

Stability and Bifurcation of Tumor Immune Model with Time Delay

Li Yangjuan*, Xiao Zhengying and Lin Jinzhong

Engineering Training Center, Putian University, Putian 351100, China

Abstract: In this paper, we investigate the effect of time delay on the stability of the tumor immune system using theoretical calculations and numerical simulations. Since it takes a certain time for immune cells to recognize tumor cells to make an appropriate response, a model of tumor-immune system interaction with time delay is established by considering time delay in this process. The four equilibrium points are solved by simplifying the model using Taylor expansion with a small time delay. Then the stability of each equilibrium point of the system under a small time delay is determined by calculating the characteristic roots of each equilibrium point with numerical simulation software. The results show that the system has a bistability phenomenon. The saddle point and stable node are not affected by the delay, while only the stability of the stable foci changes with the time delay with Hopf bifurcation. This study can help determine the optimal time for tumor treatment and provide a reference for analyzing tumor status and treatment.

1 INTRODUCTION

Tumors have become one of the top risk factors for human health. The process of tumor-immune system interaction is a very complex nonlinear kinetic process, which needs to consider not only the interaction between tumor cells and immune cells, but also the proliferation and apoptosis of the cells themselves. Experimental studies alone are not sufficient to fully understand the origin behind the phenomena, but by constructing mathematical physical models, we can effectively reflect the changing pattern of the tumor immune system, which has important theoretical and practical significance for the treatment and preventive control of tumors (Malinzi, 2019; Bashkirtseva, 2020). Kuznetsov et al. (1994) proposed a classical differential equation model of the tumor immune system, which explains phenomena such as tumor dormancy and tumor escape through theoretical analysis and comparison of experimental data. As research progresses, various tumor immune models have been established and many valuable research results have been obtained (Al-Tuwairqi et al., 2020). We have noticed that during tumor proliferation, there is usually a period of latency. Many studies have shown that time delays can disrupt the homeostasis of the human immune system and lead to altered stability (Kayan et al., 2017; Banerjee et al., 2008). Therefore, considering the time delay factor in tumor immune models better reflects the objective pattern and has important scientific significance. In this paper, we consider time delay in the deterministic tumor immune system created by Kuznetsov et al. to investigate the effect of time delay on the stability of the system in depth.

2 TUMOR IMMUNE SYSTEM MODEL WITH TIME DELAY

In order to better understand the tumor immune system, we need to consider not only the proliferation and apoptosis of tumor cells and immune cells, but also factors such as the interaction between them. The growth pattern of tumor cells conforms to the logistic curve. When tumor cells appear in the organism, they will stimulate the immune system to produce an immune response, and the immune effector cells will eliminate the tumor cells, in which some immune cells will also die out. On this basis, Kuznetsov et al. (1994) created the following model of tumor-immune cell interactions:

$$\dot{x} = f_1(x, y) = \sigma + \rho \frac{xy}{\eta + y} - \mu xy - \gamma x \quad (1)$$

$$\dot{y} = f_2(x, y) = \alpha y(1 - \beta y) - xy$$

In Equation (1), x is the number of immune effector cells, σ is the natural growth rate of immune effector cells, $\rho \frac{xy}{\eta + y}$ indicates the growth rate of immune effector cells stimulated by tumor cells, μ is the rate of reduction in the process of effector cell binding to tumor cells, and γ is the natural mortality rate of effector cells. y is the tumor cell count, α is the natural growth rate of tumor cells and β is the inverse of the environmental carrying capacity. The values of each parameter are as follows: $\sigma = 0.1181$, $\rho = 1.131$, $\eta = 20.19$,

* Corresponding author: toliyangjuan@163.com

$$\mu = 0.00311, \quad \delta = 0.3743, \quad \alpha = 1.636, \quad \beta = 0.002.$$

Since it takes time for immune cells to recognize tumor cells to respond, considering time delay in this process is more reasonable. Therefore, both $\rho \frac{xy}{\eta + y}$ and μxy in Model (1) are rewritten after including the delay as $\rho \frac{x_\tau y_\tau}{\eta + y_\tau}$ and $\mu x_\tau y_\tau$, where $x_\tau = x(t - \tau)$, $y_\tau = y(t - \tau)$. A model of the tumor immune system with time delay was obtained as follows:

$$\begin{aligned} \dot{x} &= f_1(x, x_\tau, y_\tau) = \sigma + \rho \frac{x_\tau y_\tau}{\eta + y_\tau} - \mu x_\tau y_\tau - \gamma x & (2) \\ \dot{y} &= f_2(x, y) = \alpha y(1 - \beta y) - xy \end{aligned}$$

It is difficult to analyze the tumor immune system model with time delay directly in theory, requiring an approximation method to simplify it for further study by analytical methods. If the delay time τ is short, Model (2) can be simplified by using the Taylor expansion method with a small delay to obtain:

$$\begin{aligned} f_1(x, x_\tau, y_\tau) &= f_1(x, y) - \tau \left[\frac{\partial f_1(x, x_\tau, y_\tau)}{\partial x_\tau} \dot{x} + \frac{\partial f_1(x, x_\tau, y_\tau)}{\partial y_\tau} \dot{y} \right] \Bigg|_{\substack{x_\tau=x \\ y_\tau=y}} + O(\tau^2) \\ &= f_1(x, y) - \tau \left[\frac{\partial f_1(x, x_\tau, y_\tau)}{\partial x_\tau} f_1(x, y) + \frac{\partial f_1(x, x_\tau, y_\tau)}{\partial y_\tau} f_2(x, y) \right] \Bigg|_{\substack{x_\tau=x \\ y_\tau=y}} + O(\tau^2) \end{aligned} \quad (3)$$

$O(\tau^2)$ in the above equation is a higher order infinitesimal with respect to τ . Substituting Equations (2) into (3), ignoring the higher order terms, $f_1(x, x_\tau, y_\tau)$ is obtained by taking the first order approximation:

$$\begin{aligned} f_1(x, x_\tau, y_\tau) &\approx f_1(x, y) - \\ &\tau \cdot \left(\left(\frac{\rho y}{\eta + y} - \mu y \right) f_1(x, y) + \left(\frac{\rho x \eta}{(\eta + y)^2} - \mu x \right) f_2(x, y) \right) \end{aligned}$$

Assume that:

$$f(x, y) = f_1(x, y) - \tau \cdot \left(\left(\frac{\rho y}{\eta + y} - \mu y \right) f_1(x, y) + \left(\frac{\rho x \eta}{(\eta + y)^2} - \mu x \right) f_2(x, y) \right) \quad (4)$$

Then Model (2) is reduced to:

$$\begin{aligned} \dot{x} &= f(x, y) \\ \dot{y} &= f_2(x, y) \end{aligned} \quad (5)$$

3 DELAYED EQUILIBRIUM POINT OF TUMOR IMMUNE SYSTEM

The equilibrium point of the tumor immune system with time delay satisfies the following equation:

$$\begin{aligned} \dot{x} &= f(x, y) = 0 \\ \dot{y} &= f_2(x, y) = 0 \end{aligned} \quad (6)$$

According to Equations (1), (4) and (6), the equilibrium point of the tumor immune system with a time

delay can be found with 4 significant solutions, denoted as $P_i = (x_i, y_i)$ ($i = 0, 1, 2, 3$), as follows:

$$\begin{aligned} P_0 &= (x_0, y_0) = (0.3155, 0) \\ P_1 &= (x_1, y_1) = (1.6092, 8.1897) \\ P_2 &= (x_2, y_2) = (0.7598, 267.7980) \\ P_3 &= (x_3, y_3) = (0.1730, 447.1342) \end{aligned}$$

In the equilibrium point P_0 , the number of tumor cells is 0, which is called the tumor-free equilibrium state, indicating that there are no tumor cells or tumor cells have been eliminated. Equilibrium point P_1 contains a relatively small number of tumor cells and a high level of immune effector cells, indicating the tumor dormancy state in which tumor cells coexist with immune cells. The equilibrium points P_2 and P_3 contain plenty of tumor cells, indicating a significant tumor proliferation and a gradual failure of the immune system, which can be called the equilibrium state of tumor explosion.

4 STABILITY AND BIFURCATION ANALYSIS OF EQUILIBRIUM POINTS

4.1 Stability analysis

It is important that the stability of the equilibrium point has practical significance. In the tumor immune system, an unstable equilibrium state may be transformed into other situations at any time, and only the stable equilibrium state is the best time to treat the tumor. It is difficult to derive analytical solutions for nonlinear dynamical systems with time delays, which rely heavily on numerical calculations. In the paper, the DDE-Biftool software for numerical bifurcation analysis of dynamical systems with time delay is used to analyze the stability and bifurcation of the system (Engelborghs et al., 2002).

The sign of the real part of the characteristic root of the equilibrium point can be used to determine the stability, and the method is used to analyze the stability of four equilibrium points P_0 , P_1 , P_2 and P_3 of the tumor immune system under a small time delay. Taking the small delay time $\tau = 0.1$, the characteristic roots of each equilibrium point of the system are found, as shown in Figure 1, with the vertical axis indicating the imaginary part of the characteristic root and the horizontal axis indicating the real part of the characteristic root. From figure 1, it can be seen that P_0 and P_2 have two real characteristic roots with opposite signs, which can be determined as saddle points according to nonlinear dynamics theory. The characteristic roots of the equilibrium point P_1 are a complex-conjugate pair with both negative real parts, and thus are stable foci. The characteristic roots of the equilibrium point P_3 are two negative real numbers, therefore P_3 is a stable node.

There is a bistable phenomenon in the tumor immune system under small time delays, that is, the tumor dormant equilibrium state and the tumor explosion equilibrium state. It indicates that the final state of the tumor immune system depends on the initial conditions. If the initial density of tumor cells is low, the immune cells are

activated and have some suppressive effect on the tumor, and then the system will be in a tumor dormant equilibrium state. Conversely, when the initial density of tumor cells is high and the immune system fails, the system will tend to a tumor explosion state.

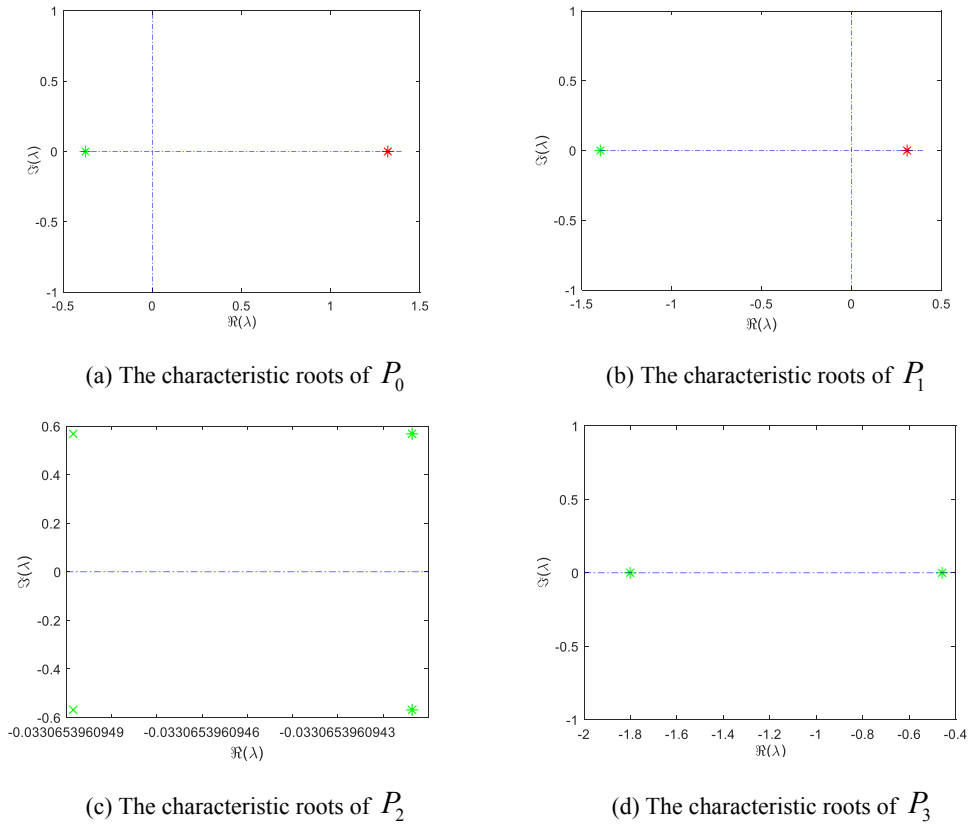


Figure 1: Approximate characteristic root (X) and modified characteristic root (*) for each equilibrium point of the system at $\tau = 0.1$.

4.2 Bifurcation analysis

Considering the time delay factor allows the tumor immune system to present a richer and more complex dynamical behavior, potentially disrupting the equilibrium state of the system and leading to changes in stability, triggering bifurcation, periodic oscillation phenomena or irregular chaotic behavior (Kayan et al., 2017; Ping et al., 2014.). Many studies have suggested that in the tumor immune system, changing the amount of time delay causes the system to exhibit different kinetic behavior (Rihan et al., 2014; Banerjee et al., 2008). Rihan et al. (2012) developed a tumor immune model containing time delay parameters and investigated the effect of time delay on the stability of the system, which can predict

tumor dormancy. Khajanchi et al. (2019) introduced time delay in the tumor immune system, using theoretical analysis and numerical simulations, and found that the time delay parameter of tumor growth can regulate the stability of the system. When the threshold is exceeded, a periodic oscillatory solution will be generated, demonstrating the phenomenon of long-term tumor recurrence. In this paper, we analyze the effect of time delay on the stability of the equilibrium point of the tumor immune system using the extended topology algorithm. We consider time delay as the change parameter, from which the equilibrium point changes with the parameter, and calculate and graph the change curve of the real part of the characteristic root at the equilibrium point with the parameter as a way to study the stability change and bifurcation of the system.

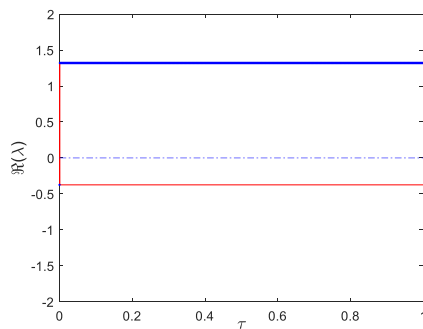


Figure 2: Variation of the real part of the characteristic root at equilibrium point P_0

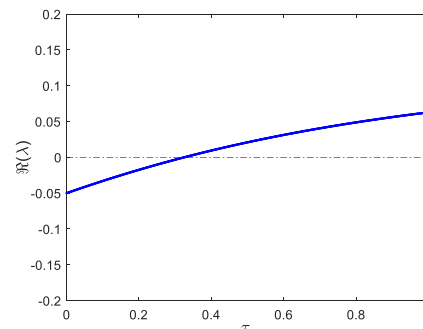


Figure 3: Variation of the real part of the characteristic root at equilibrium point P_1

Bifurcation analysis was applied to the saddle point P_0 . Figure 2 shows the variation curve of the real part of the characteristic root at the equilibrium point P_0 with time delay. As can be seen from Figure 2, the real part of the characteristic root does not alter during the change of the time delay parameter τ from 0 to 1, which remains a straight line; therefore, the stability of the equilibrium point P_0 does not change with time delay and remains a saddle point.

The bifurcation analysis is performed for the stable foci P_1 . The variation curve of the real part of the characteristic root with the time delay parameter τ is shown in Figure 3. The change of the delay parameter τ from 0 to 1 has the real part of the characteristic root crossing the zero line, which indicates the change of the real part of the characteristic root from a negative value to

0 and then from 0 to a positive value, and the stability of the system is transformed from stable to unstable. When $\tau = 0.325$, the characteristic root real part $\text{Re}(\lambda) = 0$, and the system develops a Hopf bifurcation. Hopf bifurcation is a very special kind of bifurcation where the equilibrium point changes from stable to unstable as the parameter changes past the bifurcation value, from which the limit loop is generated. Figure 4 shows the characteristic roots of this Hopf bifurcation point, and a pair of purely imaginary roots, about $\pm 0.5480i$, appear in the figure, proving the existence of the Hopf bifurcation.

Starting from this Hopf bifurcation point, a perturbation is applied and corrected to obtain the periodic solution branch of Hopf bifurcation by extension, as shown in Figure 5. This periodic solution branch exists for a certain time delay range and the amplitude of the periodic solution increases as the delay time increases until the system cannot sustain the periodic oscillation when the delay time τ is about 2.7.

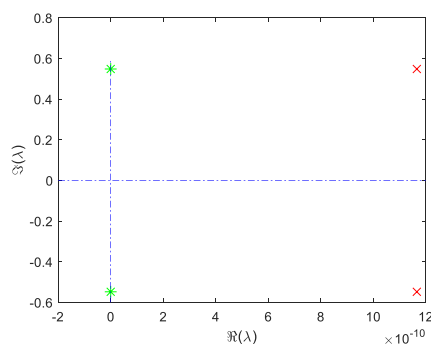


Figure 4: Characteristic root of Hopf bifurcation points

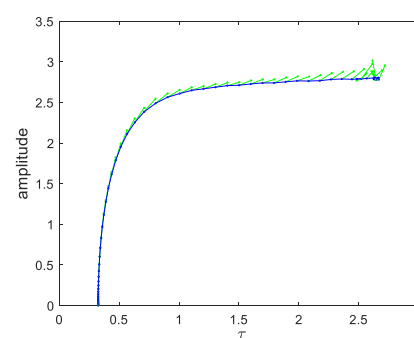


Figure 5: Hopf bifurcation periodic solution branch

Bifurcation analysis was applied to saddle point P_2 . Figure 6 shows the variation curve of the real part of the characteristic root at saddle point P_2 with the time delay parameter τ . From the figure, it can be seen that the change curve of the real part of the characteristic root does not cross the zero axis, and the number notation of the real part of the characteristic root does not change in the small delay time period; therefore, the stability of the

equilibrium point P_2 does not change with the time delay and remains as a saddle point.

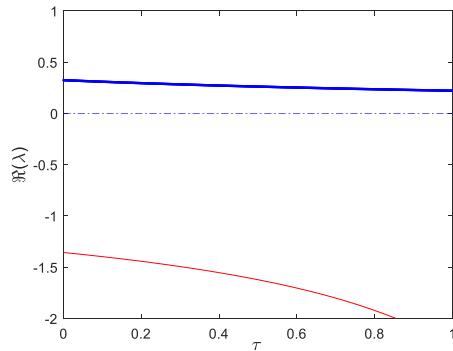


Figure 6: Variation of the real part of the characteristic root at equilibrium point P_2

For the bifurcation analysis of the stable node P_3 , it can be seen from Figure 7 that the real parts of the characteristic roots are below the zero line, all of them are negative, and the stability of the system has not changed and remains a stable node.

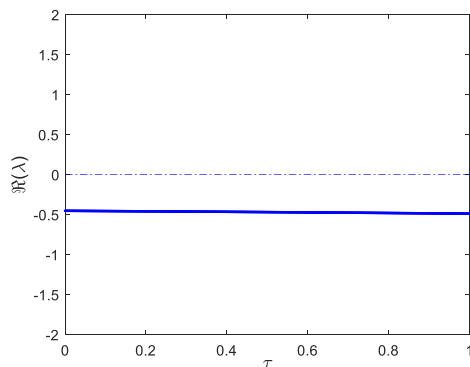


Figure 7: Variation of the real part of the characteristic root at equilibrium point P_3

5 DYNAMICS SIMULATION OF HOPF BIFURCATION

After studying the stability and bifurcation of each equilibrium point of the tumor immune system, it is known that the stability of saddle points P_0 and P_2 and stable node P_3 is not affected by the delay when the system is in a small delay time period, i.e., during the change of τ from 0 to 1. Only the stability of the stable foci P_1 changes with the time delay. At the delay parameter reaches the bifurcation critical value of 0.325, a characteristic root real part crosses the zero line and the system appears Hopf bifurcation.

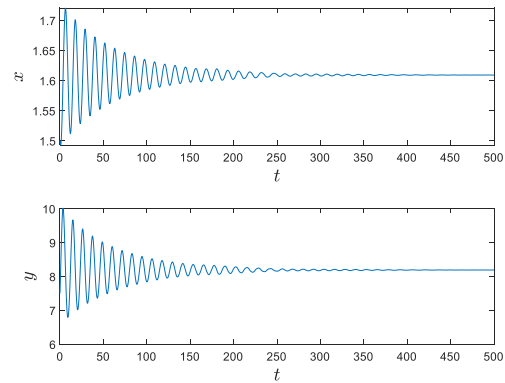


Figure 8: $\tau = 0.2$, immune effector cells x and tumor cells y converge to the equilibrium point with time.

To better understand the interaction between tumor cells and immune effector cells, kinetic simulations were performed to analyze the change of stable foci P_1 with delay. When the delay is less than the bifurcation threshold value of 0.325, take $\tau = 0.2$ for numerical simulation to obtain Figure 8, the tumor immune system manifests that the tumor cells and effector cells tend to the equilibrium point in the form of oscillation, and finally reach the equilibrium point P_1 with the increase of time. It shows that the immune system can control the growth of tumor cells inside the body at this time, and the body is in a state of balance. When the time delay $\tau = 0.325$, the system starts to develop Hopf bifurcation with a limit loop (see Figure 9(a)), and the trajectory adjacent to the stable force P_1 tends to this stable limit loop, as shown in Figure 9(b).

The kinetic behavior of the tumor immune system exhibits stable periodic oscillatory properties, as shown in Figure 10. It illustrates that there is a dynamic balance between the immune system and tumor cells in this state. The proliferation of tumor cells is inhibited by the immune system, which recognizes and eliminates tumor cells, but there may still be some tumor cells that can escape the elimination effect of the immune system and enter into a slow proliferation process, resulting in a tumor-bearing survival state in which tumors and organisms coexist. However, the equilibrium state of this tumor immune system is dynamic, and once the equilibrium is disrupted, it may lead to uncontrollable states that tumor cells explode. When the time delay τ continues to increase, the amplitude of the cycle solution rises and τ reaches about 2.7, the tumor immune system is unable to maintain a state of dynamic equilibrium, with immune cells decaying sharply and tumor cells growing substantially, and a tumor explosion occurs, as shown in Figure 11.

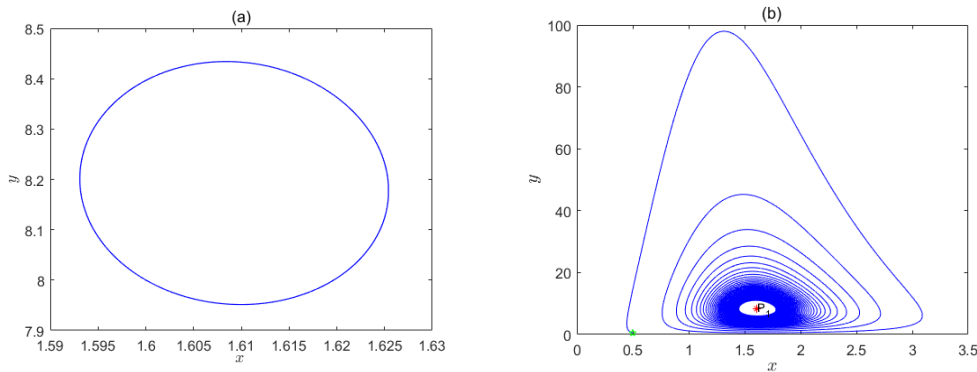


Figure 9: $\tau = 0.325$, phase graph (a) and track line graph (b).

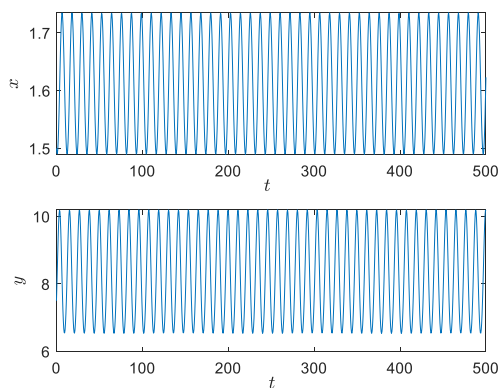


Figure 10: $\tau=0.325$, immune effector cells x and tumor cells y converge to a cyclic oscillation state with time.

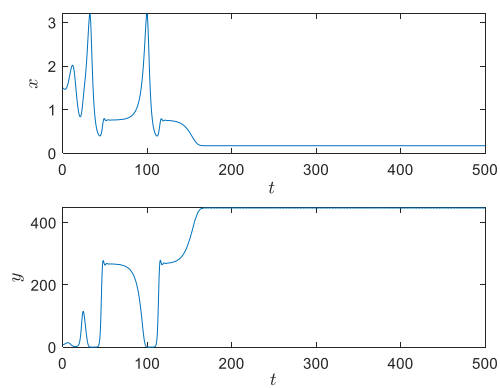


Figure 11: $\tau=2.7$, tumor explosion.

6 CONCLUSIONS

In this study, the role of time delay was considered in the tumor immune system model proposed by Kuznetsov et al. A small delay Taylor expansion was used to simplify the system to find four meaningful equilibrium points of the system, tumor-free equilibrium point P_0 , tumor dormant equilibrium point P_1 , and two tumor explosion equilibrium points P_2 and P_3 . We use the numerical simulation method to determine the stability of each equilibrium point, P_0 and P_2 are the saddle points, P_1 is the stable focus, P_3 is the stable node, and there is a bistability phenomenon in the system.

Time delay can affect the kinetic morphology of the tumor immune system. When the delay is small, the stability of saddle points P_0 and P_2 as well as the stable node P_3 is not affected by the delay. Only the stability of stable foci P_1 changes with the delay, and a Hopf bifurcation occurs. There is a dynamic balance between the immune system and the tumor cells, leading to a state of tumor-bearing survival in which the tumor and the organism coexist. As the delay continues to increase, the system is unable to maintain dynamic equilibrium,

resulting in a tumor explosion in the organism. The results of the study can help determine the optimal time for tumor treatment and provide a reference for analyzing tumor status and treatment.

ACKNOWLEDGEMENTS

This work was supported by Fujian Province Young and Middle School Teacher Education Research Project (JAT200515).

REFERENCES

1. Al-Tuwairqi S M., Al-Johani N O., Simbawa E A., 2020. Modeling dynamics of cancer radiotherapy. *Journal of Theoretical Biology*,506:110405. DOI : 10.1016/j.jtbi.2020.110405.
2. Banerjee S., Sarkar R R., 2008. Delay-induced model for tumor-immune interaction and control of malignant tumor growth. *Biosystems*, 91(1):268-288. DOI : 10.1016/j.biosystems.2007.10.002.
3. Bashkirtseva I., Ryashko L., 2020. Analysis of noise-induced phenomena in the nonlinear tumor-immune system. *Physica A: Statistical Mechanics and its Applications*, 549:123923. DOI : 10.1016/j.physa.2019.123923.
4. Engelborghs K., Luzyanina T., Roose D., 2002. Numerical bifurcation analysis of delay differential equations using

- DDE-BIFTOOL. *ACM Transactions on Mathematical Software*, 28(1):1-21. DOI : 10.1145/513001.513002.
5. Kayan Ş., Merdan H., Yafia R., et al., 2017. Bifurcation Analysis of a Modified Tumor-immune System Interaction Model Involving Time Delay. *Mathematical Modelling of Natural Phenomena*, 12(5):120-145. DOI : 10.1051/mmnp/201712508.
 6. Khajanchi S., Nieto J J., 2019. Mathematical modeling of tumor-immune competitive system, considering the role of time delay. *Applied Mathematics and Computation*, 340:180-205. DOI : 10.1016/j.amc.2018.08.018.
 7. Kuznetsov V A., Makalkin I A., Taylor M A., et al., 1994. Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. *Bulletin of Mathematical Biology*, 56(2):295-321. DOI : 10.1016/s0092-8240(05)80260-5.
 8. Malinzi J., 2019. Mathematical Analysis of a Mathematical Model of Chemovirotherapy: Effect of Drug Infusion Method. *Computational and Mathematical Methods in Medicine*, 2019:1-16. DOI : 10.1155/2019/7576591.
 9. Ping B., Xiao H., 2014. Hopf bifurcation for tumor-immune competition systems with delay. *Electronic Journal of Differential Equations*, 2014(27): 1-13. DOI : 10.1155/2014/723159.
 10. Rihan F A., Abdel Rahman D H., Lakshmanan S., et al., 2014. A time delay model of tumour-immune system interactions: Global dynamics, parameter estimation, sensitivity analysis. *Applied Mathematics and Computation*, 232:606-623. DOI : 10.1016/j.amc.2014.01.111.
 11. Rihan F A., Safan M., Abdeen M A., et al., 2012. Mathematical Modeling of Tumor cell Growth and Immune System Interactions. In: *International Conference Mathematical and Computational Biology 2011*. Malacca, Malaysia. pp:95-111. DOI : 10.1142/S2010194512005156.