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MATHEMATICAL MODELLING OF TUMOR-IMMUNE SYSTEM BY CONSIDERING THE REGULATORY T CELLS ROLE

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Abstract: The immune system has an important role in protecting the body from tumors. However, several clinical studies have shown that not all immune cells in the body work positively against tumors, such as regulatory T cells which are known to modulate the function of effector cells and inhibit their cytotoxic activity. The purpose of this paper is to analyze the mathematical model of tumor-immune system dynamics by considering the regulatory T cells role. Based on the model analysis results obtained eight equilibrium points, where two equilibrium points are unstable, namely the equilibrium point of normal, tumor, effector cells extinction and the equilibrium point of normal, tumor cells extinction, then four equilibrium points are conditionally asymptotically stable, namely the equilibrium point of normal and effector cells extinction, tumor and effector cells extinction, tumor cells extinction, and effector cells extinction, and two equilibrium points are thought to tend to be asymptotically stable when the existence conditions are satisfied, namely the equilibrium point of normal cells extinction and coexistence. The numerical simulation results show that regulatory T cells play an important role in inhibiting effector cells and promoting tumor cell growth. Furthermore, a numerical bifurcation analysis is performed which shows the presence of saddle-node bifurcation and

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bistable behavior in the system.

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1. INTRODUCTION

The number of cancer sufferers worldwide is expected to increase significantly. The World Health Organization (WHO) in 2020 estimates that over the next 20 years the number of cancer cases will increase by 60%. The World Health Organization (WHO) also informed that there were 18.1 million new cancer cases and 9.6 million deaths due to cancer in 2018 [1]. Cancer is a type of disease that has a very broad scope, involving uncontrolled cell division [2]. This uncontrolled cell division leads to the growth of tumor cells. Tumor cells can be benign or malignant. Benign tumor cells do not invade the surrounding tissue and do not spread through the blood vessels to other parts of the body. However malignant tumor cells can attack normal cells, spread to other parts of the body, and cause cancer. Tumor cells continue to proliferate until they can be detected in certain physiological spaces in the human body. Then, the immune system will be triggered into "Search and Destroy" mode [3]. Tumor cells will express antigens or substances that can be recognized by the immune system. These substances can stimulate the immune system to produce antibodies as a form of resistance against tumor cells [2].

The immune system has an important role in fighting tumor cells. It has two main components that interact with each other to defend the organism from pathogens, namely natural and adaptive components [4]. T lymphocytes is one of the adaptive component cells that plays an important role in fighting tumor cells. T lymphocytes will develop into special cells, including CD8+ T cells and CD4+ T cells. In general, CD4+ T cells can be classified into helper T cells and regulatory T cells. Helper T cells have a role in controlling adaptive immunity against pathogens and tumors by activating CD8+ T cells [4]. After activation by helper T cells, CD8+ T cells differentiate into cytotoxic T lymphocytes, which are commonly called effector cells. Regulatory T cells themselves also play an important role in suppressing excessive immune responses, but

regulatory T cells modulate the function of effector cells which makes effector cells unable to continue their cytotoxic activity and causes a weak immune response against tumor cells [5].

Many Research related to the interaction of the immune system and tumor cells has been carried out several times in several scientific fields; one of them is mathematics. By using mathematical model approach, Kuznetsov et al. [6] built a tumor growth model by analyzing the impact of effector cells on tumor cells. Kirschner and Panetta [7] introduced interleukin-2 (IL-2) to form a classical tumor immunotherapy model, then predicted several infusion effector cells and IL-2 could eradicate tumors. Wilson and Levy [8] developed a mathematical model containing regulatory T cells and studied the absence of treatment, vaccine treatment, anti-TGF-β treatment, and combination vaccine and anti-TGF-β treatment, as well as sensitivity analysis of several important parameters. Dong et al. [9] constructed a three-dimensional ordinary differential equation model focusing on the effect of helper T cells on the tumor immune system. Pang et al. [10] built a simple and realistic mathematical model of anti-tumor immune response involving the role of immature and mature lymphocytes. Makhlouf et al. [11] proposed a mathematical model of ordinary differential equations predicting the interactions of tumor cells, natural killer cells, CD4+ T cells, CD8+ T cells, circulating lymphocytes, and interleukin-2. Then Yang et al. [12] proposed a model of the interaction of the immune system and tumor cells considering regulatory T cells.

Based on these descriptions, the authors are interested to develop mathematical model by Yang et al. [12]. We add normal cells compartment on the model that compete with tumor cells and considering the inactivation of effector cells by tumor cells, as well as altering the bilinear form of the immune system and tumor cells interactions become Michaelis-Menten kinetic form. The Michaelis-Menten kinetic form can describe chemical reactions and the mechanism of interaction between the immune system and tumor cells which are known to be very complex [13]. The work is put in order as follows. In section 2, we discuss model formulation and analysis of the model. In section 3, the stability of the model is analyzed. Section 4 demonstrates the numerical results to illustrate the dynamics of the model and the conclusion is summarized in section 5.

2. Model Formulation

This section will discuss the mathematical model of the tumor-immune system by considering the regulatory T cells role. The basic model used refers to the paper written by Yang et al. [12]. The mathematical model is divided into five populations, namely the population of normal cells (N), tumor cells (T), effector cells (E), helper T cells (H), and regulatory T cells (R). The assumptions used in this mathematical model are as follows:

1. The population of normal cells and tumor cells show the rate of logistics proliferation (the process of cells multiplying naturally)
2. The population of normal cells and tumor cells compete with each other for available resources.
3. The growth rate of tumor cells is faster than normal cells.
4. The inhibition rate of normal cells by tumor cells is faster than that of tumor cells by normal cells.

Based on the assumptions, we construct the governing equations of the mathematical model of the tumor-immune system by considering the regulatory T cells role. Then lists of parameters unit used in model can be seen in the table 2.1.

The normal cell population (N) grows logistically at an intrinsic growth rate of r_1 and grows until it is limited by the maximum capacity of cells in the biological environment of $1/b_1$. The normal cell population decreased due to the rate of competition with tumor cells of β_1,

$$\frac{dN}{dt} = r_1 N(1 - b_1 N) - \beta_1 NT. \tag{1}$$

The tumor cell population (T) grows logistically at an intrinsic growth rate of r_2 and grows until it was limited by the maximum capacity of cells in the biological environment of $1/b_2$. Tumor cell population decreased due to the competition rate with normal cells of β_2, and eradication rate by effector cells of β_3, which was written in the form of Michaelis-Menten kinetics to show that the immune response was limited to tumor immunosuppressive activity due to the presence of pro-tumor factors [14],

$$\frac{\mathrm{dT}}{\mathrm{dt}} = r_2 T(1 - b_2 T) - \beta_2 NT - \frac{\beta_3 ET}{\alpha_1 + T}. \tag{2}$$

The Effector cell population (E) increased due to the activation rate by helper T cells of p. Effector cell population decreased due to the rate of inactivation by tumor cells of β_4 and the rate of inhibition by regulatory T cells of q and the natural death rate of d_1,

$$\frac{\mathrm{dE}}{\mathrm{dt}} = pEH - \beta_4 ET - qRE - d_1 E. \quad (3)$$

The Helper T cell population (H) increases due to a constant recruitment from bone marrow at rate s and the presence of tumor cell antigens identified at rate k. It was written in Michaelis-Menten kinetics form to show the growth rate of helper T cells that depend on tumor cell abundance. Helper T cell population was decreased due to a natural death rate of d_2,

$$\frac{\mathrm{dH}}{\mathrm{dt}} = s + \frac{kTH}{\alpha_2 + T} - d_2 H. \quad (4)$$

The population of regulatory T cells (R) increased due to the rate of activation by effector cells and helper T cells, a_1 and a_2, respectively. Regulatory T cells population decrease due to the natural death rate of d_3,

$$\frac{\mathrm{dR}}{\mathrm{dt}} = a_1 E + a_2 H - d_3 R. \quad (5)$$

Table 2.1 Definition of the parameters.

Parameter	Definition	Unit
r_1	Normal cell growth rate	$time^{-1}$
r_2	Tumor cell growth rate	$time^{-1}$
b_1	Normal cell carrying capacity	$cell^{-1}$
b_2	Tumor cell carrying capacity	$cell^{-1}$
β_1	Rate of competition between normal and tumor cells	$(cell \cdot time)^{-1}$
β_2	Rate of competition between tumor and normal cells	$(cell \cdot time)^{-1}$
β_3	Rate of tumor cell eradication by effector cells	$time^{-1}$
β_4	Rate of effector cells inactivation by tumor cells	$(cell \cdot time)^{-1}$
p	Rate of effector cells activation by helper T cells	$(cell \cdot time)^{-1}$
q	Rate of effector cells inhibition by regulatory T cells	$(cell \cdot time)^{-1}$
a_1	Rate of regulatory T cells activation by effector cells	$time^{-1}$

a_2	Rate of regulatory T cells activation by helper T cells	$time^{-1}$
s	The recruitment rate of helper T cells produced in the bone marrow	$cell \cdot time^{-1}$
k	Helper T cell stimulation rate due to the presence of tumor antigen	$time^{-1}$
α_1, α_2	Half saturation constant	$cell$
d_1	The natural death rate of effector cells	$time^{-1}$
d_2	The natural death rate of helper T cells	$time^{-1}$
d_3	The natural death rate of regulatory T cells	$time^{-1}$

3. Model Analysis

3.1 Equilibrium Point

In this section, the equilibrium points and the existence conditions will be determined.

a. The equilibrium point for the extinction of normal, tumor, and effector cells is obtained by

$$P_0 = (N_0, T_0, E_0, H_0, R_0) = \left(0, 0, 0, \frac{s}{d_2}, \frac{a_2 s}{d_2 d_3}\right).$$

b. The equilibrium point for the extinction of normal and tumor cells is obtained by

$$P_1 = (N_1, T_1, E_1, H_1, R_1) = \left(0, 0, \frac{d_3(ps - d_1 d_2) - q a_2 s}{q a_1 d_2}, \frac{s}{d_2}, \frac{ps - d_1 d_2}{q d_2}\right),$$

which exists when $p > \frac{d_1 d_2}{s}$ and $q < \frac{d_3(ps - d_1 d_2)}{a_2 s}$.

c. The equilibrium point for the extinction of normal and effector cells is obtained by

$$P_2 = (N_2, T_2, E_2, H_2, R_2) = \left(0, \frac{1}{b_2}, 0, \frac{s(a_2 b_2 + 1)}{d_2(a_2 b_2 + 1) - k}, \frac{a_2 H_2}{d_3}\right),$$

which exists when $k < d_2(a_2 b_2 + 1)$.

d. The equilibrium point for the extinction of tumor and effector cells is obtained by

$$P_3 = (N_3, T_3, E_3, H_3, R_3) = \left(\frac{1}{b_1}, 0, 0, \frac{s}{d_2}, \frac{a_2 s}{d_2 d_3}\right).$$

e. The equilibrium point for the extinction of tumor cells is obtained by

$$P_4 = (N_4, T_4, E_4, H_4, R_4) = \left(\frac{1}{b_1}, 0, \frac{d_3(ps - d_1 d_2) - q a_2 s}{q a_1 d_2}, \frac{s}{d_2}, \frac{ps - d_1 d_2}{q d_2}\right),$$

which exists when $p > \frac{d_1 d_2}{s}$ and $q < \frac{d_3(ps - d_1 d_2)}{a_2 s}$.

f. The equilibrium point for the extinction of effector cells is obtained by

$$P_5 = (N_5, T_5, E_5, H_5, R_5)$$

$$P_5 = \left(\frac{r_2(r_1 b_2 - \beta_1)}{r_1 b_1 r_2 b_2 - \beta_1 \beta_2}, \frac{r_1(r_2 b_1 - \beta_2)}{r_1 b_1 r_2 b_2 - \beta_1 \beta_2}, 0, \frac{s(\alpha_2(r_1 b_1 r_2 b_2 - \beta_1 \beta_2) + r_1(r_2 b_1 - \beta_2))}{d_2 \alpha_2(r_1 b_1 r_2 b_2 - \beta_1 \beta_2) + (d_2 - k)(r_1(r_2 b_1 - \beta_2))}, \frac{a_2 H_5}{d_3}\right),$$

which exists when $\beta_1 < r_1 b_2,\ \beta_2 < r_2 b_1,\ \beta_1 \beta_2 < r_1 b_1 r_2 b_2,\ k < d_2$.

g. The equilibrium point for the extinction of normal cells is obtained by

$$P_6 = (N_6, T_6, E_6, H_6, R_6)$$

where $N_6 = 0$

$E_6 = \frac{r_2(1 - b_2 T_6)(\alpha_1 + T_6)}{\beta_3}$

$H_6 = \frac{s(\alpha_2 + T_6)}{d_2(\alpha_2 + T_6) - kT_6}$

$R_6 = \frac{a_1 r_2(1 - b_2 T_6)(\alpha_1 + T_6)(d_2(\alpha_2 + T_6) - kT_6) + s a_2 \beta_3(\alpha_2 + T_6)}{d_3 \beta_3(d_2(\alpha_2 + T_6) - kT_6)}$

and T_6 is the solution of the characteristic equation

$$A_1 T_6^3 + A_2 T_6^2 + A_3 T_6 + A_4 = 0 \qquad (6)$$

where,

$A_1 = r_2 b_2 q a_1 d_2 - r_2 b_2 q a_1 k,$

$A_2 = \beta_3 \beta_4 d_3 k - \beta_3 \beta_4 d_3 d_2 + r_2 b_2 q a_1 d_2 \alpha_2 - r_2 q a_1 d_2 + r_2 b_2 \alpha_1 q a_1 d_2 + r_2 q a_1 k - r_2 b_2 \alpha_1 q a_1 k,$

$A_3 = psd_3 \beta_3 - r_2 q a_1 d_2 \alpha_2 + r_2 b_2 \alpha_1 q a_1 d_2 \alpha_2 - r_2 \alpha_1 q a_1 d_2 + r_2 \alpha_1 q a_1 k - \beta_3 \beta_4 d_3 d_2 \alpha_2 -$

$d_1 d_3 d_2 \beta_3 + d_1 d_3 \beta_3 k - q a_2 s \beta_3, A_4 = psd_3 \alpha_2 \beta_3 - d_1 d_3 d_2 \alpha_2 \beta_3 - q a_2 s \alpha_2 \beta_3 - r_2 q a_1 d_2 \alpha_2.$

The equilibrium point P_6 will exist if

$T_6 < \mu_1 \approx \min\left\{\left(\frac{1}{b_2}, \frac{d_2 \alpha_2}{k - d_2}\right)\right\}, k > d_2$ and $q < \frac{d_3 \beta_3(ps - d_1 d_2)}{r_2 a_1 d_2 + a_2 s \beta_3}$.

h. The equilibrium point of coexistence, namely $P^* = (N^*, T^*, E^*, H^*, R^*)$

where $N^* = \frac{r_1 - \beta_1 T^*}{r_1 b_1}$

$$E^* = \frac{(r_1(r_2b_1(1-b_2T^*)-\beta_2)+\beta_1\beta_2T^*)(\alpha_1+T^*)}{r_1b_1\beta_3}$$

$$H^* = \frac{s(\alpha_2+T^*)}{d_2(\alpha_2+T^*)-kT^*}$$

$$R^* = \frac{a_1(d_2(\alpha_2+T^*)-kT^*)\big((r_1(r_2b_1(1-b_2T^*)-\beta_2)+\beta_1\beta_2T^*)(\alpha_1+T^*)\big)+a_2s(\alpha_2+T^*)r_1b_1\beta_3}{r_1b_1\beta_3d_3(d_2(\alpha_2+T^*)-kT^*)}$$

where T^* is the solution of the characteristic equation

$$A_5T^{*3} + A_6T^{*2} + A_7T^* + A_8 = 0 \tag{7}$$

where,

$A_5 = -r_1r_2qa_1b_1b_2d_2 + qa_1d_2\beta_1\beta_2 + r_1r_2qa_1b_1b_2k - qa_1\beta_1\beta_2k,$

$A_6 = -r_1r_2qa_1b_1b_2d_2\alpha_2 + qa_1d_2\alpha_2\beta_1\beta_2 + r_1r_2qa_1b_1d_2 - r_1r_2qa_1d_2b_1b_2\alpha_1 - r_1qa_1d_2\beta_2 + qa_1d_2\alpha_1\beta_1\beta_2 - r_1r_2qa_1b_1k + r_1r_2qa_1b_1b_2\alpha_1k + r_1qa_1\beta_2k - qa_1\alpha_1\beta_1\beta_2k + r_1b_1d_2d_3\beta_3\beta_4 - r_1b_1d_3\beta_3\beta_4k,$

$A_7 = r_1r_2qa_1b_1d_2\alpha_2 - r_1r_2qa_1b_1b_2d_2\alpha_1\alpha_2 - r_1qa_1d_2\alpha_2\beta_2 + qa_1d_2\alpha_1\alpha_2\beta_1\beta_2T + r_1r_2qa_1b_1d_2\alpha_1 - r_1qa_1d_2\alpha_1\beta_2 - r_1r_2qa_1b_1\alpha_1k + r_1qa_1\alpha_1\beta_2k - psr_1b_1d_3\beta_3 + qsr_1a_2b_1\beta_3 + r_1b_1d_2d_3\alpha_2\beta_3\beta_4 + r_1b_1d_1d_2d_3\beta_3 - r_1b_1d_1d_3\beta_3k,$

$A_8 = r_1r_2qa_1b_1d_2\alpha_1\alpha_2 - r_1qa_1d_2\alpha_1\alpha_2\beta_2 + qsr_1a_2b_1\alpha_2\beta_3 - psr_1b_1d_3\alpha_2\beta_3 + r_1b_1d_1d_2d_3\alpha_2\beta_3.$

The equilibrium point P^* will exist if

$T^* < \mu_2 \approx \min\left\{\left(\frac{r_1}{\beta_1}, \frac{1}{b_2}, \frac{d_2\alpha_2}{k-d_2}\right)\right\}, r_2b_1(1-b_2T^*) > \beta_2, k > d_2$ and $q < \frac{b_1d_3\beta_3(ps-d_1d_2)}{a_1d_2\alpha_1(r_2b_1-\beta_2)+sa_2b_1\beta_3}$.

3.2 Stability Analysis

This section will analyze the stability of each equilibrium point that has been obtained previously. A mathematical model of the tumor-immune system by considering the regulatory T cells role is a nonlinear differential equation, so it is necessary to linearize it using the Jacobian matrix. The following Jacobian matrix is obtained:

$$J(P) = \begin{pmatrix} A_9 & -\beta_1N & 0 & 0 & 0 \\ -\beta_2T & A_{10} & -\frac{\beta_3T}{\alpha_1+T} & 0 & 0 \\ 0 & -\beta_4E & A_{11} & pE & -qE \\ 0 & A_{12} & 0 & \frac{kT}{\alpha_2+T} - d_2 & 0 \\ 0 & 0 & a_1 & a_2 & -d_3 \end{pmatrix} \tag{8}$$

where

$A_9 = r_1 - 2r_1 b_1 N - \beta_1 T$

$A_{10} = r_2 - 2r_2 b_2 T - \beta_2 N - \frac{\beta_3 E}{\alpha_1 + T} + \frac{\beta_3 ET}{(\alpha_1 + T)^2}$

$A_{11} = pH - \beta_4 T - qR - d_1$

$A_{12} = \frac{kH}{\alpha_2 + T} - \frac{kTH}{(\alpha_2 + T)^2}$

Based on the Jacobian matrix $J(P)$, the characteristic equation can be formed:

$$\det(\lambda I - J(P)) = \begin{pmatrix} \lambda - A_9 & -\beta_1 N & 0 & 0 & 0 \\ -\beta_2 T & \lambda - A_{10} & -\frac{\beta_3 T}{\alpha_1 + T} & 0 & 0 \\ 0 & -\beta_4 E & \lambda - A_{11} & pE & -qE \\ 0 & A_{12} & 0 & \lambda - \frac{kT}{\alpha_2 + T} + d_2 & 0 \\ 0 & 0 & a_1 & a_2 & \lambda + d_3 \end{pmatrix} \quad (9)$$

a. Stability of equilibrium point for the extinction of normal, tumor, and effector cells

By substituting P_0 in characteristic equation (9) are obtained:

$$(\lambda - r_1)(\lambda + d_3)(\lambda + d_2)(\lambda - r_2)\left(\lambda - \frac{ps}{d_2} - \frac{qa_2 s}{d_2 d_3} - d_1\right) = 0 \quad (10)$$

From equation (10) it can be seen that there are two positive eigenvalues. Thus, it can be concluded that the equilibrium point P_0 is unstable.

b. Stability of equilibrium point for the extinction of normal and tumor cells

By substituting P_1 in characteristic equation (9) are obtained:

$$(\lambda - r_1)(\lambda - A_{13})(\lambda + d_2)[\lambda^2 + d_3\lambda - a_1 A_{16}] = 0 \quad (11)$$

From equation (11) it can be seen that there is one positive eigenvalue. Thus, it can be concluded that the equilibrium point P_1 is unstable.

c. Stability of equilibrium point for the extinction of normal and effector cells

By substituting P_2 in characteristic equation (9) are obtained:

$$(\lambda + d_3)\left(\lambda - \frac{k}{\alpha_2 b_2 + 1} + d_2\right)(\lambda + r_2)(\lambda - B_1)(\lambda - B_2) = 0 \quad (12)$$

From equation (12) the eigenvalues are obtained

$\lambda_1 = -d_3, \lambda_2 = \frac{k}{\alpha_2 b_2 + 1} - d_2, \lambda_3 = -r_2, \lambda_4 = B_1 = r_1 - \frac{\beta_1}{b_2}$

$\lambda_5 = B_2 = \frac{psb_2 d_3(\alpha_2 b_2+1) - b_2 q a_2 s(\alpha_2 b_2+1) - \beta_4 d_3(d_2\alpha_2 b_2 + d_2 - k) - d_1 b_2 d_3(d_2\alpha_2 b_2 + d_2 - k)}{b_2 d_3(d_2\alpha_2 b_2 + d_2 - k)}$

Because λ_1 and λ_3 are negative. So, it is necessary to specify the conditions for λ_2, λ_4, and λ_5 to be negative. Thus, the equilibrium point of P_2 will be asymptotically stable if

i. $k < k_1$, where $k_1 = d_2(\alpha_2 b_2 + 1)$

ii. $\beta_1 > r_1 b_2$

iii. $p < p_1$, where $p_1 = \frac{(\beta_4 d_3 + d_1 d_3 b_2)(d_2(\alpha_2 b_2+1) - k) + q a_2 s b_2(\alpha_2 b_2+1)}{s b_2 d_3(\alpha_2 b_2+1)}$

d. Stability of equilibrium point for the extinction of tumor and effector cells

By substituting P_3 in characteristic equation (9) are obtained:

$$(\lambda + r_1)(\lambda + d_2)(\lambda + d_3)\left(\lambda - r_2 + \frac{\beta_2}{b_1}\right)\left(\lambda - \frac{ps}{d_2} + \frac{q a_2 s}{d_2 d_3} + d_1\right) = 0 \quad (13)$$

From equation (13) the eigenvalues are obtained

$\lambda_1 = -r_1, \lambda_2 = -d_2, \lambda_3 = -d_3, \lambda_4 = r_2 - \frac{\beta_2}{b_1}$ and $\lambda_5 = \frac{ps}{d_2} - \frac{q a_2 s}{d_2 d_3} - d_1$.

Because λ_1, λ_2, and λ_3 are negative. So, it is necessary to specify the conditions for λ_4 and λ_5 to be negative. Thus, the equilibrium point of P_3 will be asymptotically stable if

i. $\beta_2 > r_2 b_1$

ii. $q > q_1$, where $q_1 = \frac{d_3(ps - d_1 d_2)}{a_2 s}$

e. Stability of equilibrium point for the extinction of tumor cells

By substituting P_4 in characteristic equation (9) are obtained:

$$(\lambda + r_1)(\lambda - B_4)(\lambda + d_2)[\lambda^2 + d_3\lambda - B_7 a_1] = 0 \quad (14)$$

From equation (14) the eigenvalues are obtained

$\lambda_1 = -r_1, \lambda_2 = B_1 = \frac{r_2 b_1 \alpha_1 q a_1 d_2 - \beta_2 \alpha_1 q a_1 d_2 - \beta_3 ps d_3 b_1 + \beta_3 d_2 d_3 b_1 + \beta_3 q a_2 s b_1}{b_1 \alpha_1 q a_1 d_2}$, $\lambda_3 = -d_2$

and the roots of the following equation

$$\lambda^2 + c_3\lambda + c_4 = 0 \quad (15)$$

where,

$c_3 = d_3,\ c_4 = -B_7 a_1$

Because λ_1 and λ_3 are negative. So, it is necessary to specify the conditions for λ_2 to be negative. Then, because the eigenvalues in equation (15) are difficult to determine analytically, we use the Routh Hurwitz criteria. Based on the Routh Hurwitz criteria, the equation (15) has roots that the real part is negative, and consequently $c_3, c_4 > 0$. Thus, the equilibrium point of P_4 will be asymptotically stable if

i. $q < q_3$, where $q_3 = \frac{b_1\beta_3 d_3(ps - d_1 d_2)}{a_1\alpha_1 d_2(r_2 b_1 - \beta_2) + b_1 a_2 s\beta_3}$

ii. $q < q_1$, where $q_1 = \frac{d_3(ps - d_1 d_2)}{a_2 s}$

f. Stability of equilibrium point for the extinction of effector cells

By substituting P_5 in characteristic equation (9) are obtained:

$$(\lambda + d_3)(\lambda - F_8)(\lambda - F_6)[\lambda^2 + (-F_1 - F_4)\lambda + F_1F_4 - F_2F_3] = 0 \qquad (16)$$

From equation (16) the eigenvalues are obtained

$\lambda_1 = -d_3, \lambda_2 = F_8 = \frac{k(r_1 r_2 b_1 - \beta_2 r_1)}{\alpha_2(r_1 b_1 r_2 b_2 - \beta_1\beta_2) + r_1 r_2 b_1 - \beta_2 r_1} - d_2$

$\lambda_3 = F_6 = \frac{psD_1}{D_2} - \beta_4\left(\frac{r_1 r_2 b_1 - \beta_2 r_1}{r_1 b_1 r_2 b_2 - \beta_1\beta_2}\right) - \frac{qsa_2 D_1}{d_3 D_2} - d_1$

and the roots of the following equation

$$\lambda^2 + c_5\lambda + c_6 = 0 \qquad (17)$$

where,

$c_5 = -F_1 - F_4,\ c_6 = F_1F_4 - F_2F_3$

Because λ_1 is negative. So, it is necessary to specify the conditions for λ_2 and λ_3 to be negative. In similar way, because the eigenvalues in equation (17) are difficult to determine analytically, we use the Routh Hurwitz criteria. Based on the Routh Hurwitz criteria, the equation (17) has roots that the real part is negative, and consequently $c_5, c_6 > 0$. Thus, the equilibrium point of P_5 will be asymptotically stable if

i. $k < d_2(\alpha_2 b_2^* + 1)$, dengan $b_2^* = \frac{r_1 b_1 r_2 b_2 - \beta_1\beta_2}{r_1(r_2 b_1 - \beta_2)}$

ii. $p < p_2$, dengan $p_2 = \frac{\beta_4 r_1(r_2 b_1 - \beta_2) + qsa_2 D_1 + d_1 d_3 D_2(r_1 b_1 r_2 b_2 - \beta_1\beta_2)}{sd_3 D_1(r_1 b_1 r_2 b_2 - \beta_1\beta_2)}$

iii. $\frac{b_1 b_2 (r_1+r_2)}{b_1\beta_1+b_2\beta_2} > 1$

iv. $\beta_2 < \beta_2^*$, dengan $\beta_2^* = \frac{r_1 r_2 r_2 b_1 b_1 b_2 (r_1 b_2 - \beta_1)}{\beta_1\beta_2(r_1 b_2-\beta_1)+r_2 b_1 (r_1 r_1 b_2 b_2+\beta_1\beta_1)}$

g. Stability of equilibrium point for the extinction of normal cells

By substituting P_6 in characteristic equation (9) are obtained:

$$(\lambda - F_9)(\lambda^4 + c_7\lambda^3 + c_8\lambda^2 + c_9\lambda + c_{10}) = 0 \quad (18)$$

From equation (18) the eigenvalues are obtained

$\lambda_1 = F_9 = r_1 - \beta_1 T_6$

and the roots of the following equation

$$(\lambda^4 + c_7\lambda^3 + c_8\lambda^2 + c_9\lambda + c_{10}) = 0 \quad (19)$$

where,

$c_7 = -F_{12} - F_{10} - \frac{kT_6}{\alpha_2+T_6} + d_2 + d_3,$

$c_8 = F_{10}F_{12} + d_2(F_{12}+F_{10}) + \frac{\beta_3 F_{11} T_6}{\alpha_1+T_6} - d_3\left((F_{12}+F_{10}) + \frac{kT_6}{\alpha_2+T_6} + d_2\right) - a_1 F_{14},$

$c_9 = \frac{(F_{12}+F_{10})kT_6 - F_{10}F_{12}kT_6}{\alpha_2+T_6} - d_2F_{10}F_{12} - \frac{kF_{11}\beta_3 T_6^2}{(\alpha_2+T_6)(\alpha_1+T_6)} - \frac{d_2F_{11}\beta_3 T_6}{\alpha_1+T_6} - \frac{\beta_3 F_{13}F_{15}T_6}{\alpha_1+T_6}$
$+ d_3\left(F_{10}F_{12} + d_2(F_{12}+F_{10}) + \frac{\beta_3 F_{11}T_6}{\alpha_1+T_6}\right) + F_{14}\left(\frac{a_1 kT_6}{\alpha_2+T_6} + a_1 d_2 + a_1 F_{10}\right),$

$c_{10} = d_3\left(\frac{(F_{12}+F_{10})kT_6 - F_{10}F_{12}kT_6}{\alpha_2+T_6} - d_2F_{10}F_{12} - \frac{kF_{11}\beta_3 T_6^2}{(\alpha_2+T_6)(\alpha_1+T_6)} - \frac{d_2F_{11}\beta_3 T_6}{\alpha_1+T_6}\right.$
$\left. - \frac{\beta_3 F_{13}F_{15}T_6}{\alpha_1+T_6}\right) + \left(-\frac{a_1 kF_{10}F_{14}T_6}{\alpha_2+T_6} - a_1 d_2 F_{10}F_{14} + \frac{a_2\beta_3 F_{14}F_{15}T_6}{\alpha_1+T_6}\right)$

Because the eigenvalues in equation (19) are difficult to determine, both analytically and under the Routh Hurwitz criteria. Therefore, the equilibrium point of P_6 will be analyzed through numerical simulation.

This simulation is done by giving three different initial values for $N(0), T(0), E(0), H(0), R(0)$, and parameter values that satisfy the existence conditions. The following is a table of parameter values and initial values used

Table 3.1 Parameter values for P_3, P_4, P_6, P^*

Parameters	Value	Source
r_1	1	[13]
r_2	1.636	[9]
b_1	0.1	Assumption
b_2	1 (for P_3, P_4)	[13]
	0.1 (for P_6, P^*)	Assumption
β_1	1 (for P_3)	[13]
	0.5 (for P_6)	Assumption
	0.1 (for P^*)	Assumption
β_2	0.5 (for P_3)	[13]
	0.01 (for P_4, P_6, P^*)	Assumption
β_3	0.1	Assumption
β_4	0.01	Assumption
p	0.18 (for P_3)	Assumption
	0.48 (for P_4, P_6, P^*)	[9]
q	0.15 (for P_4)	Assumption
	0.4 (for P_3, P_6, P^*)	
s	0.38	[9]
k	0.06	Assumption
a_1	0.15	[12]
a_2	0.2	[12]
α_1	1	Assumption
α_2	10^2	Assumption
d_1	0.3743	[9]
d_2	0.055	[5]
d_3	0.55	Assumption

Table 3.2 Initial value of phase plane

Initial Value	$N(0)$	$T(0)$	$E(0)$	$H(0)$	$R(0)$	Color
1	10	3	5	4	2	Red
2	12	2.5	3.4	3.7	3	Green
3	15	3.3	5.5	3.9	1.8	Blue

This simulation is only carried out at times $t = 0$ to $t = 200$. The results of the phase plane simulation for normal cell extinction are shown in Figure 3.1. In Figure 3.1, it can be seen that the graphs of effector cells (E) − regulatory T cells (R) population tends to converge to one point $(E;\ R) = (19; 7.937)$, as well as the graphs of tumor cells (T) − helper T cells (H) population tend to converge to one point $(T;\ H) = (8.809; 7.579)$, which means that the overall dynamics of each population in the model going closer to the equilibrium point of normal cells extinction P_6, where $P_6 = (0; 8.8717; 19.0019; 7.5789; 7.9386)$. In addition, the existence condition of the equilibrium point P_6 is also fulfilled. Thus, it is concluded that the equilibrium point of normal cell extinction is thought to tend to be asymptotically stable.

h. Stability of equilibrium point of coexistence

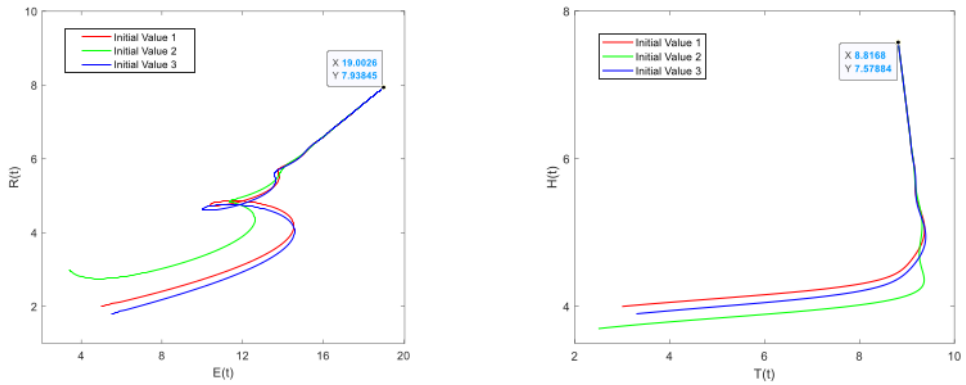
By substituting P^* in characteristic equation (9) are obtained:

$$\lambda^5 + c_{12}\lambda^4 + c_{13}\lambda^3 + c_{14}\lambda^2 + c_{15}\lambda + c_{16} = 0 = 0 \qquad (20)$$

Similar to the equilibrium point P_6, it is difficult to determine the roots of the characteristic equation (20) analytically, so this coexistence equilibrium point will be analyzed through numerical simulation. The parameter values used refer to the parameter values in Table 3.1 and the initial values used refer to Table 3.2.

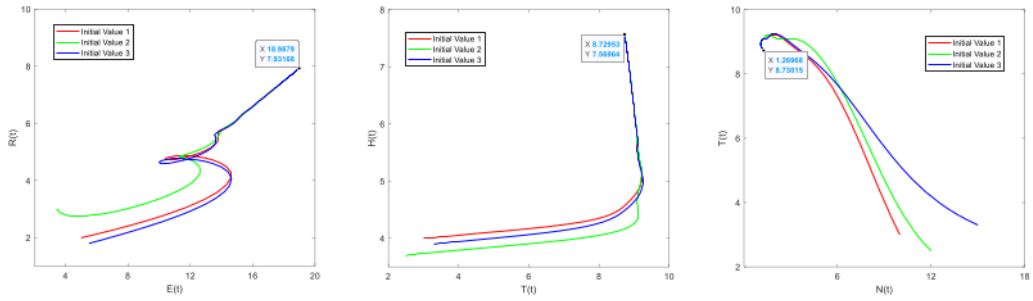
This simulation is only carried out at times $t = 0$ to $t = 200$. The results of the phase plane simulation for coexistence conditions are shown in Figure 3.2. It can be seen that the graphs of effector cells (E) − regulatory T cells (R) populations, tumor cell (T) − helper T cells (H) populations, and normal cell (N) − tumor cells (T) populations tend to converge to one

point, namely $(E;\ R) = (18.99; 7.932), (T;\ H) = (8.729; 7.57)$ and $(N;\ T) = (1.27; 8.729)$, which means the overall dynamics of each population in the model going closer to the equilibrium point of coexistence P^*, with the value $P^* = (1.2707; 8.7287; 18.9904; 7.5723; 7.9328)$. In addition, the existence condition of the equilibrium point P^* is also fulfilled. Thus, it can be concluded that the coexistence equilibrium point is thought to tend to be asymptotically stable.



(a) (b)

Figure 3.1 Graph of phase plane for the extinction of normal cells (a) $E - R$ (b) $T - H$



(a) (b) (c)

Figure 3.2 Graph of phase plane in coexistence conditions (a) $E - R$ (b) $T - H$ (c) $N - T$

The summary of the existence and stability conditions for each equilibrium point that has been obtained can be seen in Table 3.3

Table 3.3 The existence and stability conditions for each equilibrium point

Equilibrium	Existence Conditions	Stability Conditions
P_0	Always exists	Unstable
P_1	$p > \frac{d_1 d_2}{s}$	Unstable
P_2	$k < k_1$	$k < k_1$
P_3	Always exists	$\beta_2 > r_2 b_1$
P_4	$p > \frac{d_1 d_2}{s}$	$q < q_3$
P_5	$\beta_1 < r_1 b_2$	$k < d_2(\alpha_2 b_2^* + 1)$
P_6	$T_6 < \mu_1 \approx \min\left\{\left(\frac{1}{b_2}, \frac{d_2\alpha_2}{k-d_2}\right)\right\}$	asymptotically
P^*	$T^* < \mu_2 \approx \min\left\{\left(\frac{r_1}{\beta_1}, \frac{1}{b_2}, \frac{d_2\alpha_2}{k-d_2}\right)\right\}$	asymptotically

4. NUMERICAL SIMULATION

Numerical simulations will be carried out according to the conclusions of the analysis obtained in the previous section and examine the effect of the inhibitory role of effector cells by regulatory T cells on tumor cell growth. In addition, numerical bifurcation analysis and interpretation of each numerical simulation were also provided. The initial value used is $N(0) = 8, T(0) = 5, E(0) = 3, H(0) = 4, R(0) = 2$ and it is carried out at time $t = 0$ to $t = 200$. The parameter values used refer to Table 3.1 and Table 4.1.

a. Numerical simulation of normal and effector cells extinction conditions

Based on Figure 4.1 (a), it can be seen that the tumor cell population increased from $t = 5$, then constant until $t = 200$. Both normal and effector cell populations decreased from $t = 2$, then became extinct until $t = 200$. Biologically, this condition is referred to as tumor cell invasion. Tumor cells have managed to escape from effector cells and penetrate normal surrounding tissues, then proliferate until the cell's capacity is limited. Furthermore, the population of helper T cells

will continue increase due to a constant source from bone marrow. Consequently, regulatory T cells population also increasing, because helper T cells promote the activation of regulatory T cells. Neither helper T cells nor regulatory T cells can attack tumor cells, therefore helper T cells and regulatory T cells populations will persist even after the invasion of tumor cells occurs.

Table 4.1 Parameter values for P_2 *and* P_5

Parameters	Value	Source
r_1	1	[13]
r_2	1.636	[9]
b_1	0.1	Assumption
b_2	0.1	Assumption
β_1	1 (for P_2)	[13]
	0.05 (for P_5)	Assumption
β_2	0.01	Assumption
β_3	0.56	[13]
β_4	0.5	Assumption
p	0.48	[9]
q	0.48	[1]
s	0.38	[9]
k	0.035	Assumption
a_1	0.15	[12]
a_2	0.2	[12]
α_1	10^5	[11]
α_2	2.02×10^7	[11]
d_1	0.3743	[9]
d_2	0.055	[9]
d_3	0.25	[12]

b. Numerical simulation of tumor and effector cells extinction conditions

Based on Figure 4.1 (b), it can be seen that the population of normal cells, helper T cells, and

regulatory T cells increased and remained constant until $t = 200$. From a biological point of view, this condition indicates that the body's immune system is working quite effectively against tumor cells, even before tumor cells proliferate. However, effector cells decreased from $t = 15$, and finally they became extinct. The extinction of effector cells occurs due to competition against tumor cells and also an increase regulatory T cells.

c. Numerical simulation of tumor cells extinction conditions

Based on Figure 4.1 (c), it can be seen that the effector and regulatory T cells populations increased from $t = 3$, then fluctuated up to $t = 22$ and increased for certain period before reached constant value until $t = 200$. Furthermore, normal and helper T cells populations were increase from $t = 3$, then constant until $t = 200$. From a biological point of view, this condition indicates a healthy condition, where the immune system works effectively against tumor cells and maintains normal cells.

d. Numerical simulation of effector cells extinction conditions

Based on Figure 4.1 (d), it can be seen that the tumor cell population increased from $t = 4$, then constant until $t = 200$, while the normal cell population decreased from $t = 5$, then constant until $t = 200$. The effector cell population decreased and eventually became extinct. Biologically, this condition means that tumor cells are free from immune system control and expected to develop into malignant tumors, that metastasize. This condition has not yet reached tumor invasion because the normal cell population is still present in the body. Furthermore, the population of helper T cells will continue increase due to a constant source from bone marrow. Consequently, regulatory T cells population also increasing, because helper T cells promote the activation of regulatory T cells.

e. Numerical simulation of normal cells extinction conditions

Based on Figure 4.1 (e), it can be seen that tumor cells, effector cells, and regulatory T cells populations increased from $t = 3$, then fluctuated and ended constant until $t = 200$. The normal cell population decreased from $t = 2$, then got extinction. This indicates that tumor cell invasion occurs. Although effector cells are still effective against tumor cells, effector cells cannot maintain the existence of normal cells in the body. Therefore, many researchers consider the treatment of tumor disease can eradicate tumor cells and also maintain the existence of normal cells.

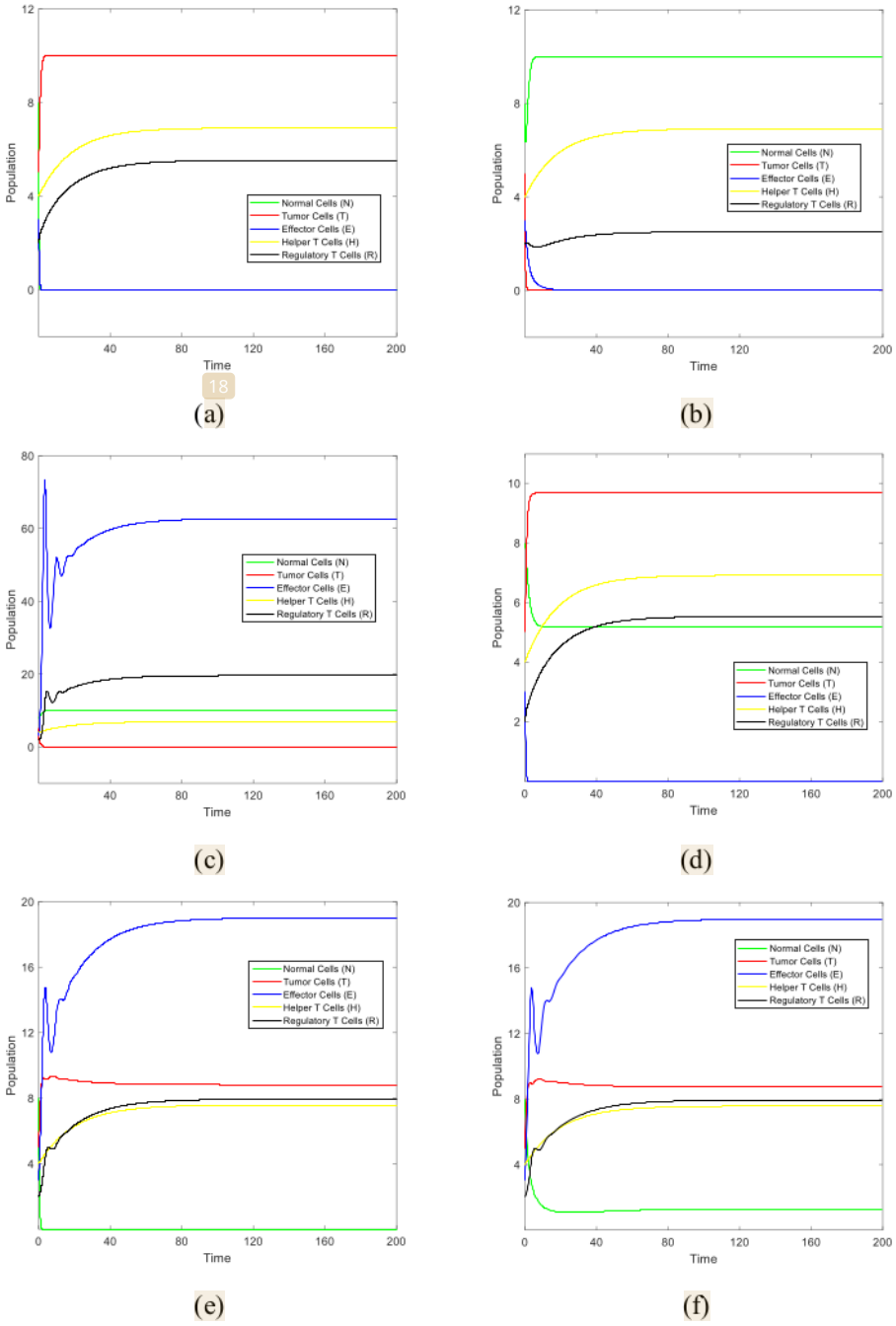


Figure 4.1 Numerical simulation graph of conditions: (a) normal and effector cells extinction (b) tumor and effector cells extinction (c) tumor cells extinction (d) effector cells extinction (e) normal cells extinction (f) coexistence

f. Numerical simulation of coexistence conditions

Based on Figure 4.1 (f), it can be seen that the effector cells and helper T cells populations increased from $t = 3$, then fluctuated and eventually grew steadily until $t = 200$. Consequently, the regulatory T cells are also increased. The tumor cells population increased from $t = 6$, then slightly decreased and ended constant until $t = 200$. Although the population of normal cells decreased, it is not going extinct. The immune system inhibits the tumor spread effectively. Clinically, this condition shows that the patient can still survive even though there are tumor cells in the body.

4.1 The inhibitory role of effector cells by regulatory T cells on Tumor cell growth

Based on Figure 4.2, it is clear that the rate of inhibition of effector cells by regulatory T cells (q) greatly affects the growth of tumor cells. The density of tumor cell populations with different q value is written in the following table:

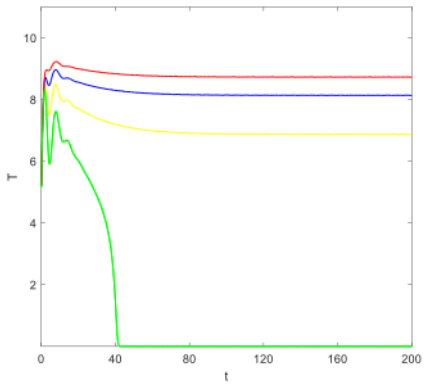


Figure 4.2 t-T graph with different q values

Table 4.2 Density of tumor cell population with different q values

q value	Tumor Cell Population Density
0.4	8.7241
0.32	8.1326
0.24	6.8751
0.18	3.47×10^{-8}

The high rate of inhibition of effector cells by regulatory T cells results high tumor cell growth. Conversely, the low rate of inhibition of effector cells by regulatory T cells results low tumor cells growth. The effector cells can perform their cytotoxic activity or fight tumor cells optimally.

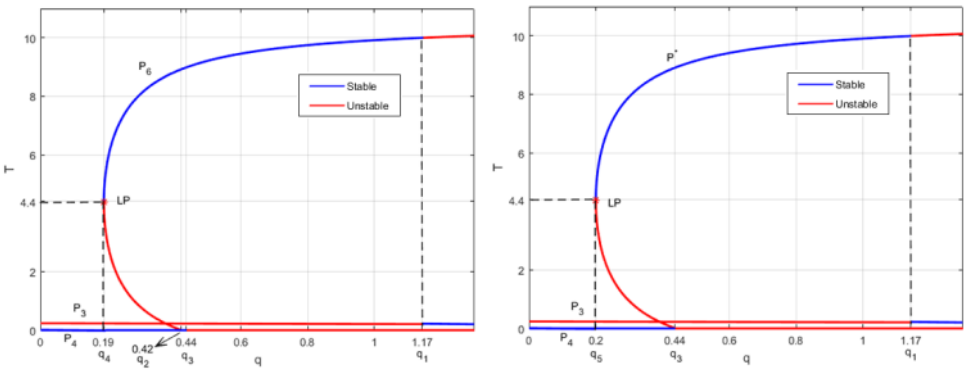
4.2 Numerical Bifurcation Analysis

Numerical bifurcation analysis was carried out to determine the effect of a parameter on the system stability. As the focus of this study, namely the tumor-immune system dynamics with considering the inhibitory role of regulatory T cells, the bifurcation diagram is plotted with a continuous value of q, which is the rate of effector cells inhibition by regulatory T cells. In this simulation, the parameter values used refer to Table 3.1 and the values of q are $q_1 = 1.1710, q_2 = 0.4218, q_3 = 0.4390$.

Figure 4.3 shows the changes in the system stability due to various q parameter values. In Figure 4.3 (a), for $0 < q < q_4$ where $q_4 = 0.19$ is a saddle-node bifurcation point, the equilibrium point P_3 exists and is unstable, P_4 exists and is stable, while the other equilibrium points do not exist. The solution of the system tends to P_4, which means the immune system works very effectively against tumor cells and maintains normal cells. For $q_4 < q < q_3$, the system has bistable behavior, because at that interval there is stability at two points, namely equilibrium points P_4 and P_6, which implies that the immune system works quite effectively against tumor cells, but cannot maintain normal cells in the body. For $q_3 < q < q_1$, both P_3 and P_4 exist and are unstable, while P_6 exists and is stable. The solution of the system tends to P_6, which means the immune system's performance against tumor cells begins to decline and causes the extinction of normal cells. For $q > q_1$, both P_4 and P_6 exist and are unstable, while P_3 exists and is stable. The solution of the system tends to P_3; It shows the inhibition by regulatory T cells causes effector cells tends to extinct and the tumor cell population increased.

Furthermore, in Figure 4.3 (b) for $0 < q < q_5$, where $q_5 = 0.2$ is the saddle-node bifurcation point, the equilibrium point P_3 exists and is unstable, P_4 exists and is stable, while the other equilibrium points do not exist. The solution of the system tends to P_4, which means the immune system works very effectively against tumor cells and maintains normal cells. For $q_5 < q < q_3$, the system has bistable behavior, because at that interval there is stability at two points, namely the equilibrium points P_4 and P^*, which implies that the immune system's performance against tumor cells is quite effective even though the population of tumor cells is not completely

extinct in the patient's body. For $q_3 < q < q_1$, P_3 and P_4 exist and are unstable, while P^* exists and is stable. The solution of the system tends to P^*, which means that the patient is still alive with the presence of tumor cells in the body. For $q > q_1$, both P_4 and P^* exist and are unstable, while P_3 exists and is stable. The solution of the system tends to P_3 and shows evidence that the inhibition by regulatory T cells causes effector cells tends to extinct and the tumor cell population increased.



(a) (b)

Figure 4.3 Bistable and Saddle-Node Bifurcation Diagram of T concerning q with a value of (a) $\beta_1 = 0.5$. (b) $\beta_1 = 0.1$

Based on above explanation, the q parameter has a significant effect on the inhibition of the immune system and tumor cell growth, as well as changes in the system stability. It is important to carry out this analysis before deciding on a suitable tumor treatment strategy so that the immune system can work optimally to reduce the inhibition by regulatory T cells. Then, tumor cells are completely eradicated from the patient's body.

5. CONCLUSION

Based on the results of the discussion that has been described in the previous section, the following conclusions are obtained:

1. The mathematical model of tumor-immune system dynamics by considering the regulatory T cells role has eight equilibrium points, namely:
   a. Two equilibrium points are unstable, namely the equilibrium point of normal, tumor, effector cells extinction (P_0) and the equilibrium point of normal cells, tumor cells extinction (P_1).
   b. Four equilibrium points are conditional asymptotically stable, namely the equilibrium point of normal and effector cells extinction (P_2), tumor and effector cells extinction (P_3), tumor cells extinction (P_4), and effector cells extinction (P_5),
   c. Two equilibrium points are supposed to be asymptotically stable when the conditions for their existence are satisfied, namely the equilibrium point of normal cell extinction (P_6) and coexist condition (P^*).
2. The numerical simulation results of a mathematical model of tumor-immune system by considering the regulatory T cells role show that the inhibition of effector cells by regulatory T cells causes tumor cells growth increased, and vice versa. In addition, a numerical bifurcation analysis was also carried out which showed the presence of saddle-node bifurcation and bistable behavior in the system. The regulatory T cells play an important role in the dynamics of the tumor-immune system, especially in inhibiting the performance of effector cells and promoting tumor cell growth.

DATA AVAILABILITY STATEMENT

The parameter data used to support the findings of this study are included within the article.

ACKOWLEDGMENTS

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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MATHEMATICAL MODELLING OF TUMOR-IMMUNE SYSTEM BY CONSIDERING THE REGULATORY T CELLS ROLE

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