Research Article

Mathematical Modelling of the Inhibitory Role of Regulatory T Cells in Tumor Immune Response

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The immune system against tumors acts through a complex dynamical process showing a dual role. On the one hand, the immune system can activate some immune cells to kill tumor cells (TCs), such as cytotoxic T lymphocytes (CTLs) and natural killer cells (NKs), but on the other hand, more evidence shows that some immune cells can help tumor escape, such as regulatory T cells (Tregs). In this paper, we propose a tumor immune interaction model based on Tregs-mediated tumor immune escape mechanism. When helper T cells' (HTCs) stimulation rate by the presence of identified tumor antigens is below critical value, the coexistence (tumor and immune) equilibrium is always stable in its existence region. When HTCs stimulation rate is higher than the critical value, the inhibition rate of effector cells (ECs) by Tregs can destabilize the coexistence equilibrium and cause Hopf bifurcations and produce a limit cycle. This model shows that Tregs might play a crucial role in triggering the tumor immune escape. Furthermore, we introduce the adoptive cellular immunotherapy (ACI) and monoclonal antibody immunotherapy (MAI) as the treatment to boost the immune system to fight against tumors. The numerical results show that ACI can control TCs more, while MAI can delay the inhibitory effect of Tregs on ECs. The result also shows that the combination of both immunotherapies can control TCs and reduce the inhibitory effect of Tregs better than a single immunotherapy can control.

1. Introduction

Tumors can be benignant (not cancerous), premalignant (precancerous), and malignant (cancerous). Every year millions of people suffer with cancer and die from this disease throughout the world [1]. It is important to understand tumor's mechanisms of establishment and destruction, cell-mediate immunity with cytotoxic T lymphocytes (CTLs), and natural killer cells (NKs), generally called effector cells (ECs) that are cytotoxic to tumor cells (TCs), and play a basic role in immune response against tumors [2, 3]. Moreover, efficient antitumor immunity requires the action of helper T cells (HTCs), which can directly activate naive CD8⁺ T cells to differentiate into CTLs [4–6]. Recently, it has been reported that regulatory T cells (Tregs) can inhibit CTLs and promote the escape of TCs [7]. Tregs suppress immune cells, and when the war

between T cells and infection is over, the Tregs signal to stop [8]. Cancer immunotherapy fights against cancer by strengthening the body's immune system, but the involvement of Tregs inhibits the immune response and turns off the anticancer effect. Tregs inhibition is important in the dynamics of the tumor immune system, which is one motivation of this work.

Adoptive T cell immunotherapy (ACI) as a common immunotherapy involves injecting adoptive T cells directly into tumor patients [9–11]. Its advantages are good destruction of tumor and persistence, while its disadvantages are serious toxic and side effects. The monoclonal antibody immunotherapy (MAI) is the immune checkpoint inhibitor [12, 13], which has the advantage of removing the suppression state of the immune system and restoring the immune function of the body to TCs and the disadvantage of having serious immune-related adverse reactions.

Tregs have become an important target in tumor immunotherapy because of their contribution to tumor immune escape. Cytotoxic T lymphocyte antigen 4 (CTLA-4) is a marker that is expressed on the surface of activated T cells and transmits inhibitory signals in the immune response [14–16]. Blocking CTLA-4 can reduce the inhibitory activity of Tregs, and the anti-CTLA-4 humanized monoclonal antibody Ipilimumab and Tremelimumab are used to treat advanced melanoma and malignant mesothelioma, respectively [17]. Similar to CTLA-4, programmed death receptor 1 (PD-1) can also promote the activation and development of Tregs [18–21]. Blocking PD-1 can prevent the development of Tregs and prevent the conversion of HTC into Tregs [22]. Currently, OPDIVO (Nivolumab), an anti-PD-1 monoclonal antibody, has been approved by the US FDA for the treatment of melanoma, renal cell carcinoma, and non-small cell lung cancer [23–25]. Establishment of a mathematical model to study the immunotherapy on the reduction of Tregs inhibition has both theoretical and practical significance.

In order to describe the mechanisms of host's own immune response to against TCs, various types of mathematical models have been proposed [26–43]. The modelling of the tumor immune system described by ordinary differential equations (ODEs) has a long history, which can be traced back to the classic research of Stepanova in 1980 [26]. In 1994, Kuznetsov et al. established the famous two-dimensional ODEs model, postulating that tumor growth follows the Logistic growth pattern. They evaluated the parameters of the model by fitting experimental data from mice [27]. In 2003, Stolorongo-Costa et al. assumed that TCs follows the exponential growth pattern and constructed a two-dimensional ODEs model. They analyzed the basic properties of the model and provided conditions for stability of the tumor-free equilibrium, explaining its epidemiological significance [28]. In 2004, Galach simplified Kuznetsov's system to account for the effect of immune delay on the tumor immune system [29]. In 2014, Dong et al. constructed a three-dimensional ODEs model focusing on the effects of HTCs on the tumor immune system [4].

In 1998, Kirschner and Panetta generalized Kuznetsov-Taylor model and illustrated the dynamics between TCs, ECs, and IL-2. They firstly introduced ACI into their model which can explain both short-term tumor oscillations in tumor sizes as well as long-term tumor relapse [11]. In 2003, in order to study the role of cytokine therapy in the activation of the immune system, Stolorongo-Costa et al. introduced cycle therapy term $F\cos^2\omega t$ and established a cycle immunotherapy model. They obtained some thresholds of the frequency and intensity of immunotherapy [28]. In 2006, de Pillis et al. constructed the six-dimensional ODEs model to investigate the effects of combined chemotherapy and immunotherapy on tumor control. They briefly analyzed the nature of the model and discussed the optimal treatment using optimal control theory [30]. In 2008, Bunimovich-Mendrazitsky et al. established a pulsed differential equation model with Bacillus Calmette-Guerin tumor immunotherapy. They obtained the critical threshold and pulse frequency of BCG injection dose that could

successfully treat superficial bladder cancer [31]. In 2012, Wilson and Levy established a mathematical model containing Tregs. They studied the absence of treatment, vaccine treatment, anti-TGF treatment, and combination vaccine and anti-TGF treatment, as well as sensitivity analysis of some important parameters [8]. In 2018, Radunskaya et al. established a mathematical model with blood, spleen, and tumor compartments to study PD-L1 inhibitors in the role of tumor immunotherapy. The model was used to fit parameters with the experimental data. The results showed that increasing the resistance of PD-L1 doses can greatly improve the clearance rate of tumor [32].

This paper investigates the role of Tregs in the tumor immune system. Therefore, we incorporate the fourth population of Tregs into the previous system in [8]. For the mathematical simplicity, a bilinear term also has been used to describe the interactions between immune response and tumor. To our knowledge, HTCs can recognize TCs and promote the growth of ECs. And ECs can provide direct protective immunity by attacking TCs. When there are more HTCs and ECs, in order to maintain immune homeostasis, the body will produce corresponding Tregs to suppress ECs, and Tregs originating from both HTCs and ECs. Then, we establish a four-dimensional ODEs model described as below:

$$\begin{cases} \frac{dT(t)}{dt} = aT(t)(1 - bT(t)) - nE(t)T(t), \\ \frac{dE(t)}{dt} = pE(t)H(t) - qR(t)E(t) - d_1E(t), \\ \frac{dH(t)}{dt} = s_2 + k_2T(t)H(t) - d_2H(t), \\ \frac{dR(t)}{dt} = r_1E(t) + r_2H(t) - d_3R(t), \end{cases} \quad (1)$$

where $T(t)$, $E(t)$, $H(t)$, and $R(t)$ represent the populations of TCs, ECs, HTCs, and Tregs, respectively. The first equation describes the rate change of TCs population. The tumor follows logistic growth dynamics with growth rate a , and the maximum capacity is $1/b$. n represents the loss rate of TCs by ECs interaction. The second equation describes the rate change of the ECs population. d_1 is the mortality rate of ECs. p is the activation rate of ECs by HTCs, and q is the inhibition rate of Tregs on ECs. The third equation describes the rate change of the HTCs population, s_2 is birth rate of HTCs produced in the bone marrow, and HTCs have a natural lifespan of an average $1/d_2$ days. k_2 is HTCs stimulation rate by the presence of identified tumor antigens. The fourth equation gives the rate change of the Tregs population, r_1 and r_2 are the activation rates of Tregs by ECs and HTCs, respectively. d_3 represents per capita decay rate of Tregs. A diagram of the various interactions between these cell populations is shown in Figure 1.

We nondimensionalize model (1) by taking the following scaling:

FIGURE 1: A diagram of interactions among the different cell populations in model (1).

$$\begin{aligned}
 t &= \frac{\tau}{nT_0}, \quad T(t) = T_0 x(\tau), \quad E(t) = E_0 y(\tau), \quad H(t) \\
 &= H_0 z(\tau), \quad R(t) = R_0 u(\tau), \quad \alpha = \frac{a}{nT_0}, \quad \beta = bT_0, \\
 \rho &= \frac{p}{n}, \quad \omega_2 = \frac{k_2}{n}, \quad \theta = \frac{qR_0}{nT_0}, \quad \delta_1 = \frac{d_1}{nT_0}, \quad \delta_2 \\
 &= \frac{d_2}{nT_0}, \quad \delta_3 = \frac{d_3}{nT_0}, \quad \sigma_2 = \frac{s_2}{nT_0 H_0}, \quad \gamma_1 = \frac{r_1}{nR_0}, \quad \gamma_2 = \frac{r_2}{nR_0},
 \end{aligned} \tag{2}$$

and we choose the scaling $T_0 = E_0 = H_0 = R_0 = 10^6$. By replacing τ by t , we obtain the following scaled model:

$$\begin{cases} \frac{dx(t)}{dt} = \alpha x(t)(1 - \beta x(t)) - x(t)y(t), \\ \frac{dy(t)}{dt} = \rho y(t)z(t) - \theta y(t)u(t) - \delta_1 y(t), \\ \frac{dz(t)}{dt} = \sigma_2 + \omega_2 x(t)z(t) - \delta_2 z(t), \\ \frac{du(t)}{dt} = \gamma_1 y(t) + \gamma_2 z(t) - \delta_3 u(t), \end{cases} \tag{3}$$

with initial conditions

$$\begin{aligned}
 x(0) &= x_0 \geq 0, \\
 y(0) &= y_0 \geq 0, \\
 z(0) &= z_0 \geq 0, \\
 u(0) &= u_0 \geq 0.
 \end{aligned} \tag{4}$$

Here, x , y , z , and u denote the dimensionless densities of TCs, ECs, HTCs, and Tregs populations, respectively.

2. Model Analysis

2.1. Well Posedness of Model (3). The following proposition establishes the well posedness of model (3) with initial conditions (4).

Proposition 1. *The solutions $(x(t), y(t), z(t), u(t))$ of model (3) with initial conditions (4) are existent, unique, and nonnegative on the interval $[0, +\infty)$.*

Proof. Since the right-hand side of model (3) is completely continuous and locally Lipschitz on the interval $[0, +\infty)$, there exists a constant $\delta > 0$ such that the solutions $(x(t), y(t), z(t), u(t))$ of model (3) with initial conditions (4) are existent and unique on the interval $[0, \delta)$, where $0 < \delta \leq +\infty$ [44].

From model (3) with initial conditions (4), we obtain

$$\begin{aligned}
 x(t) &= x_0 e^{\int_0^t (\alpha(1-\beta(s)) - y(s)) ds} \geq 0, \\
 y(t) &= y_0 e^{\int_0^t (\rho z(s) - \theta u(s) - \delta_1) ds} \geq 0, \\
 z(t) &= z_0 e^{\int_0^t (\omega_2 x(\tau) - \delta_2) d\tau} + \sigma_2 \int_0^t e^{\int_s^t (\omega_2 x(\tau) - \delta_2) d\tau} ds \geq 0, \\
 u(t) &= u_0 e^{-\delta_3 t} + \int_0^t (\gamma_1 y(s) + \gamma_2 z(s)) e^{-\delta_3(t-s)} ds \geq 0.
 \end{aligned} \tag{5}$$

It is obvious to see that the solutions $(x(t), y(t), z(t), u(t))$ of model (3) with initial conditions (4) are nonnegative for all $t \geq 0$. The proof is complete. $\square$

2.2. Existence of Equilibria. In this section, we will study the existence of various equilibria for system (3). We set $(dx/dt) = 0$, $(dy/dt) = 0$, $(dz/dt) = 0$, and $(du/dt) = 0$ in system (3), and we have

$$\begin{cases} \alpha x(1 - \beta x) - xy = 0, \\ \rho yz - \theta yu - \delta_1 y = 0, \\ \sigma_2 + \omega_2 xz - \delta_2 z = 0, \\ \gamma_1 y + \gamma_2 z - \delta_3 u = 0. \end{cases} \tag{6}$$

Putting $x = 0$ and $y = 0$ yields the tumor-free and ECs-free equilibrium, namely,

$$P_0 = (x_0, y_0, z_0, u_0) = \left(0, 0, \frac{\sigma_2}{\delta_2}, \frac{\gamma_2 \sigma_2}{\delta_2 \delta_3}\right), \tag{7}$$

which always exists.

Putting $x = 0$ and $y \neq 0$ yields the tumor-free equilibrium, namely,

$$P_1 = (x_1, y_1, z_1, u_1) = \left(0, \frac{\delta_3(\rho \sigma_2 - \delta_1 \delta_2) - \gamma_2 \theta \sigma_2}{\theta \gamma_1 \delta_2}, \frac{\sigma_2}{\delta_2}, \frac{\rho \sigma_2 - \delta_1 \delta_2}{\delta_2 \theta}\right), \tag{8}$$

which exists when $\rho > \delta_1 \delta_2 / \sigma_2$ and $\theta < \delta_3 (\rho \sigma_2 - \delta_1 \delta_2) / \gamma_2 \sigma_2 \triangleq \theta_1$.

Putting $x = 1/\beta$ yields the tumor-dominant equilibrium, namely,

$$P_2 = (x_2, y_2, z_2, u_2) = \left(\frac{1}{\beta}, 0, \frac{\beta \sigma_2}{\beta \delta_2 - \omega_2}, \frac{\beta \gamma_2 \sigma_2}{\delta_3 (\beta \delta_2 - \omega_2)} \right), \quad (9)$$

which exists when $\omega_2 < \beta \delta_2 \triangleq \omega_2^*$.

Putting $x \neq 0$ and $x \neq 1/\beta$ and eliminating y, z , and u in (6), we have

$$F(x) = Ax^2 + Bx + C = 0, \quad (10)$$

where $A = -\alpha\beta\theta\gamma_1\omega_2 < 0$, $B = \theta\alpha\gamma_1(\omega_2^* + \omega_2) + \delta_1\delta_3\omega_2 > 0$, and $C = \delta_3(\rho\sigma_2 - \delta_1\delta_2) - \theta(\alpha\gamma_1\delta_2 + \gamma_2\sigma_2)$.

Then, we have the coexistence equilibrium

$$P^* = (x^*, y^*, z^*, u^*) = \left(x^*, \alpha(1 - \beta x^*), \frac{\sigma_2}{\delta_2 - \omega_2 x^*}, \frac{\alpha\gamma_1(1 - \beta x^*)(\delta_2 - \omega_2 x^*) + \gamma_2\sigma_2}{\delta_3(\delta_2 - \omega_2 x^*)} \right), \quad (11)$$

which exists when $x^* < \mu \triangleq \min\{(1/\beta), (\delta_2/\omega_2)\}$, where x^* is the positive root of (10).

Below, we consider the existence condition of P^* :

Case (1): $C \geq 0$, i.e., $\theta \leq \delta_3(\rho\sigma_2 - \delta_1\delta_2) / \alpha\gamma_1\delta_2 + \gamma_2\sigma_2 \triangleq \theta_0$.

Since $F(1/\beta) = \theta\alpha\beta\gamma_1\delta_2 + \delta_1\delta_3\omega_2 + C\beta/\beta > 0$ and $F(\delta_2/\omega_2) = \theta\alpha\gamma_1\delta_2 + \delta_1\delta_2\delta_3 + C > 0$, we have $1/\beta < x^*$ and $\delta_2/\omega_2 < x^*$, which contradicts with $x^* < \mu$. Hence, P^* does not exist in this case.

Case (2): $C < 0$, i.e., $\theta > \theta_0$.

Let $\Delta = B^2 - 4AC = 4\alpha\beta\gamma_1\theta\omega_2(\delta_3(\rho\sigma_2 - \delta_1\delta_2) - \theta(\alpha\gamma_1\delta_2 + \gamma_2\sigma_2)) + (\theta\alpha\gamma_1(\omega_2^* + \omega_2) + \delta_1\delta_3\omega_2)^2 = [\theta\alpha\gamma_1(\omega_2 - \omega_2^*) + \delta_1\delta_3\omega_2]^2 + 4\alpha\beta\theta\gamma_1\omega_2\sigma_2(\rho\delta_3 - \theta\gamma_2)$.

If $\Delta < 0$, then (10) does not have a positive root. Hence, P^* does not exist in this case.

If $\Delta = 0$, then (10) has one positive root x^* , where $x^* = \theta\alpha\gamma_1(\omega_2^* + \omega_2) + \delta_1\delta_3\omega_2 / 2\alpha\beta\theta\gamma_1\omega_2 > \omega_2^* + \omega_2 / 2\beta\omega_2 = 1/2((\delta_2/\omega_2) + (1/\beta)) \geq \mu$, which contradicts with $x^* < \mu$. Hence, P^* does not exist in this case.

If $\Delta > 0$, then (10) has two positive roots, where $x_+^* = \theta\alpha\gamma_1(\omega_2^* + \omega_2) + \delta_1\delta_3\omega_2 + \sqrt{\Delta} / 2\alpha\beta\theta\gamma_1\omega_2$ and $x_-^* = \theta\alpha\gamma_1(\omega_2^* + \omega_2) + \delta_1\delta_3\omega_2 - \sqrt{\Delta} / 2\alpha\beta\theta\gamma_1\omega_2$. Since $x_+^* > \theta\alpha\gamma_1(\omega_2^* + \omega_2) + \delta_1\delta_3\omega_2 / 2\alpha\beta\theta\gamma_1\omega_2 > \omega_2^* + \omega_2 / 2\beta\omega_2 = (1/2)((\delta_2/\omega_2) + (1/\beta)) \geq \mu$, which contradicts with $x^* < \mu$. If $x_-^* < \mu$, i.e., $F(1/\beta) = (\delta_1\delta_3\omega_2 + \beta\delta_2(\rho\sigma_2 - \delta_1\delta_2) - \theta\beta\gamma_2\sigma_2/\beta) > 0 \Rightarrow \theta < (\delta_1\delta_3\omega_2 + \beta\delta_3(\rho\sigma_2 - \delta_1\delta_2) / \beta\gamma_2\sigma_2) \triangleq \theta_2$ and $F(\delta_2/\omega_2) = \sigma_2(\rho\delta_3 - \theta\gamma_2) > 0 \Rightarrow \theta < \rho\delta_3/\gamma_2 \triangleq \theta_3$, there exists a unique coexistence equilibrium $P^* = (x^*, y^*, z^*, u^*) = (x^*, \alpha(1 - \beta x^*), \sigma_2 / (\delta_2 - \omega_2 x^*), \alpha\gamma_1(1 - \beta x^*)(\delta_2 - \omega_2 x^*) + \gamma_2\sigma_2 / \delta_3(\delta_2 - \omega_2 x^*))$, where $x^* = x_-^*$.

The existence conditions for each equilibrium are given in Table 1.

2.3. Stability of Equilibria. In order to investigate the local stability of the above equilibria P_0, P_1, P_2 , and P^* of system (3), we linearize the system and obtain Jacobian matrix at each equilibrium $\bar{P}(\bar{x}, \bar{y}, \bar{z}, \bar{u})$:

$$J(\bar{P}) = \begin{pmatrix} \alpha - 2\alpha\beta\bar{x} - \bar{y} & -\bar{x} & 0 & 0 \\ 0 & \rho\bar{z} - \theta\bar{u} - \delta_1 & \rho\bar{y} & -\theta\bar{y} \\ \omega_2\bar{z} & 0 & \omega_2\bar{x} - \delta_2 & 0 \\ 0 & \gamma_1 & \gamma_2 & -\delta_3 \end{pmatrix}. \quad (12)$$

The corresponding characteristic equation is

$$\det(J(\bar{P}) - \lambda I) = \begin{vmatrix} \alpha - 2\alpha\beta\bar{x} - \bar{y} - \lambda & -\bar{x} & 0 & 0 \\ 0 & \rho\bar{z} - \theta\bar{u} - \delta_1 - \lambda & \rho\bar{y} & -\theta\bar{y} \\ \omega_2\bar{z} & 0 & \omega_2\bar{x} - \delta_2 - \lambda & 0 \\ 0 & \gamma_1 & \gamma_2 & -\delta_3 - \lambda \end{vmatrix} = 0. \quad (13)$$

Theorem 1. System (3) always has one tumor-free and ECs-free equilibrium P_0 , which is unstable.

Proof. At P_0 , characteristic (13) becomes

$$(\lambda - \alpha)(\lambda + \delta_2)(\lambda + \delta_3) \left(\lambda + \frac{\theta\gamma_2\sigma_2 + \delta_1\delta_2\delta_3 - \rho\sigma_2\delta_3}{\delta_2\delta_3} \right) = 0. \quad (14)$$

It can be seen that one eigenvalue α is positive. Hence, P_0 is unstable. $\square$

Theorem 2. System (3) has one tumor-free equilibrium P_1 , when $\rho > \delta_1\delta_2/\sigma_2$ and $\theta < \theta_1$, which is locally asymptotically stable (LAS) if the inequality $\theta < \theta_0$ holds.

Proof. At P_1 , characteristic (13) becomes

$$\left(\lambda - \frac{\theta(\alpha\gamma_1\delta_2 + \gamma_2\sigma_2) - \delta_3(\rho\sigma_2 - \delta_1\delta_2)}{\theta\gamma_1\delta_2} \right) (\lambda + \delta_2)(\lambda^2 + \delta_3\lambda + \theta\gamma_1\gamma_2) = 0. \quad (15)$$

TABLE 1: The existence and stability conditions of each equilibrium.

	Existence conditions	Stability conditions
P_0	Always	Unstable
P_1	$\theta < \theta_1$	$\theta < \theta_0$
P_2	$\omega_2 < \omega_2^*$	$\theta > \theta_2$
P^*	$\theta > \theta_0 \begin{cases} (i): \omega_2 \leq \omega_2^*, \theta < \theta_2 < \theta_3 \\ (ii): \omega_2 > \omega_2^*, \theta < \theta_3 < \theta_2 \end{cases}$	(20)

Then, one root of characteristic equation is $-\delta_2 < 0$. It is easily noted that as $\delta_3 > 0$, $\theta\gamma_1\gamma_1 > 0$, so $\lambda^2 + \delta_3\lambda + \theta\gamma_1\gamma_1 = 0$ has solutions with negative real parts. Therefore, P_1 is LAS when $\theta(\alpha\gamma_1\delta_2 + \gamma_2\sigma_2) - \delta_3(\rho\sigma_2 - \delta_1\delta_2)/\theta\gamma_1\delta_2 < 0$, that is, $\theta < \theta_0$. $\square$

Theorem 3. System (3) has one tumor-dominant equilibrium P_2 , when $\omega_2 < \omega_2^*$, which is LAS if the inequality $\theta > \beta\delta_3(\rho\sigma_2 - \delta_1\delta_2) + \delta_1\delta_3\omega_2/\beta\gamma_2\sigma_2 \equiv \theta_2$ holds.

Proof. At P_2 , characteristic (13) becomes

$$(\lambda + \alpha)(\lambda + \delta_3) \left(\lambda - \frac{\omega_2 - \omega_2^*}{\beta} \right) [\lambda - (\rho z_2 - \theta u_2 - \delta_1)] = 0. \quad (16)$$

The three roots of characteristic equation are $\lambda_1 = -\alpha < 0$, $\lambda_2 = -\delta_3 < 0$, and $\lambda_3 = \omega_2 - \omega_2^*/\beta < 0$, if $\omega_2 < \omega_2^*$. So, P_2 is LAS when $\lambda_4 = \rho z_2 - \theta u_2 - \delta_1 = \rho\beta\sigma_2\delta_3 - \delta_1\delta_3(\omega_2^* - \omega_2) - \theta\beta\gamma_2\sigma_2/\delta_3(\omega_2^* - \omega_2) < 0$, which is equivalent to $\theta > \theta_2$.

At P^* , characteristic (13) becomes

$$\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 = 0, \quad (17)$$

where

$$\begin{aligned} A_1 &= \alpha\beta x^* + \delta_3 + \delta_2 - \omega_2 x^* > 0, \\ A_2 &= \theta\gamma_1 y^* + \alpha\beta(\delta_2 - \omega_2 x^*)x^* + (\alpha\beta x^* + \delta_2 - \omega_2 x^*)\delta_3 > 0, \\ A_3 &= \theta\gamma_1(\alpha\beta x^* + \delta_2 - \omega_2 x^*)y^* + \alpha\beta\delta_3(\delta_2 - \omega_2 x^*)x^* \\ &\quad + \rho\omega_2 x^* y^* z^* > 0, \\ A_4 &= \theta\alpha\beta\gamma_1(\delta_2 - \omega_2 x^*)x^* y^* + (\rho\delta_3 - \theta\gamma_2)\omega_2 x^* y^* z^*. \end{aligned} \quad (18)$$

Note that $\delta_2 > \omega_2 x^*$ and $\theta < \min\{\theta_2, \theta_3\}$ are necessary for the existence of P^* , then we have $A_4 > 0$. By the Routh–Hurwitz criterion, the roots of (17) have only negative real parts if and only if

$$\begin{aligned} A_1 > 0, A_2 > 0, A_3 > 0, A_4 > 0, A_1 A_2 \\ - A_3 > 0, A_1(A_2 A_3 - A_1 A_4) - A_3^2 > 0. \end{aligned} \quad (19)$$

Hence, we obtain the sufficient conditions for stability of P^* :

$$(H1): \delta_2 > \omega_2 x^*, \theta < \min\{\theta_2, \theta_3\},$$

$$\begin{aligned} (H2): A_1 A_2 - A_3 &= \theta\gamma_1(\alpha\beta x^* + \delta_2 - \omega_2 x^*)y^* \\ &\quad + \alpha\beta\delta_3(\delta_2 - \omega_2 x^*)x^* \\ &\quad - \rho x^* y^* z^* > 0, \end{aligned}$$

$$(H3): A_1(A_2 A_3 - A_1 A_4) - A_3^2 = B_1 \theta + B_2 > 0, \quad (20)$$

where

$$\begin{aligned} B_1 &= ((\alpha\beta x^* + \delta_2 - \omega_2 x^*)^2 \delta_3 + \alpha\beta x^* + \delta_2 - \omega_2 x^*) \delta_3^2 \\ &\quad - \rho\omega_2 x^* y^* z^* (\alpha\beta x^* + \delta_2 - \omega_2 x^*) \gamma_1 y^* \\ &\quad - (\alpha\beta x^* + \delta_2 - \omega_2 x^* + \delta_3)^2 (\alpha\beta\gamma_1(\delta_2 - \omega_2 x^*)x^* y^* \\ &\quad - \omega_2 \gamma_2 x^* y^* z^*), \\ B_2 &= [((\alpha\beta x^* + \delta_2 - \omega_2 x^*)^2 \delta_3 + \alpha\beta x^* + \delta_2 - \omega_2 x^*) \delta_3^2 \\ &\quad - \rho\omega_2 x^* y^* z^* (\alpha\beta\delta_3(\delta_2 - \omega_2 x^*)x^* + \rho\omega_2 x^* y^* z^*)] \\ &\quad - (\alpha\beta x^* + \delta_2 - \omega_2 x^* + \delta_3)^2 \rho\omega_2 \delta_3 x^* y^* z^*. \end{aligned} \quad (21)$$

$\square$

Theorem 4. System (3) has a unique coexistence equilibrium P^* , when $\omega_2 \leq \omega_2^*$, $\theta_0 < \theta < \theta_2$ or $\omega_2 > \omega_2^*$, $\theta_0 < \theta < \theta_3$ hold, and P^* is LAS, when conditions (20) are satisfied.

We summarize the above results in Table 1, where $\omega_2^* = \beta\delta_2$, $\theta_0 = \delta_3(\rho\sigma_2 - \delta_1\delta_2)/\alpha\gamma_1\delta_2 + \gamma_2\sigma_2$, $\theta_1 = \delta_3(\rho\sigma_2 - \delta_1\delta_2)/\gamma_2\sigma_2$, $\theta_2 = \beta\delta_3(\rho\sigma_2 - \delta_1\delta_2) + \delta_1\delta_3\omega_2/\beta\gamma_2\sigma_2$, and $\theta_3 = \rho\delta_3/\gamma_2$.

2.4. Numerical Simulations. In this section, we choose some suitable parameters in (3) to simulate numerically the theoretical conclusions obtained in the previous sections by using the Matlab software package MATCONT [45]. We select the following parameters' set [4]:

$$\begin{aligned} \alpha &= 1.636, \beta = 0.002, \delta_1 = 0.3743, \sigma_2 = 0.38, \\ \delta_2 &= 0.055, \rho = 0.48, \gamma_1 = 0.15, \gamma_2 = 0.2, \delta_3 = 0.25. \end{aligned} \quad (22)$$

Note that $\omega_2^* = \beta\delta_2 = 0.00011$. By calculations, we have

$$\begin{aligned}
\theta_0 &= \frac{\delta_3(\rho\sigma_2 - \delta_1\delta_2)}{\alpha\gamma_1\delta_2 + \gamma_2\sigma_2} = 0.452, \\
\theta_1 &= \frac{\delta_3(\rho\sigma_2 - \delta_1\delta_2)}{\gamma_2\sigma_2} = 0.5323, \\
\theta_3 &= \frac{\rho\delta_3}{\gamma_2} = 0.6, \\
\theta_2 &= \frac{\beta\delta_3(\rho\sigma_2 - \delta_1\delta_3) + \delta_1\delta_3\omega_2}{\beta\gamma_2\sigma_2} = 615.625\omega_2 + 0.5323.
\end{aligned} \tag{23}$$

And we find the stability region of $P^* = (x^*, y^*, z^*, u^*)$ (see Figure 2). P^* is LAS in regions **I** and **II**. P^* is unstable in region **III**.

Let us denote the point in $\theta - \omega_2$ plane as $Q_i = (\theta, \omega_2)$.

Case (a): we choose a point $Q_1 = (0.48, 0.0001)$ in the region **I**; then, system (3) has one interior equilibrium:

$$P_1^* = (77.6449, 1.38195, 8.0448, 7.265). \tag{24}$$

The eigenvalues of Jacobian matrix of (12) are

$$\begin{aligned}
&-0.4623, \quad -0.049151, \quad -0.01991 - 0.378i \text{ and} \\
&-0.01991 + 0.378i,
\end{aligned} \tag{25}$$

so P_1^* is stable, as shown in Figure 3(a).

Case (b): we choose a point $Q_2 = (0.455, 0.0004)$ in the region **II**; then, system (3) has one interior equilibrium:

$$P_2^* = (2.84485, 1.62669, 7.05506, 6.62006). \tag{26}$$

The eigenvalues of Jacobian matrix of (12) are

$$\begin{aligned}
&-0.0931 + 0.301i, \quad -0.0931 - 0.301i, \quad -0.0633 \\
&+ 0.0188i \text{ and } -0.0633 - 0.0188i,
\end{aligned} \tag{27}$$

so P_2^* is stable, as shown in Figure 3(b).

Case (c): we choose a point $Q_3 = (0.48, 0.000111)$ in the region **II**; then system (3) has one interior equilibrium:

$$P_3^* = (72.569, 1.39855, 8.094, 7.314). \tag{28}$$

The eigenvalues of Jacobian matrix of (12) are

$$\begin{aligned}
&-0.458, \quad -0.0491, \quad -0.0132 + 0.383i \text{ and } -0.0132 - 0.383i,
\end{aligned} \tag{29}$$

so P_3^* is stable, as shown in Figure 3(c).

Case (d): we choose a point $Q_4 = (0.48, 0.0004)$ in the region **III**; then, system (3) has one interior equilibrium:

$$P_4^* = (26.365, 1.54973, 8.54816, 7.76837). \tag{30}$$

The eigenvalues of Jacobian matrix of (12) are

$$\begin{aligned}
&-0.4328, \quad -0.0497, \quad 0.0509 + 0.416i \text{ and } 0.0509 - 0.416i,
\end{aligned} \tag{31}$$

so P_4^* is unstable, as shown in Figure 3(d).

Below, we perform numerically bifurcation analysis of x against θ for different values of ω_2 .

Case (1): we choose $\omega_2 = 0.0001 < \omega_2^* = 0.00011$ (see Figure 4(a)).

We obtain the following result.

Proposition 2. When $0 < \theta < \theta_0$, P_0 exists and is unstable, P_1 exists and is LAS, P_2 exists and is unstable, and P^* does not exist. When $\theta_0 < \theta < \theta_1$, P_0 exists and is unstable, P_1 exists and is unstable, P_2 exists and is unstable, and P^* exists and is LAS. When $\theta_1 < \theta < \theta_2$, P_0 exists and is unstable, P_1 does not exist, P_2 exists and is unstable, and P^* exists and is LAS. When $\theta > \theta_2$, P_0 exists and is unstable, P_1 does not exist, P_2 exists and is LAS, and P^* does not exist.

Case (2): we choose $\omega_2 = 0.0004 > \omega_2^* = 0.00011$ (see Figure 4(b)).

We obtain the following result.

Proposition 3. When $0 < \theta < \theta_0$, P_0 exists and is unstable, P_1 exists and is LAS, and P^* does not exist. When $\theta_0 < \theta < \theta_4$, where $\theta_4 = 0.4657$ is a Hopf bifurcation, P_0 exists and is unstable, P_1 exists and is LAS, and P^* exists and is LAS. When $\theta_4 < \theta < \theta_1$, P_0 exists and is unstable, P_1 exists and is unstable, and P^* exists and is unstable. When $\theta_1 < \theta < \theta_3$, P_0 exists and is unstable, P_1 does not exist, and P^* exists and is unstable. When $\theta > \theta_3$, P_0 exists and is unstable, P_1 does not exist, and P^* does not exist.

Consider the case where HTC's stimulation rate (ω_2) is low by the presence of identified tumor antigens ($\omega_2 < \omega_2^*$). When the inhibition rate of Tregs to ECs θ is lower than θ_0 , the solution of system (3) approaches P_1 implying that ECs can still effectively remove TCs. When $\theta_0 < \theta < \theta_2$, the solution of system (3) approaches P^* showing the coexistence of TCs and immune cells, which means that the patient can survive with tumors. When $\theta > \theta_2$, TCs escape the control of the immune system and develop into malignant tumors.

Next consider the case where HTC's stimulation rate (ω_2) is high by the presence of identified tumor antigens ($\omega_2 > \omega_2^*$). When $\theta < \theta_0$, the solution of system (3) approaches P_1 implying that TCs can be effectively removed by ECs. When $\theta_0 < \theta < \theta_4$, the solution of system (3) approaches P^* implying that TCs can still be controlled by the immune system. When $\theta > \theta_4$, the system has a Hopf bifurcation point and induces a limit cycle (see Figure 3(e)). In the biological sense, it can be understood that the number of TCs presents a periodic change.

FIGURE 2: Stability region of P^* and Hopf bifurcation curve in $\theta - \omega_2$ parameter plane.

FIGURE 3: The other parameter values are given in (22). (a) P_1^* (77.644, 1.381, 8.044, 7.265) is LAS, $\theta = 0.48$ and $\omega_2 = 0.0001$. (b) P_2^* (2.844, 1.626, 7.055, 6.62) is LAS, $\theta = 0.455$ and $\omega_2 = 0.0004$. (c) P_3^* (72.569, 1.398, 8.094, 7.314) is LAS, $\theta = 0.48$ and $\omega_2 = 0.000111$. (d) P_4^* (26.365, 1.549, 8.548, 7.768) is unstable, $\theta = 0.48$ and $\omega_2 = 0.0004$. (e) The 3D phase portrait depicts tumor cell, ECs, and Tregs, $\theta = 0.48$ and $\omega_2 = 0.0004$.

FIGURE 4: The bifurcation diagrams of x with respect to θ for different $\omega_2 = 0.0001$ and 0.0004 , respectively. The stable state is represented by the blue curve, and the unstable one corresponds to the red curve. The equilibria are $P_0(0, 0, z_0, u_0)$, $P_1(0, y_1, z_1, u_1)$, $P_2(500, 0, z_2, u_2)$, and $P^*(x^*, y^*, z^*, u^*)$ of system (3) (in order to distinguish P_0 from P_1 , we move P_1 up a little bit). (a) $\omega_2 = 0.0001$. (b) $\omega_2 = 0.0004$.

3. Treatment Model

In order to investigate well the effect of Tregs in tumor immune response under the treatment, we follow the way in [11] to introduce the constant treatment term s_1 into the second equation of (1). Since CTLA-4 and PD-1 can inhibit the development of Tregs and prevent the transformation of HTC's into Tregs [12], the effect of CTLA4 or PD-1 on Tregs can be considered. Then, we shall establish a five-dimensional ODEs model described as below:

$$\begin{cases} \frac{dT(t)}{dt} = aT(t)(1 - bT(t)) - nE(t)T(t), \\ \frac{dE(t)}{dt} = s_1 + pE(t)H(t) - qR(t)E(t) - d_1E(t), \\ \frac{dH(t)}{dt} = s_2 + k_2T(t)H(t) - d_2H(t), \\ \frac{dR(t)}{dt} = r_1E(t) + r_2H(t) - d_3R - mR(t)W(t), \\ \frac{dW(t)}{dt} = s_3 - d_4W(t), \end{cases} \quad (32)$$

where $W(t)$ represents the concentration of monoclonal antibody in human body at time t , s_1 represents the treatment term of introducing LAK and TIL into the region of tumor localization, m represents the inhibition rate of monoclonal antibody on Tregs, s_3 represents the amount of monoclonal antibody entering human body at time t , and d_4 represents the attenuation coefficient of monoclonal antibody.

We scale those new parameters in model (32) as follows:

$$W(t) = W_0 v(\tau), \sigma_1 = \frac{s_1}{nE_0 T_0}, \xi = \frac{mW_0}{nT_0}, \sigma_3 = \frac{s_3}{nW_0 T_0}, \delta_4 = \frac{d_4}{nT_0}, \quad (33)$$

and we choose the scaling $W_0 = 10^6$. By replacing τ by t , we obtain the following scaled model with treatment:

$$\begin{cases} \frac{dx(t)}{dt} = \alpha x(t)(1 - \beta x(t)) - x(t)y(t), \\ \frac{dy(t)}{dt} = \sigma_1 + \rho y(t)z(t) - \theta y(t)u(t) - \delta_1 y(t), \\ \frac{dz(t)}{dt} = \sigma_2 + \omega_2 x(t)z(t) - \delta_2 z(t), \\ \frac{du(t)}{dt} = \gamma_1 y(t) + \gamma_2 z(t) - \delta_3 u(t) - \xi u(t)v(t), \\ \frac{dv(t)}{dt} = \sigma_3 - \delta_4 v(t), \end{cases} \quad (34)$$

with initial conditions

$$\begin{aligned} x(0) = x_0 \geq 0, y(0) = y_0 \geq 0, z(0) = z_0 \geq 0, u(0) \\ = u_0 \geq 0, v(0) = v_0 \geq 0. \end{aligned} \quad (35)$$

Here, v denotes the dimensionless concentration of monoclonal antibody.

3.1. Model Analysis. By a similar proof of Proposition 1, we can obtain the well posedness of model (34) with initial conditions (35) as follows.

Proposition 4. *The solutions $(x(t), y(t), z(t), u(t))$ of model (34) with initial conditions (35) are existent, unique, and nonnegative on the interval $[0, +\infty)$.*

Next, we discuss the effect of three types of immunotherapy on tumors such as

Case I: ACI model ($\sigma_1 > 0, \sigma_3 = 0$)

Case II: MAI model ($\sigma_1 = 0, \sigma_3 > 0$)

Case III: combined immunotherapy model ($\sigma_1 > 0, \sigma_3 > 0$)

We set $dx/dt = 0, dy/dt = 0, dz/dt = 0, du/dt = 0$, and $dv/dt = 0$ in (34), and we have

$$\begin{cases} \alpha x(1 - \beta x) - xy = 0, \\ \rho yz - \theta yu - \delta_1 y + \sigma_1 = 0, \\ \sigma_2 + \omega_2 xz - \delta_2 z = 0, \\ \gamma_1 y + \gamma_2 z - \delta_3 u - \xi uv = 0, \\ \sigma_3 - \delta_4 v = 0. \end{cases} \quad (36)$$

3.1.1. ACI Model. When $\sigma_1 > 0$ and $\sigma_3 = 0$, we put $v = 0$ and (36) becomes

$$\begin{cases} \alpha x(1 - \beta x) - xy = 0, \\ \rho yz - \theta yu - \delta_1 y + \sigma_1 = 0, \\ \sigma_2 + \omega_2 xz - \delta_2 z = 0, \\ \gamma_1 y + \gamma_2 z - \delta_3 u = 0. \end{cases} \quad (37)$$

Putting $x = 0$ yields the tumor-free equilibrium, namely,

$$E_0 = (x_0, y_0, z_0, u_0) = \left(0, y_0, \frac{\sigma_2}{\delta_2}, \frac{\gamma_1 \delta_2 y_0 + \gamma_2 \sigma_2}{\delta_2 \delta_3}\right), \quad (38)$$

where $y_0 = -B + \sqrt{B^2 - 4AC}/2A$, $A = \theta\gamma_1\delta_2 > 0$, $B = \delta_1\delta_2\delta_3 + \theta\gamma_2\sigma_2 - \rho\sigma_2\delta_3$, and $C = -\sigma_1\delta_2\delta_3 < 0$. E_0 always exists.

Putting $x \neq 0$ and eliminating y, z , and u in (37), we have

$$\begin{aligned} F(x) &= C_3 x^3 + C_2 x^2 + C_1 x + C_0 \\ C_3 &= \theta\alpha^2\beta^2\gamma_1\omega_2 > 0, \\ C_2 &= -\theta\alpha^2\beta\gamma_1\omega_2 - \alpha\beta[\theta\alpha\gamma_1(\beta\delta_2 + \omega_2) + \delta_1\delta_3\omega_2] < 0, \\ C_1 &= \theta\alpha(2\alpha\beta\gamma_1\delta_2 + \alpha\gamma_1\omega_2 + \beta\gamma_2\sigma_2) \\ &\quad + \alpha\delta_3[\delta_1\omega_2 - \beta(\rho\sigma_2 - \delta_1\delta_2)] - \sigma_1\omega_2\delta_3, \\ C_0 &= \sigma_1\delta_2\delta_3 + \alpha\delta_3(\rho\sigma_2 - \delta_1\delta_2) - \theta\alpha(\alpha\gamma_1\delta_2 + \gamma_2\sigma_2). \end{aligned} \quad (39)$$

Case (a): if $F(0)F(\mu) = C_0F(\mu) < 0$ (where $\mu = \min\{1/\beta, (\delta_2/\omega_2)\}$, due to $F(+\infty) > 0$ and $F(-\infty) < 0$, then (39) has one positive root x^* in the interval $[0, \mu]$. Therefore, system (34) has a unique coexistence equilibrium:

$$E^* = (x^*, y^*, z^*, u^*) = \left(x^*, \alpha(1 - \beta x^*), \frac{\sigma_2}{\delta_2 - \omega_2 x^*}, \frac{\alpha\gamma_1(1 - \beta x^*)(\delta_2 - \omega_2 x^*) + \gamma_2\sigma_2}{\delta_3(\delta_2 - \omega_2 x^*)}\right). \quad (40)$$

We show the existence conditions of E^* in the following:

Case (1): $C_0 > 0, F(\mu) < 0$.

Since $C_0 > 0$, we have $\theta < \sigma_1\delta_2\delta_3 + \alpha\delta_3(\rho\sigma_2 - \delta_1\delta_2)/\alpha(\alpha\gamma_1\delta_2 + \gamma_2\sigma_2) \triangleq \theta_5$. Since $F(\mu) < 0$, we have the following two cases:

Case where $1/\beta < \delta_2/\omega_2$, i.e., $\omega_2 < \beta\delta_2$. Since $\mu = 1/\beta$, we have $F(\mu) = \delta_3\sigma_1(\beta\delta_2 - \omega_2)/\beta > 0$. That is a contradiction.

Case where $1/\beta > \delta_2/\omega_2$, i.e., $\omega_2 > \beta\delta_2$. Since $\mu = \delta_2/\omega_2$, we have $F(\mu) = \alpha\sigma_2(\beta\delta_2 - \omega_2)(\gamma_2\theta - \delta_3\rho)/\omega_2 < 0$ implying $\theta > \rho\delta_3/\gamma_2 = \theta_3$. If $\theta_5 \geq \theta_3$, i.e., $\sigma_1\delta_2\delta_3 + \alpha\delta_3(\rho\sigma_2 - \delta_1\delta_2)/\alpha(\alpha\gamma_1\delta_2 + \gamma_2\sigma_2) \geq \rho\delta_3/\gamma_2$, we have $\sigma_1 \geq \alpha(\alpha\rho\gamma_1 + \delta_1\gamma_2)/\gamma_2$, there exists E^* .

Case (2): $C_0 < 0, F(\mu) > 0$.

Since $C_0 < 0$, we have $\theta > \theta_5$. Since $F(\mu) > 0$, we have the following two cases:

Case where $1/\beta < \delta_2/\omega_2$, i.e., $\omega_2 < \beta\delta_2$. Since $\mu = 1/\beta$, we have $F(\mu) = \delta_3\sigma_1(\beta\delta_2 - \omega_2)/\beta > 0$, there exists E^* .

Case where $1/\beta > \delta_2/\omega_2$, i.e., $\omega_2 > \beta\delta_2$. Since $\mu = \delta_2/\omega_2$, we have $F(\mu) = \alpha\sigma_2(\beta\delta_2 - \omega_2)(\gamma_2\theta - \delta_3\rho)/\omega_2 > 0$ implying $\theta < \theta_3$. If $\theta_3 \geq \theta_5$, i.e., $\rho\delta_3/\gamma_2 \geq \sigma_1\delta_2\delta_3 + \alpha\delta_3(\rho\sigma_2 - \delta_1\delta_2)/\alpha(\alpha\gamma_1\delta_2 + \gamma_2\sigma_2)$, we have $\sigma_1 \leq \alpha(\alpha\rho\gamma_1 + \delta_1\gamma_2)/\gamma_2$, there exists E^* .

Case (b): If $F(0)F(\mu) = C_0F(\mu) > 0$, then (39) can have two positive roots x_1^* and x_2^* in the interval $[0, \mu]$, where x_1^* and x_2^* are the roots of (39). Therefore, system (34) can have two coexistence equilibria:

$$E_1^* = (x_1^*, y_1^*, z_1^*, u_1^*) = \left(x_1^*, \alpha(1 - \beta x_1^*), \frac{\sigma_2}{\delta_2 - \omega_2 x_1^*}, \frac{\alpha\gamma_1(1 - \beta x_1^*)(\delta_2 - \omega_2 x_1^*) + \gamma_2\sigma_2}{\delta_3(\delta_2 - \omega_2 x_1^*)}\right), \quad (41)$$

$$E_2^* = (x_2^*, y_2^*, z_2^*, u_2^*) = \left(x_2^*, \alpha(1 - \beta x_2^*), \frac{\sigma_2}{\delta_2 - \omega_2 x_2^*}, \frac{\alpha\gamma_1(1 - \beta x_2^*)(\delta_2 - \omega_2 x_2^*) + \gamma_2\sigma_2}{\delta_3(\delta_2 - \omega_2 x_2^*)}\right). \quad (42)$$

In the following, we show the existence condition of E_1^* and E_2^* .

Differentiating (39), we have

$$F'(x) = 3C_3x^2 + 2C_2x + C_1 = 0, \quad (43)$$

where $C_3 > 0$ and $C_2 < 0$. If $C_1 > 0$ and $\Delta \triangleq C_2^2 - 3C_1C_3 > 0$, then (43) has two positive roots $x_1^+ = -C_2 - \sqrt{\Delta}/3C_3$ and $x_2^+ = -C_2 + \sqrt{\Delta}/3C_3$. And if $C_1 < 0$, then (43) has one positive root $x_2^+ = -C_2 + \sqrt{\Delta}/3C_3$.

Case (1): $C_0 > 0$, $F(\mu) > 0$.

Since $C_0 > 0$, we have $\theta < \theta_5$. Since $F(\mu) > 0$, we have the following two cases:

Case where $1/\beta < \delta_2/\omega_2$, i.e., $\omega_2 < \beta\delta_2$. Since $\mu = 1/\beta$, we have $F(\mu) = \delta_3\sigma_1(\beta\delta_2 - \omega_2)/\beta > 0$. If $F(x_2^+) < 0$, then there exist E_1^* and E_2^* .

Case where $1/\beta > \delta_2/\omega_2$, i.e., $\omega_2 > \beta\delta_2$. Since $\mu = \delta_2/\omega_2$, we have $F(\mu) = \alpha\sigma_2(\beta\delta_2 - \omega_2)(\gamma_2\theta - \delta_3\rho)/\omega_2 > 0$ implying $\theta < \theta_3$. Then, we have $\theta < \min\{\theta_3, \theta_5\}$. If $F(x_2^+) < 0$, then there exist E_1^* and E_2^* .

Case (2): $C_0 < 0$, $F(\mu) < 0$.

Since $C_0 < 0$, we have $\theta > \theta_5$. Since $F(\mu) > 0$, we have the following two cases:

Case where $1/\beta < \delta_2/\omega_2$, i.e., $\omega_2 < \beta\delta_2$. Since $\mu = 1/\beta$, we have $F(\mu) = \delta_3\sigma_1(\beta\delta_2 - \omega_2)/\beta > 0$. That is a contradiction.

Case where $1/\beta > \delta_2/\omega_2$, i.e., $\omega_2 > \beta\delta_2$. Since $\mu = \delta_2/\omega_2$, we have $F(\mu) = \alpha\sigma_2(\beta\delta_2 - \omega_2)(\gamma_2\theta - \delta_3\rho)/\omega_2 < 0$ implying $\theta > \theta_3$. Then, we have $\theta > \max\{\theta_3, \theta_5\}$. If $F(x_1^+) > 0$, then there exist E_1^* and E_2^* .

Next, we show the stability of the above two equilibria E_0 and E^* of system (34) with $v = 0$. We linearize the system and obtain the characteristic equation whose expression is the same as (13).

Theorem 5. System (34) with $v = 0$ always has one tumor-free equilibrium E_0 , which is LAS if the inequality $\theta < \theta_5$ holds.

Proof. At $E_0 = (x_0, y_0, z_0, u_0) = (0, y_0, \sigma_2/\delta_2, \gamma_1\delta_2y_0 + \gamma_2\sigma_2/\delta_2\delta_3)$, the characteristic equation becomes

$$(\lambda - \alpha + y_0)(\lambda + \delta_2)\left(\lambda^2 + \left(\frac{\sigma_1}{y_0} + \delta_3\right)\lambda + \theta\gamma_1y_0 + \frac{\sigma_1\delta_3}{y_0}\right) = 0, \quad (44)$$

and one root of characteristic equation is $-\delta_2 < 0$. It is easily noted that as $\sigma_1/y_0 + \delta_3 > 0$, $\theta\gamma_1y_0 + \sigma_1\delta_3/y_0 > 0$, so the solutions of $\lambda^2 + ((\sigma_1/y_0) + \delta_3)\lambda + \theta\gamma_1y_0 + (\sigma_1\delta_3/y_0) = 0$ have always negative real parts. Therefore, E_0 is LAS if and only if $\alpha - y_0 = 2\alpha A + B - \sqrt{B^2 - 4AC}/2A < 0$, that is, if and only if $\theta < \theta_5$.

At $E^* = (x^*, y^*, z^*, u^*)$, characteristic (13) becomes

$$\lambda^4 + B_1\lambda^3 + B_2\lambda^2 + B_3\lambda + B_4 = 0, \quad (45)$$

where

$$B_1 = \alpha\beta x^* + \delta_3 + \frac{\sigma_1}{y^*} + \frac{\sigma_2}{z^*} > 0,$$

$$B_2 = \left(\alpha\beta x^* + \frac{\sigma_2}{z^*}\right)\left(\frac{\sigma_1}{y^*} + \delta_3\right) + \alpha\beta x^* \frac{\sigma_2}{z^*} + \delta_3 \frac{\sigma_1}{y^*} + \theta\gamma_1 y^* > 0,$$

$$B_3 = \left(\theta\gamma_1 y^* + \delta_3 \frac{\sigma_1}{y^*}\right)\left(\alpha\beta x^* + \frac{\sigma_2}{z^*}\right) + \alpha\beta x^* \frac{\sigma_2}{z^*} \left(\delta_3 + \frac{\sigma_1}{y^*}\right) + \rho\omega_2 x^* y^* z^* > 0,$$

$$B_4 = \alpha\beta x^* \frac{\sigma_2}{z^*} \left(\theta\gamma_1 y^* + \delta_3 \frac{\sigma_1}{y^*}\right) + (\rho\delta_3 - \theta\gamma_2)\omega_2 x^* y^* z^*. \quad (46)$$

By the Routh–Hurwitz criterion, the roots of (45) have negative real parts if and only if $B_1 > 0$, $B_2 > 0$, $B_3 > 0$, $B_4 > 0$, $B_1B_2 - B_3 > 0$, and $B_1(B_2B_3 - B_1B_4) - B_3^2 > 0$.

Hence, we obtain the sufficient condition for the stability of P^* :

$$(H4): B_4 = \alpha\beta x^* \frac{\sigma_2}{z^*} \left(\theta\gamma_1 y^* + \delta_3 \frac{\sigma_1}{y^*}\right) + (\rho\delta_3 - \theta\gamma_2)\omega_2 x^* y^* z^* > 0,$$

$$(H5): B_1B_2 - B_3 = K_1\theta + K_2 > 0,$$

$$(H6): B_1(B_2B_3 - B_1B_4) - B_3^2 = B_3(K_1\theta + K_2) - B_1^2B_4 \quad (47)$$

where

$$K_1 = (\sigma_1 + \delta_3 y^*)\gamma_1,$$

$$K_2 = \left(\delta_3 + \frac{\sigma_1}{y^*} + \frac{\sigma_2}{z^*}\right)\left[\alpha^2\beta^2 x^{*2} + \left(\alpha\beta x^* + \frac{\sigma_2}{z^*}\right)\left(\frac{\sigma_1}{y^*} + \delta_3\right) + \alpha\beta x^* \frac{\sigma_2}{z^*}\right] + \delta_3 \frac{\sigma_1}{y^*} \left(\frac{\sigma_1}{y^*} + \delta_3\right) - \rho\omega_2 x^* y^* z^*,$$

$$K_3 = K_1\left(\alpha\beta x^* + \frac{\sigma_2}{z^*}\right)\gamma_1 y^*,$$

$$K_4 = \left[\left(K_2\gamma_1 y^* + K_1 \frac{\sigma_1\delta_3}{y^*}\right)\left(\alpha\beta x^* + \frac{\sigma_2}{z^*}\right) + K_1\left[\alpha\beta x^* \frac{\sigma_2}{z^*} \left(\delta_3 + \frac{\sigma_1}{y^*} - \left(\alpha\beta x^* + \delta_3 + \frac{\sigma_1}{y^*} + \frac{\sigma_2}{z^*}\right)^2 \gamma_1 y^*\right) + (\rho + \gamma_2)\omega_2 x^* y^* z^*\right],$$

$$K_5 = K_2\left(\alpha\beta x^* + \frac{\sigma_2}{z^*}\right) \frac{\sigma_1\delta_3}{y^*} - \alpha\beta x^* \frac{\sigma_2}{z^*} \left[K_2\left(\delta_3 + \frac{\sigma_1}{y^*}\right) - \left(\alpha\beta x^* + \delta_3 + \frac{\sigma_1}{y^*} + \frac{\sigma_2}{z^*}\right)^2 \frac{\sigma_1\delta_3}{y^*}\right] + (K_2 - \delta_3)\rho\omega_2 x^* y^* z^*. \quad (48)$$

□

Theorem 6. System (34) with $\nu = 0$ has a coexistence equilibrium E^* when $\omega_2 > \beta\delta_2$, $\sigma_1 \geq \alpha(\alpha\gamma_1 + \delta_1\gamma_2)/\gamma_2$, $\theta_3 < \theta < \theta_5$ or $\omega_2 > \beta\delta_2$, $\sigma_1 \leq \alpha(\alpha\gamma_1 + \delta_1\gamma_2)/\gamma_2$, $\theta_5 < \theta < \theta_3$ or $\omega_2 < \beta\delta_2$, $\theta > \theta_5$ hold. Further E^* is LAS when condition (47) is satisfied.

3.1.2. MAI Model. When $\sigma_1 = 0$, $\sigma_3 > 0$, (36) becomes

$$\begin{cases} \alpha x(1 - \beta x) - xy = 0, \\ \rho yz - \theta yu - \delta_1 y = 0, \\ \sigma_2 + \omega_2 xz - \delta_2 z = 0, \\ \gamma_1 y + \gamma_2 z - \delta_3 u - \xi uv = 0, \\ \sigma_3 - \delta_4 v = 0. \end{cases} \quad (49)$$

Equation (49) can be simplified as follows:

$$\begin{cases} \alpha x(1 - \beta x) - xy = 0, \\ \rho yz - \theta yu - \delta_1 y = 0, \\ \sigma_2 + \omega_2 xz - \delta_2 z = 0, \\ \gamma_1 y + \gamma_2 z - \delta_{31} u = 0, \end{cases} \quad (50)$$

where $\delta_{31} = \delta_3\delta_4 + \xi\sigma_3/\delta_4$.

The analysis of (50) is similar to that of (12), and the equilibria of (34) can be obtained as follows:

$$\begin{aligned} F_0 &= \left(0, 0, \frac{\sigma_2}{\delta_2}, \frac{\gamma_2\sigma_2}{\delta_2\delta_{31}}, \frac{\sigma_3}{\delta_4} \right) \\ &= \left(0, \frac{\delta_{31}(\rho\sigma_2 - \delta_1\delta_2) - \theta\gamma_2\sigma_2}{\theta\gamma_1\delta_2}, \frac{\sigma_2}{\delta_2}, \frac{\rho\sigma_2 - \delta_1\delta_2}{\theta\delta_2}, \frac{\sigma_3}{\delta_4} \right), \\ F_2 &= \left(\frac{1}{\beta}, 0, \frac{\beta\sigma_2}{\beta\delta_2 - \omega_2}, \frac{\beta\gamma_2\sigma_2}{\delta_{31}(\beta\delta_2 - \omega_2)}, \frac{\sigma_3}{\delta_4} \right), \\ F^* &= \left(x^*, \alpha(1 - \beta x^*), \frac{\sigma_2}{\delta_2 - \omega_2 x^*}, \right. \\ &\quad \left. \frac{\alpha\gamma_1(1 - \beta x^*)(\delta_2 - \omega_2 x^*) + \gamma_2\sigma_2}{\delta_{31}(\delta_2 - \omega_2 x^*)}, \frac{\sigma_3}{\delta_4} \right). \end{aligned} \quad (51)$$

Here, $x^* \in (0, \mu)$ and satisfies the equation $a_2 x^2 + a_1 x + a_0 = 0$, where coefficients are defined as $a_2 = -\theta\alpha\beta\gamma_1\omega_2 < 0$, $a_1 = \theta\alpha\gamma_1(\beta\delta_2 + \omega_2) + \delta_1\delta_{31}\omega_2 > 0$, and $a_0 = \delta_{31}(\rho\sigma_2 - \delta_1\delta_2) - \theta(\alpha\gamma_1\delta_2 + \gamma_2\sigma_2)$.

The Jacobian matrix of system (34) at any equilibrium $\bar{F}(\bar{x}, \bar{y}, \bar{z}, \bar{u}, \bar{v})$ is as follows:

$$J(\bar{F}) = \begin{pmatrix} \alpha - 2\alpha\beta\bar{x} - \bar{y} & -\bar{x} & 0 & 0 & 0 \\ 0 & \rho\bar{z} - \theta\bar{u} - \delta_1 & \rho\bar{y} & -\theta\bar{y} & 0 \\ \omega_2\bar{z} & 0 & \omega_2\bar{x} - \delta_2 & 0 & 0 \\ 0 & \gamma_1 & \gamma_2 & -\delta_3 - \xi\bar{v} & \xi\bar{u} \\ 0 & 0 & 0 & 0 & -\delta_4 \end{pmatrix} = \begin{pmatrix} \alpha - 2\alpha\beta\bar{x} - \bar{y} & -\bar{x} & 0 & 0 & 0 \\ 0 & \rho\bar{z} - \theta\bar{u} - \delta_1 & \rho\bar{y} & -\theta\bar{y} & 0 \\ \omega_2\bar{z} & 0 & \omega_2\bar{x} - \delta_2 & 0 & 0 \\ 0 & \gamma_1 & \gamma_2 & -\delta_{31} & \xi\bar{u} \\ 0 & 0 & 0 & 0 & -\delta_4 \end{pmatrix}. \quad (52)$$

The corresponding characteristic equation is

$$|J(\bar{F}) - \lambda I| = 0. \quad (53)$$

Substituting δ_{31} for δ_3 in (12), we have

$$|J(\bar{F}) - \lambda I| = (\lambda + \delta_4)|J(\bar{P}) - \lambda I| = 0. \quad (54)$$

Thus, the stability analysis of $\bar{F}$ is similar to that of $\bar{P}$.

Substituting δ_{31} for δ_3 in (20) to get new conditions for the stability of F^* :

$$(h1): A_4 = \theta\alpha\beta\gamma_1(\delta_2 - \omega_2 x^*)x^* y^* + (\rho\delta_{31} - \theta\gamma_2)\omega_2 x^* y^* z^* > 0,$$

$$(h2): A_1 A_2 - A_3 = \theta\gamma_1(\alpha\beta x^* + \delta_2 - \omega_2 x^*)y^* + \alpha\beta\delta_{31}(\delta_2 - \omega_2 x^*)x^* - \rho x^* y^* z^* > 0,$$

$$(h3): A_1(A_2 A_3 - A_1 A_4) - A_3^2 = B_1 \theta + B_2 > 0, \quad (55)$$

where

$$\begin{aligned} B_1 &= ((\alpha\beta x^* + \delta_2 - \omega_2 x^*)^2 \delta_{31} + (\alpha\beta x^* + \delta_2 - \omega_2 x^*) \delta_{31}^2 \\ &\quad - \rho\omega_2 x^* y^* z^*)(\alpha\beta x^* + \delta_2 - \omega_2 x^*)\gamma_1 y^* \\ &\quad - (\alpha\beta x^* + \delta_2 - \omega_2 x^* + \delta_{31})^2 (\alpha\beta\gamma_1(\delta_2 - \omega_2 x^*)x^* y^* \\ &\quad - \omega_2\gamma_2 x^* y^* z^*), \\ B_2 &= ((\alpha\beta x^* + \delta_2 - \omega_2 x^*)^2 \delta_{31} + (\alpha\beta x^* + \delta_2 - \omega_2 x^*) \delta_{31}^2 \\ &\quad - \rho\omega_2 x^* y^* z^*)(\alpha\beta\delta_{31}(\delta_2 - \omega_2 x^*)x^* + \rho\omega_2 x^* y^* z^*) \\ &\quad - (\alpha\beta x^* + \delta_2 - \omega_2 x^* + \delta_{31})^2 \rho\omega_2 \delta_{31} x^* y^* z^*. \end{aligned} \quad (56)$$

We set

$$\begin{aligned}
\theta_{70} &= \frac{\delta_{31}(\rho\sigma_2 - \delta_1\delta_2)}{\alpha\gamma_1\delta_2 + \gamma_2\sigma_2}, \\
\theta_{71} &= \frac{\delta_{31}(\rho\sigma_2 - \delta_1\delta_2)}{\gamma_2\sigma_2}, \\
\theta_{72} &= \frac{\beta\delta_{31}(\rho\sigma_2 - \delta_1\delta_2) + \delta_1\delta_{31}\omega_2}{\beta\gamma_2\sigma_2}, \\
\theta_{73} &= \frac{\rho\delta_{31}}{\gamma_2},
\end{aligned} \tag{57}$$

and we obtain the following results.

Theorem 7. System (34) always has one tumor-free and ECs-free equilibrium F_0 , which is unstable.

Theorem 8. System (34) has one tumor-free equilibrium F_1 when $\rho > \delta_1\delta_2/\sigma_2$ and $\theta < \theta_{71}$, which is LAS if the inequality $\theta < \theta_{70}$ holds.

Theorem 9. System (34) has one tumor-dominant equilibrium F_2 when $\omega_2 < \omega_2^*$, which is LAS if the inequality $\theta > \theta_{72}$ holds.

Theorem 10. System (34) has a unique coexistence equilibrium F^* when $\omega_2 < \omega_2^*$, $\theta_0 < \theta < \theta_2$ or $\omega_2 > \omega_2^*$, $\theta_0 < \theta < \theta_3$ hold. Further F^* is LAS, when condition (55) is satisfied.

3.1.3. Combined Immunotherapy Model. When $\sigma_1 > 0$ and $\sigma_3 > 0$, (36) can be simplified as follows:

$$\begin{cases}
\alpha x(1 - \beta x) - xy = 0, \\
\rho yz - \theta yu - \delta_1 y + \sigma_1 = 0, \\
\sigma_2 + \omega_2 xz - \delta_2 z = 0, \\
\gamma_1 y + \gamma_2 z - \delta_{31} u = 0,
\end{cases} \tag{58}$$

where $\delta_{31} = \delta_3\delta_4 + \xi\sigma_3/\delta_4$.

The analysis of (58) is similar to that of (37), and the equilibria of (34) can be obtained as follows:

$$N_0 = (x_0, y_0, z_0, u_0, v_0) = \left(0, y_0, \frac{\sigma_2}{\delta_2}, \frac{\gamma_1\delta_2 y_0 + \gamma_2\sigma_2}{\delta_2\delta_{31}}, \frac{\sigma_3}{\delta_4}\right), \tag{59}$$

where $y_0 = -B + \sqrt{B^2 - 4AC}/2A$ with $A = \theta\gamma_1\delta_2 > 0$, $B = \delta_{31}(\delta_1\delta_2 - \rho\sigma_2) + \theta\gamma_2\sigma_2$, and $C = -\sigma_1\delta_2\delta_{31} < 0$.

$$N^* = (x^*, y^*, z^*, u^*, v^*) = \left(x^*, \alpha(1 - \beta x^*), \frac{\sigma_2}{\delta_2 - \omega_2 x^*}, \right.$$

$$\left. \frac{\alpha\gamma_1(1 - \beta x^*)(\delta_2 - \omega_2 x^*) + \gamma_2\sigma_2}{\delta_{31}(\delta_2 - \omega_2 x^*)}, \frac{\sigma_3}{\delta_4}\right), \tag{60}$$

where $x^* \in (0, \mu)$ and satisfies the equation $c_3 x^3 + c_2 x^2 + c_1 x + c_0 = 0$ with coefficients

$$\begin{aligned}
c_3 &= \theta\alpha^2\beta^2\gamma_1\omega_2 > 0, \\
c_2 &= -\theta\alpha^2\beta\gamma_1\omega_2 - \alpha\beta[\theta\alpha\gamma_1(\beta\delta_2 + \omega_2) + \delta_1\delta_{31}\omega_2] < 0, \\
c_1 &= \theta\alpha(2\alpha\beta\gamma_1\delta_2 + \alpha\gamma_1\omega_2 + \beta\gamma_2\sigma_2) + \alpha\delta_{31}[\delta_1\omega_2 \\
&\quad - \beta(\rho\sigma_2 - \delta_1\delta_2)] - \sigma_1\omega_2\delta_{31}, \\
c_0 &= \sigma_1\delta_2\delta_{31} + \alpha\delta_{31}(\rho\sigma_2 - \delta_1\delta_2) - \theta\alpha(\alpha\gamma_1\delta_2 + \gamma_2\sigma_2).
\end{aligned} \tag{61}$$

For system (34) at $N_0 = (x_0, y_0, z_0, u_0, v_0)$, Jacobian matrix is expressed as follows:

$$J(N_0) = \begin{pmatrix} \alpha - y_0 & 0 & 0 & 0 & 0 \\ 0 & -\frac{\sigma_1}{y_0} & \rho y_0 & -\theta y_0 & 0 \\ \omega_2 z_0 & 0 & -\delta_2 & 0 & 0 \\ 0 & \gamma_1 & \gamma_2 & -\delta_{31} & \xi u_0 \\ 0 & 0 & 0 & 0 & -\delta_4 \end{pmatrix}. \tag{62}$$

The corresponding characteristic equation is

$$|J(N_0) - \lambda I| = (\lambda + \delta_4)|J(E_0) - \lambda I| = 0. \tag{63}$$

Thus, the stability analysis of N_0 is similar to that of E_0 . Set $\theta_8 = \alpha\delta_{31}(\rho\sigma_2 - \delta_1\delta_2) + \sigma_1\delta_2\delta_{31}/\alpha(\alpha\gamma_1\delta_2 + \sigma_2\gamma_2)$, and we can get the following result.

Theorem 11. System (34) always has one tumor-free equilibrium N_0 , which is LAS if the inequality $\theta < \theta_8$ holds.

For system (34) at $N^* = (x^*, y^*, z^*, u^*, v^*)$, Jacobian matrix is given as follows:

$$J(N^*) = \begin{pmatrix} -\alpha\beta x^* & -x^* & 0 & 0 & 0 \\ 0 & -\frac{\sigma_1}{y^*} & \rho y^* & -\theta y^* & 0 \\ \omega_2 z^* & 0 & \omega_2 x^* - \delta_2 & 0 & 0 \\ 0 & \gamma_1 & \gamma_2 & -\delta_{31} & \xi u^* \\ 0 & 0 & 0 & 0 & -\delta_4 \end{pmatrix}. \tag{64}$$

The corresponding characteristic equation is

$$|J(N^*) - \lambda I| = (\lambda + \delta_4)|J(E^*) - \lambda I| = 0. \tag{65}$$

Thus, the stability analysis of N^* is similar to that of E^* . Set $\theta_9 = \rho\delta_{31}/\gamma_2$ and substitute δ_{31} for δ_3 in (47) to get new conditions:

$$(h4): B_4 = \alpha\beta x^* \frac{\sigma_2}{z^*} \left(\theta\gamma_1 y^* + \delta_{31} \frac{\sigma_1}{y^*} \right) + (\rho\delta_{31} - \theta\gamma_2)\omega_2 x^* y^* z^* > 0,$$

$$(h5): B_1 B_2 - B_3 = k_1 \theta + k_2 > 0,$$

$$(h6): B_1 (B_2 B_3 - B_1 B_4) - B_3^2 = B_3 (k_1 \theta + k_2) - B_1^2 B_4 = k_3 \theta^2 + k_4 \theta + k_5 > 0, \quad (66)$$

where

$$\begin{aligned} k_1 &= (\sigma_1 + \delta_{31} y^*) \gamma_1, \\ k_2 &= \left(\delta_{31} + \frac{\sigma_1}{y^*} + \frac{\sigma_2}{z^*} \right) \left[\alpha^2 \beta^2 x^{*2} + \left(\alpha\beta x^* + \frac{\sigma_2}{z^*} \right) \left(\frac{\sigma_1}{y^*} + \delta_{31} \right) \right. \\ &\quad \left. + \alpha\beta x^* \frac{\sigma_2}{z^*} \right] + \delta_{31} \frac{\sigma_1}{y^*} \left(\frac{\sigma_1}{y^*} + \delta_{31} \right) - \rho\omega_2 x^* y^* z^*, \\ k_3 &= k_1 \left(\alpha\beta x^* + \frac{\sigma_2}{z^*} \right) \gamma_1 y^*, \\ k_4 &= \left[\left(k_2 \gamma_1 y^* + k_1 \frac{\sigma_1 \delta_{31}}{y^*} \right) \left(\alpha\beta x^* + \frac{\sigma_2}{z^*} \right) \right. \\ &\quad \left. + k_1 \left[\alpha\beta x^* \frac{\sigma_2}{z^*} \left(\delta_{31} + \frac{\sigma_1}{y^*} - \left(\alpha\beta x^* + \delta_{31} + \frac{\sigma_1}{y^*} + \frac{\sigma_2}{z^*} \right)^2 \gamma_1 y^* \right) \right. \right. \\ &\quad \left. \left. + (\rho + \gamma_2)\omega_2 x^* y^* z^* \right], k_5 = k_2 \left(\alpha\beta x^* + \frac{\sigma_2}{z^*} \right) \frac{\sigma_1 \delta_{31}}{y^*} \right. \\ &\quad \left. - \alpha\beta x^* \frac{\sigma_2}{z^*} \left[k_2 \left(\delta_{31} + \frac{\sigma_1}{y^*} \right) - \left(\alpha\beta x^* + \delta_{31} + \frac{\sigma_1}{y^*} + \frac{\sigma_2}{z^*} \right)^2 \frac{\sigma_1 \delta_{31}}{y^*} \right] \right. \\ &\quad \left. + (k_2 - \delta_{31})\rho\omega_2 x^* y^* z^* \right]. \end{aligned} \quad (67)$$

Therefore, we can obtain the following result.

Theorem 12. System (34) has a coexistence equilibrium N^* when $\omega_2 > \beta\delta_2, \sigma_1 \geq \alpha(\alpha\gamma_1 + \delta_1\gamma_2)/\gamma_2, \theta_9 < \theta < \theta_8$ or $\omega_2 > \beta\delta_2, \sigma_1 \leq \alpha(\alpha\gamma_1 + \delta_1\gamma_2)/\gamma_2, \theta_8 < \theta < \theta_9$ or $\omega_2 < \beta\delta_2, \theta > \theta_8$ hold. Further N^* is LAS when condition (66) is satisfied.

3.2. Numerical Simulations

3.2.1. ACI Model ($\sigma_1 > 0, \sigma_3 = 0$). We conduct numerical simulations of the ACI model. We choose $\omega_2 = 0.0004$ and the other parameter values are given in (22). We find the stability region of $E^* = (x^*, y^*, z^*, u^*)$, as shown in Figure 5(a). E^* is stable in region I and unstable in region II.

Case (a): we choose a point $G_1 = (\sigma_1, \theta) = (0.4, 0.5)$ in the region I, then system (34) has one coexistence equilibrium:

$$E^* = (11.560, 1.598, 7.543, 6.993). \quad (68)$$

The eigenvalues of characteristic equation of (47) are

$$-0.269, -0.041, -0.1388 + 0.334i \text{ and } -0.1388 - 0.334i, \quad (69)$$

so E^* is stable, as shown in Figure 6(b).

Case (b): we choose a point $G_2 = (\sigma_1, \theta) = (0.4, 0.55)$ in the region II; then, system (34) has one coexistence equilibrium:

$$E^* = (69.131, 1.409, 13.895, 11.962). \quad (70)$$

The eigenvalues of characteristic equation of (47) are

$$-0.830, -0.021, 0.0326 + 0.6039i \text{ and } 0.0326 - 0.6039i, \quad (71)$$

so E^* is unstable, as shown in Figures 6(c) and 6(d).

According to the stability condition of tumor-free equilibrium E_0 in Theorem 5, ACI curve can be obtained as

$$\theta = \frac{\alpha\delta_3(\rho\sigma_2 - \delta_1\delta_2) + \sigma_1\delta_2\delta_3}{\alpha(\alpha\gamma_1\delta_2 + \gamma_2\sigma_2)} = 0.09391\sigma_1 + 0.452. \quad (72)$$

We find the stability region of $E_0 = (0, y_0, z_0, u_0)$ shown in Figure 5(b). E_0 is stable in the region III and unstable in the region IV. With the increase of σ_1 , region III gradually increases, while region IV gradually decreases.

Case (c): we choose a point $G_3 = (\sigma_1, \theta) = (0.4, 0.48)$ in the region III; then, system (34) has a tumor-free equilibrium:

$$E_0 = (0, 1.782, 6.909, 6.596). \quad (73)$$

The eigenvalues of Jacobian matrix of E_0 are

$$-0.055, -0.146, -0.237 + 0.358i \text{ and } -0.237 - 0.358i, \quad (74)$$

so E_0 is stable, as shown in Figure 6(a).

Case (d): we choose a point $G_4 = (\sigma_1, \theta) = (0.4, 0.53)$ in the region IV; then, system (34) has a tumor-free equilibrium:

$$E_0 = (0, 1.141, 6.909, 6.212). \quad (75)$$

The eigenvalues of Jacobian matrix of E_0 are

$$0.494, -0.055, -0.3 + 0.297i \text{ and } -0.3 - 0.297i, \quad (76)$$

so E_0 is unstable.

We choose ACI parameter $\sigma_1 = 0.4$ to study the relationship between the number of TCs x and the parameter θ (see Figure 5(c)). By some calculations, we have $\theta_3 = \rho\delta_3/\gamma_2 =$

FIGURE 5: (a) Stability region of E^* and Hopf bifurcation curve in $\theta - \sigma_1$ parameter plane. E^* is stable in region I and unstable in region II. (b) ACI curve. E_0 is stable in region III and unstable in region IV. (c) The bifurcation diagram of x with respect to θ for fixed $\sigma_1 = 0.4$. Hopf bifurcation point appears at $\theta_{ACI}^* = 0.5354$. (d) The bifurcation diagram of x with respect to θ for different $\sigma_1 = 0, 0.1, 0.3, 0.5, 0.7, 0.9$ (the blue curves represent the stable steady states of system (34), while the red curves represent the unstable steady states).

$0.6, \theta_5 = \alpha\delta_3(\rho\sigma_2 - \delta_1\delta_2) + \sigma_1\delta_2\delta_3/\alpha(\alpha\gamma_1\delta_2 + \gamma_2\sigma_2) = 0.489$. And Hopf bifurcation point appears at $\theta_{ACI}^* = 0.5354$. We can obtain the following result.

Proposition 5. When $0 < \theta < \theta_5$, E_0 exists and is LAS, and E^* is nonexistent. When $\theta_5 < \theta < \theta_{ACI}^*$, E_0 exists and is unstable, and E^* exists and is LAS. When $\theta_{ACI}^* < \theta < \theta_3$, E_0 exists and is unstable, and E^* exists and is unstable. When $\theta > \theta_3$, E_0 exists and is unstable, and E^* is nonexistent.

Next, we choose different ACI parameters $\sigma_1 = 0, 0.1, 0.3, 0.5, 0.7, 0.9$, to study the relationship between the number of TCs x and the parameter θ (see Figure 5(d)).

By comparing the curves in Figure 5(d), we see that, as σ_1 increases gradually, the stable region of tumor-free equilibrium E_0 of system (34) gradually increases (the intersection point of the curve and the x -coordinate gradually moves to the right) and the stability region of equilibrium E^* in system (34) gradually increases (the blue curve gradually moves upward). This indicates that increasing the injection volume of adoptive T cells can not only delay the inhibitory effect of Tregs on tumor immune response but also help the immune system to

remove more TCs. It also helps the immune system to control more TCs, keeping them at a stable state.

3.2.2. MAI Model ($\sigma_1 = 0, \sigma_3 > 0$). We conduct numerical simulations of the MAI model. We choose $\omega_2 = 0.0004$, $\xi = 0.05$, and $\delta_4 = 0.25$ and the other parameter values are given in (22). We find the stability region of $F^* = (x^*, y^*, z^*, u^*)$, as shown in Figure 7(a). F^* is stable in region I and unstable in region II.

Case (a): we choose a point $M_1 = (\sigma_3, \theta) = (0.4, 0.6)$ in region I; then, system (34) has one coexistence equilibrium:

$$F^* = (2.413, 1.628, 7.032, 5.002, 1.6). \quad (77)$$

The eigenvalues of Jacobian matrix of F^* are

$$\begin{aligned} &-0.25, -0.146 + 0.336i, -0.146 - 0.336i, -0.0499 \\ &+ 0.033i \text{ and } -0.0499 - 0.033i, \end{aligned} \quad (78)$$

FIGURE 6: Choose $\sigma_1 = 0.4$, and the other parameter values are given in (22). (a) When $\theta = 0.48$, $E_0(0, 1.782, 6.909, 6.596)$ is LAS. (b) When $\theta = 0.50$, $E^*(11.560, 1.598, 7.543, 6.993)$ is LAS. (c) When $\theta = 0.55$, $E^*(69.131, 1.409, 13.895, 11.962)$ is unstable. (d) When $\theta = 0.55$, the 3D phase portrait depicts TCs, ECs, and Tregs.

so F^* is stable, as shown in Figure 8(b).

Case (b): we choose a point $M_2 = (\sigma_3, \theta) = (0.4, 0.635)$ in region **II**; then, system (34) has one coexistence equilibrium:

$$F^* = (27.345, 1.546, 8.624, 5.93, 1.6). \quad (79)$$

The eigenvalues of Jacobian matrix of F^* are

$$\begin{aligned} &-0.4334, -0.25, -0.0644, 0.0172 \\ &+ 0.429i \text{ and } 0.0172 - 0.429i, \end{aligned} \quad (80)$$

so F^* is unstable, as shown in Figures 8(c) and 8(d).

According to the stability condition of tumor-free equilibrium F_1 in Theorem 7, MAI curve can be obtained as

$$\theta = (\delta_3 \delta_4 + \xi \sigma_3)(\rho \sigma_2 - \delta_1 \delta_2) / (\alpha \gamma_1 \delta_2 + \sigma_2 \gamma_2) \quad (81)$$

$$\delta_4 = 0.3616 \sigma_3 + 0.452.$$

We find the stability region of F_1 , as shown in Figure 7(b). F_0 is stable in region **III** and unstable in region **IV**. With the increase of σ_3 , region **III** gradually increases, while region **IV** gradually decreases.

Case (c): we choose a point $M_3 = (\sigma_3, \theta) = (0.4, 0.5)$ in region **III**; then, system (34) has a tumor-free equilibrium:

$$F_1 = (0, 2.556, 6.909, 5.349, 1.6). \quad (82)$$

The eigenvalues of Jacobian matrix of F_1 are

FIGURE 7: (a) Stability region of F^* and Hopf bifurcation curve in $\theta - \sigma_3$ parameter plane. F^* is stable in region I and unstable in region II. (b) MAI curve. F_1 is stable in region III and unstable in region IV. (c) The bifurcation diagram of x with respect to θ for fixed $\sigma_3 = 0.4$. Hopf bifurcation point appears at $\theta_{MAI}^* = 0.627$. (d) The bifurcation diagrams of x with respect to θ for different $\sigma_3 = 0, 0.1, 0.3, 0.5, 0.7, 0.9$ (the blue curves represent the stable steady states of system (34), while the red curves represent the unstable steady states).

$$-0.92, -0.25, -0.055, -0.164 + 0.428i \text{ and } -0.164 - 0.428i, \quad (83)$$

so F_1 is stable, as shown in Figure 8(a).

Case (d): we choose a point $M_4 = (\sigma_3, \theta) = (0.4, 0.6)$ in region IV; then, system (34) has a tumor-free equilibrium:

$$F_1 = (0, 1.575, 6.909, 4.903, 1.6). \quad (84)$$

The eigenvalues of Jacobian matrix of F_1 are

$$0.061, -0.25, -0.055, -0.164 + 0.338i \text{ and } -0.164 - 0.338i, \quad (85)$$

so F_1 is unstable.

We choose MAI parameter $\sigma_3 = 0.4$ to study the relationship between the number of TCs x and the parameter θ (see Figure 7(c)). By some calculations, we have $\theta_{70} = \delta_{31}(\rho\sigma_2 - \delta_1\delta_2)/\alpha\gamma_1\delta_2 + \gamma_2\sigma_2 = 0.597$, $\theta_{71} = \delta_{31}(\rho\sigma_2 - \delta_1\delta_2)/\gamma_2\sigma_2 = 0.703$, and $\theta_{73} = \rho\delta_{31}/\gamma_2 = 0.792$. And Hopf bifurcation point appears at $\theta_{MAI}^* = 0.627$. We can obtain the following result.

Proposition 6. When $0 < \theta < \theta_{70}$, F_0 exists and is unstable, F_1 exists and is LAS, and F^* exists and is LAS. When

$\theta_{70} < \theta < \theta_{MAI}^*$, F_0 exists and is unstable, F_1 exists and is unstable, and F^* exists and is unstable. When $\theta_{MAI}^* < \theta < \theta_{71}$, F_0 exists and is unstable, F_1 exists and is unstable, and F^* exists and is unstable. When $\theta_{71} < \theta < \theta_{73}$, F_0 exists and is unstable, F_1 is nonexistent, and F^* exists and is unstable. When $\theta > \theta_{73}$, F_0 exists and is unstable, F_1 is nonexistent, and F^* is nonexistent.

Next, we choose different MAI parameters $\sigma_3 = 0, 0.1, 0.3, 0.5, 0.7, 0.9$, to study the relationship between the number of TCs x and the parameter θ (see Figure 7(d)).

By comparing the curves in Figure 7(d), we can find that, with the gradual increase of σ_3 , the stability region of the tumour-free equilibrium F_1 of system (34) gradually increases (the intersection point of curves and x -coordinate gradually moves to the right). This shows that the increase of antibody injection quantity can help to slow down Tregs inhibition of tumor immune responses. The stability region of equilibrium F^* of system (34) gradually increases (the blue curve gradually moves upward), which means that increasing the amount of antibody injected can help the immune system to control more TCs. By comparing Figures 5 and 7, we find that the effect of MAI is better than that of AIC in delaying the inhibitory effect of Tregs on tumor immune response (at the same injection dose, the intersection point of curves and x -coordinate in Figure 7 moves to the right more widely than that in Figure 5). AIC is more effective than MAI in controlling TCs (the blue

FIGURE 8: Choose $\sigma_3 = 0.4$, and the other parameter values are given in (22). (a) When $\theta = 0.5$, $F_1(0, 2.556, 6.909, 5.349, 1.6)$ is LAS. (b) When $\theta = 0.6$, $F^*(2.413, 1.628, 7.032, 5.002, 1.6)$ is LAS. (c) When $\theta = 0.635$, $F^*(27.345, 1.546, 8.624, 5.93, 1.6)$ is unstable. (d) When $\theta = 0.635$, the 3D phase portrait depicts TCs, ECs, and Treg.

curve in Figure 7 moves up more than the blue curves in Figure 5 at the same injection dose).

3.2.3. Combined Immunotherapy Model ($\sigma_1 > 0$, $\sigma_3 > 0$). We conduct numerical simulations of the combined immunotherapy model. We choose $\omega_2 = 0.0004$, $\xi = 0.05$, and $\delta_4 = 0.25$, and the other parameter values are given in (22). We find the stability region of $N^* = (x^*, y^*, z^*, u^*, v^*)$, as shown in Figure 9(a). When σ_3 increases gradually, the stability region of N^* also increases gradually.

Case (a): we choose a point $L_1 = (\theta, \sigma_1) = (0.7, 0.4)$ on the left of the curve $\sigma_3 = 0.5$; then, system (34) has one coexistence equilibrium:

$$N^* = (11.56, 1.59, 7.54, 4.99, 2). \quad (86)$$

The eigenvalues of Jacobian matrix of (64) are

$$-0.06, -0.176, -0.25, -0.22 - 0.37i \text{ and } -0.22 + 0.37i, \quad (87)$$

so N^* is stable, as shown in Figure 10(b).

Case (b): we choose a point $L_2 = (\theta, \sigma_1) = (0.78, 0.4)$ on the right of the curve $\sigma_3 = 0.5$; then, system (34) has one coexistence equilibrium:

$$N^* = (77.887, 1.381, 15.936, 9.698, 2). \quad (88)$$

FIGURE 9: (a) Choose different $\sigma_3 = 0.1, 0.5, 0.8$. Stability region of N^* and Hopf bifurcation curve in $\theta - \sigma_1$ parameter plane. N^* is stable to the left of the curve and unstable to the right of the curve. (b) Combined immunotherapy surface. N_0 is stable below the surface and unstable above the surface. (c) When $\sigma_1 = 0.4$ and $\sigma_3 = 0.4$, the bifurcation diagram of x with respect to θ for system (34). Hopf bifurcation point appears at $\theta_{CI}^* = 0.727$. (d) Choose different $(\sigma_1, \sigma_3) = (0.4, 0), (0, 0.4), (0.4, 0.4), (0.7, 0.7)$. The bifurcation diagram of x with respect to θ (the stable steady state is represented by the blue curve, and the unstable one corresponds to the red curve).

The eigenvalues of Jacobian matrix of (64) are

$$\begin{aligned} & -0.906238, -0.0248, -0.25, 0.00641 \\ & -0.66i \text{ and } 0.00641 + 0.66i, \end{aligned} \quad (89)$$

so N^* is unstable, as shown in Figures 10(c) and 10(d).

According to the stability condition of tumor-free equilibrium N_0 in Theorem 11, combined immunotherapy surface can be obtained as

$$\begin{aligned} \theta &= \frac{\alpha\delta_{31}(\rho\sigma_2 - \delta_1\delta_2) + \sigma_1\delta_2\delta_{31}}{\alpha(\alpha\gamma_1\delta_2 + \sigma_2\gamma_2)} \\ &= (0.055\sigma_1 + 0.2647)(1.366\sigma_3 + 1.707). \end{aligned} \quad (90)$$

Therefore, the stability region of tumor-free equilibrium N_0 of system (34) is obtained (see Figure 9(b)).

Case (c): we choose a point $L_3 = (\sigma_1, \sigma_2, \theta) = (0.5, 0.5, 0.4)$ below surface (90); then, system (34) has a tumor-free equilibrium:

$$N_0 = (0, 8.3, 6.909, 7.505, 2). \quad (91)$$

The eigenvalues of Jacobian matrix of (64) are

$$\begin{aligned} & -6.664, -0.055, -0.25, -0.204 + 0.69i \text{ and } -0.204 - 0.69i, \end{aligned} \quad (92)$$

so N_0 is stable, as shown in Figure 10(a).

Case (d): we choose a point $L_4 = (\sigma_1, \sigma_2, \theta) = (0.5, 0.5, 0.8)$ above surface (90); then, system (34) has a tumor-free equilibrium:

$$N_0 = (0, 0.886, 6.909, 4.32, 2). \quad (93)$$

The eigenvalues of Jacobian matrix of (64) are

$$\begin{aligned} & 0.75, -0.055, -0.25, -0.453 + 0.311i \text{ and } \\ & -0.453 - 0.311i, \end{aligned} \quad (94)$$

so N_0 is unstable.

We choose combined immunotherapy parameter $\sigma_1 = 0.4$ and $\sigma_3 = 0.4$ to study the relationship between the number of TCs x and the parameter θ (see Figure 9(c)). By some calculations, we have $\theta_8 = \alpha\delta_{31}(\rho\sigma_2 - \delta_1\delta_2) +$

FIGURE 10: (a) When $\sigma_1 = \sigma_3 = 0.5$, $\theta = 0.4$, $N_0(0, 8.3, 6.909, 7.505, 2)$ is LAS. (b) When $\sigma_1 = 0.4$, $\sigma_3 = 0.5$, $\theta = 0.7$, $N^*(11.56, 1.59, 7.54, 4.99, 2)$ is LAS. (c) When $\sigma_1 = 0.4$, $\sigma_3 = 0.5$, $\theta = 0.78$, $N^*(77.887, 1.381, 15.936, 9.698, 2)$ is unstable. (d) When $\sigma_1 = 0.4$, $\sigma_3 = 0.5$, $\theta = 0.78$, the 3D phase portrait depicts TCs, ECs, and Tregs.

$\sigma_1 \delta_2 \delta_{31} / (\alpha (\gamma_1 \delta_2 + \sigma_2 \gamma_2)) = 0.646$, and $\theta_9 = \rho \delta_{31} / \gamma_2 = 0.791$. And Hopf bifurcation point appears at $\theta_{CI}^* = 0.727$. We can obtain the following result.

Proposition 7. When $0 < \theta < \theta_8$, N_0 exists and is LAS, and N^* is nonexistent. When $\theta_8 < \theta < \theta_{CI}^*$, N_0 exists and is unstable, and N^* exists and is LAS. When $\theta_{CI}^* < \theta < \theta_9$, N_0 exists and is unstable, and N^* exists and is unstable. When $\theta > \theta_9$, N_0 exists and is unstable, and N^* is nonexistent.

For combined immunotherapy, by comparing the curves in Figure 9(d), we know that, with the increase of σ_1 and σ_3 , the stability region of the tumour-free equilibrium of N_0 of system (34) gradually increases (the intersection point of curves and x -coordinate gradually moves to the right), and the stability region of equilibrium N^* of system (34) gradually increases (the blue curve gradually moves upward). By comparing Figure 9 with Figures 5 and 7, it can be

seen that combined immunotherapy has better effects on delaying the inhibitory effect of Tregs on tumor immune response and helps the immune system to control more TCs than ACI or MAI.

4. Discussion and Conclusion

Tregs-mediated tumor immune escape is one of the core mechanisms of tumor immune regulation. And Tregs have been found to mediate tumor evasion and immune escape in many different solid tumors [46]. The study on Tregs has a very high research value and application prospect in the immunotherapy of tumors. If the activity of Tregs is controlled or blocked during the tumor immune response, or a barrier is set to prevent Tregs from migrating into the tumor microenvironment, then the effect of tumor immunotherapy can be improved [47].

First, we developed a mathematical model to study the inhibitory role of Tregs in the tumor immune system. For the lower recognition of tumor antigens by the immune system, the stronger the inhibition effect of Tregs on ECs, TCs can easily escape the control of the immune system (see Figure 4(a)). When the immune system is highly sensitive to tumor antigens, the immune system activates ECs; the stronger the inhibition effect of Tregs on ECs, the more complicated interactions between TCs and immune cells (see Figure 4(b)).

Second, we incorporated the previous mathematical model with three types of immunotherapy to obtain ACI model, MAI model, and combined both ACI and MAI model. Through the theoretical analysis and numerical simulations, we found that ACI can control more TCs, but have no obvious effects on reducing the inhibitory effect of Tregs on ECs (see Figure 5). MAI can effectively reduce the inhibitory effect of Tregs on ECs, but cannot control more TCs (see Figure 7). However, combination immunotherapy with ACI and MAI is more effective than single immunotherapy. It can not only significantly reduce the inhibitory effect of Tregs on ECs but also help the immune system to kill TCs to the maximum extent (see Figure 9). Therefore, we recommend the use of combined immunotherapy in the treatment of tumors. Besides, clinical trials are needed to further evaluate the safety and efficacy of combined immunotherapy.

This paper focused on the general process of tumor immune response with negative feedback. Using the mathematical model, it is possible to simulate the state of tumors in the immune system at different inhibition states. The results of the study can contribute to the understanding of tumor immunity; at the same time, it also provides new ideas for the treatment of tumors. However, due to the complexity and heterogeneity of tumor microenvironment, there is still a certain gap between the mathematical model and the description of the real interactions between the tumor and immune system. Therefore, specific tumor microenvironment and heterogeneous tumoral populations should be considered in practical application to make the model more realistic [34]. In addition to the bilinear incidence model considered in this paper, non-bilinear model with saturation incidence should be employed in the further study [35]. Besides, other important factors such as immune activation delays [36–38, 48], stochastic effects [39, 40, 49], and impulsive perturbations [41, 42, 50] can be considered in the modelling of the tumor immune system. The tumor immune response dynamics in vivo is very complex and not well understood primarily because the measurements of the necessary parameters are difficult in vivo [43].

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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