DYNAMIC ANALYSIS OF A MATHEMATICAL MODEL OF THE ANTI-TUMOR IMMUNE RESPONSE

Usman Pagalay[1], *Juhari*[1], and *Sindi* Ayuna Hustani[1]

[1]Program Studi Matematika, Universitas Islam Negeri Maulana Malik Ibrahim Malang, Malang, East Java, Indonesia

Abstract. This study discusses the dynamic analysis, the Hopf bifurcation, and numerical simulations. The mathematical model of the anti-tumor immune response consists of three compartments namely Immature T Lymphocytes (L_1), Mature T Lymphocytes (L_2) and Tumor Cells (T). This research was conducted to represent the behavior between immune cells and tumor cells in the body with five γ conditions. Where γ is the intrinsic growth rate of mature T lymphocytes. This study produces $R_0 > 1$ in conditions 1 to 4 while in condition 5 produces $R_0 < 1$. The disease-free equilibrium point is stable only in condition 5, while the endemic equilibrium point is stable only in conditions 2 and 4. Hopf bifurcation occurs at the endemic equilibrium point. Numerical simulation graph in condition 1 shows that tumor cells will increase uncontrollably. In condition 2 the graph show that the endemic equilibrium point for large tumors is stable. In condition 3 the graph show that there will be a bifurcation from the endemic equilibrium point by the disturbance of the parameter value γ. In condition 4 the graph show the small tumor endemic equilibrium point is stable. Finally, in condition 5, the graph show a stable disease-free equilibrium point.

1. INTRODUCTION

Health is one of the most important things in supporting human activities. Charles-Edward Amory Winslow, a public health expert in the United States, stated that publichealth is the science and art of preventing disease, extending life span and improving health status through organizing efforts of the general public [1]. At present public health is very disturbed by diseases that are starting to occur a lot, one of which is tumor disease.

A tumor is an abnormal growth of a group of cells in the body. Tumors originate from a disturbance that occurs in the control of growth regulation of normal cells during the DNA mutation process, resulting in excessive and uncoordinated proliferation (division) and apoptosis (cell death) significantly decreased [7]. In short, tumor is a pathological disorder of cell growth characterized by excessive and uncontrolled cell proliferation, which can be solid or filled with fluid [10]. In medical language, tumors are known as neoplasia. Neoplasia is a condition where cells in tissues proliferate abnormally and are invasive [9]. In general, body cells have two main tasks, namely carrying out their functional activities and

multiplying by dividing. However, in the case of tumor cells, almost all of the cell's energy is used solely for proliferating activities [7]. Tumors are divided into two major groups, namely there are benign tumors (clear) and there are malignant tumors (malignant) or called cancer [3].

In our body there is already an immune system that plays a role in dealing with various diseases that attack the body. One of the immune systems that has an important role in the body is lymphocytes, because of their influence on the immune response, such as infectious microorganisms and other foreign bodies [8]. Lymphocytes are an important component of the immune response and originate from the hemopoietic stem. Common lymphoid stem cells undergo differentiation and proliferation to become B cells, which mediate humoral or antibody-mediated immunity, and T cells (processed in the thymus), which mediate cellular immunity [5]. T lymphocytes have two growth stages, namely young T lymphocytes and mature T lymphocytes. Young T lymphocytes are cells that have not found their specific antigen, most of which originate from bone marrow stem cells. Meanwhile, mature T lymphocytes are cells that have recognized their specific antigen, which will then proliferate and differentiate into one of several subsets of effector T lymphocytes [2].

Efforts to understand and study tumor disease can be done by constructing problems using mathematical modeling. Mathematical modeling is a system of equations used to describe a complex problem being observed [6]. In more detail, mathematical modeling can be defined as a field of mathematics that seeks to present and describe physical systems or problems in the real world in mathematical statements so that a more precise understanding of the problem is obtained. This process of elaborating or representing is referred to as modeling or modeling which is a logical thinking process [11]. The problem system involving young lymphocytes, mature lymphocytes, and tumors is very complex at the microscopic to macroscopic level.

The formulated model represents the intended complexity so that tumor immune dynamics can be studied. Models that have been successfully formed can be analyzed further by performing dynamic analysis.

Dynamic Analysis is the observation of object activity by providing the behavior of complex dynamical systems, usually by using differential equations or different equations to be studied or studied in detail. Dynamic behavior analysis is carried out to determine whether a mathematical model is valid or not. The stability of the mathematical model can be done by analyzing the equilibrium point, then by calculating the eigenvalues of the mathematical model equation, the type of stability will be known [12]. Dynamic analysis is usually used to analyze models of a disease, so that the development of the disease can be observed.

There are several previous studies that discuss tumor immune dynamics. Bell (1973) applied the classical predator-prey interaction system to describe the response of effector cells to tumor cell growth. Kuznetsov et al (1994) considered tumor cell penetration by effector cells and presented a mathematical model of the Cytotoxic T lymphocyte (CTL) cell response to immunogenic tumor growth. Pillis et al (2000) applieda mathematical model to investigate the mechanism of interaction between tumor cells and various immune effector cells, and applied numerical computations to discuss the treatment effect of different therapy regimens. Liu et al (2012) developed a mathematical model of tumor cells eliciting an immune response proposed by delisi and Rescigno (1977), to investigate the dynamics of the interaction of tumors and the immune system. Liu and Ruan made a more realistic model assumption by requiring lymphocytes to go through two stages of development, namely immature lymphocytes and mature lymphocytes, and claimed that only lymphocytes in the second stage, namely mature lymphocytes, were effective in killing tumor cells.

In this discussion, research will be carried out following the ideas from the modeling

provided by Liu and Ruan, but the difference is that this study prefers to build a simple but reasonable mathematical model to describe some of the phenomena observed clinically according to the model provided by Liuyong Pang, et al. Furthermore, with the model provided by Liuyong Pang, et al, a dynamic analysis will be carried out to find the stability of the equilibrium point, then a bifurcation analysis will be carried out, and a numerical simulation will be carried out to describe the stability of the balance and the existence of a stable periodic solution using the ode45 method.

This will allow results to reflect clinically observed phenomena, and understand the key factors influencing the outcome of the antitumor response as clearly as possible.

2. METHOD

2.1. Research Stages

1. Perform a dynamic analysis of the mathematical model of the anti-tumor immune response according to the model equation given in the article Liuyong Pang, Sanhong Liu, Xinan Zhang, Tianhai Tian (2019).
   a. Determine the disease-free equilibrium point. At this stage the mathematical model of the anti-tumor immune response is in a state of equilibrium, meaningthat there is no rate of disease spread in the body.
   b. Determining the endemic equilibrium point. At this stage, the mathematical model of the anti-tumor immune response in conditions of disease in the body.
   c. Determining the basic reproduction number in a mathematical model of the anti-tumor immune response
   d. Analyzing the stability of the disease-free equilibrium point. Stability analysis is carried out by looking at the eigenvalues
   e. Analyzing the stability of the endemic equilibrium point. Stability analysis is carried out by looking at the eigenvalues
2. Perform a Hopf bifurcation analysis
   a. Determine the parameter value for the Hopf bifurcation, namely the parametervalue at the eigenvalue of the purely imaginary equilibrium point.
   b. Calculate the transversal condition to be more certain that the Hopf bifurcation occurs at the internal equilibrium point.
3. Numerical simulation
   Completion of the mathematical model of the anti-tumor immune response was carried out using ode45 with the help of MATLAB software.

3. Results and Discussion

3.1 Dynamic Analysis

Based on the mathematical model of the anti-tumor immune response according to the model written by Liuyong Pang, Sanhong Liu, Xinan Zhang, Tianhai Tian (2019) in the journal entitled Mathematical Modeling and Dynamic Analysis of Anti-Tumor Immune Response, namely

$$\frac{dL_1}{dt} = -\lambda_1 \left(L_1 - \frac{\lambda_0}{\lambda_1} L_0 \right) + \frac{a_1 T L_2}{\eta + T} \tag{1}$$

$$\frac{dL_2}{dt} = \lambda_1 L_1 - a_3 L_2 \tag{2}$$

$$\frac{dT}{dt} = \lambda_2 T - a_2 T L_2 \tag{3}$$

Next, we will look for the equilibrium point or fixed point of tumor disease in this case. The equilibrium point is obtained when equations (1) to (3) satisfy $\frac{dL_1}{dt} = 0, \frac{dL_2}{dt} = 0, \frac{dT}{dt} = 0$. However, to simplify the work, equations (1) to (3) will be simplified by substituting $L_1 - \frac{\lambda_0}{\lambda_1} L_0 = \frac{a_1}{a_2} x, L_2 = \frac{\lambda_1}{a_2} y, T = \eta z$ and $t = \frac{1}{\lambda_1}\tau$. So we have a simple system, namely

$$\frac{dx}{d\tau} = -x + \frac{yz}{1+z} \tag{4}$$

$$\frac{dy}{d\tau} = ax - \beta y + \gamma \tag{5}$$

$$\frac{dz}{d\tau} = \delta z - zy \tag{6}$$

3.2 Disease Free Equilibrium Point

The disease-free equilibrium point in tumors states that the equilibrium state is obtained in the absence of infection. In other words, there are no tumor cells in the body, so we can assume a value of $z = 0$. Disease-free equilibrium can be expressed by $E_0 = (x^*, y^*, z^*)$. By doing the calculations for equations (4) to (6), the disease-free equilibrium point of the anti-tumor immune response model is obtained

$$E_0 = (x^0, y^0, z^0) = \left(0, \frac{\gamma}{\beta}, 0\right)$$

3.3 Endemic Equilibrium Point

Endemic equilibrium points in tumor disease can be obtained when class z≠0. When the z value is not equal to zero, it means that there are tumor cells in the human body. Endemic equilibrium points can be expressed by $E_1 = (x^*, y^*, z^*)$. By doing the calculations for equations (4) to (6), the endemic equilibrium point of the anti-tumor immune response model is obtained

$$E_1 = (x^*, y^*, z^*) = \left(\frac{\beta\delta - \gamma}{a}, \delta, \frac{\beta\delta - \gamma}{\gamma + \alpha\delta - \beta\delta}\right)$$

3.4 Basic Reproduction Number

The basic reproduction number is a threshold condition for determining whether a population is endemic or free from disease.

The basic reproduction number will be found using the next generation matrix. It is known that the infected compartment in the system of equations (4) to (6) is z. So that the basic reproduction number (R_0) obtained from theanti-tumor immune response model is

$$R_0 = \frac{\delta\beta}{\gamma} \tag{7}$$

Based on the parameter values in this study, the basic reproduction numbers from the system of equations (4) to (6) are obtained for each condition, which can be seen in the following table.

Table 1. R_0 Value of Mathematical Model of Anti-Tumor Immune Response

No	Condition	R_0 Value	Information
1	When $\gamma < (\beta - \alpha)\delta$	3.00	$R_0 > 1$
2	When $(\beta - \alpha)\delta < \gamma < \gamma_1^*$	1.71	$R_0 > 1$
3	When $\gamma_1^* < \gamma < \gamma_2^*$	1.50	$R_0 > 1$
4	When $\gamma_2^* < \gamma < \beta\delta$	1.20	$R_0 > 1$
5	When $\gamma > \beta\delta$	0.97	$R_0 < 1$

From the table above it can be seen that for conditions 1 to condition 4 the value of $R_0 > 1$, this means that there is disease in the body and it will be endemic.

So for conditions 1 to 4, the endemic equilibrium point is stable. Meanwhile, for condition 5, the value of $R_0 < 1$, means that the disease is not present in the body. So for condition 5, the disease-free equilibrium point is stable.

3.5 Stability of the Disease-Free Equilibrium Point

Analysis of the stability of the equilibrium point is carried out based on the eigenvalues obtained from the Jacobi matrix using the linearization method around the equilibrium point.

The jacobi matrix E_0 from the system of equations (4) to (6) is

$$J(E_0) = \begin{bmatrix} -1 & 0 & \frac{\gamma}{\beta} \\ \alpha & -\beta & 0 \\ 0 & 0 & \delta - \frac{\gamma}{\beta} \end{bmatrix}$$

The characteristic equation of (E_0) is

$$f(\lambda) = (-1 - \lambda)(-\beta - \lambda)\left(\delta - \frac{\gamma}{\beta} - \lambda\right) \quad (8)$$

So that the eigen values are obtained, namely

$$\lambda_1 = -1$$
$$\lambda_2 = -\beta$$
$$\lambda_3 = -\frac{\gamma - \beta\delta}{\beta}$$

If the parameter values used in this research are substituted into the eigenvalue equation obtained, then the eigenvalues are obtained.

Table 2. Eigenvalues of the Disease-Free Equilibrium Point

No	Condition	Eigen Value		
		λ_1	λ_2	λ_3
1	When $\gamma < (\beta - \alpha)\delta$	$-1 < 0$	$-0.6 < 0$	$6.67 > 0$
2	When $(\beta - \alpha)\delta < \gamma < \gamma_1^*$	$-1 < 0$	$-0.6 < 0$	$4.17 > 0$
3	When $\gamma_1^* < \gamma < \gamma_2^*$	$-1 < 0$	$-0.6 < 0$	$3.33 > 0$
4	When $\gamma_2^* < \gamma < \beta\delta$	$-1 < 0$	$-0.6 < 0$	$1.67 > 0$
5	When $\gamma > \beta\delta$	$-1 < 0$	$-0.6 < 0$	$-0.33 < 0$

Based on the table above, it is known that in conditions 1 to condition 4, $\lambda_1, \lambda_2 < 0$ dan $\lambda_3 > 0$are obtained. While in condition 5 obtained $\lambda_1, \lambda_2, \lambda_3 < 0$. So that the stability of the

disease-free equilibrium point in the anti-tumor immune response model in conditions 1 to 4 is unstable while in condition 5 is stable.

3.6 Stability of Endemic Equilibrium Points

Analysis of the stability of the equilibrium point was carried out based on the eigenvalues obtained from the Jacobi matrix using the linearization method around the equilibrium point.

The Jacobi matrix E_1 from the system of equations (4) to (6) is

$$J(E_1) = \begin{bmatrix} -1 & \frac{\beta\delta-\gamma}{\alpha\delta} & \frac{\delta}{\left(1+\frac{\beta\delta-\gamma}{\gamma+\alpha\delta-\beta\delta}\right)^2} \\ \alpha & -\beta & 0 \\ 0 & \left(\frac{\beta\delta-\gamma}{\gamma+\alpha\delta-\beta\delta}\right) & \delta-\frac{\gamma}{\beta} \end{bmatrix}$$

The characteristic equation of (E_1) is

$$(\lambda) = k_0\lambda^3 + k_1\lambda^2 + k_2\lambda + k_3 \quad (9)$$

with

$$k_0 = 1$$
$$k_1 = 1+\beta$$
$$k_2 = \frac{\gamma}{\delta}$$
$$k_3 = \frac{(\beta\delta-\gamma)(\gamma+\alpha\delta-\beta\delta)}{\alpha\delta}$$

The root value of the characteristic equation above can be analyzed for stability using the Routh Hurwitz criteria if it meets the conditions

$D_1 = k_1 > 0, D_2 = k_1k_2 - k_0k_3 > 0, D_3 = k_3D_2 > 0$ or $D_1, D_2, D_3 > 0$

If the parameter values used in this study are entered into D_1, D_2, and D_3, the resultingvalues are as follows:

Table 3. Stability of the Endemic Equilibrium Point According to the Routh Hurwitz Criteria

No	Condition	Routh Hurwitz Criteria		
		D_1	D_1	D_1
1	When $\gamma < (\beta-\alpha)\delta$	1.6 > 0	1.65 > 0	−2.20 < 0
2	When $(\beta-\alpha)\delta < \gamma < \gamma_1^*$	1.6 > 0	0.14 > 0	0.05 > 0
3	When $\gamma_1^* < \gamma < \gamma_2^*$	1.6 > 0	−0.02 < 0	−0.01 < 0
4	When $\gamma_2^* < \gamma < \beta\delta$	1.6 > 0	0.13 > 0	0.08 > 0
5	When $\gamma > \beta\delta$	1.6 > 0	1.20 > 0	−0.25 < 0

Based on the calculation results using the Routh Hurwitz criteria in table (3) above.It is known that the endemic equilibrium point is stable in condition 2 and condition 4 because the values D_1, D_2, $D_3 > 0$, which means that condition 1 and condition 4 meet the requirements of the Routh Hurwitz criteria. Meanwhile, during condition 1, condition 3 and condition 5, the endemic equilibrium point is unstable because there is a D value that is less than zero.

Next, by substituting the parameter values in each case at the endemic equilibrium point, the eigenvalues are obtained

Table 4. Eigenvalues of Endemic Equilibrium Points

No	Condition	Eigen Value
1	When $\gamma < (\beta-\alpha)\delta$	$\lambda_1 = -1.16 + 0.72I$ $\lambda_2 = -1.16 - 0.72I$

		$\lambda_3 = 0.72$
2	When $(\beta - \alpha)\delta < \gamma < \gamma_1^*$	$\lambda_1 = -0.03 + 0.52I$ $\lambda_2 = -0.03 - 0.52I$ $\lambda_3 = -1.55$
3	When $\gamma_1^* < \gamma < \gamma_2^*$	$\lambda_1 = 0.004 + 0.64I$ $\lambda_2 = 0.004 - 0.64I$ $\lambda 3 = -1.61$
4	When $\gamma_2^* < \gamma < \beta\delta$	$\lambda 1 = -0.02 + 0.65I$ $\lambda 2 = -0.02 - 0.65I$ $\lambda 3 = -1.55$
5	When $\gamma > \beta\delta$	$\lambda 1 = -0.91 + 0.43I$ $\lambda 2 = -0.91 - 0.43I$ $\lambda 3 = 0.21$

Based on the eigenvalues in table (4) above, it is known that in condition 1 there is a value of $\lambda_3 > 0$, then the type of stability at the endemic equilibrium point is unstable. In condition 2, because the values $\lambda_{1,2} = x \pm yi$ with $k < 0$ and $\lambda_3 < 0$, the type of stability at the endemic equilibrium point is stable.

In condition 3, because the value $\lambda_{1,2} = x \pm yi$ with $k > 0$ and $\lambda_3 < 0$, the type of stability at the endemic equilibrium point is unstable. In condition 4, because the values $\lambda_{1,2} = x \pm yi$ with $k < 0$ and $\lambda_3 < 0$, the type of stability at the endemic equilibrium point is stable. In condition 5 there is a value of $\lambda_3 > 0$, so the type of stability at the endemic equilibrium point is unstable. Overall it can be concluded that in condition 2 and condition 4 the type of stability at the endemic equilibrium point is stable, while in condition 1, condition 3 and condition 5 the type of stability at the endemic equilibrium point is unstable.

3.7 Bifurcation Analysis

Based on the Routh Hurwitz criterion, it is known that all roots of equation (9) are negative or have a negative real part if and only if the determinant of all Routh Hurwitz matrices is positive, in other words $k_1k_2 - k_3 > 0$. If otherwise $k_1k_2 - k_3 < 0$ then the endemic equilibrium point is unstable, whereas if $k_1k_2 - k_3 = 0$ it cannot be determined. However, equation (9) always has at least one negative real root whatever the sign of $k_1k_2 - k_3$.

We assume $k_1k_2 - k_3 = 0$ or $(\gamma) = 0$, then it is clear that (E_1) has one negative eigenvalue $\lambda_1 = -k_1$ and two pure imaginary eigenvalues $\lambda_{2,3} = \pm\omega i$ (dimana $\omega = \sqrt{k_2} > 0$), which shows that the system of equations (4) to (6) can experience a Hopf bifurcation around the equilibrium point E_1. We will cite useful lemmas in analyzing the Hopf bifurcation.

Lemma 1:

Let $\Omega \in \mathbb{R}^3$ be an open set containing $O(x_1, x_2, x_3)$ and let $S \subseteq \mathbb{R}$ be an open set with $0 \in S$. Let $f: \Omega \times S \to \mathbb{R}^3$ be an analytical function such that $(0, \rho) = 0$ for every $\rho \in S$. Assume that the variational matrix $Df(0, \rho)$ of f has one real eigenvalue $\gamma(\rho)$ and two conjugate imaginary eigenvalues $\alpha(\rho) \pm i\beta(\rho)$ with $\gamma(0) < 0$, $\alpha(0) = 0$, $\beta(0) > 0$. Next, suppose that the eigenvalues cross the imaginary axis with a non-zero speed, namely $\frac{d\alpha(0)}{dp} \neq 0$. So the differential system follows

$$\dot{X} = f(X, p)$$

Experiencing a Hopf bifurcation near the equilibrium point O at $\rho = 0$

We choose the intrinsic growth rate γ as the perturbation parameter. We know that $k_1k_2 - k_3 = 0$ or $f(\gamma) = 0$, has two positive roots which are denoted by $\gamma_{1,2}^*$ satisfies that $(k_1k_2 - k)|\rho = 0 = 0$. We also need to determine the sign of the real part of $\frac{d\lambda}{d\rho}$ at $\rho = 0$ when the above equation is valid. Differentiating equation (9) with respect to ρ, we have

$$3\lambda^2\frac{d\lambda}{d\rho} + 2A_1\lambda\frac{d\lambda}{d\rho} + \frac{1}{\delta}\lambda + A_2\frac{d\lambda}{d\rho} + \frac{-(2\gamma-2\beta\delta+\alpha\delta)}{\alpha\delta} = 0 \quad (10)$$

which leads to

$$\frac{d\lambda}{d\rho} = -\frac{\alpha\lambda-(2\gamma-2\beta+\alpha\delta)}{\alpha\delta(3\lambda^2+2A_1\lambda+A_2)} \quad (11)$$

Therefore

$$V_c = sign\left\{-Re\left(\frac{d\lambda}{d\rho}\middle|\rho = 0\right)\right\}$$
$$V_c = sign\left\{-Re\left(\frac{\alpha\omega i-(2\gamma-2\beta\delta+\alpha\delta)}{\alpha\delta(-3A_2+2A_1\omega i+A_2)}\middle|\gamma = \gamma_{1,2}^*\right)\right\}$$
$$V_c = sign\left\{-Re\left(\frac{\alpha\omega i-(2\gamma-2\beta\delta+\alpha\delta)}{-A_2+A_1\omega i}\middle|\gamma = \gamma_{1,2}^*\right)\right\}$$
$$V_c = sign\{-[2\gamma + \alpha(1+\beta) + \alpha\delta - 2\beta\delta]|\gamma = \gamma_{1,2}^*\}$$
$$= sign\left\{-\frac{df(\gamma)}{d\gamma}\middle|\gamma = \gamma_{1,2}^*\right\}$$
$$= -1$$

It can be concluded that when $\gamma = \gamma_1^*$ or $\gamma = \gamma_2^*$ the system of equations (4) to (6) experiences a non-degenerate Hopf bifurcation at the endemic equilibrium point.

4. Numerical Simulation

Next, a numerical simulation will be carried out from the mathematical model equation of the anti-tumor immune response using the ODE45 method with the help of the MATLAB application, with the initial values used $x = 4$, $y = 10$, $z = 1.5$ and using the equation parameter values contained in table [5] , so that a comparison of several conditions will be obtained. In this study, there were five γ treatments in each condition.

Table 5. Parameters and Values of the Mathematical Model of Anti-Tumor Immune Response

No	Parameter	Value	Unit
1	α	0.3	/day
2	β	0.6	/day
3	δ	10	/day
4	γ_1^*	3.88	/day
5	γ_2^*	4.64	/day

4.1 Numerical Simulation of Models When Value γ=2

Based on the parameter values used in this research, a graph is obtained for the firstcondition, namely when $\gamma < (\beta - \alpha)$ and the parameter value $\gamma = 2$ is taken as follows

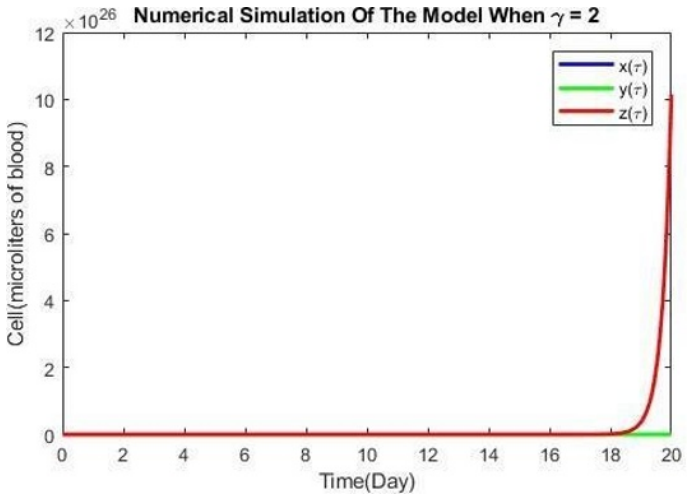

Fig. 1. Simulation of the System of Equations (4) to (6) when $\gamma < (\beta - \alpha)$ by taking $\gamma = 2$, and initial values (4,10,1.5)

From the picture above we can conclude that, when the normal flow rate of immune cells γ is less than the threshold value $(\beta - \alpha)$, then tumor cells will increase uncontrollably. This indicates that tumor development is no longer controlled by the immune system.

4.2 Numerical Simulation of Models When Value $\gamma = 3.5$

Based on the parameter values used in this research, a graph is obtained for the second condition, namely when $(\beta - \alpha) < \gamma < \gamma_1^*$ and the parameter value $\gamma = 3.5$ is taken as follows

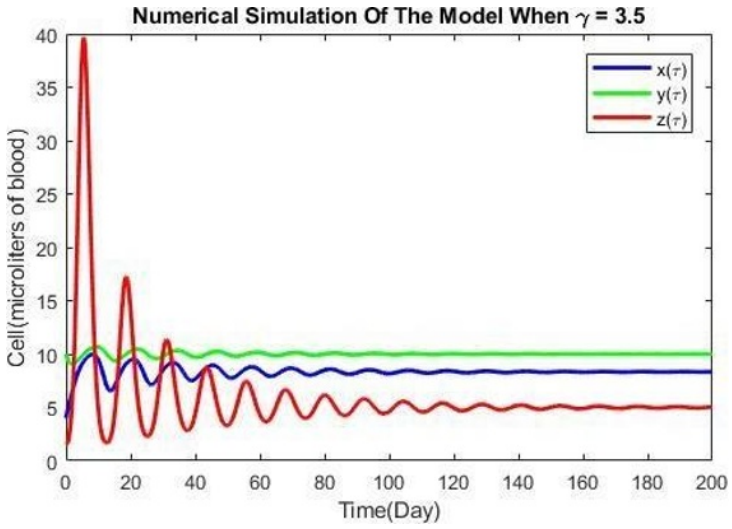

Fig. 2. Simulation of the System of Equations (4) to (6) when $(\beta - \alpha) < \gamma < \gamma_1^*$ by taking $\gamma = 3.5$, and initial value (4,10,1.5)

From the picture above we can conclude that, when the normal flow rate of immune cells γ between $(\beta - \alpha)$ and γ_1^* shows a stable endemic equilibrium point, which means that the level of tumor cells does not change.

4.3 Numerical Simulation of Models When Value $\gamma = 4$

Based on the parameter values used in this research, a graph is obtained for thesecond condition, namely when $\gamma_1^* < \gamma < \gamma_2^*$ and the parameter value $\gamma = 4$ is taken as follow

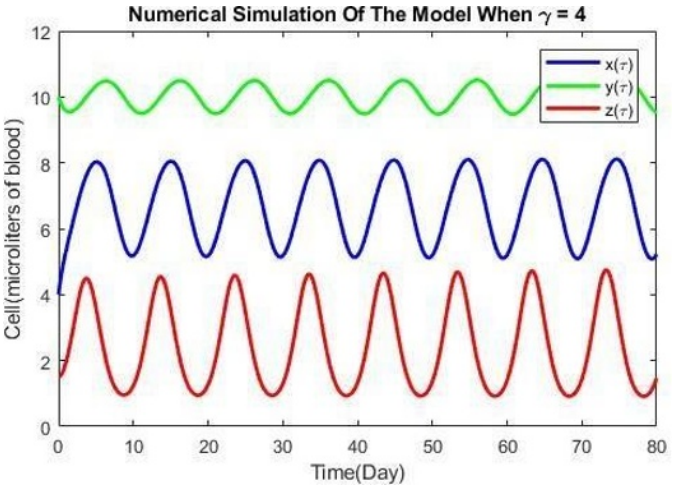

Fig. 3. Simulation of the System of Equation (4) to (6) when $\gamma_1^* < \gamma < \gamma_2^*$ by taking $\gamma = 4$, ad initial values (4,10,1.5)

From the picture above we can conclude that, when the normal flow rate of immune cells γ is in the interval $[\gamma_1^*, \gamma_2^*]$, then the limit cycle will experience bifurcation from the ndemic equilibrium point by disturbances from parameter values γ which are close to a value of 4.64, which indicates that the periodic orbit of the system of equations (4) to (6) occurs at the endemic equilibrium point.

4.4 Numerical Simulation of Models When Value $\gamma = 5$

Based on the parameter values used in this study, a graph for the second condition is obtained, namely when $\gamma_2^* < \gamma < \beta\delta$ and the parameter value $\gamma = 5$ is taken as follows

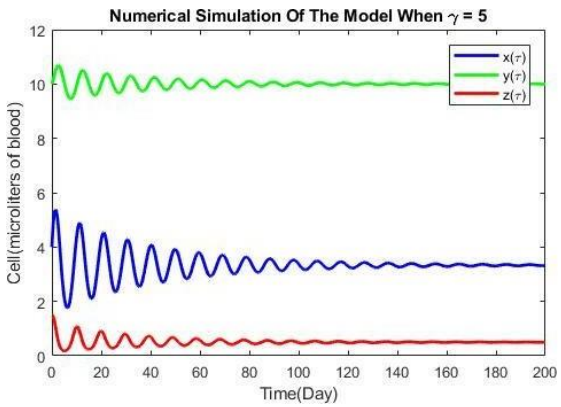

Fig. 4. Simulation of the System of Equations (4) to (6) when $\gamma_2^* < \gamma < \beta\delta$ by taking $\gamma = 5$, and initial values (4,10,1.5)

From the picture above we can conclude that, when the normal flow rate of immune cells γ is between γ_2^* and $\beta\delta$, it shows that the endemic equilibrium point for small tumors willbe stable. This means that the level of tumor cells does not change.

4.5 Numerical Simulation of Models When Value $\gamma = 6.2$

Based on the parameter values used in this study, a graph is obtained for the second condition, namely when $\gamma > \beta\delta$ and the parameter value $\gamma = 6.2$ is taken as follows

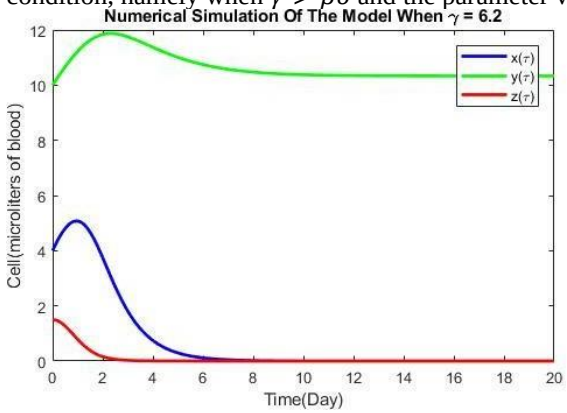

Fig. 5. Simulation of the System of Equations (4) to (6) when $\gamma > \beta\delta$ by taking $\gamma = 5$, and the initial value (4,10,1.5)

From the picture above we can conclude that, when the normal flow rate of immune cells γ is more than the value $\beta\delta$ then the disease-free equilibrium point E_0 is stable, this meansthat tumors will not exist in the body.

5. Conclusion

Based on the objectives and results of the discussion in the previous chapter, the following conclusions are obtained:

1. Based on dynamic analysis of the mathematical model the anti-tumor immune response is obtained
   a. The disease-free equilibrium point results in a point $E_0 = (x^0, y^0, z^0) = (0, \frac{\gamma}{\beta}, 0)$. Based on table (2) it is known that in conditions 1 to condition 4, $\lambda_1, \lambda_2 < 0$ and $\lambda_3 > 0$ are obtained. While in condition 5 obtained $\lambda_1, \lambda_2, \lambda_3 < 0$. So the stability of the disease-free equilibrium point in conditions 1 to 4 is unstable, while in condition 5 it is stable.
   b. The endemic equilibrium point produces point $E_1 = (x^*, y^*, z^*) = \left(\frac{\beta\delta-\gamma}{\alpha}, \delta, \frac{\beta\delta-\gamma}{\gamma+\alpha\delta-\beta\delta}\right)$. Based on the calculation results with the Routh Hurwitz criteria in the table (3) and the eigenvalues in the table (4). It can ben concluded that in condition 2 and condition 4 the type of stability at the endemic equilibrium point is stable. Whereas in condition 1, condition 3, and condition 5 the type of stability at the endemic equilibrium point in unstable.

   c. From table (1) it can be seen that for conditions 1 to condition 4, the value $R_0 > 1$ is obtained, so it can be concluded that there is a tumor in the body. Meanwhile, for condition 5, the $R_0 < 1$ is obtained, so it can be concluded that there is no tumor in the body.

2. The system of equations (4) to (6) of the mathematical model of the anti-tumor immune response experiences a non-degenerate Hopf bifurcation at the endemic equilibrium point, when $\gamma = \gamma_1^*$ atau $\gamma = \gamma_2^*$..
3. Based on numerical simulations of the mathematical model of the anti-tumor immune response using the ode45 method, it is obtained:
   a. For condition 1, that is when $\gamma < (\beta - \alpha)\delta$ and the parameter value $\gamma = 2$ is taken, and by substituting the parameter values in the table (5), the conclusion based on the graphic results is that tumor cells will increase uncontrollably. This indicates that tumor development is no longer controlled by the immune system, which is consistent with the clinically observed phenomen of immune escape.
   b. For condition 2, namely when $(\beta - \alpha)\delta < \gamma < \gamma_1^*$ and the parameter value $\gamma = 3.5$ is taken, and by substituting the parameter values in the table (5), a conclusion is obtained based on the graphic results, namely that it shows a stable endemic equilibrium point, which means that the level of tumor cells does not change.
   c. For condition 3, that is when $\gamma_1^* < \gamma < \gamma_2^*$ and the parameter value $\gamma = 4$ is taken, and by substituting the parameter values in the table (5), a conclusion is obtained based on the graphical results, namely that the boundary cycle will experience a bifurcation from the endemic equilibrium point by the disturbance of the value of the parameter γ which is close to the value of 4.64, which indicates that the periodic orbit of the system of equations (4) to (6) occurs at the endemic equilibrium point.
   d. For conditions 4, namely when $\gamma_2^* < \gamma < \beta\delta$ and the parameter value $\gamma = 5$ is taken, and by substituting the parameter values in the table (5), a conclusion is obtained based on the graphic results, namely that it shows that the endemic equilibrium point for small tumors will be stable. This means the level of tumor cells has not changed.
   e. For condition 5, namely when $\gamma > \beta\delta$ and the parameter value $\gamma = 6.2$, is taken, and by substituting the parameter values in table (5), a conclusion is obtained based on the graphic results, namely that the disease-free equilibrium point is stable, this means that the tumor is not in the body.

References

1 D. Liu, Ruan, S., Zhu, D., Math. Biosci. Eng. **9**, 347–368 (2012)

2 Eryati Darwin, Dwitya Elvira, dan Eka Fithra Elfi, *Imunologi Dan Infeksi*, (Padang: Andalas University Press, 2021)

3 G. E. Yojanvia, Hubungan Antara Asupan Lemak dan Obesitas dengan Kejadian Kanker Payudara di RSUD Kota Yogyakarta, (Yogyakarta: Jurusan Gizi Politeknik Kesehatan Kementerian Kesehatan Yogyakarta, 2019)

4 Liuyong Pang, Liu Sanghong, Xinan Zhang, and Tianhai Tian, Mathematical Modeling and Dynamic analysis of Anti-Tumor Immune Response, Korea: Journal of Applied Mathematics and Computing, 2019.

5 Mehta Atul dan A. Victor Hoffbrand, At a Glance Hematologi Edisi 2, (Jakarta: Erlangga, 2006)

6 Meksianis, Pemodelan Matematika, (PT. Nasya Expanding Management, Pekalongan, 2022)

7 M.M. Prameswari, Kinematika Imunoterapi pada Tumor, Skripsi tidak dipublikasikan, Bogor: Institut Pertanian Bogor, 2011.

8 O. Orakpoghenor, D. O. Avazi, T. P. Markus, and O. S. Olaolu, Lymphocytes : A Brief Review, **3**, pp. 4–8 (2019)

9 S. Ariani, Stop Kanker, (Istana Media, Yogyakarta, 2015)

10 Sinta, Jurnal Keluarga Sehat Sejahtera, 13, 26, (2018)

11 Usman Pagalay, Mathematical Modelling, Malang: UIN Press, 2009.

12 W.E Boyce & DiPrima, R.C., Elementary Differential Equations and Boundary Value Problems, (Von Hoffmann Press, New York, 2001)