is determined by fitting a curve to vasculature growth data taken from [60] where the carrying capacity $1/b_e$ is assumed to be very large. The angiogenesis recruitment rate for endothelial cells $\rho_{et}$ was calculated by transforming the Hahnfeldt model [26] from volume to number of cells with the conversion that a single endothelial cell can be considered a cylinder with volume between $7.85 \cdot 10^{-8}$ and $6.28 \cdot 10^{-7}$ mm$^3$ [41].
Table 2. Values of parameters for combined therapy.

| Parameter | Description                  | Value       | Units    | Source       |
|-----------|------------------------------|-------------|----------|--------------|
| $\xi_t$  | AAT effect on tumor carrying capacity | 8.9-10^{-1} | no units | estimated   |
| $\xi_e$  | AAT effect on endothelial cells | 9.088-10^{-1} | no units | estimated   |
| $\lambda_t$ | Clearance rate of AAT agent | ln(2) / $\tau_t$ | day^{-1} | [15]         |
| $\tau_t$ | Half life of AAT agent       | 0.833 - 19.6 day | [61] [27] |
| $\epsilon_h$ | Chemotherapy effect on immune cells | 4.999-10^{-2} | day^{-1} | estimated   |
| $\epsilon_i$ | Chemotherapy effect on tumor cells | 7.494-10^{-2} | day^{-1} | estimated   |
| $\epsilon_e$ | Chemotherapy effect on endothelial cells | 4.999-10^{-2} | day^{-1} | estimated   |
| $\lambda_t$ | Clearance rate of chemotherapy agent | ln(2) / $\tau_e$ | day^{-1} | [15]         |
| $\tau_e$ | Half life of chemotherapy agent | 0.417 - 2.08 day | [61]      |

2.2. Mathematical model with therapy. We now incorporate the combined effects of AAT and chemotherapy into our model. To simplify the analysis, we do not include the standard linear pharmacokinetics equations that describe the dynamics of the dose rates [52]. Instead, we identify the dose rates with the concentration of the agent by introducing chemotherapy parameters $\epsilon_k$ for $k = h, i, t, e$ and AAT parameters $\xi_j$ for $j = t, e$ and assume a clearance of the drug dose that decays exponentially [61] until the next dose is administered at which point the previous dose is set to zero. Thus, the modified system of ODEs contains time-dependent therapy parameters which are now described in detail.

We use mass action terms to represent the influence of the chemotherapy agent on the tumor microenvironment of the form

$$-\epsilon_h Q_h(t) H,$$
$$-\epsilon_i Q_i(t) T,$$
$$-\epsilon_e Q_e(t) E,$$

for the host, tumor, and endothelial cells, respectively, where

$$Q_n(t) = \begin{cases} 
  e^{-\lambda_e (t - q_{n-1})} & \text{if } q_{n-1} \leq t < q_n, \\
  0 & \text{otherwise},
\end{cases}$$

$$Q_e(t) = \sum_{n=1}^{N} Q_n(t).$$

$Q_e(t)$ incorporates the administration of $N$ doses of chemotherapy given at times $q_n = q_0, \ldots, q_{N-1}$ with clearance rate $\lambda_e$.

In regard to the effect of chemotherapy on the immune system, Wu [59] noted in their mouse study of tumor re-population that the presence of chemotherapeutic
agents – cisplatin, in this instance – increased the amount of T cells in the tumor microenvironment. Therefore, we include a positive mass action term of the form
\[ + \epsilon_t Q_e(t)I \] (10)
to model the stimulatory effect of chemotherapy on the immune system.

The primary targets of AAT are the stimulation receptors of the tumor vasculature. These inhibitors bind to these receptors preferentially in comparison to VEGF so that the vasculature will not grow towards the tumor. The goal of this is to cut off the tumor from necessary nutrients and oxygen provided by the vasculature. We incorporate this effect into our model by modifying the growth rate of the endothelial cells due to the presence of tumor cells into the form
\[ Z_{\xi_e}(t)\rho_{te}T \] (11)
where
\[ S_m(t) = \begin{cases} e^{-\lambda_{\xi_e}(t-s_m-1)} & \text{if } s_{m-1} \leq t < s_m, \\ 0 & \text{otherwise}, \end{cases} \] (12)
\[ S_{\xi}(t) = \sum_{m=1}^{M} S_m(t), \] (13)
\[ Z_{\xi_e}(t) = (1 - (1 - \xi_e)S_{\xi}(t)), \] (14)
and \( \xi_e < 1 \). \( S_{\xi}(t) \) incorporates the administration of \( M \) doses of AAT given at times \( s_m = s_0, \ldots, s_{M-1} \) with clearance rate \( \lambda_{\xi_e} \).

Liu [39] noted that in the presence of angiogenic inhibitors, a tumor only grows to 72% of the maximum volume of a control tumor without such inhibitors. This corresponds to a reduction in the carrying capacity dependent on endothelial cells, and therefore, the carrying capacity of the tumor cells becomes
\[ K_{te} + Z_{\xi_e}(t)\gamma_{te}E \] (15)
where
\[ Z_{\xi_e}(t) = (1 - (1 - \xi_e)S_{\xi}(t)) \] (16)
and setting \( \xi_t < 1 \) accounts for the reduction in tumor growth as noted in [39]. We note that
\[ \lim_{t \to \infty} Z_{\xi_e}(t) = \lim_{t \to \infty} Z_{\xi_t}(t) = 1 \]
so that the system returns to the model without therapy in the long run.

The resulting system with therapy is given by
\[ \dot{H} = r_h H (1 - b_h H) - 6_{hi} HT - \epsilon_h Q_e(t)H, \] (17)
\[ \dot{I} = \sigma_i + \alpha_{ii} IT (1 - \beta_{ii} T) - \delta_i I + \epsilon_i Q_e(t)I, \] (18)
\[ \dot{T} = r_t T \left(1 - \frac{T}{K_{te} + Z_{\xi_e}(t)\gamma_{te}E}\right) - \alpha_{ti} TI - \epsilon_i Q_e(t)T, \] (19)
\[ \dot{E} = r_e E \left(1 - b_e E + Z_{\xi_e}(t)\rho_{e}T - \epsilon_e Q_e(t)E. \right) \] (20)

Due to recent developments in the ability of these cytotoxic agents to be tumor-preferential targeting, we reduce the effect on host and endothelial cells by a factor of 1/2 in comparison with the effect on tumor cells [37] so that \( \epsilon_h = \epsilon_i = \epsilon_t/2 \). The values for \( \epsilon_t \) and \( \epsilon_i \) are calculated by simulating our model without therapy and determining the values that reproduce the results in [59], specifically, by increasing the number of immune cells present in the tumor microenvironment by 5% and
reducing the volume of the tumor, assumed to be proportional to the number of tumor cells, by 10%. Using a modified 2D system of only tumor and endothelial cells with AAT, we obtain $\xi_t$ and $\xi_e$ by iterating over values until $T^*$ was reduced by 72% in comparison to $T^*$ without therapy, matching the results observed in [39].

We calculate all chemotherapy and AAT parameters independently of each other by assuming the linear log-kill hypothesis [53], i.e., by setting $\lambda_e = \lambda_t = 0$ so that there is a constant presence of each agent at all times. This assumption leads to lower values for the chemotherapy parameters and larger values for the AAT parameters than would otherwise be calculated by including the exponential decay of each agent. The calculated values for all therapy parameters are listed in Table 2. It is worth mentioning that in the particular case of assuming a constant presence of each agent, the model with therapy can be reduced to the model without therapy in which the system parameters are modified by the effect of the combined therapy but remain constant. Thus, a linear stability analysis of the model without therapy or with continuously constant therapy yields the same results.

3. Linear stability analysis without therapy. The equilibrium solutions $E^* = (H^*, I^*, T^*, E^*)$ of our model without therapy are obtained by setting the equations given in (1)−(4) equal to zero and solving for $H$, $I$, $T$, and $E$. The Jacobian matrix of the system in (1)−(4) is given by

$$J(E^*) =
\begin{bmatrix}
    r_h(1 - 2b_h H^*) & -\alpha_h H^* & 0 & 0 \\
    0 & \alpha_i T^*(1 - \beta_i T^*) - \delta_i & \alpha_i I^*(1 - 2\beta_i T^*) & 0 \\
    0 & -\alpha_t T^* & r_t(1 - \rho_a(\gamma_e + \gamma_i E^*)^2 - \alpha_t I^*) & 0 \\
    0 & 0 & 0 & -r_e(1 - 2b_e E^*).
\end{bmatrix}
$$

which will allow us to perform a linear stability analysis.

We note that all relevant equilibrium solutions can be conveniently divided into two groups: those with and without tumor cells. We first consider the four tumor-free equilibrium solutions without therapy that exist for all values of the parameters and then examine equilibrium solutions in which the population of tumor cells is nonzero. We end this section with a discussion of transcritical bifurcations that occur as certain parameters vary.

3.1. Tumor-free equilibrium solutions. All tumor-free equilibrium solutions require the immune cell count to be $I^* = \sigma_i/\delta_i$. Three of these solutions are unstable states:

1. $E_1 = (0, \sigma_i/\delta_i, 0, 0)$ with eigenvalues

$$r_h, -\delta_i, r_t - \frac{\sigma_i \alpha t}{\delta_i}, r_e.$$

2. $E_2 = (1/b_h, \sigma_i/\delta_i, 0, 0)$ with eigenvalues

$$-r_h, -\delta_i, r_t - \frac{\sigma_i \alpha t}{\delta_i}, r_e.$$

3. $E_3 = (0, \sigma_i/\delta_i, 0, 1/b_e)$ with eigenvalues

$$r_h, -\delta_i, r_t - \frac{\sigma_i \alpha t}{\delta_i}, -r_e.$$


The stability of the equilibrium solution $E_4 = (1/b_h, \sigma_i/\delta_i, 0, 1/b_c)$ depends upon its environment as exhibited in the following theorem.

**Theorem 3.1.** The tumor-free equilibrium solution $E_4$ is stable if and only if the inequality

\[ r_t < \frac{\sigma_i \alpha_{it}}{\delta_i} \]  

(22)

is satisfied.

**Proof.** The linearization yields eigenvalues $-r_h$, $-\delta_i$, $r_t - \frac{\sigma_i \alpha_{it}}{\delta_i}$, and $-r_c$, and the result follows immediately. $\square$

This result demonstrates that if the tumor cell growth rate is below a certain threshold, then immune surveillance is capable of eradicating the tumor, supporting the current viewpoint that both the innate and adaptive immune responses can recognize and eliminate tumors \[10\], \[46\], \[49\]. Further, this threshold depends on the immune response due the presence of tumor cells, constant influx of immune cells, and death rate of immune cells.

### 3.2. Nonzero-tumor equilibrium solutions

For the nonzero-tumor equilibrium solutions, setting (1)–(4) equal to zero yields host, immune, and tumor cell counts in terms of the endothelial cell count given by

\[ H^* = \frac{1}{b_h} (1 - \frac{\alpha_{ht} T^*}{r_h}) = \frac{1}{b_h} (1 - \frac{r_c \alpha_{ht} E^* (b_c E^* - 1)}{r_h \rho_{ct}}) \]  

(23a)

\[ H^* = 0, \]  

(23b)

\[ I^* = \frac{r_t}{\alpha_{ti}} \left( 1 - \frac{T^*}{K_{te} + \gamma_{te} E^*} \right) = \frac{r_t}{\alpha_{ti}} \left( 1 - \frac{r_c E^* (b_c E^* - 1)}{\rho_{ct} (K_{te} + \gamma_{te} E^*)} \right) \]  

(24)

\[ T^* = \frac{r_c}{\rho_{ct}} E^* (b_c E^* - 1), \]  

(25)

where $E^*$ is a root of the following sixth degree polynomial equation

\[ A_6 E^6 + A_5 E^5 + A_4 E^4 + A_3 E^3 + A_2 E^2 + A_1 E + A_0 = 0 \]  

(26)

and

\[ A_6 = \frac{r_t b_c^2 r_c^3 \alpha_{it} \gamma_{it}}{\rho_{ct}^2 \alpha_{ti}} \]  

(27)

\[ A_5 = -\frac{r_t b_c^2 r_c^3 \alpha_{it} \gamma_{it} (3r_c + \rho_{et} \mu_{te})}{\rho_{ct}^3 \alpha_{ti}}, \]  

(28)

\[ A_4 = -\frac{r_t b_c r_c^2 \alpha_{it} \left( r_c \rho_{et} (b_c (\gamma_{it} \beta_{te} + 1) - 2 \gamma_{it} \mu_{te}) - 3 r_c \gamma_{it} \right)}{\rho_{ct}^3 \alpha_{ti} \alpha_{it}}, \]  

(29)

\[ A_3 = \frac{r_c r_t \alpha_{it} \left( r_c \rho_{et} (2b_c (\gamma_{it} \beta_{te} + 1) - \gamma_{it} \mu_{te}) + b_c \rho_{ct}^2 \mu_{te} - r_c^2 \gamma_{it} \right)}{\rho_{ct}^3 \alpha_{ti}}, \]  

(30)

\[ A_2 = \frac{r_c r_t \left( \rho_{et} (b_c (\delta_i + \alpha_{it} \beta_{te}) - \alpha_{it} \mu_{te}) - r_c \alpha_{it} (\gamma_{it} \beta_{te} + 1) \right)}{\rho_{ct}^2 \alpha_{ti}}, \]  

(31)

\[ A_1 = \frac{\rho_{et} \mu_{te} (\sigma_i \alpha_{ti} - \delta_i r_t) - r_c r_t (\delta_i + \alpha_{it} \beta_{te})}{\rho_{ct} \alpha_{ti}}, \]  

(32)

\[ A_0 = \beta_{te} \left( \sigma_i - \frac{\delta_i r_t}{\alpha_{ti}} \right). \]  

(33)
Clearly, there are six roots of (26) counting multiplicity, and thus, at most six biologically relevant equilibrium values for the endothelial cell count or twelve possible biologically relevant equilibrium solutions since the host cell count is either zero or nonzero as displayed in (23a)–(23b). By Descartes rule of signs, there is always the possibility of a positive root of (26) since \( A_6 > 0 \) and \( A_5 < 0 \), and any positive root of (26) must also yield positive values of host, immune, and tumor cell counts in \((23a)-(25)\). To this end, we present the following theorem.

**Theorem 3.2.** Given a positive root \( E^* \) to (26), the equilibrium solution \( E^* = (H^*, I^*, T^*, E^*) \) is positive if and only if the following inequalities are satisfied:

\[
\frac{1}{b_c} < E^* < \frac{1 + \sqrt{1 + (4r_h b_c \rho_{et})/(r_c \alpha_{ht})}}{2b_c}, \quad (34)
\]

\[
E^* < \frac{r_c + \rho_{et} \gamma_{te} + \sqrt{(r_c + \rho_{et} \gamma_{te})^2 + 4r_c b_c \rho_{et} K_{te}}}{2r_c b_c}, \quad (35)
\]

**Proof.** The lower bound in (34) is clearly required for the tumor cell count given in (25) to be positive. Now consider the function

\[
f(E) = -b_c E^2 + E + \frac{r_h \rho_{et}}{r_c \alpha_{ht}}\]

The positivity of \( H^* \) is equivalent to the positivity of \( f(E) \), which occurs between its roots given by

\[
r_{1,2} = \frac{1 \pm \sqrt{1 + (4r_h b_c \rho_{et})/(r_c \alpha_{ht})}}{2b_c}, \quad (37)
\]

and the upper bound in (34) is now established. Similarly, the positivity of \( I^* \) is determined by the positivity of the function

\[
g(E) = -r_c b_c E^2 + (r_c + \rho_{et} \gamma_{te}) E + \rho_{et} K_{te}, \quad (38)
\]

The roots of (38) are given by

\[
r_{1,2} = \frac{r_c + \rho_{et} \gamma_{te} \pm \sqrt{(r_c + \rho_{et} \gamma_{te})^2 + 4r_c b_c \rho_{et} K_{te}}}{2r_c b_c}, \quad (39)
\]

and the positive root in (39) is evidently the upper bound in (35).

| Equilibrium Solution | Eigenvalues |
|----------------------|-------------|
| \( E_1 = (0, 1.429 \cdot 10^6, 0, 0) \) | \((-0.007, 0.18, 0.19, 0.215)\) |
| \( E_2 = (1.000 \cdot 10^5, 1.429 \cdot 10^6, 0, 0) \) | \((-0.18, -0.007, 0.19, 0.215)\) |
| \( E_3 = (0, 1.429 \cdot 10^6, 0, 1.000 \cdot 10^7) \) | \((-0.215, -0.007, 0.18, 0.19)\) |
| \( E_4 = (1.000 \cdot 10^5, 1.429 \cdot 10^6, 0, 1.000 \cdot 10^7) \) | \((-2.15, -0.18, -0.007, 0.19)\) |
| \( E_5 = (9.962 \cdot 10^5, 3.126 \cdot 10^6, 1.422 \cdot 10^6, 2.520 \cdot 10^8) \) | \((-10.62, -0.18, -0.0022 \pm 0.035)\) |
| \( E_6 = (9.204 \cdot 10^5, 3.045 \cdot 10^6, 2.986 \cdot 10^7, 1.137 \cdot 10^9) \) | \((-48.67, -0.17, -0.16, 0.16)\) |
| \( E_7 = (0, 1.48 \cdot 10^{-1}, 2.746 \cdot 10^{10}, 3.432 \cdot 10^{10}) \) | \((-67464.4, -14756.4, -13, -0.17)\) |

The nonzero tumor equilibrium solutions cannot be determined algebraically, and thus, we perform a numerical investigation using Mathematica, which also allows us to check linear stability. If the default parameter values in Table 1 and a tumor doubling time of \( \tau_t = 2 \) days indicative of an aggressive tumor are substituted
In addition to the four tumor-free equilibrium solutions, there are three nonzero solutions into (1) representing a transcritical bifurcation at \( \alpha = 4 \).

Simulation results and discussion. Numerical simulations of the governing systems given in Eqs. (1)–(4) and Eqs. (17)–(20) are presented using the Python function ODE from the SciPy suite of numerical integrators for ODEs [2]. Within the host of ODE solvers for this suite, we utilize the LSODA method which is a real-valued variable-coefficient ODE solver with fixed-leading-coefficient implementation. LSODA automatically switches between the Adams method for solving non-stiff ODEs and backwards differentiation formulas (BDF) for solving stiff ODEs by utilizing information at the end of each step of the integration and then deciding which method is most efficient [47].

The default parameter values for this system are given in Table 1. We choose two different values of the tumor doubling time \( \tau_t \) that fall within the realistic range
of values [50]. The default initial conditions for our simulations are as follows:

\[
\begin{align*}
H(0) &= 1 \cdot 10^7, \\
I(0) &= 2.5 \cdot 10^6, \\
T(0) &= 1.2 \cdot 10^7, \\
E(0) &= 9.55 \cdot 10^7.
\end{align*}
\]  

(40)

Figure 1. Bifurcation diagram for tumor doubling time versus tumor cell count using default parameter values given in Table 1. A transcritical bifurcation occurs when \( \tau_t = 4.4069303 \) days.

Figure 2. Bifurcation diagram for immune cell killing rate of tumor cells versus tumor cell count using default parameter values given in Table 1 and \( \tau_t = 10 \) days. A transcritical bifurcation occurs when \( \alpha_{ti} = 4.852032 \cdot 10^{-8} \) cell\(^{-1}\) day\(^{-1}\).
4.1. Simulations without therapy. Theorem 3.1 provides conditions in which the immune response is capable of eliminating the tumor without therapy. In particular, if the tumor growth rate is low, the immune system is able to eliminate the tumor for the default parameter values and initial conditions used in our study. As the tumor growth rate increases, the immune system is still effective at controlling tumor growth although the tumor cannot be eliminated. Furthermore, if we modify the initial conditions by decreasing the number of initial immune cells, our model exhibits tumor escape, the phase of immunoediting in which the tumor evades the immune system and grows to a level that cannot be treated. In this subsection, we modify the initial conditions and tumor doubling time to allow our system without therapy to illustrate all three of these scenarios.

When the tumor growth rate is low and the initial number of immune cells is sufficient, the immune system is able to eradicate the tumor cells without a need for therapy. This process of elimination is shown in Fig. 3 where the system approaches the tumor-free equilibrium solution $E_4$ given in Table 4. Since $\tau_t$ satisfies the inequality (22) of Theorem 3.1, $E_4$ is stable, and thus, a realistic outcome. Fig. 4 represents a case where the immune system is ineffective at fighting off the tumor. Here the tumor inactivates the immune cells and beats out the host cells for oxygen and nutrients so that it can grow to a carrying capacity $K + \gamma E^*$ that depends on the equilibrium endothelial cell count. In this instance, the system approaches the equilibrium solution $E_7$ of Table 4, which corresponds to tumor escape and is numerically determined to be stable.

In Fig. 5 the immune cells are able to prevent the tumor from growing out of control, but the tumor growth rate is large enough so that it can replace cells that are
Figure 4. Numerical simulation using parameter values given in Table 1 with $\tau_t = 10$ days, $I(0) = 1.0 \cdot 10^5$ cells and all other initial conditions given in (40). The immune response is unable to eliminate the tumor so that the system approaches the equilibrium solution $E_7$ given in Table 4.

Figure 5. Numerical simulation using parameter values given in Table 1 with initial conditions given in (40) and $\tau_t = 2$ days. The immune response is unable to eliminate the tumor so that the system approaches the equilibrium solution $E_6$ in Table 3, which corresponds to the equilibrium phase of immunoediting.
Numerical simulations using parameter values given in Table 1 and initial conditions given by Eqn. (40), where $\tau_t = 2$ days and the system is simulated for 250 days, showing a ‘zoomed-in’ view of Fig. 5.

Eventually the system approaches the equilibrium solution $E_6$ in Table 3, a scenario representing the equilibrium phase of immunoediting in which the tumor volume is small but nonzero.

4.2. **Realistic treatment timelines.** A full simulation using initial conditions given in (40) and the protocol outlined in [12] and [29] is performed for the model with therapy given by Eqns. (17)–(20). This corresponds to administering one dose of chemotherapy agents and one dose of AAT agents every three weeks for 4 cycles [12], [29]. The system is then allowed to recover for 7 days, after which an additional 2 cycles of therapy are administered before the system comes to rest at the end of 250 days.

This protocol is implemented mathematically via Eqns. (8)–(9) and (12)–(13) where $N = M = 6$ and $q_n = s_m = 0, 21, 42, 63, 91, 112, 250$. We assume a clearance of the drug dose that decays exponentially [61] until the next dose is administered at which point the previous dose is set to zero. We choose the tumor doubling time to be below the bifurcation value so that tumor elimination is not a possible scenario without therapy in order to assess the efficacy of the combined therapy.

In Fig. 6, the system without therapy shows an immune response that is effective at killing cancer cells, but the cancer cells are able to grow again near the end of the simulation. This system with initial conditions given in (40) and $\tau_t = 2$ days will eventually approach the equilibrium solution $E_5$ given in Table 3 as illustrated in Fig. 5. This shows that a healthy immune system may provide tumor control for fast growing cancers, such as late stage mesothelioma, under the right conditions without treatment.

Fig. 7 shows that the addition of combined therapy boosts the immune response enough to completely eradicate the cancer. There are six cycles of therapy applied
Figure 7. Numerical simulations for the system undergoing 6 cycles of combined chemoangiogenesis therapy described in Sect. 4 using initial conditions given in Eqn. (40). We set \( \tau_\epsilon = 1.25 \) days, \( \tau_\xi = 19.6 \) days, and \( \tau_t = 2 \) days, and all other parameter values as listed in Tables 1–2.

with a seven day rest period after cycle four, the effects of which are most apparent in the plots for host and immune cells which oscillate out of phase due to the administration of chemotherapy agents at times specified in the protocol before approaching equilibrium values given in E4 in Table 3.

4.3. Analysis of chemotherapy effects on immune system. Eqn. (18) was constructed under the assumption that the increase of immune cells noted in [59] were effective at combating the tumor. The reality is much more complicated than that. The presence of immune cells in the tumor microenvironment does not necessarily correspond to immune cells fighting back the cancer. Even the presence of regulatory T cells or CTLA-4 cells may not actually be able to fight back mesothelioma once they are inside the tumor. Chu [14] discusses many ways in which mesothelioma is able to resist the body’s immune response. Therefore, two additional scenarios regarding the effects of chemotherapy on the immune response are investigated:

1. Chemotherapy does not improve the immune response to the tumor so that \( \epsilon_i = 0 \).
2. Chemotherapy hurts the immune response by damaging CTLA-4 and regulatory T cells before they infiltrate the tumor. We make the assumption that chemotherapy hurts the tumor preferentially so that \( \epsilon_t = -\frac{\epsilon_i}{2} \).

Fig. 8 represents Case 1 in which chemotherapy has no effect on the immune system. In this instance, the initial spike of the tumor cells is roughly 30% larger than the initial spike in Fig. 7 and the tumor cells are not fully eliminated, leading to a second spike at the end of the simulation. The therapy also exhibits some
Figure 8. Numerical simulation for the system in which chemotherapy has no affect on the immune system using initial conditions given in (40). We set $\epsilon_i = 0$, $\tau_\epsilon = 1.25$ days, $\tau_\xi = 19.6$ days, $\tau_\xi = 2$ days, and all other parameter values as listed in Tables 1–2.

tumor control, lowering the magnitude of the first peak by 25%. Additionally, the therapy pushes the system towards the equilibrium solution $E_6$ faster than the case of no therapy as evidenced in Fig. 6.

Case 2, in which chemotherapy adversely effects the immune system, is represented in Fig. 9. The chemotherapy allows the tumor to grow 25% larger by the first peak than seen in Fig. 6 by damaging the immune system early on. Although the system still approaches $E_6$ after the therapeutic effects decay away, there is the potential that the increased volume of the initial peak has pushed the cancer into a stage where metastases could occur, increasing the mortality of the patient.

4.4. Sensitivity analysis of half life of drugs. The half life of a chemotherapy agent and an angiogenesis inhibitor depends on the drug being used, the metabolism of the patient, and a variety of other factors. It is therefore necessary to consider how sensitive the model proposed is to the effective half life of each drug. To this end, the half life values, $\tau_\epsilon$ and $\tau_\xi$, are varied to the extreme of each range and the effects on the system are analyzed. Since the results of Sect. 4.3 show that the effect of chemotherapy on the immune system will directly affect the outcome of the therapy on the tumor remission, we only consider the immune and tumor cell counts in our analysis.

Fig. 10 illustrates the effects of the biological half life of the chemotherapy and AAT on the system by plotting the immune and tumor cell counts for various values of $\tau_\epsilon$ and $\tau_\xi$. The combined therapy approach described in this paper is modeled such that the AAT cannot kill the tumor on its own — it can only reduce the size of the tumor. Therefore, the fact that the tumor grows back for a quickly decaying chemotherapy, as seen in (a) and (c) of Fig. 10, is to be expected. On the other hand, if the chemotherapy agents decay slowly, then the combined therapy is capable of
Figure 9. Numerical simulation for the system in which chemotherapy has an adverse affect on the immune system at half the effectiveness as the tumor using initial conditions given in (40). We set $\epsilon_i = -\frac{\epsilon_t}{2}$, $\tau_\epsilon = 1.25$ days, $\tau_\xi = 19.6$ days, $\tau_t = 2$ days, and all other parameter values as listed in Tables 1−2. The tumor has a second peak early on that is not seen in Figs. 6−8, indicating that chemotherapy which harms the immune system makes the therapy more harmful to the patient than no therapy at all.

Figure 10. Numerical simulations of the system with therapy for (a) $\tau_\epsilon = 0.417$ days and $\tau_\xi = 0.833$ day, (b) $\tau_\epsilon = 2.08$ days and $\tau_\xi = 0.833$ days, (c) $\tau_\epsilon = 0.417$ days and $\tau_\xi = 19.6$ days, (d) $\tau_\epsilon = 2.08$ days and $\tau_\xi = 19.6$ days.
driving the system to the tumor-free equilibrium solution as can be seen in Fig. 10b and Fig. 10d. Moreover, an increased presence of AAT decreases the tumor carrying capacity as seen in Eqn. (19), and so, for a fixed decay rate of chemotherapy agents, we expect the system to approach the tumor-free equilibrium solution at an earlier time for AAT agents that decay more slowly. However, Fig. 10b and Fig. 10d both depict a system that approaches the tumor-free equilibrium solution in the same amount of time, estimated to be $t^* = 103.9$ days, despite a 23-fold increase in the half life of the AAT. These results lead us to conclude that for the AAT to be effective, there must be some critical half life for the chemotherapy, $\tau^c$, that drives the system to the tumor-free equilibrium solution.

To determine an approximate value of $\tau^c$, we analyze a system with only chemotherapy that iterates through values of $\tau_c$ to find $\tau^c_{\text{CM}}$, which we define to be the minimum biological half-life of the chemotherapy agent that makes the tumor cell count go to zero

$$\tau^c = \min \{\tau_c, T^* \to 0\}. \quad (41)$$

This metric becomes satisfied for

$$\tau^c_{\text{CM}} = 1.075 \text{ days}, \quad (42)$$

and is the upper bound on $\tau^c$.

**Proposition 4.1.** Given that there is a bifurcation, the bifurcation value $\tau^c$ depends on the decay rate of AAT, and thus an upper bound for the bifurcation will necessarily be the value when no AAT is administered, denoted by $\tau^c_{\text{CM}}$.

Justification: For $\tau^c_{\text{CM}}$ to be the upper bound on the bifurcation parameter $\tau^c$, the bifurcation value must be lower when AAT is considered in the simulation. To determine the value of $\tau^c$ with combined therapy, we simulate Eqns. (17)–(20) with therapy terms defined by Eqns. (5)–(15) as $\tau_\xi \to \infty$, which represents continuously constant AAT. Iterating through values of $\tau_c$ until Eqn. (41) is satisfied yields the bifurcation value

$$\tau^c_{\text{CM}} = 0.9421 \text{ days}. \quad (43)$$

Since the presence of continuously constant AAT has reduced the value of $\tau^c$, it is a lower bound, and thus $\tau^c_{\text{CM}}$ must necessarily be an upper bound.

The critical half life chemotherapy terms, $\tau^c_\xi$, for all other values of $\tau_\xi$, such as the range listed in Table 2, will therefore lie in the interval

$$0.9421 \leq \tau^c_\xi \leq 1.075, \quad (44)$$

where the left bound, $\tau^c_{\text{CM}}$, corresponds to $\tau_\xi \to \infty$ and the right bound, $\tau^c_{\text{CM}}$, corresponds to $\tau_\xi \to 0$.

5. **Conclusion.** We have presented new mechanistic mathematical models in terms of ordinary differential equations to describe the interactions within a tumor microenvironment with and without combined therapy. We have performed a dynamical systems analysis of all biologically relevant equilibrium solutions. Our analysis demonstrates that our model without therapy is able to capture the three phases of cancer immunoediting: elimination, equilibrium, and escape. In addition, we present transcritical bifurcations for the tumor doubling time and the immune cell killing rate of tumor cells that correspond to the progression from the elimination phase to the equilibrium phase.
We have run simulations of the model without therapy to validate our numerical algorithm by matching the results seen in Figs. 3–5 to the analytical results discussed in Section 3. Simulations were then run to analyze the system with therapy using realistic treatment timelines and protocol which revealed that the mathematical implementation of a combined therapy was sufficient at providing tumor suppression early in the therapy and tumor elimination by the end of the protocol. Fig. 9 showed that therapy can eliminate a tumor for the case in which chemotherapy boosts the immune system for parameter values and initial conditions that would otherwise lead to the equilibrium phase of immunoediting as seen in Figs. 7–8.

The sensitivity of the model to produce these results were then analyzed by first considering different ways in which the chemotherapy agents might affect the immune response to the tumor’s presence. It has been shown in Figs. 8–9 that if the chemotherapy agents either have no effect on or harm the immune system, then tumor elimination is no longer possible. In addition, Fig. 10 illustrated that the stability of the tumor-free equilibrium solution is insensitive to the biological half-life of AAT agents but is very sensitive to the biological half-life of chemotherapy agents resulting in a bifurcation. In particular, we found that there are upper and lower bounds on the bifurcation value $\tau_c^*$ where the upper bound corresponds to no administration of AAT and the lower bound corresponds to AAT having a continuously constant effect.

The models presented in this article demonstrated that, although the anti-tumor immune response is the most important aspect for tumor elimination, there are many other interesting aspects in the mathematical modeling of tumor-immune dynamics that can have a significant effect on the outcome, including the intrinsic growth rate of the tumor represented by the tumor doubling time, whether the effect of chemotherapy on the immune system represented by the parameter $\epsilon_i$ is helpful, hurtful or neutral, and the half-life corresponding to the decay of each type of therapy once it is administered. In future work, we plan on further investigating the apparent bifurcations associated with $\epsilon_i$ and $\tau$ that were found in the numerical simulations. In addition, since we took a neutral position on the hypothesis that normalization of the vasculature improves chemotherapy efficacy, we would like to include this feature in our model with therapy to assess patient outcomes for different scenarios related to this highly debated topic.

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Received April 2020; revised August 2020.

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