

THE INFLUENCE OF DELAYS AND INJECTION TREATMENTS ON THE DYNAMICS OF TUMOR-IMMUNE SYSTEM*

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Abstract We propose a tumor-CD4⁺-cytokine-host system with two delays and injection treatments, where two delays denote activation delays for CD4⁺ T cells and cytokines respectively and host cells compete with tumor cells. First we prove the positivity and boundedness of solutions without injection treatments, the positivity means that tumor cells always exist, the boundedness means that immune cells can control the increase of tumor cells, then we discuss the influence of two delays on the dynamics of system, that is as any of the delays is sufficiently small, the corresponding interior positive equilibrium point is locally stable, as the delay increases to critical value, Hopf bifurcation occurs and periodic solution bifurcates from the equilibrium point, which means the relapse of tumor cells occurs, furthermore base on center manifold and normal form, we study the property of Hopf bifurcation, at last, in absence of delay, we study the influence of relative parameters on the volume of tumor cells and feasibility of injection treatments of CD4⁺ T cells and cytokines on eradication of tumor cells, that is the tumor cells can be eradicated if the dose of injection treatment of CD4⁺ T cells or cytokines is sufficiently large. All the results are supported by simulations.

Keywords Immunotherapy, tumor-immune-host system, delays, Hopf bifurcation, stability, cytokine.

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1. Introduction

As we know, malignant tumor has the feature of unregulated proliferation, rapid growth and deadly impact, which causes many deaths worldwide. American cancer report 2018 showed that more than 15.5 million patients of tumor arise and tumor is the second cause of death in USA. The tumor cells [35] grow uncontrollably and invade distant parts of body, our immune system can recognize tumor antigen and initiate anti-tumor response, we call the mechanism “Tumor-Immune-Surveillance” Hypothesis [7], which was formulated in 1957 and showed that immune system has the ability of eliminating tumor cells before they grow with clinical feature.

There are several therapies [14, 31] toward malignant tumor, such as immunotherapy, chemotherapy, radiation therapy, where immunotherapy depends on white blood cells, especially CD8⁺ T cell, Natural Killer cells and macrophages [27]. Some works [1, 28] demonstrated that immune cells can lyse tumor cells effectively. For all the vertebrates, the major histocompatibility complex (MHC) denotes the molecules on cell surface, which are encoded by a

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large gene family, the MHC can be divided into three subgroups: Class I-III. The Cytotoxic T lymphocytes (CTLs), such as $CD8^+$ T cells can recognize tumor antigen [25] in association with molecules of MHC class I on tumor cells. However some evidences have shown that tumor cells can evade recognition by CTLs, for certain tumor cells [25] do not express MHC class I antigen on the cell surface. $CD4^+$ T cells are always considered as a helper role, which activate $CD8^+$ to kill tumor cell, but some works [5, 25, 38] showed that $CD4^+$ cells play more direct role on eradicating tumor cells by producing cytokines and chemokines [25, 38], furthermore, in absence of $CD8^+$ T cells and Natural Killer cells, $CD4^+$ T cells can kill tumor cells, that is tumor cells may be eradicated by tumoricidal myeloid cells or anti-angiogenic cytokines, such as IL-4 secreted by $CD4^+$ T cells [25, 38].

Eftimie [8] proposed a model consisting of either six or seven ordinary differential equations, which included tumor cells, $CD4^+$ T cells, cytokines of suppressing tumor, cytokines of promoting tumor, type 1 (by Th 1 cells) cytokines, type 2 (by Th 2 cells) cytokines and other immune cells, they studied the eradication of skin tumor by $CD4^+$ T cells, where $CD4^+$ T cells can be divided into Th1 cells and Th2 cells, by data [25] and simulation, they demonstrated the effective role of $CD4^+$ T cells in tumor eradication depends on the feedback between Th2 cells and eosinphils. Mattes [25] demonstrated that $CD4^+$ T cells can recognize tumor antigen and secrete cytokines with profile characteristic of Th 2 cells, the cytokines can clear established lung and visceral metastases of melanoma, which is resistant to CTLs. Perez-Diez et al. [5] compared the role of $CD4^+$ T cells and $CD8^+$ cells on eradication of tumor, they concluded that $CD4^+$ T cells play more effect than $CD8^+$, even when tumor cells express molecules of MHC class I but not MHC class II.

There are many works [2, 6, 12, 13, 17, 29, 34, 39] about the dynamics of tumor-immune system, L. Anderson [2] thought that $CD4^+$ T cells secrete cytokines to eradicate tumor cells, the production of $CD4^+$ cells depends on the interaction between $CD4^+$ T cells and tumor cells, they proposed the following tumor- $CD4^+$ -cytokine system:

$$\begin{cases} \frac{dx}{dt} = rx(1 - \frac{x}{K}) - \frac{\delta xz}{m+x}, \\ \frac{dy}{dt} = \frac{\beta xy}{k+x} - ay, \\ \frac{dz}{dt} = \frac{\alpha xy}{b+x} - \mu z, \end{cases} \quad (1.1)$$

where $x(t)$ denotes the volume of tumor cells, $y(t)$ denotes the volume of $CD4^+$ T cells, $z(t)$ denotes the volume of cytokines secreted by $CD4^+$ T cells, they investigated the role of $CD4^+$ T cells on eradication of tumor, studied the injection treatments of $CD4^+$ T cells and cytokines and concluded that the doses of injection treatments are critical for eradication of tumor.

In tumor micro-environment, for the cellular differentiation, chemical transportation and exchanged chemical signal is not instantaneous, besides immune cells take some time to identify tumor and react properly [21], delays always exist in tumor-immune system [4, 6, 19, 20, 32, 33], delay bring rich dynamics, such as Hopf bifurcation.

The interaction between immune cells and tumor cells is complicate, the immune cells require time to react after recognizing tumor cells, Sardar et al. [33] pointed out time delays play important role on the interaction among immune cells, cytokines and tumor cells, they can accurately represent the intricate and delayed nature of immune response by introducing time delays into tumor-immune system. The dynamics of delayed immune-tumor system were discussed [4, 19, 20] by many researchers, some works [19, 20] thought the growth and differentiation of immune cells

by tumor cells require time, so they introduced delay into system and demonstrated the delay can induce periodic oscillation, Dehingia et al. [4] thought that the proliferation of hunting T cells depends on the interaction between hunting T cells and resting T cells, they introduced delay into system, where the delay denotes the time required for the interaction, they showed that the delay also induces periodic oscillation of system.

For activation of immune cells by tumor cells need some time, Dong et al. [6] proposed the following tumor-immune system with two delays:

$$\begin{cases} \frac{dT}{dt} = aT(t)(1 - bT(t)) - nE(t)T(t), \\ \frac{dE}{dt} = s_1 + k_1T(t - t_1)E(t - t_1) - d_1E(t) + pE(t)H(t), \\ \frac{dH}{dt} = s_2 + k_2T(t - t_2)H(t - t_2) - d_2H(t), \end{cases} \quad (1.2)$$

where $T(t)$, $E(t)$, $H(t)$ denote the volume of tumor cells, effect T cells and helper T cells, two delays τ_1, τ_2 denote activation delays of effect T cells and Helper T cells respectively, they established the stability of tumor-free and immune-control equilibrium points and the existence of Hopf bifurcation caused by two delays, the results showed that both delays do not affect the stability of tumor-free equilibrium point, but destabilize the immune-control equilibrium point and cause periodic oscillation, the authors numerically illustrated how two delays can change the stability region of immune-control equilibrium point and display the different impacts on the control of tumor cells.

The competition of cells exists in some species, such as mammals [24], for survival and growth, near blood vessels, tumor cells compete with health cells for nutrients and oxygen, the tumor cells appear from single transformed cells by mutation, the nearby host cells always spatially inhibit them [9], the winner cells during competition fill in the vacated space of nearly failed cells and continue to proliferate, when tumor cells win, they can propagate within normal tissue [23], on the other hand, the health cells inhibit tumor cells and cause the death of oncogenic mutant cells within tissue [23], competition of cells exists and plays great role on the dynamics of biological system, introducing competition between tumor cells and host cells should be valuable, Fujita [9] pointed out that competition of anti-tumor occurs only when the tumor cells encounter host cells, while the immune cells do not participate, the classical Lotka-Volterra equation was used to describe the competition between tumor cells and host cells regardless of immune cells, which means the host cells battle with tumor cells for territories and nutrients [26].

Activated by above works, we take some changes about system (1.1):

- (i) Some works [13, 36] thought that $CD4^+$ T cells are a kind of T lymphocyte cells and can be activated by cytokines such as $IFN-\gamma$, the proliferation of $CD4^+$ T cells is up-regulated by cytokines and the tumor cells, we take the same expression.
- (ii) Similar to [6], we introduce two discrete delays, one is the activation delay of $CD4^+$ T cells, the other is activation delay of cytokines.
- (iii) For the tumor cells and normal tissue cells compete for resource and space [35], besides signaling interactions between neoplastic and stromal tissues are important for tumor production [10], so compare with [2], we add host cells to system (1.1), obtain the following tumor- $CD4^+$ -cytokine-host system with two delays:

$$\begin{cases} \frac{dx}{dt} = r_1x(1 - \frac{x}{k_1}) - \frac{a_1xz}{b_1+x} - d_1xw, \\ \frac{dy}{dt} = \frac{a_2x(t-\tau_1)z(t-\tau_1)}{b_2+x(t-\tau_1)} - c_1y - d_2xy, \\ \frac{dz}{dt} = \frac{a_3x(t-\tau_2)y(t-\tau_2)}{b_3+x(t-\tau_2)} - c_2z, \\ \frac{dw}{dt} = r_2w(1 - \frac{w}{k_2}) - d_3xw, \end{cases} \quad (1.3)$$

with initial conditions

$$\begin{aligned} x(\theta) = \phi_1(\theta) \geq 0, y(\theta) = \phi_2(\theta) \geq 0, z(\theta) = \phi_3(\theta) \geq 0, w(\theta) = \phi_4(\theta) \geq 0, \\ \theta \in [-\tau, 0], \tau = \max\{\tau_1, \tau_2\}, \phi_i(\theta) \in C([-\tau, 0], R^+), i = 1, 2, 3, 4 \end{aligned} \quad (1.4)$$

where $x(t), y(t), z(t), w(t)$ denote the volume of tumor cells, CD4⁺ T cells, cytokines and host cells respectively, some works [8, 13] thought that cytokines directly destroy tumor cells and has limited property of lysing tumor cells, so they took Michaelis Menten kinetics $\frac{a_1xz}{b_1+x}$ to describe the eradication of tumor by cytokines, both the tumor cells and host cells grow logistically. r_1, r_2 denote the intrinsic growth rates of tumor and host cells respectively, k_1, k_2 denote the carrying capacity of tumor cells and host cells respectively, b_1, b_2, b_3 are the half saturation constants of response function, a_1 denotes the killing rate of tumor cells by cytokines, a_2 denotes production rate of CD4⁺ T cells induced by cytokines, a_3 denotes production rate of cytokines secreted by CD4⁺ T cells, d_1 denotes killing rate of tumor cells by host cells, d_2 denotes the loss rate of CD4⁺ T cells by tumor cells, d_3 denotes killing rate of host cells by tumor cells, c_1, c_2 denote the natural death rates of CD4⁺ T cells and cytokines respectively, we will discuss the positivity and boundedness of solutions of system (1.3), reveal the influence of delays on the dynamics of system (1.3), the influence of relative parameters on the volume of tumor cells without delays. In absence of delays, we will discuss the feasibility of injection treatments of CD4⁺ T cells and cytokines on eradication of tumor cells.

This paper is organized as follows, first we study the existence of equilibrium points, the positivity and boundedness of solutions of system (1.3), then around interior positive equilibrium point, we study the influence of two delays on the dynamics of system (1.3), the influence of relative parameters on the volume of tumor cells without delays. At last, in absence of delays, under three cases: (1) Injection treatment of only CD4⁺ T cells, (2) injection treatment of only cytokines, (3) injection treatments of both CD4⁺ T cells and cytokines, the feasibility of injection treatment on eradication of tumor cells, all the results are supported by simulation.

2. Existence of equilibrium points, positivity and boundedness of solutions of system

Before our discussion, we give the existence of equilibrium points:

- (1) Equilibrium points $E_0(0, 0, 0, 0)$, $E_1(k_1, 0, 0, 0)$, $E_2(0, 0, 0, k_2)$ always exist.
- (2) Equilibrium point $E_3(x_3, 0, 0, w_3) = (\frac{k_1r_2(d_1k_2-r_1)}{d_1d_3k_1k_2-r_1r_2}, 0, 0, \frac{k_2r_1(d_3k_1-r_2)}{d_1d_3k_1k_2-r_1r_2})$ exists if

$$d_1k_2 - r_1 > 0, d_3k_1 - r_2 > 0, d_1d_3k_1k_2 - r_1r_2 > 0,$$

hold.

Table 1. The values of parameters.

Parameter	Value	Unit
r_1	0.514 [8]	day ⁻¹
k_1	9.8039×10^8 [8]	day
a_1	0.2 [8]	cell(day) ⁻¹ × (pg/ml) ⁻¹
b_1	10^5 [18]	cells
d_1	1.1×10^{-10} [22]	(cell day) ⁻¹
a_2	(0.008, 1.008) [8]	cell(day) ⁻¹
b_2	10^3 [3]	cells
c_1	0.1 [2]	day ⁻¹
d_2	10^{-7} [8]	(cell day) ⁻¹
a_3	5.4 [8]	pg/ml × (cell day) ⁻¹
b_3	10^3 [8]	cells
c_2	34 [8]	day ⁻¹
r_2	0.18 [22]	day ⁻¹
k_2	10^9 [22]	day
d_3	4.8×10^{-10} [22]	(cell day) ⁻¹

(3) For equilibrium points $E_4(x_4, y_4, z_4, 0)$, where

$$y_4 = \frac{a_2 x_4 z_4}{(b_2 + x_4)(c_1 + d_2 x_4)}, \quad z_4 = \frac{r_1}{a_1} \left(1 - \frac{x_4}{k_1}\right) (b_1 + x_4),$$

and x_4 satisfies

$$\begin{aligned} & c_2 d_2 x_4^3 + (b_2 c_2 d_2 + b_3 c_2 d_2 - a_2 a_3 + c_1 c_2) x_4^2 \\ & + (b_2 b_3 c_2 d_2 + b_2 c_1 c_2 + b_3 c_1 c_2) x_4 + b_2 b_3 c_1 c_2 = 0. \end{aligned} \quad (2.1)$$

$E_4(x_4, y_4, z_4, 0)$ exists if equation (2.1) has positive root x_4 .

(4) For equilibrium points $E_5(x_5, y_5, z_5, w_5)$, where

$$y_5 = \frac{c_2 z_5 (b_3 + x_5)}{a_3 x_5}, \quad w_5 = -\frac{k_2}{r_2} (d_3 x_5 - r_2),$$

where x_5, z_5 satisfy

$$A_{11}(x_5)^2 + A_{12}x_5 + A_{13}z_5 + A_{14} = 0, \quad (2.2)$$

$$A_{21}(x_5)^3 + A_{22}(x_5)^2 + A_{23}x_5 + A_{24} = 0, \quad (2.3)$$

where

$A_{11} = d_1 d_3 k_1 k_2 - r_1 r_2$, $A_{12} = b_1 d_1 d_3 k_1 k_2 - d_1 k_1 k_2 r_2 - b_1 r_1 r_2 + k_1 r_1 r_2$, $A_{13} = -a_1 k_1 r_2$, $A_{14} = b_1 k_1 r_1 r_2 - b_1 d_1 k_1 k_2 r_2$, $A_{21} = -c_2 d_2$, $A_{22} = a_2 a_3 - b_2 c_2 d_2 - b_3 c_2 d_2 - c_1 c_2$, $A_{23} = -(b_2 b_3 c_2 d_2 + b_2 c_1 c_2 + b_3 c_1 c_2)$, $A_{24} = -b_2 b_3 c_1 c_2$.

$E_5(x_5, y_5, z_5, w_5)$ exists if equations (2.2) and (2.3) have positive roots x_5, z_5 and $d_3 x_5 < r_2$.

Now we discuss the positivity and boundedness of solutions of system (1.3).

From the first equation,

$$\begin{aligned}\frac{dx}{dt} &= (r_1(1 - \frac{x}{k_1}) - \frac{a_1 z}{b_1 + x} - d_1 w)dt \\ \Rightarrow x(t) &= x(0)e^{\int_0^t (r_1(1 - \frac{x(s)}{k_1}) - \frac{a_1 z(s)}{b_1 + x(s)} - d_1 w(s))ds} > 0, t > 0,\end{aligned}$$

similarly, from the fourth equation, we get

$$\frac{dw}{dt} = (r_2(1 - \frac{w}{k_2}) - d_3 x)dt \Rightarrow w(t) = w(0)e^{\int_0^t (r_2(1 - \frac{w(s)}{k_2}) - d_3 x(s))ds} > 0, t > 0,$$

let $d = \min\{\tau_1, \tau_2\}$, when $t \in [0, d] \Rightarrow t - \tau_1 \in [-\tau_1, d - \tau_1]$, so $x(t - \tau_1) > 0$, $z(t - \tau_1) > 0$, we have

$$\frac{dy}{dt} \geq -c_1 y - d_2 x y \Rightarrow y(t) \geq y(0)e^{\int_0^t (-c_1 - d_2 x(s))ds} > 0,$$

$t - \tau_2 \in [-\tau_2, d - \tau_2] \Rightarrow x(t - \tau_2) > 0, y(t - \tau_2) > 0$, we have

$$\frac{dz}{dt} \geq -c_2 z \Rightarrow z(t) \geq z(0)e^{-c_2 t} > 0,$$

when $t \in [d, 2d] \Rightarrow t - \tau_1 \in [d - \tau_1, 2d - \tau_1]$, for $2d - \tau_1 < d$, $x(t - \tau_1) > 0$, $z(t - \tau_1) > 0$, so

$$\frac{dy}{dt} \geq -c_1 y - d_2 x y \Rightarrow y(t) \geq y(d)e^{\int_d^t (-c_1 - d_2 x(s))ds} > 0,$$

$t - \tau_2 \in [d - \tau_2, 2d - \tau_2]$, $2d - \tau_2 < d \Rightarrow x(t - \tau_2) > 0, y(t - \tau_2) > 0$, so

$$\frac{dz}{dt} \geq -c_2 z \Rightarrow z(t) \geq z(d)e^{-c_2(t-d)} > 0,$$

so when $t \in [nd, (n+1)d]$, $n \in N$, $y(t) > 0, z(t) > 0$, that is $y(t) > 0, z(t) > 0, t > 0$.

From $\frac{dx}{dt} \leq r_1 x(1 - \frac{x}{k_1}) \Rightarrow \limsup_{t \rightarrow +\infty} x(t) \leq k_1$, similarly, $\frac{dw}{dt} \leq r_2 w(1 - \frac{w}{k_2}) \Rightarrow \limsup_{t \rightarrow +\infty} w(t) \leq k_2$.

Define $A(t) = \mu x(t - \tau_1) + y(t)$, where $\mu > 0$ satisfies $a_2 b_1 - \mu a_1 b_2 < 0$, $a_2 - \mu a_1 < 0$, we have

$$\begin{aligned}\frac{dA}{dt} &\leq r_1 \mu x(t - \tau_1)(1 - \frac{x(t - \tau_1)}{k_1}) - \frac{a_1 \mu x(t - \tau_1) z(t - \tau_1)}{b_1 + x(t - \tau_1)} \\ &\quad + \frac{a_2 x(t - \tau_1) z(t - \tau_1)}{b_2 + x(t - \tau_1)} - c_1 y \\ &= \frac{a_2 b_1 - \mu a_1 b_2 + (a_2 - \mu a_1) x(t - \tau_1)}{b_2 + x(t - \tau_1)} \times \frac{x(t - \tau_1) z(t - \tau_1)}{b_1 + x(t - \tau_1)} \\ &\quad + r_1 \mu x(t - \tau_1) - \frac{r_1 \mu x^2(t - \tau_1)}{k_1} - c_1 y \\ &\leq (r_1 \mu + c_1 \mu) x(t - \tau_1) - \frac{r_1 \mu x^2(t - \tau_1)}{k_1} - c_1 A(t) \\ &\leq \frac{(r_1 + c_1)^2 \mu k_1}{4r_1} - c_1 A(t),\end{aligned}$$

from which

$$0 < A(t) < \frac{(r_1 + c_1)^2 \mu k_1}{4r_1 c_1} (1 - e^{-c_1 t}) + A(0)e^{-c_1 t},$$

so

$$\limsup_{t \rightarrow +\infty} A(t) \leq \frac{(r_1 + c_1)^2 \mu k_1}{4r_1 c_1} \Rightarrow \limsup_{t \rightarrow +\infty} y(t) \leq \frac{(r_1 + c_1)^2 \mu k_1}{4r_1 c_1},$$

from the third equation,

$$\begin{aligned} \frac{dz}{dt} &\leq \frac{a_3 x(t - \tau_2) y(t - \tau_2)}{b_3 + x(t - \tau_2)} - c_2 z \\ &\leq a_3 y(t - \tau_2) - c_2 z \\ &\leq \frac{(r_1 + c_1)^2 a_3 \mu k_1}{4r_1 c_1} - c_2 z, \end{aligned}$$

we have

$$0 < z(t) \leq \frac{(r_1 + c_1)^2 a_3 \mu k_1}{4r_1 c_1 c_2} (1 - e^{-c_2 t}) + z(0)e^{-c_2 t},$$

so

$$\limsup_{t \rightarrow +\infty} z(t) \leq \frac{(r_1 + c_1)^2 a_3 \mu k_1}{4r_1 c_1 c_2}.$$

The proof is completed.

3. The influence of delays on the dynamics of tumor-immune system

We discuss the influence of two delays on the dynamics of system (1.3) around positive interior equilibrium point $E_5(x_5, y_5, z_5, w_5)$, the Jacobian matrix at $E_5(x_5, y_5, z_5, w_5)$ is

$$\begin{pmatrix} \gamma_1 & 0 & \gamma_2 & \gamma_3 \\ \gamma_4 + \gamma_6 e^{-\lambda \tau_1} & \gamma_5 & \gamma_7 e^{-\lambda \tau_1} & 0 \\ \gamma_9 e^{-\lambda \tau_2} & \gamma_{10} e^{-\lambda \tau_2} & \gamma_8 & 0 \\ \gamma_{11} & 0 & 0 & \gamma_{12} \end{pmatrix} \quad (3.1)$$

where

$$\begin{aligned} \gamma_1 &= -\frac{r_1 x_5}{k_1} + \frac{a_1 x_5 z_5}{(b_1 + x_5)^2}, \quad \gamma_2 = -\frac{a_1 x_5}{b_1 + x_5}, \quad \gamma_3 = -d_1 x_5, \quad \gamma_4 = -d_2 y_5, \quad \gamma_5 = -d_2 x_5 - c_1, \quad \gamma_6 = \frac{a_2 b_2 z_5}{(b_2 + x_5)^2}, \\ \gamma_7 &= \frac{a_2 x_5}{b_2 + x_5}, \quad \gamma_8 = -c_2, \quad \gamma_9 = \frac{a_3 b_3 y_5}{(b_3 + x_5)^2}, \quad \gamma_{10} = \frac{a_3 x_5}{b_3 + x_5}, \quad \gamma_{11} = -d_3 w_5, \quad \gamma_{12} = -\frac{r_2 w_5}{k_2}. \end{aligned}$$

The characteristic equation of (3.1) is

$$\begin{aligned} \lambda^4 + a_1 \lambda^3 + a_2 \lambda^2 + a_3 \lambda + a_4 + (a_5 \lambda^2 + a_6 \lambda + a_7) e^{-\lambda \tau_2} \\ + (a_8 \lambda^2 + a_9 \lambda + a_{10}) e^{-\lambda(\tau_1 + \tau_2)} = 0, \end{aligned} \quad (3.2)$$

where

$$\begin{aligned} a_1 &= -\gamma_1 - \gamma_5 - \gamma_8 - \gamma_{12}, \quad a_2 = \gamma_1\gamma_{12} + \gamma_1\gamma_5 + \gamma_1\gamma_8 - \gamma_3\gamma_{11} + \gamma_5\gamma_{12} + \gamma_8\gamma_{12} + \gamma_5\gamma_8, \quad a_3 = \\ &= -\gamma_1\gamma_5\gamma_{12} - \gamma_1\gamma_8\gamma_{12} - \gamma_1\gamma_8\gamma_5 + \gamma_3\gamma_5\gamma_{11} + \gamma_3\gamma_8\gamma_{11} - \gamma_5\gamma_8\gamma_{12}, \quad a_4 = \gamma_1\gamma_5\gamma_8\gamma_{12} - \gamma_3\gamma_5\gamma_8\gamma_{11}, \quad a_5 = \\ &= -\gamma_2\gamma_9, \quad a_6 = -\gamma_2\gamma_4\gamma_{10} + \gamma_2\gamma_9\gamma_{12} + \gamma_2\gamma_5\gamma_9, \quad a_7 = \gamma_2\gamma_4\gamma_{10}\gamma_{12} - \gamma_2\gamma_5\gamma_9\gamma_{12}, \quad a_8 = -\gamma_7\gamma_{10}, \quad a_9 = \\ &= \gamma_1\gamma_7\gamma_{10} + \gamma_7\gamma_{10}\gamma_{12} - \gamma_2\gamma_6\gamma_{10}, \quad a_{10} = -\gamma_1\gamma_7\gamma_{10}\gamma_{12} + \gamma_3\gamma_7\gamma_{10}\gamma_{11} + \gamma_2\gamma_6\gamma_{10}\gamma_{12}. \end{aligned}$$

When the delays do not exist, that is $\tau_1 = \tau_2 = 0$, the characteristic equation (3.2) becomes

$$\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 = 0, \quad (3.3)$$

where

$A_1 = a_1$, $A_2 = a_2 + a_5 + a_8$, $A_3 = a_3 + a_6 + a_9$, $A_4 = a_4 + a_7 + a_{10}$, by Routh-Hurwitz criterion, all the roots of equation of (3.3) have negative real parts when

$$(H_1) : A_1 > 0, A_1A_2 - A_3 > 0, (A_1A_2 - A_3)A_3 - A_1^2A_4 > 0.$$

When two delays coexist, we study the influence of two delays under 4 cases:

Case (1) $\tau_1 = 0, \tau_2 > 0$, the characteristic equation (3.2) becomes

$$\lambda^4 + \alpha_{11}\lambda^3 + \alpha_{12}\lambda^2 + \alpha_{13}\lambda + \alpha_{14} + (\beta_{11}\lambda^2 + \beta_{12}\lambda + \beta_{13})e^{-\lambda\tau_2} = 0, \quad (3.4)$$

where

$\alpha_{11} = a_1$, $\alpha_{12} = a_2$, $\alpha_{13} = a_3$, $\alpha_{14} = a_4$, $\beta_{11} = a_5 + a_8$, $\beta_{12} = a_6 + a_9$, $\beta_{13} = a_7 + a_{10}$, let $\lambda = i\omega_2 (\omega_2 > 0)$ be the root of equation (3.4),

$$\begin{cases} (\beta_{13} - \beta_{11}\omega_2^2) \cos(\omega_2\tau_2) + \beta_{12}\omega_2 \sin(\omega_2\tau_2) = -\omega_2^4 + \alpha_{12}\omega_2^2 - \alpha_{14}, \\ \beta_{12}\omega_2 \cos(\omega_2\tau_2) + (\beta_{11}\omega_2^2 - \beta_{13}) \sin(\omega_2\tau_2) = \alpha_{11}\omega_2^3 - \alpha_{13}\omega_2, \end{cases} \quad (3.5)$$

from which we get

$$\omega_2^8 + p_{11}\omega_2^6 + p_{12}\omega_2^4 + p_{13}\omega_2^2 + p_{14} = 0, \quad (3.6)$$

where

$p_{11} = \alpha_{11}^2 - 2\alpha_{12}$, $p_{12} = -2\alpha_{11}\alpha_{13} + \alpha_{12}^2 - \beta_{11}^2 + 2\alpha_{14}$, $p_{13} = -2\alpha_{12}\alpha_{14} + \alpha_{13}^2 + 2\beta_{11}\beta_{13} - \beta_{12}^2$, $p_{14} = -\beta_{13}^2 + \alpha_{14}^2$, denotes $v_2 = \omega_2^2$, (3.6) becomes

$$v_2^4 + p_{11}v_2^3 + p_{12}v_2^2 + p_{13}v_2 + p_{14} = 0, \quad (3.7)$$

denotes

$$f_2(v_2) = v_2^4 + p_{11}v_2^3 + p_{12}v_2^2 + p_{13}v_2 + p_{14}.$$

(H_2): There exist finite positive roots for $f_2(v_2) = 0$, without generality, denote v_{21} , v_{22} , v_{23} , v_{24} , we have $\omega_{2k} = \sqrt{v_{2k}}$, $k = 1, 2, 3, 4$ and the critical value

$$\begin{aligned} \tau_{2k}^{(j)} &= \frac{1}{\omega_{2k}} \arccos\left(\frac{B_{11}\omega_{2k}^6 + B_{12}\omega_{2k}^4 + B_{13}\omega_{2k}^2 + B_{14}}{C_{11}\omega_{2k}^4 + C_{12}\omega_{2k}^2 + C_{13}}\right) + \frac{2\pi j}{\omega_{2k}}, \\ &(k = 1, 2, 3, 4, j = 0, 1, 2, \dots) \end{aligned}$$

where

$B_{11} = \beta_{11}$, $B_{12} = \alpha_{11}\beta_{12} - \alpha_{12}\beta_{11} - \beta_{13}$, $B_{13} = \alpha_{12}\beta_{13} - \alpha_{13}\beta_{12} + \alpha_{14}\beta_{11}$, $B_{14} = -\alpha_{14}\beta_{13}$,

$C_{11} = \beta_{11}^2$, $C_{12} = -2\beta_{11}\beta_{13} + \beta_{12}^2$, $C_{13} = \beta_{13}^2$, differentiate the left side of (3.4) with respect to τ_2 , we have

$$\left(\frac{d\lambda}{d\tau_2}\right)^{-1} = -\frac{4\lambda^3 + 3\alpha_{11}\lambda^2 + 2\alpha_{12}\lambda + \alpha_{13}}{\lambda(\lambda^4 + \alpha_{11}\lambda^3 + \alpha_{12}\lambda^2 + \alpha_{13}\lambda + \alpha_{14})} + \frac{2\beta_{11}\lambda + \beta_{12}}{\lambda(\beta_{11}\lambda^2 + \beta_{12}\lambda + \beta_{13})} - \frac{\tau_2}{\lambda},$$

let $\tau_{20} = \min_{k=1,2,3,4} \tau_{2k}^{(0)}$, when $\tau_2 = \tau_{20}$, we have

$$\begin{aligned} & Re\left(\frac{d\lambda}{d\tau_2}\right)^{-1}_{\tau_2=\tau_{20}} \\ &= \frac{4\omega_{20}^6 + (3\alpha_{11}^2 - 6\alpha_{12})\omega_{20}^4 + (-4\alpha_{11}\alpha_{13} + 2\alpha_{12}^2 + 4\alpha_{14})\omega_{20}^2 + (-2\alpha_{12}\alpha_{14} + \alpha_{13}^2)}{\omega_{20}^8 + (\alpha_{11}^2 - 2\alpha_{12})\omega_{20}^6 + (-2\alpha_{11}\alpha_{13} + \alpha_{12}^2 + 2\alpha_{14})\omega_{20}^4 + (-2\alpha_{12}\alpha_{14} + \alpha_{13}^2)\omega_{20}^2 + \alpha_{14}^2} \\ &+ \frac{-2\beta_{11}^2\omega_{20}^2 + (2\beta_{11}\beta_{13} - \beta_{12}^2)}{\beta_{11}^2\omega_{20}^4 + (-2\beta_{11}\beta_{13} + \beta_{12}^2)\omega_{20}^2 + \beta_{13}^2}, \end{aligned}$$

from (3.6), we have

$$\begin{aligned} & \omega_{20}^8 + (\alpha_{11}^2 - 2\alpha_{12})\omega_{20}^6 + (-2\alpha_{11}\alpha_{13} + \alpha_{12}^2 + 2\alpha_{14})\omega_{20}^4 + (-2\alpha_{12}\alpha_{14} + \alpha_{13}^2)\omega_{20}^2 + \alpha_{14}^2 \\ &= \beta_{11}^2\omega_{20}^4 + (-2\beta_{11}\beta_{13} + \beta_{12}^2)\omega_{20}^2 + \beta_{13}^2, \end{aligned}$$

from which we have

$$Re\left(\frac{d\lambda}{d\tau_2}\right)^{-1}_{\tau_2=\tau_{20}} = \frac{f'_2(\omega_{20}^2)}{\beta_{11}^2\omega_{20}^4 + (-2\beta_{11}\beta_{13} + \beta_{12}^2)\omega_{20}^2 + \beta_{13}^2},$$

therefore $Re\left(\frac{d\lambda}{d\tau_2}\right)^{-1}_{\tau_2=\tau_{20}} \neq 0$ when (H_3) : $f'_2(\omega_{20}^2) \neq 0$, so for system (1.3), if (H_1) , (H_2) , (H_3) hold, the interior positive equilibrium point $E_5(x_5, y_5, z_5, w_5)$ is asymptotically stable for $\tau_2 \in (0, \tau_{20})$, Hopf bifurcation occurs and a periodic solution bifurcates from $E_5(x_5, y_5, z_5, w_5)$ at $\tau_2 = \tau_{20}$.

(2) $\tau_2 = 0$, $\tau_1 > 0$, the characteristic equation (3.2) becomes

$$\lambda^4 + \alpha_{21}\lambda^3 + \alpha_{22}\lambda^2 + \alpha_{23}\lambda + \alpha_{24} + (\beta_{21}\lambda^2 + \beta_{22}\lambda + \beta_{23})e^{-\lambda\tau_1} = 0, \quad (3.8)$$

where

$\alpha_{21} = a_1$, $\alpha_{22} = a_2 + a_5$, $\alpha_{23} = a_3 + a_6$, $\alpha_{24} = a_4 + a_7$, $\beta_{21} = a_8$, $\beta_{22} = a_9$, $\beta_{23} = a_{10}$, let $\lambda = i\omega_1$ ($\omega_1 > 0$) be the root of equation (3.8),

$$\begin{cases} (\beta_{23} - \beta_{21}\omega_1^2) \cos(\omega_1\tau_1) + \beta_{22}\omega_1 \sin(\omega_1\tau_1) = -\omega_1^4 + \alpha_{22}\omega_1^2 - \alpha_{24}, \\ \beta_{22}\omega_1 \cos(\omega_1\tau_1) - (\beta_{23} - \beta_{21}\omega_1^2) \sin(\omega_1\tau_1) = \alpha_{21}\omega_1^3 - \alpha_{23}\omega_1, \end{cases} \quad (3.9)$$

from which we get

$$\omega_1^8 + p_{21}\omega_1^6 + p_{22}\omega_1^4 + p_{23}\omega_1^2 + p_{24} = 0, \quad (3.10)$$

where

$p_{21} = \alpha_{21}^2 - 2\alpha_{22}$, $p_{22} = -2\alpha_{21}\alpha_{23} + \alpha_{22}^2 - \beta_{21}^2 + 2\alpha_{24}$, $p_{23} = -2\alpha_{22}\alpha_{24} + \alpha_{23}^2 + 2\beta_{21}\beta_{23} - \beta_{22}^2$, $p_{24} = \alpha_{24}^2 - \beta_{23}^2$, denotes $v_1 = \omega_1^2$, (3.10) becomes

$$v_1^4 + p_{21}v_1^3 + p_{22}v_1^2 + p_{23}v_1 + p_{24} = 0, \quad (3.11)$$

denotes

$$f_1(v_1) = v_1^4 + p_{21}v_1^3 + p_{22}v_1^2 + p_{23}v_1 + p_{24}.$$

(H_4): There exist finite positive roots for $f_1(v_1) = 0$, without generality, denote the roots as $v_{11}, v_{12}, v_{13}, v_{14}$, so $\omega_{1k} = \sqrt{v_{1k}}, k = 1, 2, 3, 4$, the critical value

$$\tau_{1k}^{(j)} = \frac{1}{\omega_{1k}} \arccos\left(\frac{B_{21}\omega_{1k}^6 + B_{22}\omega_{1k}^4 + B_{23}\omega_{1k}^2 + B_{24}}{C_{21}\omega_{1k}^4 + C_{22}\omega_{1k}^2 + C_{23}}\right) + \frac{2\pi j}{\omega_{1k}},$$

$$(k = 1, 2, 3, 4, j = 0, 1, \dots)$$

where

$B_{21} = \beta_{21}$, $B_{22} = \alpha_{21}\beta_{22} - \alpha_{22}\beta_{21} - \beta_{23}$, $B_{23} = \alpha_{22}\beta_{23} - \alpha_{23}\beta_{22} + \alpha_{24}\beta_{21}$, $B_{24} = -\alpha_{24}\beta_{23}$, $C_{21} = \beta_{21}^2$, $C_{22} = -2\beta_{21}\beta_{23} + \beta_{22}^2$, $C_{23} = \beta_{23}^2$, differentiate the left side of (3.8) with respect to τ_1 ,

$$\left(\frac{d\lambda}{d\tau_1}\right)^{-1} = -\frac{4\lambda^3 + 3\alpha_{21}\lambda^2 + 2\alpha_{22}\lambda + \alpha_{23}}{\lambda(\lambda^4 + \alpha_{21}\lambda^3 + \alpha_{22}\lambda^2 + \alpha_{23}\lambda + \alpha_{24})} + \frac{2\beta_{21}\lambda + \beta_{22}}{\lambda(\beta_{21}\lambda^2 + \beta_{22}\lambda + \beta_{23})} - \frac{\tau_1}{\lambda},$$

let $\tau_{10} = \min_{k=1,2,3,4} \tau_{1k}^{(0)}$, when $\tau_1 = \tau_{10}$, we get

$$\begin{aligned} & Re\left(\frac{d\lambda}{d\tau_1}\right)^{-1}_{\tau_1=\tau_{10}} \\ &= \frac{4\omega_{10}^6 + (3\alpha_{21}^2 - 6\alpha_{22})\omega_{10}^4 + (-4\alpha_{21}\alpha_{23} + 2\alpha_{22}^2 + 4\alpha_{24})\omega_{10}^2 + (-2\alpha_{22}\alpha_{24} + \alpha_{23}^2)}{\omega_{10}^8 + (\alpha_{21}^2 - 2\alpha_{22})\omega_{10}^6 + (-2\alpha_{21}\alpha_{23} + \alpha_{22}^2 + 2\alpha_{24})\omega_{10}^4 + (-2\alpha_{22}\alpha_{24} + \alpha_{23}^2)\omega_{10}^2 + \alpha_{24}^2} \\ &+ \frac{-2\beta_{21}^2\omega_{10}^2 + (2\beta_{21}\beta_{23} - \beta_{22}^2)}{\beta_{21}^2\omega_{10}^4 + (-2\beta_{21}\beta_{23} + \beta_{22}^2)\omega_{10}^2 + \beta_{23}^2} \\ &= \frac{f_1'(\omega_{10}^2)}{\beta_{21}^2\omega_{10}^4 + (-2\beta_{21}\beta_{23} + \beta_{22}^2)\omega_{10}^2 + \beta_{23}^2}, \end{aligned}$$

therefore $Re\left(\frac{d\lambda}{d\tau_1}\right)^{-1}_{\tau_1=\tau_{10}} \neq 0$ when (H_5): $f_1'(\omega_{10}^2) \neq 0$, so for system (1.3), if (H_1), (H_4), (H_5) hold, the interior positive equilibrium point $E_5(x_5, y_5, z_5, w_5)$ is asymptotically stable when $\tau_1 \in (0, \tau_{10})$, Hopf bifurcation occurs and a periodic solution bifurcates from $E_5(x_5, y_5, z_5, w_5)$ when $\tau_1 = \tau_{10}$.

(3) $\tau_1 \in (0, \tau_{10})$, $\tau_2 > 0$, τ_2 is considered as bifurcation parameter, let $\lambda = i\omega_2^*(\omega_2^* > 0)$ be the root of equation (3.2),

$$\begin{cases} E_{31} \cos(\omega_2^* \tau_2) + E_{32} \sin(\omega_2^* \tau_2) = E_{33}, \\ E_{32} \cos(\omega_2^* \tau_2) - E_{31} \sin(\omega_2^* \tau_2) = E_{34}, \end{cases} \quad (3.12)$$

where

$E_{31} = (a_{10} - a_8(\omega_2^*)^2) \cos(\omega_2^* \tau_1) + a_9\omega_2^* \sin(\omega_2^* \tau_1) + a_7 - a_5(\omega_2^*)^2$, $E_{32} = a_9\omega_2^* \cos(\omega_2^* \tau_1) + (a_8(\omega_2^*)^2 - a_{10}) \sin(\omega_2^* \tau_1) + a_6\omega_2^*$, $E_{33} = -(\omega_2^*)^4 + a_2(\omega_2^*)^2 - a_4$, $E_{34} = a_1(\omega_2^*)^3 - a_3\omega_2^*$, from which we get

$$F_1(\omega_2^*) + F_2(\omega_2^*) \cos(\omega_2^* \tau_1) + F_3(\omega_2^*) \sin(\omega_2^* \tau_1) = 0, \quad (3.13)$$

where

$F_1(\omega_2^*) = (\omega_2^*)^8 + (a_1^2 - 2a_2)(\omega_2^*)^6 + (-2a_1a_3 + a_2^2 - a_5^2 - a_8^2 + 2a_4)(\omega_2^*)^4 + (2a_8a_{10} - 2a_2a_4 + a_3^2$

$$\begin{aligned}
& + 2a_5a_7 - a_6^2 - a_9^2\omega_2^* - a_{10}^2 + a_4^2 - a_7^2, \\
F_2(\omega_2^*) &= -2a_5a_8(\omega_2^*)^4 + (2a_5a_{10} + 2a_7a_8 - 2a_6a_9)(\omega_2^*)^2 - 2a_7a_{10}, \\
F_3(\omega_2^*) &= (2a_5a_9 - 2a_6a_8)(\omega_2^*)^3 + (2a_6a_{10} - 2a_7a_9)\omega_2^*.
\end{aligned}$$

(H_6): There exist finite positive roots of equation (3.13) w_{2k}^* , ($k = 1, 2, \dots, l_2$), the critical value of delay is

$$\tau_{2k}^{*(j)} = \arccos\left(\frac{E_{31}E_{33} + E_{32}E_{34}}{E_{31}^2 + E_{32}^2}\right) + \frac{2\pi j}{\omega_{2k}^*}, k = 1, 2, \dots, l_2, j = 0, 1, 2, \dots,$$

differentiate the left side of (3.2) with respect to τ_2 , we get

$$\left(\frac{d\lambda}{d\tau_2}\right)^{-1} = \frac{1}{\lambda} \frac{f_{10}(\lambda) + f_{11}(\lambda)e^{-\lambda\tau_2} + f_{12}(\lambda)e^{-\lambda(\tau_1+\tau_2)}}{f_{13}(\lambda)e^{-\lambda\tau_2} + f_{14}(\lambda)e^{-\lambda(\tau_1+\tau_2)}}$$

where

$$\begin{aligned}
f_{10}(\lambda) &= 4\lambda^3 + 3a_1\lambda^2 + 2a_2\lambda + a_3, f_{11}(\lambda) = -a_5\tau_2\lambda^2 + (2a_5 - a_6\tau_2)\lambda + (a_6 - a_7\tau_2), f_{12}(\lambda) = -(\tau_1 + \tau_2)a_8\lambda^2 + (2a_8 - (\tau_1 + \tau_2)a_9)\lambda + a_9 - a_{10}(\tau_1 + \tau_2), \\
f_{13}(\lambda) &= a_5\lambda^2 + a_6\lambda + a_7, f_{14}(\lambda) = a_8\lambda^2 + a_9\lambda + a_{10}, \\
\text{let } \tau_{20}^* &= \min_{k=1,2,\dots,l_2} \tau_{2k}^{*(0)}, \text{ when } \tau_2 = \tau_{20}^*, \text{ we have}
\end{aligned}$$

$$Re\left(\frac{d\lambda}{d\tau_2}\right)^{-1}_{\tau_2=\tau_{20}^*} = Re\left(\frac{F_{31} + iF_{32}}{F_{33} + iF_{34}}\right) = \frac{F_{31}F_{33} + F_{32}F_{34}}{F_{33}^2 + F_{34}^2},$$

where

$$\begin{aligned}
F_{31} &= -3a_1(\omega_{20}^*)^2 + a_3 + (a_5\tau_{20}^*(\omega_{20}^*)^2 + a_6 - a_7\tau_{20}^*)\cos(\omega_{20}^*\tau_{20}^*) + (2a_5 - a_6\tau_{20}^*)\omega_{20}^*\sin(\omega_{20}^*\tau_{20}^*) \\
&\quad + (2a_8 - a_9\tau_1 - a_9\tau_{20}^*)\omega_{20}^*\sin(\omega_{20}^*\tau_{20}^*)\cos(\omega_{20}^*\tau_1) + (2a_8 - a_9\tau_1 - a_9\tau_{20}^*)\omega_{20}^*\cos(\omega_{20}^*\tau_{20}^*) \\
&\quad \times \sin(\omega_{20}^*\tau_1) + (-a_{10}\tau_{20}^* + a_9 + a_8\tau_1(\omega_{20}^*)^2 + a_8\tau_{20}^*(\omega_{20}^*)^2 - a_{10}\tau_1)\cos(\omega_{20}^*\tau_{20}^*)\cos(\omega_{20}^*\tau_1) \\
&\quad + (a_{10}\tau_{20}^* + a_{10}\tau_1 - a_9 - a_8\tau_1(\omega_{20}^*)^2 - a_8\tau_{20}^*(\omega_{20}^*)^2)\sin(\omega_{20}^*\tau_{20}^*)\sin(\omega_{20}^*\tau_1), \\
F_{32} &= 2a_2\omega_{20}^* - 4(\omega_{20}^*)^3 + (2a_5 - a_6\tau_{20}^*)\omega_{20}^*\cos(\omega_{20}^*\tau_{20}^*) + (a_7\tau_{20}^* - a_6 - a_5\tau_{20}^*(\omega_{20}^*)^2)\sin(\omega_{20}^*\tau_{20}^*) \\
&\quad + (-a_9 - a_8\tau_1(\omega_{20}^*)^2 - a_8\tau_{20}^*(\omega_{20}^*)^2 + a_{10}\tau_1 + a_{10}\tau_{20}^*)\cos(\omega_{20}^*\tau_{20}^*)\sin(\omega_{20}^*\tau_1) \\
&\quad + (-a_9 - a_8\tau_1(\omega_{20}^*)^2 - a_8\tau_{20}^*(\omega_{20}^*)^2 + a_{10}\tau_{20}^* + a_{10}\tau_1)\sin(\omega_{20}^*\tau_{20}^*)\cos(\omega_{20}^*\tau_1) \\
&\quad + (2a_8 - a_9\tau_1 - a_9\tau_{20}^*)\omega_{20}^*\cos(\omega_{20}^*\tau_{20}^*)\cos(\omega_{20}^*\tau_1) \\
&\quad + (a_9\tau_1 + a_9\tau_{20}^* - 2a_8)\omega_{20}^*\sin(\omega_{20}^*\tau_{20}^*)\sin(\omega_{20}^*\tau_1), \\
F_{33} &= -(\omega_{20}^*)^2a_5 + \omega_{20}^*a_7\sin(\omega_{20}^*\tau_{20}^*) - (\omega_{20}^*)^2a_6\cos(\omega_{20}^*\tau_{20}^*) \\
&\quad + (-\omega_{20}^*)^3a_8 + \omega_{20}^*a_{10}\cos(\omega_{20}^*\tau_{20}^*)\sin(\omega_{20}^*\tau_1) + (\omega_{20}^*a_{10} - (\omega_{20}^*)^3a_8)\sin(\omega_{20}^*\tau_{20}^*)\cos(\omega_{20}^*\tau_1) \\
&\quad - (\omega_{20}^*)^2a_9\cos(\omega_{20}^*\tau_{20}^*)\cos(\omega_{20}^*\tau_1) + (\omega_{20}^*)^2a_9\sin(\omega_{20}^*\tau_{20}^*)\sin(\omega_{20}^*\tau_1), \\
F_{34} &= (\omega_{20}^*)^2a_6\sin(\omega_{20}^*\tau_{20}^*) + (a_7\omega_{20}^* - a_5(\omega_{20}^*)^3)\cos(\omega_{20}^*\tau_{20}^*) + (\omega_{20}^*)^2a_9\cos(\omega_{20}^*\tau_{20}^*)\sin(\omega_{20}^*\tau_1) \\
&\quad + (\omega_{20}^*)^2a_9\sin(\omega_{20}^*\tau_{20}^*)\cos(\omega_{20}^*\tau_1) + (a_{10}\omega_{20}^* - a_8(\omega_{20}^*)^3)\cos(\omega_{20}^*\tau_{20}^*)\cos(\omega_{20}^*\tau_1) \\
&\quad + ((\omega_{20}^*)^3a_8 - \omega_{20}^*a_{10})\sin(\omega_{20}^*\tau_{20}^*)\sin(\omega_{20}^*\tau_1).
\end{aligned}$$

(H_7): $F_{31}F_{33} + F_{32}F_{34} \neq 0$, therefore if (H_1), (H_6), (H_7) hold, so for system (1.3), the interior positive equilibrium point $E_5(x_5, y_5, z_5, w_5)$ is asymptotically stable when $\tau_2 \in (0, \tau_{20}^*)$, Hopf bifurcation occurs and a periodic solution bifurcates from $E_5(x_5, y_5, z_5, w_5)$ when $\tau_2 = \tau_{20}^*$.

(4) $\tau_2 \in (0, \tau_{20})$, $\tau_1 > 0$, τ_1 is considered as bifurcation parameter, let $\lambda = i\omega_1^*$ ($\omega_1^* > 0$) be the root of equation (3.2),

$$\begin{cases} E_{41}\cos(\omega_1^*\tau_1) + E_{42}\sin(\omega_1^*\tau_1) = E_{43}, \\ E_{42}\cos(\omega_1^*\tau_1) - E_{41}\sin(\omega_1^*\tau_1) = E_{44}, \end{cases} \quad (3.14)$$

where

$$E_{41} = -a_8(\omega_1^*)^2\cos(\omega_1^*\tau_2) + a_9\omega_1^*\sin(\omega_1^*\tau_2) + a_{10}\cos(\omega_1^*\tau_2), \quad E_{42} = a_8(\omega_1^*)^2\sin(\omega_1^*\tau_2) + a_9\omega_1^*$$

$\times \cos(\omega_1^* \tau_2) - a_{10} \sin(\omega_1^* \tau_2)$, $E_{43} = -(\omega_1^*)^4 + a_2(\omega_1^*)^2 - a_4 + (a_5(\omega_1^*)^2 - a_7) \cos(\omega_1^* \tau_2) - a_6 \omega_1^* \sin(\omega_1^* \tau_2)$, $E_{44} = a_1(\omega_1^*)^3 - a_3 \omega_1^* + (a_7 - a_5(\omega_1^*)^2) \sin(\omega_1^* \tau_2) - a_6 \omega_1^* \cos(\omega_1^* \tau_2)$, from which we have

$$G_1(\omega_1^*) + G_2(\omega_1^*) \cos(\omega_1^* \tau_2) + G_3(\omega_1^*) \sin(\omega_1^* \tau_2) = 0, \quad (3.15)$$

where

$$\begin{aligned} G_1(\omega_1^*) &= (\omega_1^*)^8 + (a_1^2 - 2a_2)(\omega_1^*)^6 + (-2a_1a_3 + a_2^2 + a_5^2 - a_8^2 + 2a_4)(\omega_1^*)^4 + (2a_8a_{10} - 2a_2a_4 \\ &\quad + a_3^2 - 2a_5a_7 + a_6^2 - a_9^2)(\omega_1^*)^2 - a_{10}^2 + a_4^2 + a_7^2, \\ G_2(\omega_1^*) &= -2a_5(\omega_1^*)^6 + (-2a_1a_6 + 2a_2a_5 + 2a_7)(\omega_1^*)^4 + (-2a_2a_7 + 2a_3a_6 - 2a_4a_5)(\omega_1^*)^2 + 2a_4a_7, \\ G_3(\omega_1^*) &= (-2a_1a_5 + 2a_6)(\omega_1^*)^5 + (2a_1a_7 - 2a_2a_6 + 2a_3a_5)(\omega_1^*)^3 + (-2a_3a_7 + 2a_4a_6)\omega_1^*. \end{aligned}$$

(H₈): There exist finite positive roots ω_{1k}^* , ($k = 1, 2, \dots, l_1$) for equation (3.15), the critical value is

$$\tau_{1k}^{*(j)} = \frac{1}{\omega_{1k}^*} \arccos\left(\frac{E_{41}E_{43} + E_{42}E_{44}}{E_{41}^2 + E_{44}^2}\right) + \frac{2\pi j}{\omega_{1k}^*}, \quad (k = 1, 2, \dots, l_1, j = 0, 1, 2, \dots)$$

differentiate the left side of (3.2) with respect to τ_1 , we get

$$\left(\frac{d\lambda}{d\tau_1}\right)^{-1} = \frac{1}{\lambda} \frac{f_{20}(\lambda) + f_{21}(\lambda)e^{-\lambda\tau_2} + f_{22}(\lambda)e^{-\lambda(\tau_1+\tau_2)}}{f_{23}(\lambda)e^{-\lambda(\tau_1+\tau_2)}},$$

where

$$\begin{aligned} f_{20}(\lambda) &= 4\lambda^3 + 3a_1\lambda^2 + 2a_2\lambda + a_3, \quad f_{21}(\lambda) = -\tau_2a_5\lambda^2 + (2a_5 - \tau_2a_6)\lambda + (a_6 - \tau_2a_7), \quad f_{22}(\lambda) = \\ &= -(\tau_1 + \tau_2)a_8\lambda^2 + (2a_8 - (\tau_1 + \tau_2)a_9)\lambda + a_9 - (\tau_1 + \tau_2)a_{10}, \quad f_{23}(\lambda) = a_8\lambda^2 + a_9\lambda + a_{10}, \quad \text{let} \\ \tau_{10}^* &= \min_{k=1,2,\dots,l_1} \tau_{1k}^{*(0)}, \quad \text{when } \tau_1 = \tau_{10}^*, \text{ we have} \end{aligned}$$

$$Re\left(\frac{d\lambda}{d\tau_1}\right)^{-1}_{\tau_1=\tau_{10}^*} = Re\left(\frac{F_{41} + iF_{42}}{F_{43} + iF_{44}}\right) = \frac{F_{41}F_{43} + F_{42}F_{44}}{F_{43}^2 + F_{44}^2},$$

the computation of F_{41} , F_{42} , F_{43} , F_{44} is similar to case (3), we omit here.

(H₉): $F_{41}F_{43} + F_{42}F_{44} \neq 0$, therefore if (H₁), (H₈), (H₉) hold, the interior positive equilibrium point $E_5(x_5, y_5, z_5, w_5)$ is asymptotically stable when $\tau_1 \in (0, \tau_{10}^*)$, Hopf bifurcation occurs and a periodic solution bifurcates from $E_5(x_5, y_5, z_5, w_5)$ when $\tau_1 = \tau_{10}^*$.

4. Direction and stability of Hopf bifurcation

Bases on center manifold theorem and normal form, we study property of Hopf bifurcation about case (4): $\tau_2 \in (0, \tau_{20})$, $\tau_1 > 0$.

Transfer equilibrium point $E_5(x_5, y_5, z_5, w_5)$ to origin by $u_1(t) = x(t) - x_5$, $u_2(t) = y(t) - y_5$, $u_3(t) = z(t) - z_5$, $u_4(t) = w(t) - w_5$, system (1.3) becomes

$$\begin{cases} \frac{du_1}{dt} = \gamma_1 u_1 + \gamma_2 u_3 + \gamma_3 u_4 + F_1, \\ \frac{du_2}{dt} = \gamma_4 u_1 + \gamma_5 u_2 + \gamma_6 u_1(t - \tau_1) + \gamma_7 u_3(t - \tau_1) + F_2, \\ \frac{du_3}{dt} = \gamma_8 u_3 + \gamma_9 u_1(t - \tau_2) + \gamma_{10} u_2(t - \tau_2) + F_3, \\ \frac{du_4}{dt} = \gamma_{11} u_1 + \gamma_{12} u_4 + F_4, \end{cases} \quad (4.1)$$

where

$$\begin{aligned} F_1 &= l_1 u_1^2 + l_2 u_1 u_3 + l_3 u_1 u_4 + l_4 u_1^3 + l_5 u_1^2 u_3, \\ F_2 &= k_1 u_1^2(t - \tau_1) + k_2 u_1 u_2 + k_3 u_1(t - \tau_1) u_3(t - \tau_1) + k_4 u_1^3(t - \tau_1) + k_5 u_1^2(t - \tau_1) u_3(t - \tau_1), \\ F_3 &= m_1 u_1^2(t - \tau_2) + m_2 u_1(t - \tau_2) u_2(t - \tau_2) + m_3 u_1^3(t - \tau_2) + m_4 u_1^2(t - \tau_2) u_2(t - \tau_2), \\ F_4 &= n_1 u_4^2 + n_2 u_1 u_4, \end{aligned}$$

where

$$\begin{aligned} l_1 &= -\frac{r_1}{k_1} + \frac{a_1 b_1 z_5}{(b_1 + x_5)^3}, \quad l_2 = -\frac{a_1 b_1}{(b_1 + x_5)^2}, \quad l_3 = -d_1, \quad l_4 = \frac{a_1 b_1 z_5}{(b_1 + x_5)^4}, \quad l_5 = \frac{a_1 b_1}{(b_1 + x_5)^3}, \\ k_1 &= -\frac{a_2 b_2 z_5}{(b_5 + x_5)^3}, \quad k_2 = -d_2, \quad k_3 = \frac{a_2 b_2}{(b_2 + x_5)^2}, \quad k_4 = \frac{a_2 b_2 z_5}{(b_3 + x_5)^4}, \quad k_5 = -\frac{a_2 b_2}{(b_2 + x_5)^3}, \\ m_1 &= -\frac{a_3 b_3 y_5}{(b_3 + x_5)^3}, \quad m_2 = \frac{a_3 b_3}{(b_3 + x_5)^2}, \\ m_3 &= \frac{a_3 b_3 y_5}{(b_3 + x_5)^4}, \quad m_4 = -\frac{a_3 b_3}{(b_3 + x_5)^3}, \quad n_1 = -\frac{\tau_2}{k_2}, \quad n_2 = -d_3. \end{aligned}$$

We conclude that Hopf bifurcation around equilibrium point $E_5(x_5, y_5, z_5, w_5)$ occurs as $\tau_1 = \tau_{10}^*$, without generality, assume $\tau_{10}^* > \tau_2$, let $\tau_1 = \tau_{10}^* + \mu$, $t = s\tau_1$, then $u_1(s\tau_1) = \tilde{u}_1(s)$, $u_2(s\tau_1) = \tilde{u}_2(s)$, $u_3(s\tau_1) = \tilde{u}_3(s)$, $u_4(s\tau_1) = \tilde{u}_4(s)$, denote $\tilde{u}_1(s)$, $\tilde{u}_2(s)$, $\tilde{u}_3(s)$, $\tilde{u}_4(s)$ as $u_1(t)$, $u_2(t)$, $u_3(t)$, $u_4(t)$, system (4.1) can be written as FDE in $C = C([-1, 0], R^4)$:

$$\dot{u}(t) = L_\mu u(t) + f(\mu, u_t), \quad (4.2)$$

where $u(t) = (u_1(t), u_2(t), u_3(t), u_4(t)) \in R^4$, $L_\mu(\phi) : C \rightarrow R^4$ and $f(\mu, u_t)$ are given by

$$L_\mu(\phi) = (\tau_{10}^* + \mu)(A_1 \phi(0) + A_2 \phi(-\frac{\tau_2}{\tau_{10}^*}) + A_3 \phi(-1)), \quad (4.3)$$

where

$$A_1 = \begin{pmatrix} \gamma_1 & 0 & \gamma_2 & \gamma_3 \\ \gamma_4 & \gamma_5 & 0 & 0 \\ 0 & 0 & \gamma_8 & 0 \\ \gamma_{11} & 0 & 0 & \gamma_{12} \end{pmatrix}, \quad A_2 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \gamma_9 & \gamma_{10} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \quad A_3 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ \gamma_6 & 0 & \gamma_7 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$f(\mu, \phi) = (\tau_{10}^* + \mu) \begin{pmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \end{pmatrix},$$

where

$$\begin{aligned} f_1 &= l_1 \phi_1^2(0) + l_2 \phi_1(0) \phi_3(0) + l_3 \phi_1(0) \phi_4(0) + l_4 \phi_1^3(0) + l_5 \phi_1^2(0) \phi_3(0), \\ f_2 &= k_1 \phi_1^2(-1) + k_2 \phi_1(0) \phi_2(0) + k_3 \phi_1(-1) \phi_3(-1) + k_4 \phi_1^3(-1) + k_5 \phi_1^2(-1) \phi_3(-1), \\ f_3 &= m_1 \phi_1^2(-\frac{\tau_2}{\tau_{10}^*}) + m_2 \phi_1(-\frac{\tau_2}{\tau_{10}^*}) \phi_2(-\frac{\tau_2}{\tau_{10}^*}) + m_3 \phi_1^3(-\frac{\tau_2}{\tau_{10}^*}) + m_4 \phi_1^2(-\frac{\tau_2}{\tau_{10}^*}) \phi_2(-\frac{\tau_2}{\tau_{10}^*}), \\ f_4 &= n_1 \phi_4^2(0) + n_2 \phi_1(0) \phi_4(0), \end{aligned}$$

by Riesz representation theorem, there exists a function $\eta(\theta, \mu)$ of bounded variation for $\theta \in [-1, 0]$ such that $L_\mu \phi = \int_{-1}^0 d\eta(\mu, \theta) \phi(\theta)$, where $\phi \in C([-1, 0], R^4)$, we choose

$$\eta(\theta, \mu) = \begin{cases} (\tau_{10}^* + \mu)(A_1 + A_2 + A_3), \theta = 0, \\ (\tau_{10}^* + \mu)(A_2 + A_3), \theta \in [-\frac{\tau_2}{\tau_{10}^*}, 0), \\ (\tau_{10}^* + \mu)A_3, \theta \in (-1, -\frac{\tau_2}{\tau_{10}^*}), \\ 0, \theta = -1. \end{cases}$$

For $\phi \in C^1([-1, 0], R^4)$, define

$$A(\mu)\phi = \begin{cases} \frac{d\phi(\theta)}{d\theta}, \theta \in [-1, 0), \\ \int_{-1}^0 d\eta(\mu, s)\phi(s), \theta = 0, \end{cases}$$

and

$$R(\mu)\phi = \begin{cases} 0, \theta \in [-1, 0), \\ f(\mu, \phi), \theta = 0, \end{cases}$$

system (4.2) becomes

$$\dot{u}_t = A(\mu)u_t + R(\mu)u_t,$$

for $\theta \in [-1, 0]$, $\psi \in C^1([0, 1], (R^4)^*)$, define

$$A^*\psi(s) = \begin{cases} -\frac{d\psi(s)}{ds}, s \in (0, 1], \\ \int_{-1}^0 d\eta^\top(t, 0)\psi(-s), s = 0 \end{cases}$$

and a bilinear inner production

$$\langle \psi(s), \phi(\theta) \rangle = \bar{\psi}(0)\phi(0) - \int_{-1}^0 \int_{\xi=0}^{\theta} \bar{\psi}(\xi - \theta) d\eta(\theta)\phi(\xi) d\xi,$$

where $\eta(\theta) = \eta(\theta, 0)$, then $A(0), A^*$ are adjoint operator, we know $\pm i\omega_{10}^*\tau_{10}^*$ are eigenvalues of $A(0)$, thus they are also eigenvalues of A^* , we computer the eigenvector of $A(0)$ and A^* corresponding to $i\omega_{10}^*\tau_{10}^*$ and $-i\omega_{10}^*\tau_{10}^*$.

Suppose $q(\theta) = (1, q_2, q_3, q_4)^\top e^{i\omega_{10}^*\tau_{10}^*\theta}$ is the eigenvector of $A(0)$ corresponding to $i\omega_{10}^*\tau_{10}^*$, we get

$$\begin{aligned} q_2 &= \frac{\gamma_2\gamma_4\gamma_{12} - i\gamma_2\gamma_4\omega_{10}^* + (f_{11} + if_{12})e^{-i\omega_{10}^*\tau_{10}^*}}{\gamma_{12}(\omega_{10}^*)^2 - \gamma_2\gamma_5\gamma_{12} + i(\gamma_2\gamma_5\omega_{10}^* + \gamma_2\gamma_{12}\omega_{10}^*)}, \\ q_3 &= \frac{\gamma_1\gamma_{12} - \gamma_3\gamma_{11} - (\omega_{10}^*)^2 - i(\gamma_1\omega_{10}^* + \gamma_{12}\omega_{10}^*)}{-\gamma_2\gamma_{12} + i\gamma_2\omega_{10}^*}, \\ q_4 &= \frac{\gamma_{11}}{i\omega_{10}^* - \gamma_{12}}, \end{aligned}$$

where

$$f_{11} = \gamma_7(\omega_{10}^*)^2 + \gamma_2\gamma_6\gamma_{12} + \gamma_3\gamma_7\gamma_{11} - \gamma_1\gamma_7\gamma_{12}, f_{12} = \gamma_1\gamma_7\omega_{10}^* + \gamma_7\gamma_{12}\omega_{10}^* - \gamma_2\gamma_6\omega_{10}^*,$$

on the other hand, suppose $q^*(s) = D(1, q_2^*, q_3^*, q_4^*)e^{\omega_{10}^*\tau_{10}^*s}$, we get

$$\begin{aligned} q_2^* &= \frac{\gamma_2\gamma_{10}e^{i\omega_{10}^*\tau_2}}{\gamma_5\gamma_8 - (\omega_{10}^*)^2 - \gamma_7\gamma_{10}e^{i\omega_{10}^*(\tau_2+\tau_{10}^*)} + i(\gamma_5\omega_{10}^* + \gamma_8\omega_{10}^*)}, \\ q_3^* &= \frac{\gamma_2\gamma_5 + i\gamma_2\omega_{10}^*}{(\omega_{10}^*)^2 - \gamma_5\gamma_8 + \gamma_7\gamma_{10}e^{i\omega_{10}^*(\tau_2+\tau_{10}^*)} - i(\gamma_5\omega_{10}^* + \gamma_8\omega_{10}^*)}, \\ q_4^* &= -\frac{\gamma_3}{i\omega_{10}^* + \gamma_{12}}, \end{aligned}$$

from $\langle q^*, q \rangle = 1$, $\langle q^*, \bar{q} \rangle = 0$, we get

$$\bar{D} = \frac{1}{1 + q_2\bar{q}_2^* + q_3\bar{q}_3^* + q_4\bar{q}_4^* + (\bar{q}_3^*\gamma_9 + \bar{q}_3^*q_2\gamma_{10})\tau_2e^{-i\omega_{10}^*\tau_2} + (\bar{q}_2^*\gamma_6 + \bar{q}_2^*q_3\gamma_7)\tau_{10}^*e^{-i\omega_{10}^*\tau_{10}^*}}.$$

We computer the center manifold C_0 at $\mu = 0$, let u_t be the solution of system (4.2), define

$$z(t) = \langle q^*, u_t \rangle, W(t, \theta) = u_t(\theta) - 2Re(z(t)q(\theta)),$$

on the center manifold C_0 , we get

$$W(t, \theta) = W(z, \bar{z}, \theta) = W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\bar{z} + W_{02}(\theta)\frac{\bar{z}^2}{2} + \cdots,$$

where $z, \bar{z}$ are local coordinates for center manifold C_0 in the direction of q^* and $\bar{q}^*$. Note that $W(t, \theta)$ is real if u_t is real, we consider only real solution, for solution $u_t \in C_0$ of (4.2), since $\mu = 0$,

$$\begin{aligned} \dot{z}(t) &= \langle q^*, A(0)u_t \rangle + \langle q^*, R(0)u_t \rangle \\ &= i\omega_{10}^*\tau_{10}^*z(t) + \langle \bar{q}^*(0), f(0, W(z, \bar{z}, \theta) + 2Re(zq(\theta))) \rangle \\ &= i\omega_{10}^*\tau_{10}^*z(t) + \bar{q}^*(0)f(0, W(z, \bar{z}, \theta) + 2Re(z, q(0))) \\ &= i\omega_{10}^*\tau_{10}^*z(t) + \bar{q}(0)f_0(z, \bar{z}), \end{aligned}$$

write this equation as

$$\dot{z}(t) = i\omega_{10}^*\tau_{10}^*z(t) + g(z, \bar{z}),$$

where

$$g(z, \bar{z}) = \bar{q}^*f_0(z, \bar{z}) = g_{20}\frac{z^2}{2} + g_{11}z\bar{z} + g_{02}\frac{\bar{z}^2}{2} + g_{21}\frac{z^2\bar{z}}{2!} + \cdots, \quad (4.4)$$

we get

$$g(z, \bar{z}) = \bar{q}^*(0)f_0(z, \bar{z}) = \bar{D}\tau_{10}^*(1, \bar{q}_2^*, \bar{q}_3^*, \bar{q}_4^*)(f_1, f_2, f_3, f_4)^\top, \quad (4.5)$$

from

$$q(\theta) = (1, q_2, q_3, q_4)e^{i\omega_{10}^*\tau_{10}^*\theta},$$

$$u_t(\theta) = (u_{1t}(\theta), u_{2t}(\theta), u_{3t}(\theta), u_{4t}(\theta)) = W(t, \theta) + zq(\theta) + \bar{z}\bar{q}(\theta),$$

we get

$$\begin{aligned} u_{1t}(0) &= z + \bar{z} + W_{20}^{(1)}(0) \frac{z^2}{2} + W_{11}^{(1)}(0) z\bar{z} + W_{02}^{(1)}(0) \frac{\bar{z}^2}{2} + O(|z, \bar{z}|^3), \\ u_{2t}(0) &= q_2 z + \bar{q}_2 \bar{z} + W_{20}^{(2)}(0) \frac{z^2}{2} + W_{11}^{(2)}(0) z\bar{z} + W_{02}^{(2)}(0) \frac{\bar{z}^2}{2} + O(|z, \bar{z}|^3), \\ u_{3t}(0) &= q_3 z + \bar{q}_3 \bar{z} + W_{20}^{(3)}(0) \frac{z^2}{2} + W_{11}^{(3)}(0) z\bar{z} + W_{02}^{(3)}(0) \frac{\bar{z}^2}{2} + O(|z, \bar{z}|^3), \\ u_{4t}(0) &= q_4 z + \bar{q}_4 \bar{z} + W_{20}^{(4)}(0) \frac{z^2}{2} + W_{11}^{(4)}(0) z\bar{z} + W_{02}^{(4)}(0) \frac{\bar{z}^2}{2} + O(|z, \bar{z}|^3), \\ u_{1t}\left(-\frac{\tau_2}{\tau_{10}^*}\right) &= ze^{-i\omega_{10}^* \tau_2} + \bar{z}e^{i\omega_{10}^* \tau_2} + W_{20}^{(1)}\left(-\frac{\tau_2}{\tau_{10}^*}\right) \frac{z^2}{2} + W_{11}^{(1)}\left(-\frac{\tau_2}{\tau_{10}^*}\right) z\bar{z} \\ &\quad + W_{02}^{(1)}\left(-\frac{\tau_2}{\tau_{10}^*}\right) \frac{\bar{z}^2}{2} + O(|z, \bar{z}|^3), \\ u_{2t}\left(-\frac{\tau_2}{\tau_{10}^*}\right) &= q_2 ze^{-i\omega_{10}^* \tau_2} + \bar{q}_2 \bar{z}e^{i\omega_{10}^* \tau_2} + W_{20}^{(2)}\left(-\frac{\tau_2}{\tau_{10}^*}\right) \frac{z^2}{2} + W_{11}^{(2)}\left(-\frac{\tau_2}{\tau_{10}^*}\right) z\bar{z} \\ &\quad + W_{02}^{(2)}\left(-\frac{\tau_2}{\tau_{10}^*}\right) \frac{\bar{z}^2}{2} + O(|z, \bar{z}|^3), \\ u_{3t}\left(-\frac{\tau_2}{\tau_{10}^*}\right) &= q_3 ze^{-i\omega_{10}^* \tau_2} + \bar{q}_3 \bar{z}e^{i\omega_{10}^* \tau_2} + W_{20}^{(3)}\left(-\frac{\tau_2}{\tau_{10}^*}\right) \frac{z^2}{2} + W_{11}^{(3)}\left(-\frac{\tau_2}{\tau_{10}^*}\right) z\bar{z} \\ &\quad + W_{02}^{(3)}\left(-\frac{\tau_2}{\tau_{10}^*}\right) \frac{\bar{z}^2}{2} + O(|z, \bar{z}|^3), \\ u_{4t}\left(-\frac{\tau_2}{\tau_{10}^*}\right) &= q_4 ze^{-i\omega_{10}^* \tau_2} + \bar{q}_4 \bar{z}e^{i\omega_{10}^* \tau_2} + W_{20}^{(4)}\left(-\frac{\tau_2}{\tau_{10}^*}\right) \frac{z^2}{2} + W_{11}^{(4)}\left(-\frac{\tau_2}{\tau_{10}^*}\right) z\bar{z} \\ &\quad + W_{02}^{(4)}\left(-\frac{\tau_2}{\tau_{10}^*}\right) \frac{\bar{z}^2}{2} + O(|z, \bar{z}|^3), \\ u_{1t}(-1) &= ze^{-i\omega_{10}^* \tau_{10}^*} + \bar{z}e^{i\omega_{10}^* \tau_{10}^*} + W_{20}^{(1)}(-1) \frac{z^2}{2} + W_{11}^{(1)}(-1) z\bar{z} \\ &\quad + W_{02}^{(1)}(-1) \frac{\bar{z}^2}{2} + O(|z, \bar{z}|^3), \\ u_{2t}(-1) &= q_2 ze^{-i\omega_{10}^* \tau_{10}^*} + \bar{q}_2 \bar{z}e^{i\omega_{10}^* \tau_{10}^*} + W_{20}^{(2)}(-1) \frac{z^2}{2} + W_{11}^{(2)}(-1) z\bar{z} \\ &\quad + W_{02}^{(2)}(-1) \frac{\bar{z}^2}{2} + O(|z, \bar{z}|^3), \\ u_{3t}(-1) &= q_3 ze^{-i\omega_{10}^* \tau_{10}^*} + \bar{q}_3 \bar{z}e^{i\omega_{10}^* \tau_{10}^*} + W_{20}^{(3)}(-1) \frac{z^2}{2} + W_{11}^{(3)}(-1) z\bar{z} \\ &\quad + W_{02}^{(3)}(-1) \frac{\bar{z}^2}{2} + O(|z, \bar{z}|^3), \\ u_{4t}(-1) &= q_4 ze^{-i\omega_{10}^* \tau_{10}^*} + \bar{q}_4 \bar{z}e^{i\omega_{10}^* \tau_{10}^*} + W_{20}^{(4)}(-1) \frac{z^2}{2} + W_{11}^{(4)}(-1) z\bar{z} \\ &\quad + W_{02}^{(4)}(-1) \frac{\bar{z}^2}{2} + O(|z, \bar{z}|^3), \end{aligned}$$

from (4.4) and (4.5), we get

$$g(z, \bar{z}) = \bar{D}\tau_{10}^*(1, \bar{q}_2^*, \bar{q}_3^*, \bar{q}_4^*) \times \begin{pmatrix} K_{11}z^2 + K_{12}z\bar{z} + K_{13}\bar{z}^2 + K_{14}z^2\bar{z} \\ K_{21}z^2 + K_{22}z\bar{z} + K_{23}\bar{z}^2 + K_{24}z^2\bar{z} \\ K_{31}z^2 + K_{32}z\bar{z} + K_{33}\bar{z}^2 + K_{34}z^2\bar{z} \\ K_{41}z^2 + K_{42}z\bar{z} + K_{43}\bar{z}^2 + K_{44}z^2\bar{z} \end{pmatrix}$$

where

$$\begin{aligned} K_{11} &= l_1 q^{(1)}(0) + l_2 q^{(3)}(0) + l_3 q^{(4)}(0), \\ K_{12} &= 2l_1 q^{(1)}(0) + l_2 (\bar{q}^{(3)}(0) + q^{(3)}(0)) + l_3 (q^{(4)}(0) + \bar{q}^{(4)}(0)), \\ K_{13} &= l_1 q^{(1)}(0) + l_2 \bar{q}^{(3)}(0) + l_3 \bar{q}^{(4)}(0), \\ K_{14} &= l_1 (W_{20}^{(1)}(0) + 2W_{11}^{(1)}(0)) + l_2 (\frac{1}{2}W_{20}^{(1)}(0)\bar{q}^{(3)}(0) + W_{11}^{(1)}(0)q^{(3)}(0) + W_{11}^{(3)}(0) + \frac{1}{2}W_{20}^{(3)}(0)) \\ &\quad + l_3 (\frac{1}{2}W_{20}^{(4)}(0) + W_{11}^{(4)}(0) + \frac{1}{2}W_{20}^{(1)}(0)\bar{q}^{(4)}(0) + W_{11}^{(1)}(0)q^{(4)}(0)) + 3l_4 q^{(1)}(0) + l_5 (2q^{(3)}(0) \\ &\quad + \bar{q}^{(3)}(0)), \\ K_{21} &= k_1 (q^{(1)}(-1))^2 + k_2 q^{(2)}(0) + k_3 q^{(3)}(0)(q^{(1)}(-1))^2, \\ K_{22} &= 2k_1 + k_2 (q^{(2)}(0) + \bar{q}^{(2)}(0)) + k_3 (q^{(3)}(0) + \bar{q}^{(3)}(0)), \\ K_{23} &= k_1 (\bar{q}^{(1)}(-1))^2 + k_2 \bar{q}^{(2)}(0) + k_3 \bar{q}^{(3)}(-1)\bar{q}^{(1)}(-1), \\ K_{24} &= k_1 (2W_{11}^{(1)}(-1)q^{(1)}(-1) + W_{20}^{(1)}(-1)\bar{q}^{(1)}(-1)) + k_2 (\frac{1}{2}W_{20}^{(2)}(0) + W_{11}^{(2)}(0) + W_{11}^{(1)}(0)q^{(2)}(0) \\ &\quad + \frac{1}{2}W_{20}^{(1)}(0)\bar{q}^{(2)}(0)) + k_3 (\frac{1}{2}W_{20}^{(3)}(-1)\bar{q}^{(1)}(-1) + W_{11}^{(3)}(-1)q^{(1)}(-1) + \frac{1}{2}W_{20}^{(1)}(-1)\bar{q}^{(3)}(-1) \\ &\quad + W_{11}^{(1)}(-1)q^{(3)}(-1)) + 3k_4 q^{(1)}(-1) + k_5 (2q^{(3)}(-1) + \bar{q}^{(3)}(0)q^{(1)}(-1)), \\ K_{31} &= m_1 (q^{(1)}(-\frac{\tau_2}{\tau_{10}^*}))^2 + m_2 q^{(1)}(-\frac{\tau_2}{\tau_{10}^*})q^{(2)}(-\frac{\tau_2}{\tau_{10}^*}), \\ K_{32} &= 2m_1 + m_2 (q^{(2)}(0) + \bar{q}^{(2)}(0)), \\ K_{33} &= m_1 (\bar{q}^{(1)}(-\frac{\tau_2}{\tau_{10}^*}))^2 + m_2 \bar{q}^{(2)}(-\frac{\tau_2}{\tau_{10}^*})\bar{q}^{(1)}(-\frac{\tau_2}{\tau_{10}^*}), \\ K_{34} &= m_1 (W_{20}^{(1)}(-\frac{\tau_2}{\tau_{10}^*})\bar{q}^{(1)}(-\frac{\tau_2}{\tau_{10}^*}) + 2W_{11}^{(1)}(-\frac{\tau_2}{\tau_{10}^*})q^{(1)}(-\frac{\tau_2}{\tau_{10}^*})) + m_2 (\frac{1}{2}W_{20}^{(1)}(-\frac{\tau_2}{\tau_{10}^*})\bar{q}^{(2)}(-\frac{\tau_2}{\tau_{10}^*}) \\ &\quad + W_{11}^{(1)}(-\frac{\tau_2}{\tau_{10}^*})q^{(2)}(-\frac{\tau_2}{\tau_{10}^*}) + W_{11}^{(2)}(-\frac{\tau_2}{\tau_{10}^*})q^{(1)}(-\frac{\tau_2}{\tau_{10}^*}) + \frac{1}{2}W_{20}^{(2)}(-\frac{\tau_2}{\tau_{10}^*})\bar{q}^{(1)}(-\frac{\tau_2}{\tau_{10}^*})) + 3m_3 q^{(1)}(-\frac{\tau_2}{\tau_{10}^*}) \\ &\quad + m_4 (2q^{(2)}(-\frac{\tau_2}{\tau_{10}^*}) + \bar{q}^{(2)}(0)q^{(1)}(-\frac{\tau_2}{\tau_{10}^*})), \\ K_{41} &= n_1 (q^{(4)}(0))^2 + n_2 q^{(4)}(0), \\ K_{42} &= 2n_1 q^{(4)}(0)\bar{q}^{(4)}(0) + n_2 (q^{(4)}(0) + \bar{q}^{(4)}(0)), \\ K_{43} &= n_1 (\bar{q}^{(4)}(0))^2 + n_2 \bar{q}^{(4)}(0), \\ K_{44} &= n_1 (2W_{11}^{(4)}(0)q^{(4)}(0) + W_{20}^{(4)}(0)\bar{q}^{(4)}(0)) + n_2 (\frac{1}{2}W_{20}^{(1)}(0)\bar{q}^{(4)}(0) + W_{11}^{(4)}(0) + \frac{1}{2}W_{20}^{(4)}(0) \\ &\quad + W_{11}^{(1)}(0)q^{(4)}(0)), \end{aligned}$$

comparing the coefficients with (4.4), we obtain

$$\begin{aligned} g_{20} &= 2\tau_{10}^* \bar{D}(K_{11} + \bar{q}_2^* K_{21} + \bar{q}_3^* K_{31} + \bar{q}_4^* K_{41}), \quad g_{11} = \tau_{10}^* \bar{D}(K_{12} + \bar{q}_2^* K_{22} + \bar{q}_3^* K_{32} + \bar{q}_4^* K_{42}), \\ g_{02} &= 2\tau_{10}^* \bar{D}(K_{13} + \bar{q}_2^* K_{23} + \bar{q}_3^* K_{33} + \bar{q}_4^* K_{43}), \quad g_{21} = 2\tau_{10}^* \bar{D}(K_{14} + \bar{q}_2^* K_{24} + \bar{q}_3^* K_{34} + \bar{q}_4^* K_{44}), \end{aligned}$$

with

$$\begin{aligned} W_{20}(\theta) &= \frac{ig_{20}}{\omega_{10}^* \tau_{10}^*} q(0) e^{i\omega_{10}^* \tau_{10}^* \theta} + \frac{i\bar{g}_{02}}{3\omega_{10}^* \tau_{10}^*} \bar{q}(0) e^{-i\omega_{10}^* \tau_{10}^* \theta} + E_1 e^{2i\omega_{10}^* \tau_{10}^* \theta}, \\ W_{11}(\theta) &= -\frac{ig_{11}}{\omega_{10}^* \tau_{10}^*} q(0) e^{i\omega_{10}^* \tau_{10}^* \theta} + \frac{i\bar{g}_{11}}{\omega_{10}^* \tau_{10}^*} \bar{q}(0) e^{-i\omega_{10}^* \tau_{10}^* \theta} + E_2, \end{aligned}$$

where E_1, E_2 are determined by

$$\begin{pmatrix} 2i\omega_{10}^* - \gamma_1 & 0 & -\gamma_2 & -\gamma_3 \\ -\gamma_4 - \gamma_6 e^{-2i\omega_{10}^* \tau_{10}^*} & 2i\omega_{10}^* - \gamma_5 & -\gamma_7 e^{-2i\omega_{10}^* \tau_{10}^*} & 0 \\ -\gamma_9 e^{-2i\omega_{10}^* \tau_2} & -\gamma_{10} e^{-2i\omega_{10}^* \tau_2} & 2i\omega_{10}^* - \gamma_8 & 0 \\ -\gamma_{11} & 0 & 0 & 2i\omega_{10}^* - \gamma_{12} \end{pmatrix} E_1 = 2 \begin{pmatrix} K_{11} \\ K_{21} \\ K_{31} \\ K_{41} \end{pmatrix}$$

and

$$\begin{pmatrix} \gamma_1 & 0 & \gamma_2 & \gamma_3 \\ \gamma_4 + \gamma_6 & \gamma_5 & \gamma_7 & 0 \\ \gamma_9 & \gamma_{10} & \gamma_8 & 0 \\ \gamma_{11} & 0 & 0 & \gamma_{12} \end{pmatrix} E_2 = - \begin{pmatrix} K_{12} \\ K_{22} \\ K_{32} \\ K_{42} \end{pmatrix},$$

according to above calculation, we can obtain the following values:

$$\begin{aligned} C_1(0) &= \frac{i}{2\omega_{10}^* \tau_{10}^*} (g_{11}g_{20} - 2 |g_{11}|^2 - \frac{|g_{02}|^2}{3}) + \frac{g_{21}}{2}, \\ \mu_2 &= -\frac{Re(C_1(0))}{Re\lambda'(\tau_{10}^*)}, \beta_2 = 2Re(C_1(0)), \\ T_2 &= -\frac{ImC_1(0) + \mu_2 Im\lambda'(\tau_{10}^*)}{\omega_{10}^* \tau_{10}^*}, \end{aligned}$$

from [11], we obtain

- (i) The bifurcation is supercritical (subcritical) as $\mu_2 > 0 (< 0)$.
- (ii) The bifurcating periodic solution is unstable (stable) as $\beta_2 > 0 (< 0)$.
- (iii) The period of bifurcating periodic solution increases (decreases) as $T_2 > 0 (< 0)$, where T_2 determines the period of bifurcating periodic solution.

5. The influence of infusion of $CD4^+$ T cells and cytokines in absence of delays

In this Section, we study the influence of injection treatments of both $CD4^+$ T cells and cytokines on the volume of tumor cells in absence of delays, introducing the injection treatments, system (1.3) becomes

$$\begin{cases} \frac{dx}{dt} = r_1 x \left(1 - \frac{x}{k_1}\right) - \frac{a_1 x z}{b_1 + x} - d_1 x w, \\ \frac{dy}{dt} = \frac{a_2 x z}{b_2 + x} - c_1 y - d_2 x y + I_1, \\ \frac{dz}{dt} = \frac{a_3 x y}{b_3 + x} - c_2 z + I_2, \\ \frac{dw}{dt} = r_2 w \left(1 - \frac{w}{k_2}\right) - d_3 x w, \end{cases} \quad (5.1)$$

where doses of infusion treatments of $CD4^+$ T cells and cytokines are described by constants $I_1 \geq 0$ and $I_2 \geq 0$ respectively, so the injection treatments are constant on time, Hu and R.-J. Jang [13] and Yu, et al. [37] also take the same treatment, the stability of tumor-extinction equilibrium points $(0, *, *, *)$ of system (5.1) should be interesting, for the stability means that tumor-eradication can be realized by injection treatments.

Immunotherapy (cytokine immunotherapy, cellular immunotherapy, etc.) is a rapid developing approach in cancer treatment, it help immune system to inhibit tumor cells. For the mathematical model of chemotherapy, it is important to frame an optimal control problem about the minimum dose of drug, chemotherapy has damaging side effects, which can weaken immune system of patients, the patients may be prone to infection, so using theory of optimal control is important for chemotherapy/immunotherapy toward tumor. There are works [15, 16, 30] about optimal control in medical model, the optimal control is very important to better visualize the intricate dynamics of tumor-immune system. Here we discuss the minimum dose of injection treatment of cytokines on eradication of tumor cells and study the stability of tumor-extinction equilibrium points under three injection treatments:

(1) $I_1 > 0, I_2 = 0$, that is infusion treatment of only $CD4^+$ cells, there are tumor-extinction equilibrium points $E_{11}(0, \frac{I_1}{c_1}, 0, 0)$, $E_{12}(0, \frac{I_1}{c_1}, 0, k_2)$, the Jacobian matrix at E_{11} is

$$\begin{pmatrix} r_1 & 0 & 0 & 0 \\ -\frac{d_2 I_1}{c_1} - c_1 & 0 & 0 & 0 \\ \frac{a_3 I_1}{b_3 c_1} & 0 & -c_2 & 0 \\ 0 & 0 & 0 & r_2 \end{pmatrix} \quad (5.2)$$

the eigenvalues are $r_1, -c_1, -c_2, r_2$, so it is always a saddle, similarly the eigenvalues of E_{12} are $r_1 - d_1 k_2, -c_1, -c_2, -r_2$, so it is locally asymptotically stable when $r_1 < d_1 k_2$, that is if the growth rate of tumor cells is small, the killing rate of tumor cells by host cells or the carrying capacity of host cells is large, the tumor cells can be eradicated when the volume of tumor cells is small.

From the second equation of (5.1) and $\limsup_{t \rightarrow \infty} x(t) \leq k_1$, we get $\frac{dy}{dt} \geq -c_1 y - d_2 x y + I_1$, so $\liminf_{t \rightarrow \infty} y(t) \geq \frac{I_1}{c_1 + d_2 k_1}$, that is the $CD4^+$ cells always exist and the volume is larger than $\frac{I_1}{c_1 + d_2 k_1}$ for injection treatment of only $CD4^+$ cells.

With condition $r_2 > d_3 k_1$, $r_1 < d_1 k_2$, we discuss the globally asymptotically stability of tumor-extinction equilibrium point $E_{12}(0, \frac{I_1}{c_1}, 0, k_2)$, that is if the host cells grow fast and tumor cells grow slowly, the tumor cells can be eradicated for large initial volume, we have

Theorem 5.1. *For injection treatments of only $CD4^+$ T cells, that is $I_1 > 0, I_2 = 0$, the tumor-extinction equilibrium point $E_{12}(0, \frac{I_1}{c_1}, 0, k_2)$ is globally asymptotically stable if $r_2 > d_3 k_1$, $r_1 < d_1 k_2$ holds.*

Proof. from system (5.1), we have $\frac{dx}{dt} \leq r_1 x(1 - \frac{x}{k_1}) - d_1 x w$, $\frac{dw}{dt} \geq r_2 w(1 - \frac{w}{k_2}) - d_3 x w$, consider system

$$\begin{cases} \frac{dA}{dt} = r_1 A(1 - \frac{A}{k_1}) - d_1 AB, \\ \frac{dB}{dt} = r_2 B(1 - \frac{B}{k_2}) - d_3 AB, \end{cases} \quad (5.3)$$

with initial condition $A(0) = x(0) > 0$, $B(0) = y(0) > 0$, we have

$$A(t) = A(0)e^{\int_0^t (r_1(1 - \frac{A(s)}{k_1}) - d_1 B(s)) ds} > 0, B(t) = B(0)e^{\int_0^t (r_2(1 - \frac{B(s)}{k_2}) - d_3 A(s)) ds} > 0,$$

from $\frac{dA}{dt} \leq r_1 A(1 - \frac{A}{k_1})$, $\frac{dB}{dt} \leq r_2 B(1 - \frac{B}{k_2})$, we have

$$\limsup_{t \rightarrow +\infty} A(t) \leq k_1, \limsup_{t \rightarrow +\infty} B(t) \leq k_2,$$

that is the solutions of system (5.3) are positive and bounded.

By comparison argument, $x(t) \leq A(t)$, $w(t) \geq B(t)$ for $t > 0$, system (5.3) always has equilibrium points $(k_1, 0)$, $(0, k_2)$, the interior positive equilibrium point

$$(A_1, B_1) = \left(\frac{k_1 r_2 (d_1 k_2 - r_1)}{d_1 d_3 k_1 k_2 - r_1 r_2}, \frac{k_2 r_1 (d_3 k_1 - r_2)}{d_1 d_3 k_1 k_2 - r_1 r_2} \right)$$

exists if $r_1 > d_1 k_2, r_2 > d_3 k_1$ or $r_1 < d_1 k_2, r_2 < d_3 k_1$ holds, by condition $r_2 > d_3 k_1, r_1 < d_1 k_2$, the interior positive equilibrium point (A_1, B_1) does not exist, the Jacobian matrixes at $(k_1, 0)$, $(0, k_2)$ are

$$\begin{pmatrix} -r_1 & -d_1 k_1 \\ 0 & r_2 - d_3 k_1 \end{pmatrix}, \begin{pmatrix} r_1 - d_1 k_2 & 0 \\ -d_3 k_2 & -r_2 \end{pmatrix}$$

respectively, so the eigenvalues of $(k_1, 0)$ are $-r_1, r_2 - d_3 k_1$, the eigenvalues of $(0, k_2)$ are $r_1 - d_1 k_2, -r_2$, so $(k_1, 0)$ is always saddle and $(0, k_2)$ is locally asymptotically stable.

Taking $l(A, B) = \frac{1}{AB}$, we have

$$\begin{aligned} & \frac{\partial}{\partial A} \left(\frac{dA}{dt} l(A, B) \right) + \frac{\partial}{\partial B} \left(\frac{dB}{dt} l(A, B) \right) \\ &= \frac{\partial}{\partial A} \left(\frac{r_1}{B} \left(1 - \frac{A}{k_1} \right) - d_1 \right) + \frac{\partial}{\partial B} \left(\frac{r_2}{A} \left(1 - \frac{B}{k_2} \right) - d_3 \right) \\ &= -\frac{r_1}{B k_1} - \frac{r_2}{A k_2} \\ &< 0, \end{aligned}$$

Dulac criterion ensures that system (5.3) does not have nontrivial positive periodic solutions, by Poincare-Bendixson Theorem, for interior positive equilibrium point does not exists, so the equilibrium point $(0, k_2)$ is global asymptotically stable in the first quadrant, that is $\lim_{t \rightarrow +\infty} A(t) = 0$, $\lim_{t \rightarrow +\infty} B(t) = k_2$, so $\limsup_{t \rightarrow +\infty} x(t) \leq 0$, $\liminf_{t \rightarrow +\infty} w(t) \geq k_2$, $\lim_{t \rightarrow \infty} x(t) = 0$, $\lim_{t \rightarrow +\infty} w(t) = k_2$, from which we conclude $\lim_{t \rightarrow +\infty} y(t) = \frac{I_1}{c_1}$, $\lim_{t \rightarrow +\infty} z(t) = 0$, that is when $r_2 > d_3 k_1, r_1 < d_1 k_2$, equilibrium point $E_{12} = (0, \frac{I_1}{c_1}, 0, k_2)$ is global asymptotically stable. $\square$

(2) $I_1 = 0, I_2 > 0$, that is infusion treatment of only cytokines, there are tumor-extinction equilibrium points $E_{21}(0, 0, \frac{I_2}{c_2}, 0)$, $E_{22}(0, 0, \frac{I_2}{c_2}, k_2)$, the Jacobian matrix at E_{21} is

$$\begin{pmatrix} r_1 - \frac{a_1 I_2}{b_1 c_2} & 0 & 0 & 0 \\ \frac{a_2 I_2}{b_2 c_2} & -c_1 & 0 & 0 \\ 0 & 0 & -c_2 & 0 \\ 0 & 0 & 0 & r_2 \end{pmatrix} \quad (5.4)$$

the eigenvalues of E_{21} are $r_1 - \frac{a_1 I_2}{b_1 c_2}$, $-c_1$, $-c_2$, r_2 , so it is always a saddle, similarly the eigenvalues of E_{22} are $r_1 - \frac{a_1 I_2}{b_1 c_2} - d_1 k_2$, $-c_1$, $-c_2$, $-r_2$, so it is locally asymptotically stable when $r_1 < \frac{a_1 I_2}{b_1 c_2} + d_1 k_2$, that is if the growth rate of tumor cells is small, the tumor cells can be eradicated by infusion of only cytokines when the volume of tumor cells is small.

From the third equation of (5.1), we get $\frac{dz}{dt} \geq -c_2 z + I_2$, so $\liminf_{t \rightarrow \infty} z(t) \geq \frac{I_2}{c_2}$, that is the cytokines always exist and the volume is larger than $\frac{I_2}{c_2}$ for injection treatment of only cytokines.

Now we discuss the globally asymptotically stability of tumor-extinction equilibrium point $E_{22}(0, 0, \frac{I_2}{c_2}, k_2)$, that is the tumor cells can be eradicated for large initial volume, define $I_2^c = \frac{r_1 c_2 (b_1 + k_1)}{a_1}$, we have:

Theorem 5.2. *For injection treatment of only cytokines, that is $I_1 = 0, I_2 > 0$, the tumor-extinction equilibrium point $E_{22}(0, 0, \frac{I_2}{c_2}, k_2)$ is globally asymptotically stable if $I_2 > I_2^c$ holds.*

Proof. for $\limsup_{t \rightarrow +\infty} x(t) \leq k_1$ and $\liminf_{t \rightarrow +\infty} z(t) \geq \frac{I_2}{c_2}$, there exist $t_1 > 0$, when $t > t_1$, $x(t) < k_1$, $z(t) > \frac{I_2}{c_2} + \epsilon$ hold, where $\epsilon > 0$ is sufficiently small, for $I_2 > I_2^c$, $r_1 - \frac{a_1 (\frac{I_2}{c_2} + \epsilon)}{b_1 + k_1} < 0$ holds, so when $t > t_1$, $\frac{dx}{dt} \leq r_1 x - \frac{a_1 x z}{b_1 + x} \leq x(r_1 - \frac{a_1 (\frac{I_2}{c_2} + \epsilon)}{b_1 + k_1})$ holds, that is $\frac{dx}{dt} \leq \gamma x$, where $\gamma = r_1 - \frac{a_1 (\frac{I_2}{c_2} + \epsilon)}{b_1 + k_1} < 0$, from which we conclude $\lim_{t \rightarrow +\infty} x(t) = 0$, $\lim_{t \rightarrow +\infty} y(t) = 0$, $\lim_{t \rightarrow +\infty} z(t) = \frac{I_2}{c_2}$, $\lim_{t \rightarrow +\infty} w(t) = k_2$, besides $I_2 > I_2^c \Rightarrow r_1 - \frac{a_1 I_2}{b_1 c_2} - d_1 k_2 < r_1 - \frac{r_1 (b_1 + k_1)}{b_1} - d_1 k_2 < 0$, that is $r_1 < \frac{a_1 I_2}{b_1 c_2} + d_1 k_2$, so $E_{22}(0, 0, \frac{I_2}{c_2}, k_2)$ is globally asymptotically stable. $\square$

(3) $I_1 > 0, I_2 > 0$, that is infusion treatments of both $CD4^+$ cells and cytokines, there are tumor-extinction equilibrium points $E_{31}(0, \frac{I_1}{c_1}, \frac{I_2}{c_2}, 0)$, $E_{32}(0, \frac{I_1}{c_1}, \frac{I_2}{c_2}, k_2)$, the Jacobian matrix at $E_{31}(0, \frac{I_1}{c_1}, \frac{I_2}{c_2}, 0)$ is

$$\begin{pmatrix} r_1 - \frac{a_1 I_2}{b_1 c_2} & 0 & 0 & 0 \\ \frac{a_2 I_2}{b_2 c_2} - \frac{d_2 I_1}{c_1} & -c_1 & 0 & 0 \\ \frac{a_3 I_1}{b_3 c_1} & 0 & -c_2 & 0 \\ 0 & 0 & 0 & r_2 \end{pmatrix} \quad (5.5)$$

the eigenvalues of E_{31} are $r_1 - \frac{a_1 I_2}{b_1 c_2}$, $-c_1$, $-c_2$, r_2 , it is always a saddle, similarly the eigenvalues of E_{32} are $r_1 - \frac{a_1 I_2}{b_1 c_2} - d_1 k_2$, $-c_1$, $-c_2$, $-r_2$, so it is locally asymptotically stable when $r_1 < \frac{a_1 I_2}{b_1 c_2} + d_1 k_2$, that is when the growth rate of tumor cells is small, the tumor cells can be eradicated by infusion of both $CD4^+$ T cells and cytokines when the volume of tumor cells is small.

From the second, third equation (5.1) and $\limsup_{t \rightarrow +\infty} x(t) \leq k_1$, we get $\liminf_{t \rightarrow +\infty} y(t) \geq \frac{I_1}{c_1 + d_2 k_1}$, $\liminf_{t \rightarrow +\infty} z(t) \geq \frac{I_2}{c_2}$, that is $CD4^+$ T cells and cytokines always exist and the volumes of them are larger than $\frac{I_1}{c_1 + d_2 k_1}$ and $\frac{I_2}{c_2}$ for injection treatments of both $CD4^+$ T cells and cytokines.

Similarly for the globally asymptotically stability of tumor-extinction equilibrium point $E_{32}(0, \frac{I_1}{c_1}, \frac{I_2}{c_2}, k_2)$, that is the tumor cells can be eradicated for large initial volume, we have

Theorem 5.3. *For injection treatments of both $CD4^+$ T cells and cytokines, that is $I_1 > 0, I_2 > 0$, the tumor-extinction equilibrium point $E_{32}(0, \frac{I_1}{c_1}, \frac{I_2}{c_2}, k_2)$ is globally asymptotically stable if $I_2 > I_2^c$ holds.*

Proof. similar to Theorem 5.2, for $I_2 > I_2^c$, we get $\lim_{t \rightarrow +\infty} x(t) = 0$, $\lim_{t \rightarrow +\infty} y(t) = \frac{I_1}{c_1}$, $\lim_{t \rightarrow +\infty} z(t) = \frac{I_2}{c_2}$, $\lim_{t \rightarrow +\infty} w(t) = k_2$ and $r_1 < \frac{a_1 I_2}{b_1 c_2} + d_1 k_2$, so $E_{32}(0, \frac{I_1}{c_1}, \frac{I_2}{c_2}, k_2)$ is globally asymptotically stable. $\square$

6. Simulation

Based on values of parameters of table-1, taking $a_2 = 0.99$, the time unit is a day, we compute the equilibrium points of system (1.3):

- (1) Equilibrium points $E_0(0, 0, 0, 0)$, $E_1(9.8039 \times 10^8, 0, 0, 0)$, $E_2(0, 0, 0, 10^9)$ always exist.
- (2) For $d_1 k_2 - r_1 = -0.404 < 0$, $d_3 k_1 - r_2 = 0.29058 > 0$, $d_1 d_3 k_1 k_2 - r_1 r_2 = -0.040755 < 0$, so equilibrium points $E_3(x_3, 0, 0, w_3)$ does not exists.
- (3) Equation (2.1) becomes

$$3.4 \times 10^{-6} x_4^3 - 1.9392 x_4^2 + 6803.4 x_4 + 3.4 \times 10^6 = 0,$$

which has two positive roots: $x_{41} = 3976.9499$, $x_{42} = 5.66819 \times 10^5$, so there are two equilibrium points $E_4(x_4, y_4, z_4, 0)$: $E_{41}(3976.9499, 2.1055 \times 10^6, 2.67 \times 10^5, 0)$, $E_{42}(5.66819 \times 10^5, 1.08 \times 10^7, 1.7127 \times 10^6, 0)$.

- (4) Equation (2.2) and (2.3) become

$$\begin{aligned} -0.040755 x_5^2 + 7.128988 \times 10^7 x_5 - 3.529404 \times 10^7 z_5 + 7.12939 \times 10^{12} &= 0, \\ -3.4 \times 10^{-6} x_5^3 + 1.9392 x_5^2 - 6803.4 x_5 - 3.4 \times 10^6 &= 0, \end{aligned}$$

which have two solutions $(x_{51}, z_{51}) = (3976.9499, 2.10032 \times 10^5)$, $d_3 x_{51} - r_2 = -0.179998 < 0$, $(x_{52}, z_{52}) = (5.66819 \times 10^5, 1.3465 \times 10^6)$, $d_3 x_{52} - r_2 = -0.1797279 < 0$, so there are two interior positive equilibrium points $E_5(x_5, y_5, z_5, w_5)$: $E_{51}(3976.9499, 1.6549 \times 10^6, 2.10032 \times 10^5, 9.9998 \times 10^8)$, $E_{52}(5.66819 \times 10^5, 8.49316 \times 10^6, 1.3465 \times 10^6, 9.98488 \times 10^8)$.

In absence of delays, the eigenvalues of E_{51} are -34.01978 , -0.17999 , $-0.03258 \pm 0.12275i$, the eigenvalues of E_{52} are 0.39835 , -0.05662 , -0.1798 , -34.15532 , so E_{51} is local asymptotically stable, E_{52} is always a saddle.

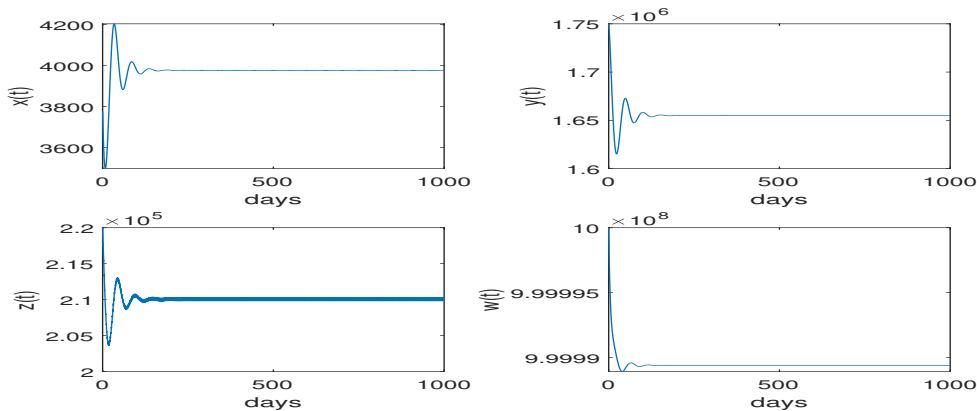


Figure 1. With ode45 solver, when $\tau_1 = \tau_2 = 0$, time evolution of tumor cells x , $CD4^+$ T cells y , cytokines z and host cells w .

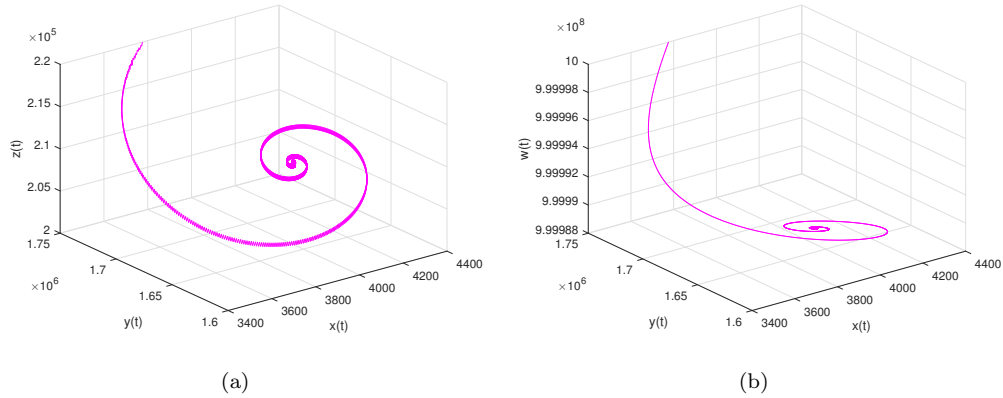


Figure 2. With ode23 solver, when $\tau_1 = \tau_2 = 0$, (a) phase portrait diagram of tumor cells x , CD4⁺ T cells y and cytokines z ; (b) phase portrait diagram of tumor cells x , CD4⁺ T cells y and host cells w .

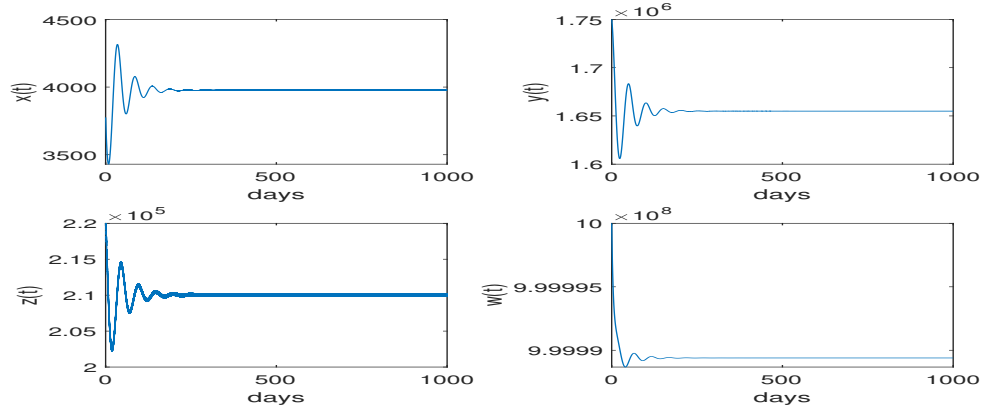


Figure 3. With dde23 solver, when $\tau_1 = 0, \tau_2 = 1 < \tau_{20}$, time evolution of tumor cells x , CD4⁺ T cells y , cytokines z and host cells w .

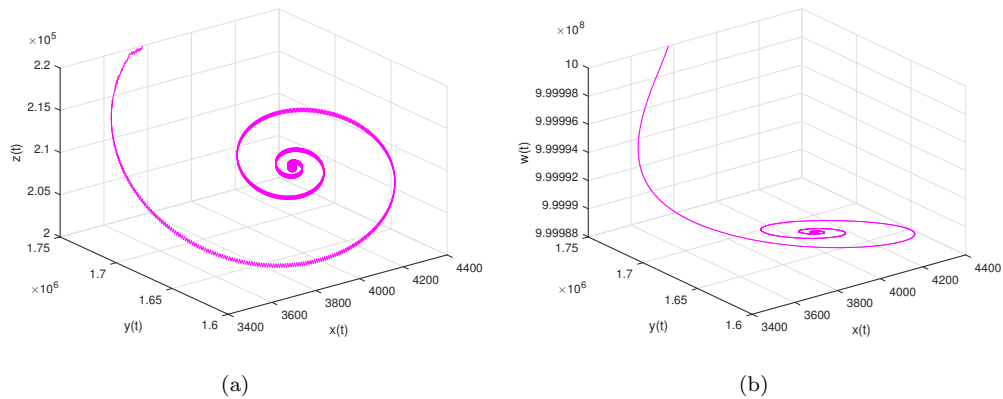


Figure 4. With dde23 solver, when $\tau_1 = 0, \tau_2 = 1 < \tau_{20}$, (a) phase portrait diagram of tumor cells x , CD4⁺ T cells y and cytokines z ; (b) phase portrait diagram of tumor cells x , CD4⁺ T cells y and host cells w .

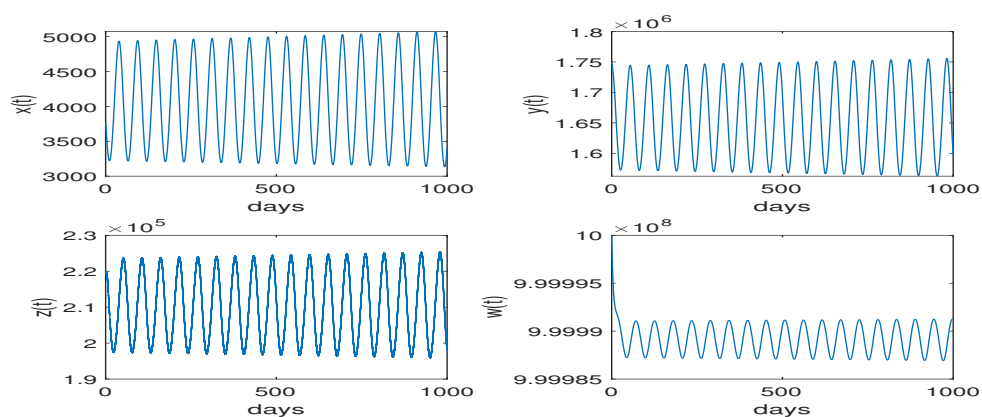


Figure 5. With dde23 solver, when $\tau_1 = 0, \tau_2 = 3.95 > \tau_{20}$, time evolution of tumor cells x , CD4⁺ T cells y , cytokines z and host cells w .

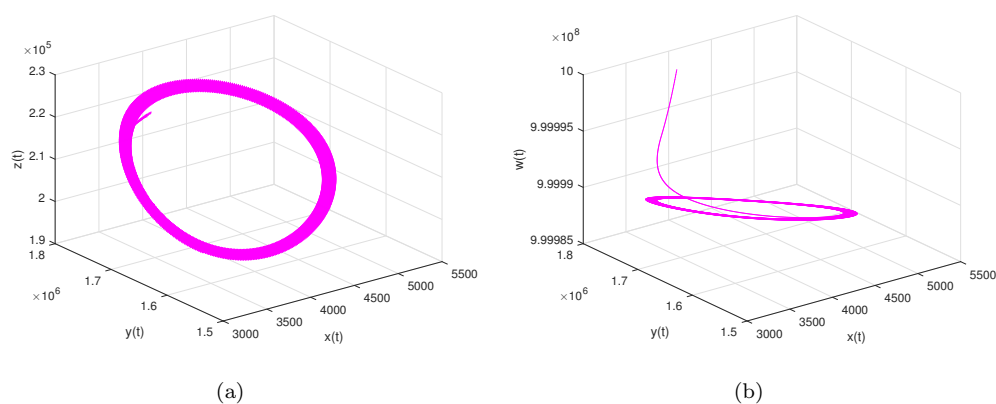


Figure 6. With dde23 solver, when $\tau_1 = 0, \tau_2 = 3.95 > \tau_{20}$, (a) phase portrait diagram of tumor cells x , CD4⁺ T cells y and cytokines z ; (b) phase portrait diagram of tumor cells x , CD4⁺ T cells y and host cells w .

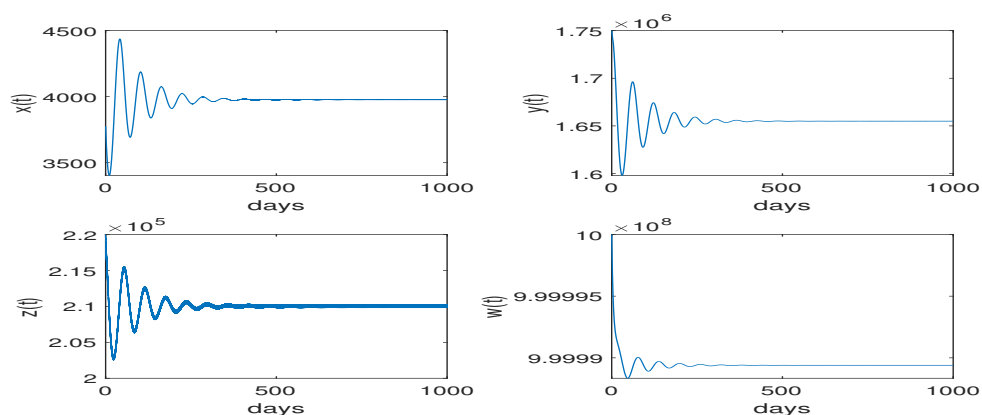


Figure 7. With dde23 solver, when $\tau_2 = 0, \tau_1 = 4 < \tau_{10}$, time evolution of tumor cells x , CD4⁺ T cells y , cytokines z and host cells w .

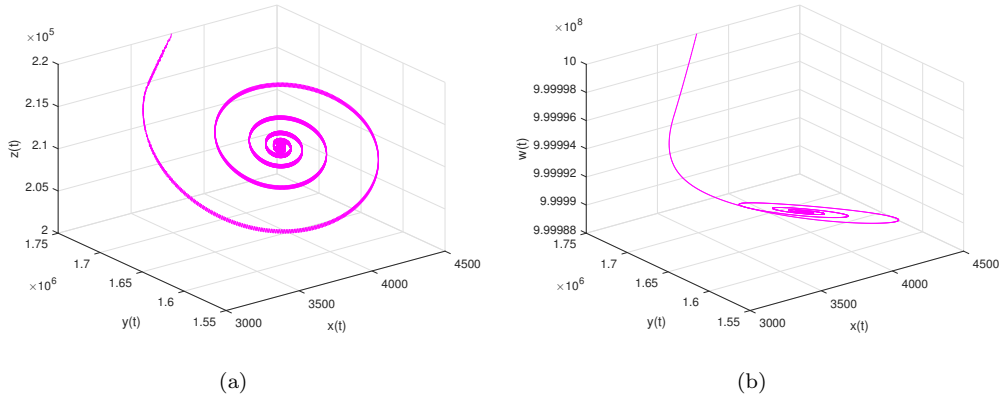


Figure 8. With dde23 solver, when $\tau_2 = 0, \tau_1 = 4 < \tau_{10}$, (a) phase portrait diagram of tumor cells x , $CD4^+$ T cells y and cytokines z ; (b) phase portrait diagram of tumor cells x , $CD4^+$ T cells y and host cells w .

For positive equilibrium point E_{51} , $A_1 = 34.264945$, $A_2 = 8.36828$, $A_3 = 0.950654$, $A_4 = 0.098767$, $A_1 A_2 - A_3 = 285.7881 > 0$, $(A_1 A_2 - A_3) A_3 - A_1^2 A_4 = 155.72393 > 0$, (H_1) holds, with initial condition $(3776, 1.75 \times 10^6, 2.2 \times 10^5, 10^9)$ and $t \in [0, 1000]$, we get E_{51} is locally asymptotically stable, which is illustrated by Figure 1 and Figure 2.

With $t \in [0, 1000]$, we give the influence of delays on the dynamics of system (1.3) around E_{51} :

For case (1), with history function $(3776, 1.75 \times 10^6, 2.2 \times 10^5, 10^9), \theta \in [-\tau_2, 0]$, we obtain $\tau_{20} = 3.4$, when $\tau_2 = 1 < \tau_{20}$, E_{51} is locally asymptotically stable, when $\tau_2 = 3.95 > \tau_{20}$, Hopf bifurcation occurs and a periodic solution bifurcates from E_{51} , which is illustrated by Figure 3, Figure 4, Figure 5 and Figure 6.

For case (2), with history function $(3776, 1.75 \times 10^6, 2.2 \times 10^5, 10^9), \theta \in [-\tau_1, 0]$, we obtain $\tau_{10} = 8.1$, when $\tau_1 = 4 < \tau_{10}$, E_{51} is locally asymptotically stable, when $\tau_1 = 13.7 > \tau_{10}$, Hopf bifurcation occurs and a periodic solution bifurcates from E_{51} , which is illustrated by Figure 7, Figure 8, Figure 9 and Figure 10.

For case (3), with history function $(3776, 1.75 \times 10^6, 2.2 \times 10^5, 10^9), \theta \in [-\tau, 0], \tau = \max\{\tau_1, \tau_2\}$, fixing $\tau_1 = 7 \in (0, \tau_{10})$, we obtain $\tau_{20}^* = 0.95$, when $\tau_2 = 0.2 < \tau_{20}^*$, E_{51} is locally asymptotically stable, when $\tau_2 = 2.1 > \tau_{20}^*$, Hopf bifurcation occurs and a periodic solution bifurcates from E_{51} , which is illustrated by Figure 11, Figure 12, Figure 13 and Figure 14.

For case (4), with history function $(3776, 1.75 \times 10^6, 2.2 \times 10^5, 10^9), \theta \in [-\tau, 0], \tau = \max\{\tau_1, \tau_2\}$, fixing $\tau_2 = 2 \in (0, \tau_{20})$, we obtain $\tau_{10}^* = 3.6$, when $\tau_1 = 3 < \tau_{10}^*$, E_{51} is locally asymptotically stable, when $\tau_1 = 7 > \tau_{10}^*$, Hopf bifurcation occurs and a periodic solution bifurcates from E_{51} , which is illustrated by Figure 15, Figure 16, Figure 17 and Figure 18.

With $t \in [0, 1000]$, we give the influence of delays on the volumes of tumor cells, $CD4^+$ T cells, cytokines and host cells around E_{51} :

When $\tau_1 = 0, \tau_2 \in (0, 4)$, with history function $(3776, 1.75 \times 10^6, 2.2 \times 10^5, 10^9), \theta \in [-\tau_2, 0]$, as τ_2 increases from 0 to 3.4, the volumes of tumor cells, $CD4^+$ T cells, cytokines and host cells keep stable, as $\tau_2 = 3.4$, periodic oscillations occur, the amplitudes of oscillations increase as τ_2 increases, which are illustrated by Figure 19(a)(b) and Figure 20(a)(b).

When $\tau_2 = 0, \tau_1 \in (0, 14)$, with history function $(3776, 1.75 \times 10^6, 2.2 \times 10^5, 10^9), \theta \in [-\tau_1, 0]$, as τ_1 increases from 0 to 8.1, the volumes of tumor cells, $CD4^+$ T cells, cytokines and host cells

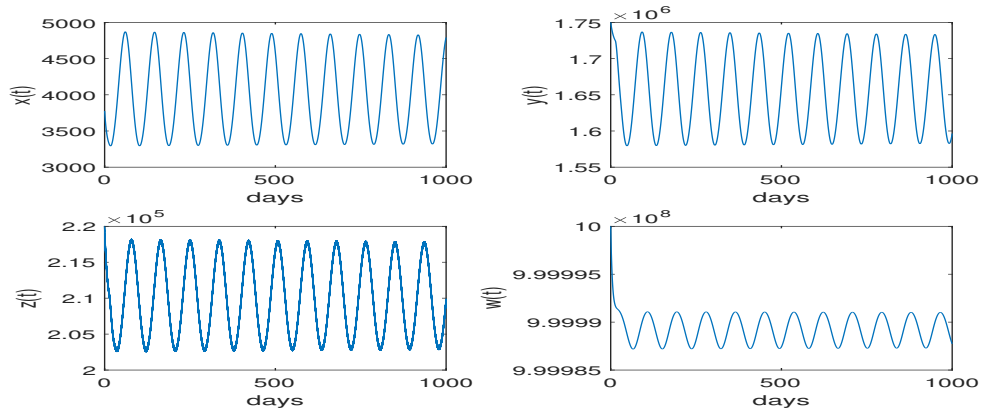


Figure 9. With dde23 solver, when $\tau_2 = 0, \tau_1 = 13.7 > \tau_{10}$, time evolution of tumor cells x , CD4⁺ T cells y , cytokines z and host cells w .

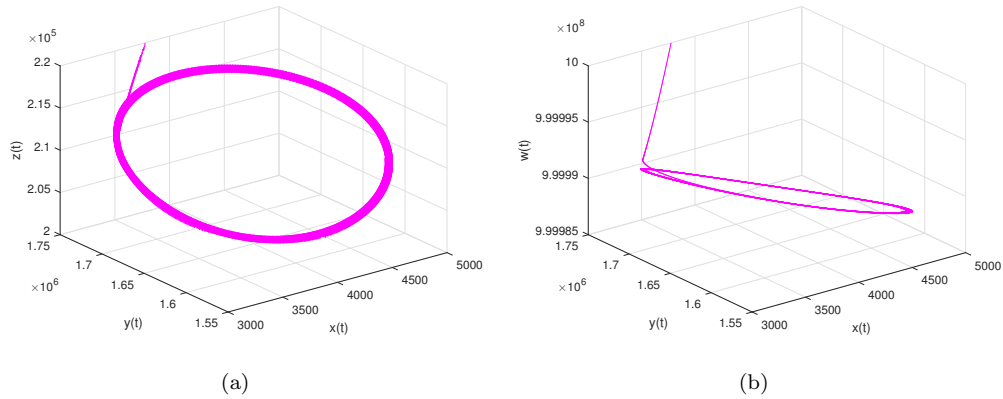


Figure 10. With dde23 solver, when $\tau_2 = 0, \tau_1 = 13.7 > \tau_{10}$, (a) phase portrait diagram of tumor cells x , CD4⁺ T cells y and cytokines z ; (b) phase portrait diagram of tumor cells x , CD4⁺ T cells y and host cells w .

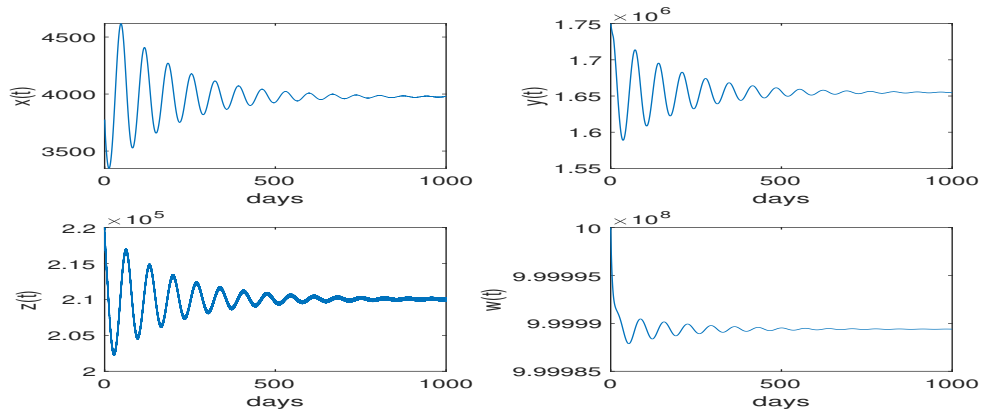


Figure 11. With dde23 solver, when $\tau_1 = 7 \in (0, \tau_{10}), \tau_2 = 0.2 < \tau_{20}^*$, time evolution of tumor cells x , CD4⁺ T cells y , cytokines z and host cells w .

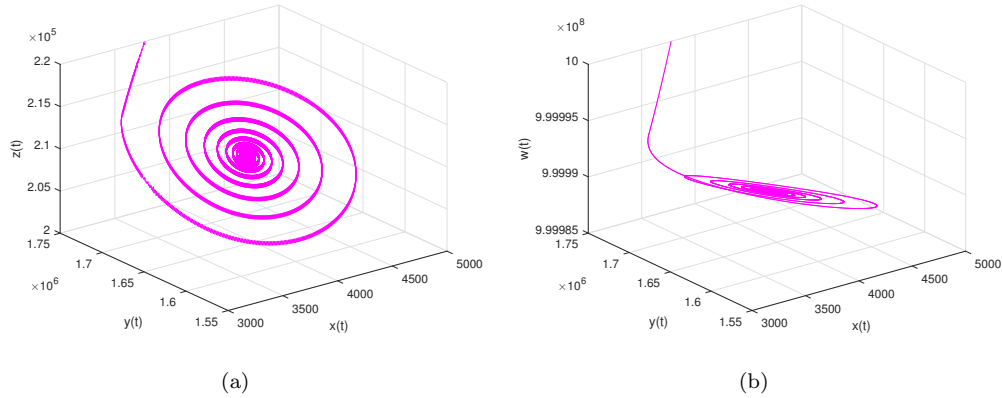


Figure 12. With dde23 solver, when $\tau_1 = 7 \in (0, \tau_{10})$, $\tau_2 = 0.2 < \tau_{20}^*$, (a) phase portrait diagram of tumor cells x , CD4⁺ T cells y and cytokines z ; (b) phase portrait diagram of tumor cells x , CD4⁺ T cells y and host cells w .

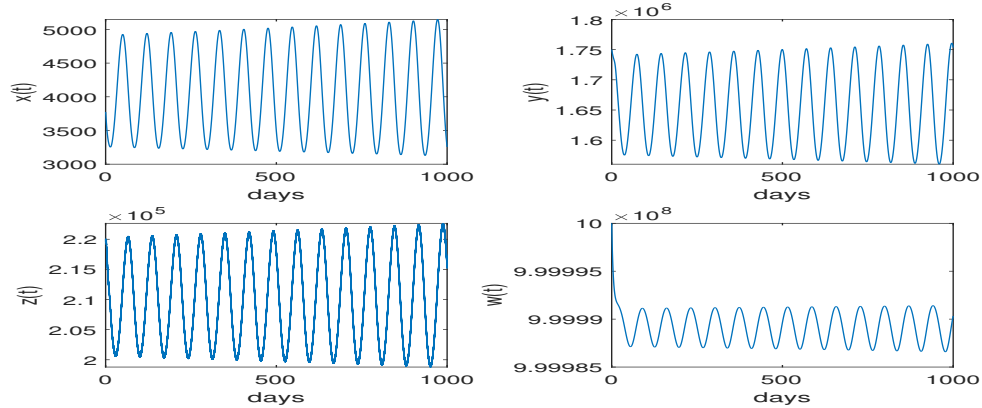


Figure 13. With dde23 solver, when $\tau_1 = 7 \in (0, \tau_{10})$, $\tau_2 = 2.1 > \tau_{20}^*$, time evolution of tumor cells x , CD4⁺ T cells y , cytokines z and host cells w .

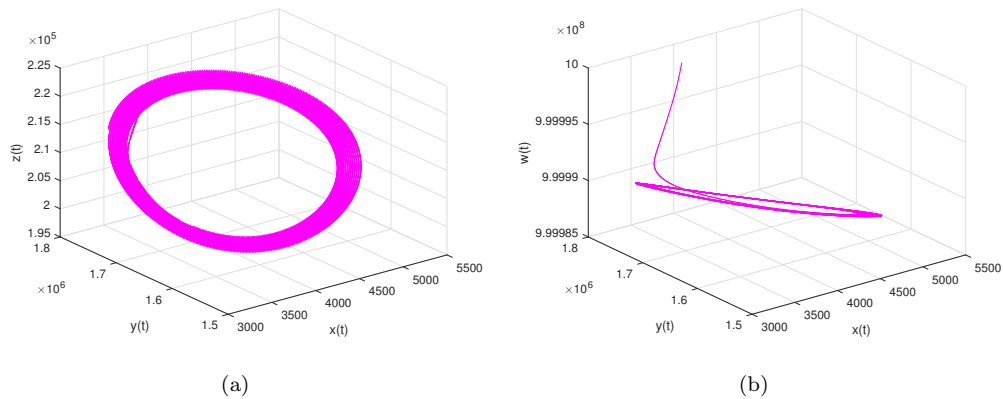


Figure 14. With dde23 solver, when $\tau_1 = 7 \in (0, \tau_{10})$, $\tau_2 = 2.1 > \tau_{20}^*$, (a) phase portrait diagram of tumor cells x , CD4⁺ T cells y and cytokines z ; (b) phase portrait diagram of tumor cells x , CD4⁺ T cells y and host cells w .

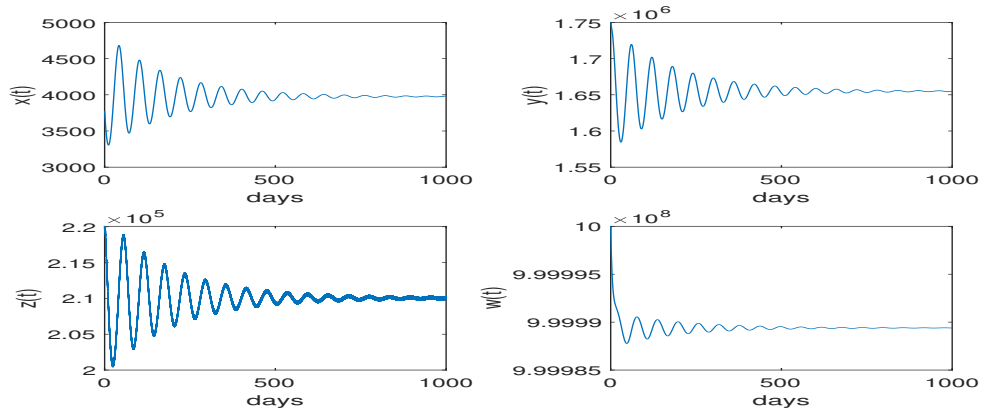


Figure 15. With dde23 solver, when $\tau_2 = 2 \in (0, \tau_{20})$, $\tau_1 = 3 < \tau_{10}^*$, time evolution of tumor cells x , CD4⁺ T cells y , cytokines z and host cells w .

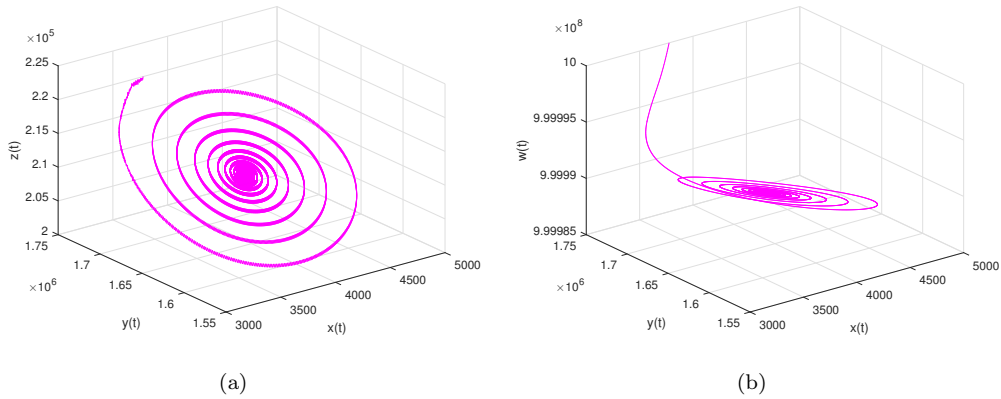


Figure 16. With dde23 solver, when $\tau_2 = 2 \in (0, \tau_{20})$, $\tau_1 = 3 < \tau_{10}^*$, (a) phase portrait diagram of tumor cells x , CD4⁺ T cells y and cytokines z ; (b) phase portrait diagram of tumor cells x , CD4⁺ T cells y and host cells w .

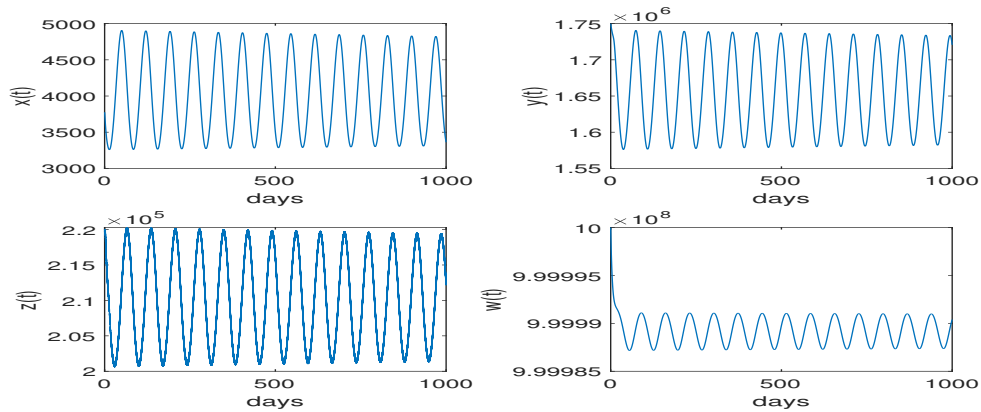


Figure 17. With dde23 solver, when $\tau_2 = 2 \in (0, \tau_{20})$, $\tau_1 = 7 > \tau_{10}^*$, time evolution of tumor cells x , CD4⁺ T cells y , cytokines z and host cells w .

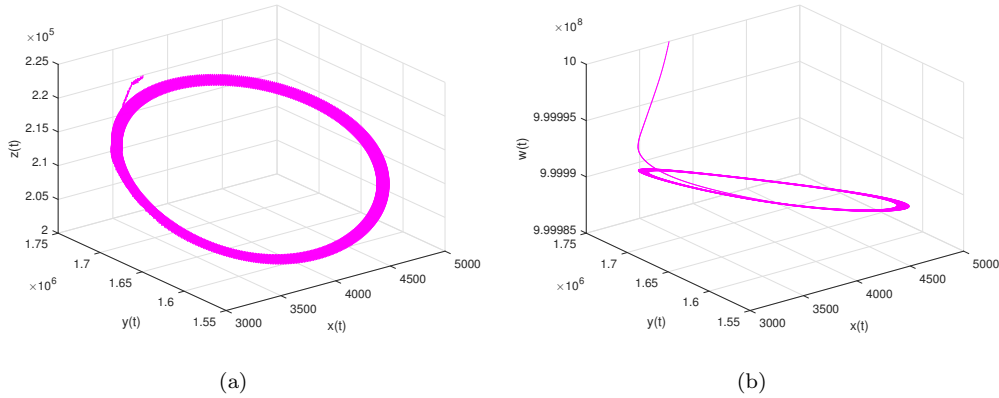


Figure 18. With dde23 solver, when $\tau_2 = 2 \in (0, \tau_{20})$, $\tau_1 = 7 > \tau_{10}^*$, (a) phase portrait diagram of tumor cells x , $CD4^+$ T cells y and cytokines z ; (b) phase portrait diagram of tumor cells x , $CD4^+$ T cells y and host cells w .

keep stable, as $\tau_1 = 8.1$, periodic oscillations occur, the amplitudes of oscillations increase as τ_1 increases, which are illustrated by Figure 21(a)(b) and Figure 22(a)(b).

When $\tau_1 = 7 \in (0, \tau_{10})$, $\tau_2 \in (0, 2.5)$, with history function $(3776, 1.75 \times 10^6, 2.2 \times 10^5, 10^9)$, $\theta \in [-\tau, 0]$, $\tau = \max\{\tau_1, \tau_2\}$, as τ_2 increases from 0 to 0.95, the volumes of tumor cells, $CD4^+$ T cells, cytokines and host cells keep stable, as $\tau_2 = 0.95$, periodic oscillations occur, the amplitudes of oscillations increase as τ_2 increases, which are illustrated by Figure 23(a)(b) and Figure 24(a)(b).

When $\tau_2 = 2 \in (0, \tau_{20})$, $\tau_1 \in (0, 7)$, with history function $(3776, 1.75 \times 10^6, 2.2 \times 10^5, 10^9)$, $\theta \in [-\tau, 0]$, $\tau = \max\{\tau_1, \tau_2\}$, as τ_1 increases from 0 to 3.6, the volumes of tumor cells, $CD4^+$ T cells, cytokines and host cells keep stable, as $\tau_1 = 3.6$, periodic oscillations occur, the amplitudes of oscillations increase as τ_1 increases; which are illustrated by Figure 25(a)(b) and Figure 26(a)(b).

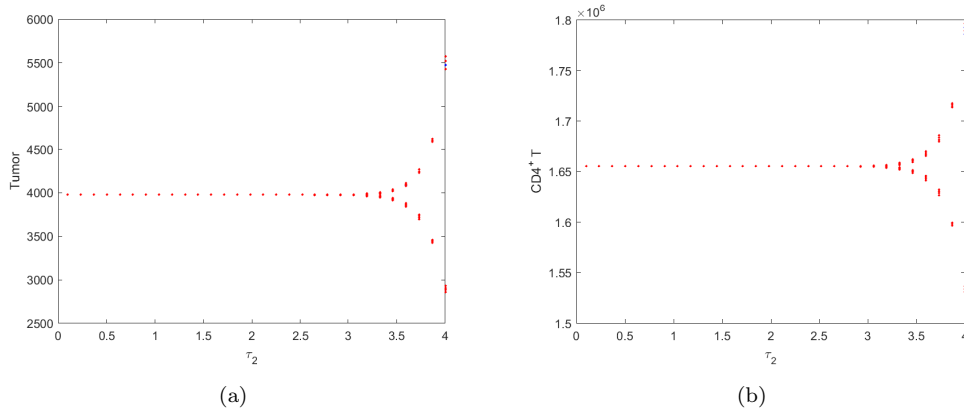


Figure 19. With dde23 solver, when $\tau_1 = 0$, $\tau_2 \in (0, 4)$, (a) the influence of delay τ_2 on the volume of tumor cells; (b) the influence of delay τ_2 on the volume of $CD4^+$ T cells.

In absence of delays, with initial condition $(3776, 1.75 \times 10^6, 2.2 \times 10^5, 10^9)$ and $t \in [0, 1000]$, we give the influence of relative parameters on the volume of tumor cells of system (1.3) around E_{51} :

The influence of production rate of $CD4^+$ T cells $a_2 \in (0.8, 1)$ and production rate of cy-

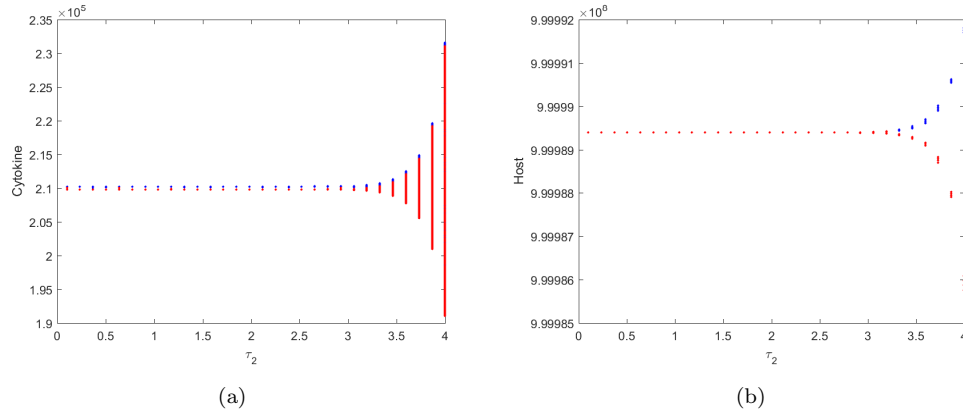


Figure 20. With dde23 solver, when $\tau_1 = 0, \tau_2 \in (0, 4)$, (a) the influence of delay τ_2 on the volume of cytokines; (b) the influence of delay τ_2 on the volume of host cells.

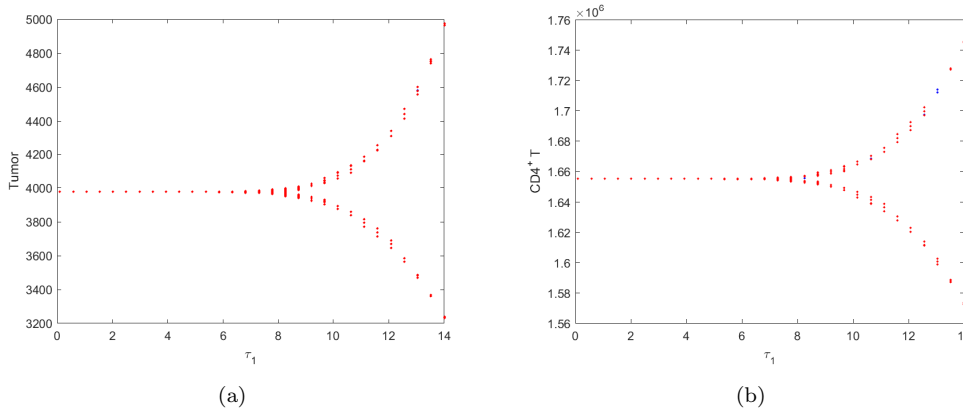


Figure 21. With dde23 solver, when $\tau_2 = 0, \tau_1 \in (0, 14)$, (a) the influence of delay τ_1 on the volume of tumor cells; (b) the influence of delay τ_1 on the volume of CD4⁺ T cells.

tokines $a_3 \in (4.5, 6.5)$ on the volume of tumor cells are illustrated by Figure 27(a) and Figure 27(b) respectively, we conclude that both the production rate of CD4⁺ T cells and cytokines reduce the volume of tumor cells.

The influence of natural death rate of CD4⁺ T cells $c_1 \in (0.01, 0.12)$ and natural death rate of cytokines $c_2 \in (25, 40)$ on the volume of tumor cells are illustrated by Figure 28(a) and Figure 28(b) respectively, we conclude that both the death rate of CD4⁺ T cells and cytokines increase the volume of tumor cells.

The influence of killing rate of tumor cells by cytokines $a_1 \in (0.1, 0.5)$ and intrinsic growth rate of host cells $r_2 \in (0.1, 0.5)$ on the volume of tumor cells are illustrated by Figure 29(a) and Figure 29(b) respectively, we conclude that both the killing rate of tumor cells by cytokines and intrinsic growth rate of host cells only cause slight oscillation and nearly do not change the volume of tumor cells.

The influence of intrinsic growth rate of tumor cells $r_1 \in (0.15, 0.6)$ and loss rate of CD4⁺ T cells by tumor cells $d_2 \in (10^{-8}, 10^{-6})$ on the volume of tumor cells are illustrated by Figure 30(a) and Figure 30(b) respectively, we conclude that as $r_1 \in (0.15, 0.18)$, there is periodic oscillation

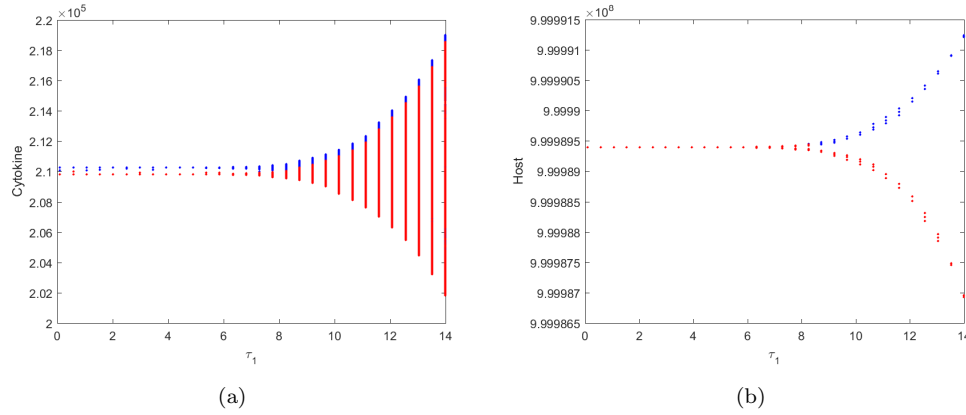


Figure 22. With dde23 solver, when $\tau_2 = 0, \tau_1 \in (0, 14)$, (a) the influence of delay τ_1 on the volume of cytokines; (b) the influence of delay τ_1 on the volume of host cells.

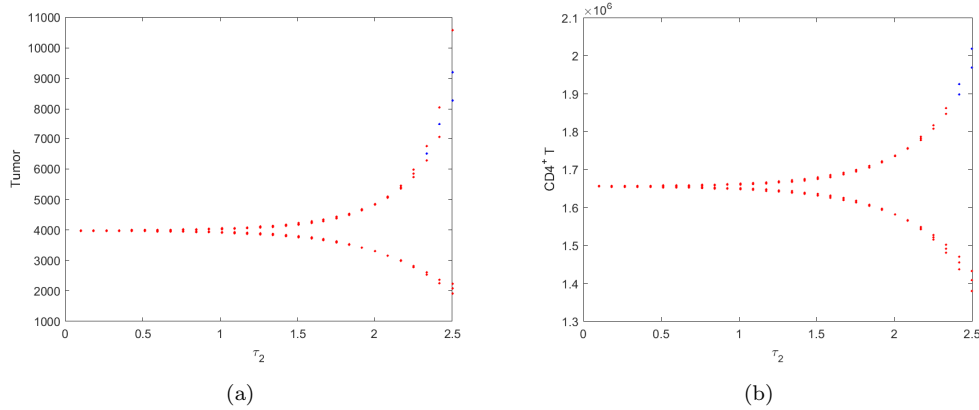


Figure 23. With dde23 solver, when $\tau_1 = 7, \tau_2 \in (0, 2.5)$, (a) the influence of delay τ_2 on the volume of tumor cells; (b) the influence of delay τ_2 on the volume of CD4⁺ T cells.

for tumor cells, as $r_1 = 0.18$, Hopf bifurcation occurs and periodic oscillation disappears, as $r_1 \in (0.18, 0.6)$, the volume of tumor cells keeps stable, the loss rate of CD4⁺ T cells by tumor cells increases the volume of tumor cells.

In absence of delays, we give the influence of injection treatments of both CD4⁺ T cells and cytokines on the volume of tumor cells:

Without injection treatment of CD4⁺ T cells and cytokines, for different initial conditions: $(8.5 \times 10^3, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$ and $(8.5 \times 10^6, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$, when $\text{day} \in [0, 300]$, the stable volumes of tumor cells are 4800 at day 180 and $9.8 \cdot 10^8$ at day 40 respectively, from which we conclude that when the initial volume of tumor cells is lower, the stable volume of tumor cells is also lower, which is illustrated by Figure 31(a) and Figure 31(b).

For $I_1 > 0, I_2 = 0$, that is injection treatment of only CD4⁺ T cells, for different initial conditions $(8.5 \times 10^3, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$, $(8.5 \times 10^6, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$ and the same injection treatment of CD4⁺ T cells $I_1 = 10^5$, when $\text{day} \in [0, 30]$, we conclude that the stable volumes of tumor cells are 1500 at day 30 and 9.8×10^8 at day 30 respectively, for the same initial condition $(8.5 \times 10^6, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$, as the injection treatment $I_1 = 1.6 \times 10^8$

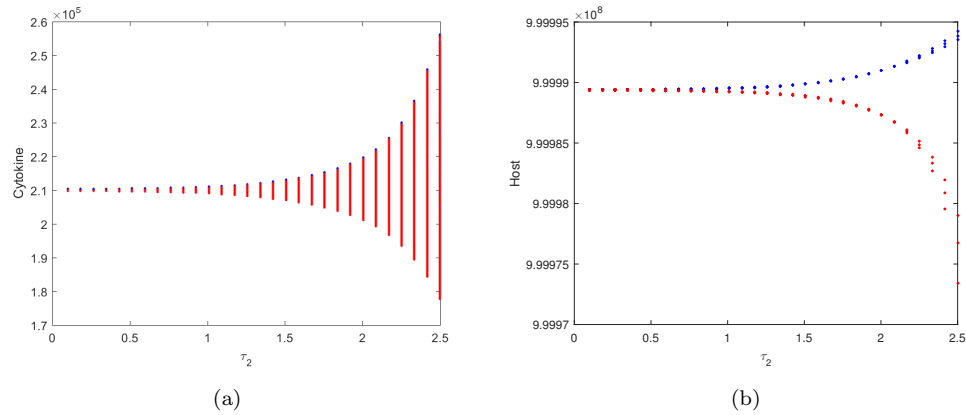


Figure 24. With dde23 solver, when $\tau_1 = 7, \tau_2 \in (0, 2.5)$, (a) the influence of delay τ_2 on the volume of cytokines; (b) the influence of delay τ_2 on the volume of host cells.

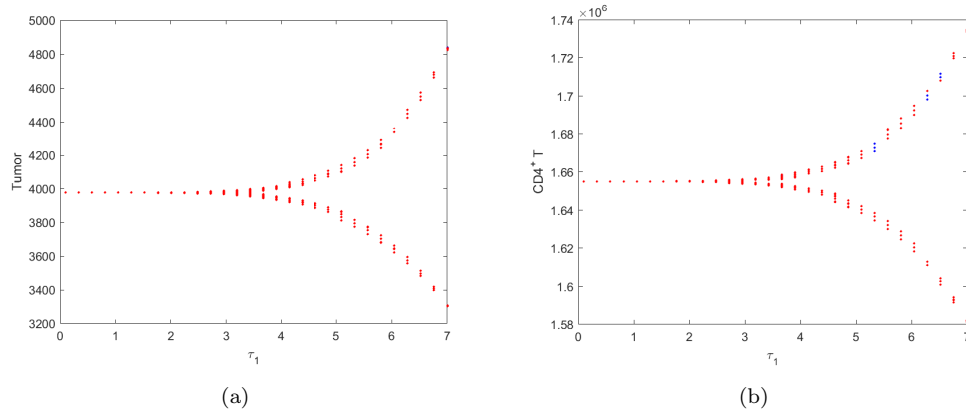


Figure 25. With dde23 solver, when $\tau_2 = 2, \tau_1 \in (0, 7)$, (a) the influence of delay τ_1 on the volume of tumor cells; (b) the influence of delay τ_1 on the volume of CD4⁺ T cells.

is sufficiently large, when $\text{day} \in [0, 30]$, the tumor cells can be eradicated at day 14, which are illustrated by Figure 32(a), Figure 32(b) and Figure 32(c) respectively.

For $I_1 = 0, I_2 > 0$, that is injection treatment of only cytokines, for different initial conditions $(8.5 \times 10^3, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$, $(8.5 \times 10^6, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$ and the same injection treatment of cytokines $I_2 = 10^4$, when $\text{day} \in [0, 200]$, we conclude that the stable volumes of tumor cells are 4800 at day 160 and 9.8×10^8 at day 40, for the same initial condition $(8.5 \times 10^6, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$, as the injection treatment $I_2 = 10^9$ is sufficiently large, when $\text{day} \in [0, 20]$, the tumor cells can be eradicated at day 2, which are illustrated by Figure 33(a), Figure 33(b) and Figure 33(c) respectively.

For $I_1 > 0, I_2 > 0$, that is injection treatments of both CD4⁺ T cells and cytokines, for the same initial condition $(8.5 \times 10^6, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$, as both injection treatments $I_1 = 10^4, I_2 = 10^5$ are small, when $\text{day} \in [0, 200]$, the stable volume of tumor cells 9.8×10^8 is large at day 30, as both injection treatments increase to $I_1 = 10^7, I_2 = 10^8$, when $\text{day} \in [0, 200]$, the stable volume of tumor cells 9.8×10^8 is also large at day 30, as both injection treatments $I_1 = 10^7, I_2 = 6 \times 10^8$ are sufficiently large, when $\text{day} \in [0, 20]$, the tumor cells can be eradicated

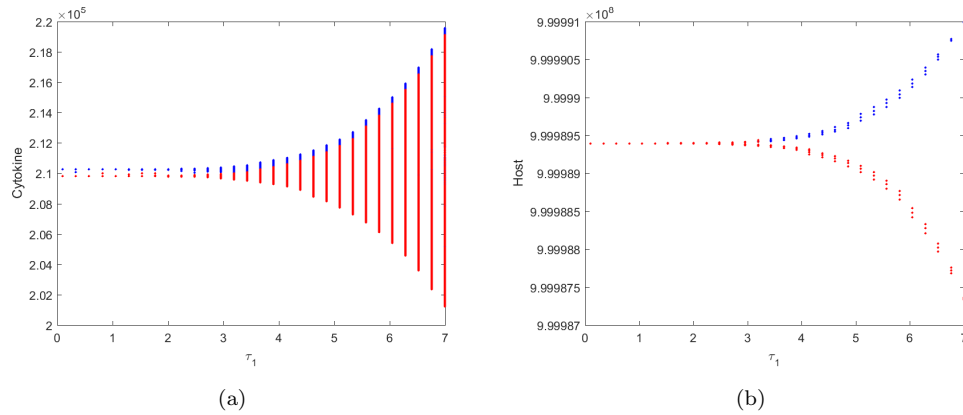


Figure 26. With dde23 solver, when $\tau_2 = 2$, $\tau_1 \in (0, 7)$, (a) the influence of delay τ_1 on the volume of cytokines; (b) the influence of delay τ_1 on the volume of host cells.

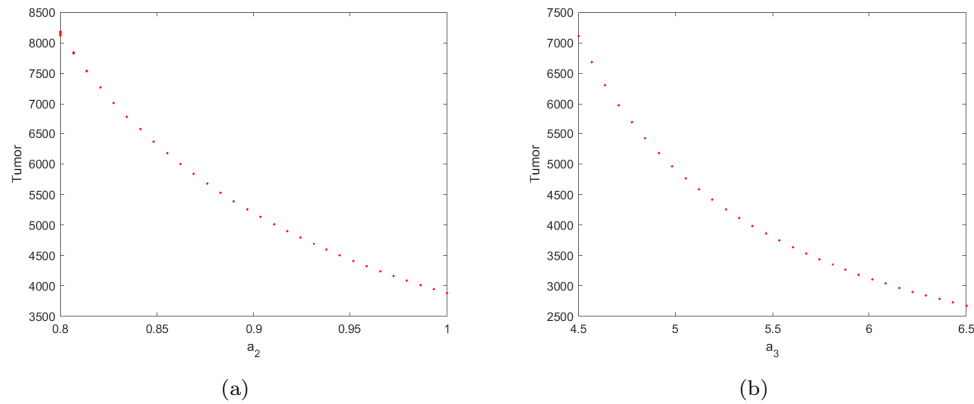


Figure 27. With ode45 solver, in absence of delay, (a) the influence of production rate of CD4⁺ T cells $a_2 \in (0.8, 1)$ on the volume of tumor cells; (b) the influence of production rate of cytokines $a_3 \in (4.5, 6.5)$ on the volume of tumor cells.

at day 5, which are illustrated by Figure 34(a), Figure 34(b) and Figure 34(c) respectively.

All the figures are drawn by software MATLAB, when time t is sufficiently large, the volume (Tumor cells, CD4⁺ T cells, Cytokines, Host cells) keeps invariant, that is stability, the volume (Tumor cells, CD4⁺ T cells, Cytokines, Host cells) has maximum and minimum, that is periodic oscillation, when the volume of tumor cells is zero, that is tumor eradication.

7. Conclusion

In this paper, we propose a tumor-CD4⁺-cytokine-host model with two delays and injection treatments, where two delays denote activation delays for CD4⁺ T cells and cytokines respectively, we compute the equilibrium points, prove the positivity and boundedness of solutions, the positivity means that tumor cells always exist without treatment, boundedness means that the immune cells can control the increase of tumor cells.

In tumor micro-environment, delay really exist for the molecule production, differentiation,

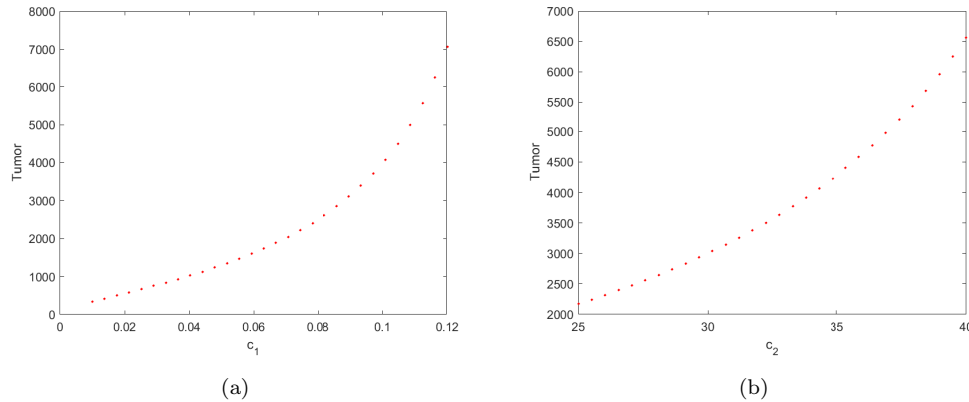


Figure 28. With ode45 solver, in absence of delay, (a) the influence of natural death rate of CD4⁺ T cells $c_1 \in (0.01, 0.12)$ on the volume of tumor cells; (b) the influence of natural death rate of cytokines $c_2 \in (25, 40)$ on the volume of tumor cells.

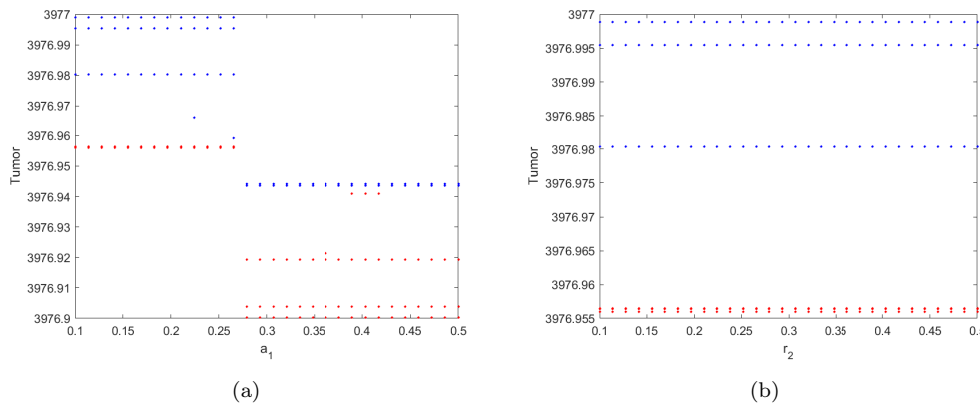


Figure 29. With ode45 solver, in absence of delay, (a) the influence of tumor-killing rate by cytokines $a_1 \in (0.1, 0.5)$ on the volume of tumor cells; (b) the influence of intrinsic growth of host cells $r_2 \in (0.1, 0.5)$ on the volume of tumor cells.

proliferation and transportation is not instantaneous, the dynamics of delayed tumor-immune system should be more real, under four cases: (1) $\tau_1 = 0, \tau_2 > 0$, (2) $\tau_2 = 0, \tau_1 > 0$, (3) $\tau_1 \in (0, \tau_{10}), \tau_2 > 0$, (4) $\tau_2 \in (0, \tau_{20}), \tau_1 > 0$, we discuss the influence of two delays on the dynamics of system (1.3) around interior positive equilibrium point E_{51} , besides we also discuss the influence of delays on the volumes of tumor cells, CD4⁺ T cells, cytokines and host cells, from which we conclude that equilibrium point E_{51} is stable when the delay is sufficiently small, Hopf bifurcation occurs and periodic solution bifurcates from equilibrium point E_{51} when any of the delays reaches the critical value, the results show that delay can destabilize the equilibrium point and cause periodic oscillation, stability of equilibrium point means that the proliferation of tumor cells is controlled, periodic oscillation means that relapse of tumor cells occurs, that is the tumor cells are invasive or malignant for large delays, the situations of patients depend on the delays, so controlling relative delay should be important for immunotherapy toward tumor cells.

In absence of delays, we give the influence of relative parameters on the volume of tumor

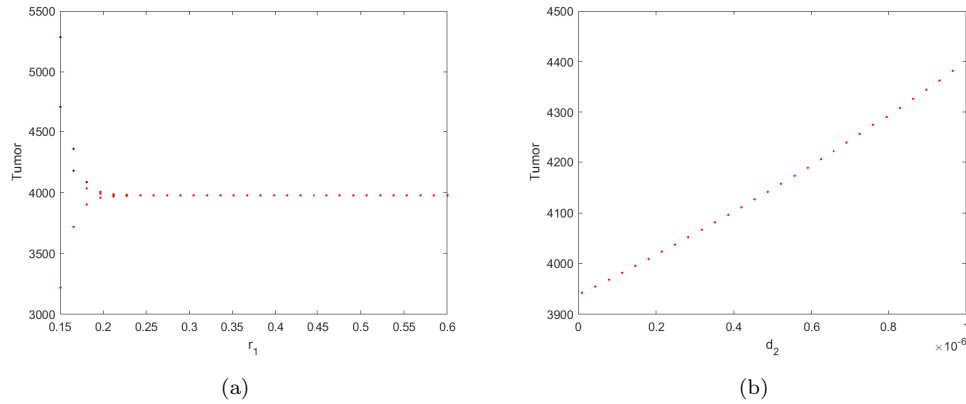


Figure 30. With ode45 solver, in absence of delay, (a) the influence of intrinsic growth rate of tumor cells $r_1 \in (0.15, 0.6)$ on the volume of tumor cells; (b) the influence of loss rate of $CD4^+$ T cells by tumor cells $d_2 \in (10^{-8}, 10^{-6})$ on the volume of tumor cells.

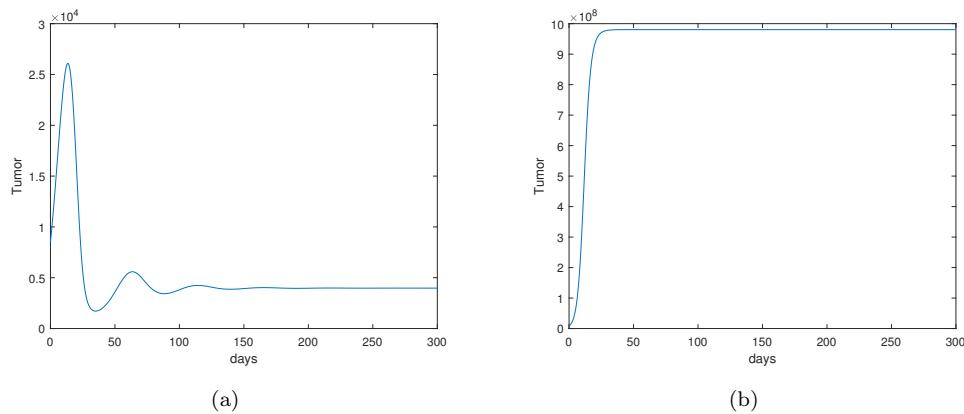


Figure 31. With ode45 solver, in absence of delays, without injection treatment, (a) the influence of initial values $(8.5 \times 10^3, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$ on the volume of tumor cells at day 300; (b) the influence of initial values $(8.5 \times 10^6, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$ on the volume of tumor cells at day 300.

cells around interior positive equilibrium point E_{51} , besides we discuss the feasibility of injection treatments of $CD4^+$ T cells and cytokines on eradication of tumor cells, from which we conclude that both the initial condition and the doses of injection treatment play important role on the volume of tumor cells, the tumor cells can be eradicated if the dose of injection treatment of $CD4^+$ T cells or cytokines is sufficiently large, all the results are supported by simulation. Comparing to works [2, 36], we introduce host cells into tumor-immune system, comparing to works [2, 13, 36, 37], we introduce two delays into tumor-immune system and study the influence of two delays on the dynamics of system, our work should be improvement of above works.

From the results, we conclude:

(i) Delay causes rich dynamics for tumor-immune system, when the delay is sufficiently small, the interior positive equilibrium point E_{51} is locally asymptotically stable, as any of the delay reaches to critical value, Hopf bifurcation occurs and periodic solution bifurcates from E_{51} , the amplitude of oscillation increases as the delay increases.

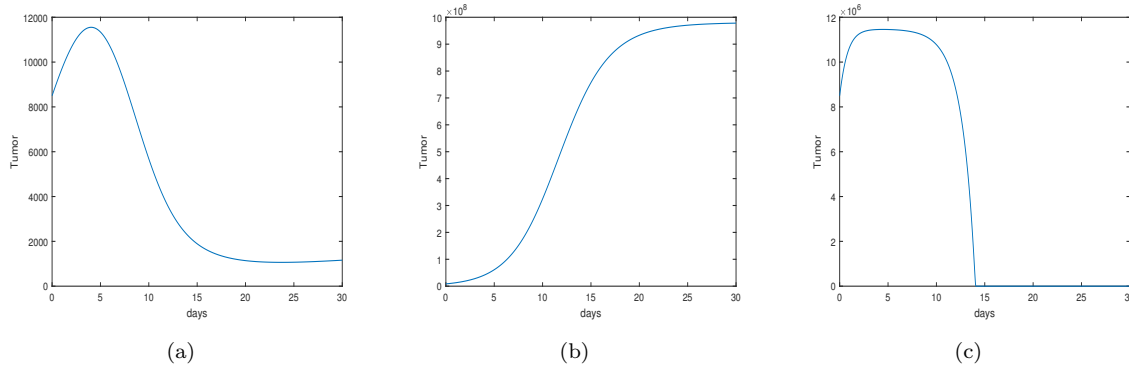


Figure 32. With ode45 solver, in absence of delays, (a) the influence of injection treatment of only $CD4^+$ T cells $I_1 = 10^5$, $I_2 = 0$ and initial values $(8.5 \times 10^3, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$ on the volume of tumor cells at day 30; (b) the influence of injection treatment of only $CD4^+$ T cells $I_1 = 10^5$, $I_2 = 0$ and initial values $(8.5 \times 10^6, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$ on the volume of tumor cells at day 30; (c) the influence of injection treatment of only $CD4^+$ T cells $I_1 = 1.6 \times 10^8$, $I_2 = 0$ and initial values $(8.5 \times 10^6, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$ on the volume of tumor cells at day 30.

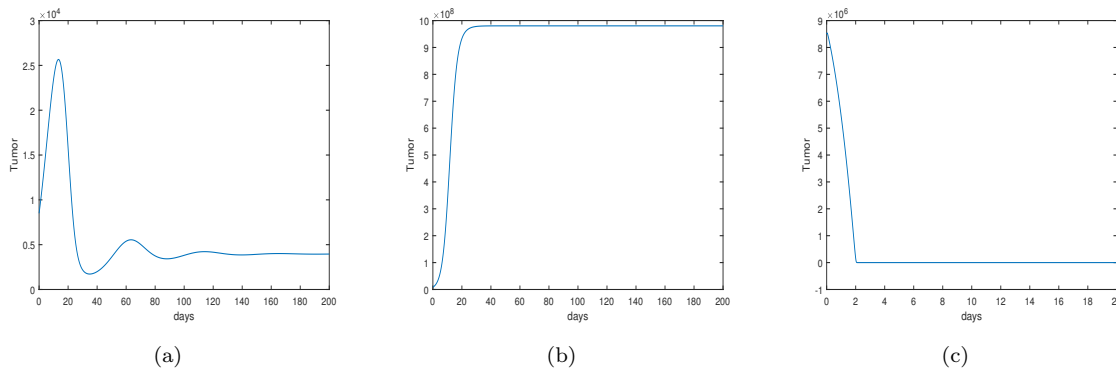


Figure 33. With ode45 solver, in absence of delays, (a) the influence of injection treatment of only cytokines $I_1 = 0$, $I_2 = 10^4$ and initial values $(8.5 \times 10^3, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$ on the volume of tumor cells at day 200; (b) the influence of injection treatment of only cytokines $I_1 = 0$, $I_2 = 10^4$ and initial values $(8.5 \times 10^6, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$ on the volume of tumor cells at day 200; (c) the influence of injection treatment of only cytokines $I_1 = 0$, $I_2 = 10^9$ and initial values $(8.5 \times 10^6, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$ on the volume of tumor cells at day 20.

(ii) In absence of delay, some parameters play important role on the volume of tumor cells, that is production rates of $CD4^+$ T cells and cytokines reduce the volume of tumor cells, natural death rates of $CD4^+$ T cells and cytokines, loss rate of $CD4^+$ T cells by tumor cells increase the volume of tumor cells, so immunity inhibits the tumor cells, on the other hand, intrinsic growth rate of tumor cells can cause periodic oscillation, killing rate of tumor cells by cytokines and intrinsic growth rate of host cells play little influence on the volume of tumor cells.

(iii) In absence of delays, we discuss the injection treatments of both $CD4^+$ T cells and cytokines, the results show that initial condition has important influence on the stable volume of tumor cells, the tumor cells can be eradicated if the dose of injection treatment of $CD4^+$ T cells or cytokines is sufficiently large, so injection treatment is valid immunotherapy toward tumor.

As we know, the immune checkpoint [12, 34, 36, 37] always exists in tumor-immune system,

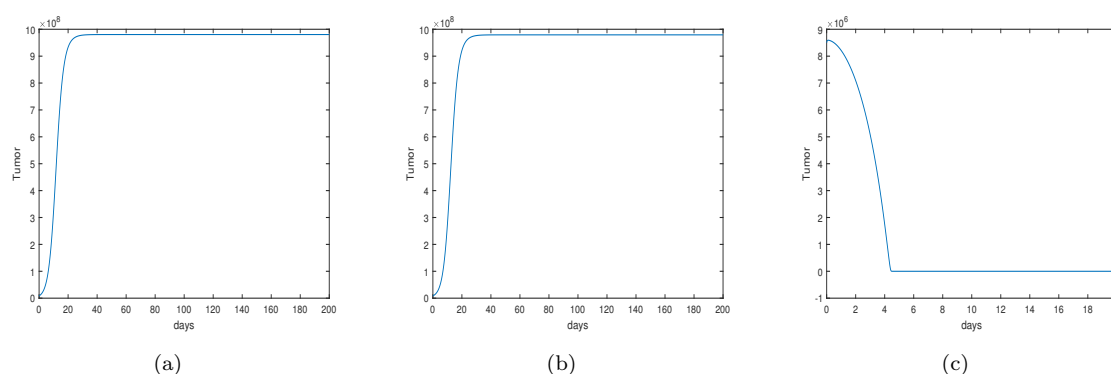


Figure 34. With ode45 solver, in absence of delays, with the same initial condition $(8.5 \times 10^6, 10^6, 1.5 \times 10^5, 9.5 \times 10^8)$, (a) the influence of injection treatments of both $CD4^+$ T cells and cytokines $I_1 = 10^4, I_2 = 10^5$ on the volume of tumor cells at day 200; (b) the influence of injection treatments of both $CD4^+$ T cells and cytokines $I_1 = 10^7, I_2 = 10^8$ on the volume of tumor cells at day 200; (c) the influence of injection treatments of both $CD4^+$ T cells and cytokines $I_1 = 10^7, I_2 = 6 \times 10^8$ on the volume of tumor cells at day 20.

which inhibits the role of immune cells against tumor cells, J.-L. Yu et al. [36] revealed that blockade of immune checkpoint is revolutionary strategy against tumor cells, so introducing immune checkpoint into tumor-immune system (1.3) should be valuable, we will discuss the dynamics of tumor-immune system with delays and immune checkpoint in the future.

Declaration of competing interest

We declare that there is no conflict of interest in this manuscript.

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