Dynamics of a tumor-immune model considering targeted chemotherapy

Peng Liu [a,b,*], Xijun Liu [a,b]

[a] Department of Mechanics, Tianjin University, Tianjin, 300354, PR China
[b] Tianjin Key Laboratory of Nonlinear Dynamics and Chaos Control, Tianjin, 300072, PR China

ARTICLE INFO

ABSTRACT

Considering the targeted chemotherapy, a mathematical model of tumor-immune system was constructed on the basis of de Pillis's model. In this paper, we conducted qualitative analysis on the mathematical model, including the positivity and boundedness of solutions, local stability and global stability of equilibrium solutions. Some numerical simulations were given to illustrate the analytic results. Comparing the targeted chemotherapy model with regular chemotherapy model, we found that the targeted chemotherapy was benefit to kill tumor cells.

© 2017 Elsevier Ltd. All rights reserved.

1. Introduction

Cancer is a disease, which can start from everywhere in human body. Normally, human cells are ordered by gene to grow and divide to form tissues and organs, i.e., the liver, the heart and the lungs. However, the order of the gene may be broken down in sometime, then the cells grow fast and disorderly to form tumors. According to the statistic data from Canadian Cancer Society, it is estimated that 41,000 Canadian men and 37,000 Canadian women will die from cancer in 2015.

Even though the high death rate, up to now, we have several types of tumor treatment such as surgery, radiation therapy, chemotherapy and immunotherapy. Each treatment has its advantages and disadvantages. Surgery is used to treat solid tumors that are contained in fixed area such as lung tumor, liver tumor. The risks of surgery include pain, infection, bleeding and damage to nearby. Radiation therapy is a treatment that uses high doses of radiation to kill tumor cells. However, radiation kill not only tumor cells, but also normal human cells to cause side effect, i.e., fatigue. Immunotherapy is a type of treatment to help human's immune system fight tumor cells, while immunotherapy can also cause side effects, such as skin reactions at the needle site, fever, pain and so on.

Chemotherapy is a treatment that uses drugs to kill tumor cells. The basic idea of chemotherapy is to stop or slow the tumor cells which grow and divide quickly, hence, chemotherapy may kill the normal cells which grow and divide quickly to induce the side effects, i.e., hair loss, mouth sores and nausea. To avoid these side effects, oncologists establish a new treatment: targeted chemotherapy. 'Targeted' means this treatment can target the changes in tumor cells that help them grow, divide and spread [1,2]. There are two types targeted chemotherapy: small-molecule drugs and monoclonal antibodies drugs. Small-molecule drugs can enter tumor cells easily [3–7], and monoclonal antibodies drugs can attach to specific targets on the outer surface of tumor cells [8–10]. Recently, more and more progress in monoclonal antibodies drugs have been made. For example, a paper published in 2015 in Nature Communications [11] gave a new targeted drug delivery method by using genetically engineered diatom biosilica, which can display specific antibodies. The drug-loaded nanoparticles can be sorbed with the diatom biosilica to kill the tumor cells. The experimental results showed that 91% of tumor cells were killed without harming the healthy ones around them.

Tumor therapy is not only a hot topic in oncology, but also focused by mathematicians. A large numbers of mathematical models have been proposed on tumor system (see in [12–17]). Among these models, the interactions between the immune system and a growing tumor are involved, since the presence of an immune component is essential for producing clinically observed phenomena such as tumor dormancy and spontaneous tumor regression [16]. Base on the tumor-immune model, some researchers established chemotherapy model to simulate the effects of the drugs (see in [18–21]). To the authors' knowledge, the modeling of targeted chemotherapy is barely to find.

---

* Corresponding author.
  E-mail address: liupeng823@tju.edu.cn (P. Liu).

Table 1
Parameter values for model (2.1).

Parameter	Definition	Value	Units	Source
a	Tumor growth rate	4.31×10^{-1}	day^{-1}	[18]
b	$1/b$ is tumor carrying capacity	1.02×10^{-14}	cells^{-1}	[18]
c_1	Fractional tumor cells killed by effector cells	3.41×10^{-10}	cells^{-1} day^{-1}	[18]
μ	Death rate of effector cells	4.12×10^{-2}	day^{-1}	[18]
g	Maximum effector cells recruitment rate by tumor cells	1.50×10^{-2}	day^{-1}	[18]
s	Steepness coefficient of the effector cells recruitment	2.02×10^{1}	cell	[18]
K_C	Fractional circulating lymphocytes killed by chemotherapy	6.00×10^{-1}	day^{-1}	[18]
K_N	Fractional effectors cells killed by chemotherapy	6.00×10^{-1}	day^{-1}	[18]
K_T	Fractional tumor cells killed by chemotherapy	8.00×10^{-1}	day^{-1}	[18]
k_T	Combination rate of chemotherapy drug with tumor cells	3.2×10^{-9}	day^{-1}	
p	Effector cells inactivation rate by tumor cells	2.00×10^{-11}	cells^{-1} day^{-1}	[18]
α_1	Constant source of effector cells	1.20×10^{4}	cells day^{-1}	[18]
α_2	Constant source of circulating lymphocytes	7.50×10^{8}	cells day^{-1}	[18]
β	Death rate of circulating lymphocytes	1.20×10^{-2}	day^{-1}	[18]
γ	Rate of chemotherapy drug decay	9.00×10^{-1}	day^{-1}	[18]
V_M	Chemotherapy treatment	$0 \leq V_M \leq 1$	day^{-1}	[18]
η	Efficacy of chemotherapy	$0 \leq \eta \leq 1$		

In this paper, we will propose a new mathematical model to reflect the effect of the monoclonal antibodies targeted chemotherapy. We will investigate the difference between untargeted chemotherapy and targeted chemotherapy. Our model is established on the model built by De Pillis in [18], which tracks three cell populations and one drug concentration in the tissue, as follows,

$$
\begin{aligned}
\dot{T} &= aT(1 - bT) - c_1 NT - K_T MT, \\
\dot{N} &= \alpha_1 + g\frac{T}{s+T}N - \mu N - pTN - K_N MN, \\
\dot{C} &= \alpha_2 - \beta C - K_C MC, \\
\dot{M} &= -\gamma M + V_M,
\end{aligned}
\tag{1.1}
$$

the meaning of the notations in which will be given in next section.

The rest of paper is organized as follows. In Section 2, we present the modeling process of the targeted chemotherapy model, and summarize some results obtained by previous papers. Then we prove that the solutions of the model are well-posed and bounded in Section 3. In Section 4, we give the expressions of the equilibrium solutions and study their stability, further, we perform some numerical simulation to illustrate the analytic results. In Section 5, we draw a conclusion and compare the result with the result summary in Section 2 to show the advantage of targeted chemotherapy.

2. Modeling

In this section, we construct a mathematical model of tumor-immune system with targeted chemotherapy, which is based on de Pillis's model in [18]. The model is built on the base of interactions among tumor cells, effector immune cells, circulating lymphocytes and chemotherapeutics, which is presented by the following ordinary differential equations,

$$
\begin{aligned}
\dot{T} &= aT(1 - bT) - c_1 NT - K_T MT, \\
\dot{N} &= \alpha_1 + g\frac{T}{s+T}N - \mu N - pTN - K_N(1-\eta)MN, \\
\dot{C} &= \alpha_2 - \beta C - K_C(1-\eta)MC, \\
\dot{M} &= -\gamma M + V_M - k_T TM,
\end{aligned}
\tag{2.1}
$$

where T, N and C is tumor cell population, effector immune cell population and circulating lymphocyte population, respectively, M is concentration of chemotherapeutic drugs in tissue, the dot denotes differentiation with respect to t, all parameter values in (2.1) are non-negative, which are shown in Table 1.

There are some considerations and assumptions in this modelling.

A1: We only consider all cells in a small volume of tissue.
A2: Tumor cells can not grow without bound, hence we select logistic growth law to describe the population growth of tumor cells, which are represented by $aT(1 - bT)$ in the first equation, where a denotes the growth rate of tumor cells, b represents the inverse of carrying capacity for tumor cells.
A3: The interaction between tumor cells and effector immune cells can result in death of both cells, which are represented by $-c_1 NT$ in the first equation and $-pTN$ in the second equation, where c_1 and p denote the fractional tumor cells killed by effector cells and effector cells inactivation rate by tumor cells respectively.
A4: The presence of tumor cells stimulates the immune response, which is described by the positive nonlinear growth term for the effector immune cells: $g\frac{T}{s+T}N$, where g denotes the maximum effector immune cell recruitment rate by tumor cells, s denotes the steepness coefficient of the effector cells recruitment.
A5: The source of effector immune cells and circulating lymphocyte is considered from outside of tissue and with constant input rate α_1 and α_2 respectively. In the absence of tumor cells, effector immune cells die at a per capita rate μ, circulating lymphocytes die at a per capita rate β.
A6: Chemotherapeutics kill tumor cells, effector immune cells and circulating lymphocytes, which is represented by $-K_T MT$ in the first equation of (2.1), $-K_N(1-\eta)MN$ in the second equation of (2.1) and $-K_C(1-\eta)MC$ in the third equation of (2.1), respectively, where K_T, K_N and K_C denotes the fractional tumor cells killed by chemotherapy, the fractional effectors cells killed by chemotherapy and the fractional circulating lymphocytes killed by chemotherapy, η is efficacy of chemotherapy.
A7: The targeted chemotherapeutics drugs are injected into tissue at constant rate V_M and decay at rate γ. Since monoclonal antibodies targeted drugs can attach to specific targets on the outer surface of tumor cells, the attachment between drugs and tumor cells consume drugs, which is represented in the last equation by $-k_T TM$, where k_T denotes the combination rate of chemotherapy drug with tumor cells.

Comparing the model (2.1) with the regular chemotherapy model (1.1), we introduce a parameter η to describe the effectiveness of the targeted chemotherapy, and add a term $-k_T TM$ in the four equation to represent the characteristic of monoclonal antibodies targeted drugs. For the convenience of comparison between model (2.1) and model (1.1), we summarize the results obtained by de Pillis in [18] and Valle in [22].

The tumor free equilibrium of system (1.1) is

$$E_e : (T_e, N_e, C_e, M_e) = \left(0, \frac{\alpha_1\gamma}{\gamma\mu + K_N V_M}, \frac{\alpha_2\gamma}{\beta\gamma + K_C V_M}, \frac{V_M}{\gamma}\right).$$

Then,

(i) E_e is locally asymptotically stable whenever

$$B_1 V_M^2 + B_2 V_M + B_3 < 0, \tag{2.2}$$

where $B_1 = -K_N K_T$, $B_2 = a\gamma K_N - K_T \gamma\mu$ and $B_3 = a\gamma^2\mu - c_1\alpha_1\gamma^2$;

(ii) E_e is globally asymptotically stable if provided initial value $M(0) = V_M$ and the following conditions are fulfilled,

$$\mu - g > 0 \quad \text{and} \quad A_1 V_M^2 + A_2 V_M + A_3 < 0, \tag{2.3}$$

where $A_1 = -bK_N K_T$, $A_2 = abK_N - \gamma K_T(p + \mu b)$ and $A_3 = \gamma(ap + \mu ab - \alpha_1 c_1 b)$.

3. Non-negativeness and boundness of solutions and equilibria

Due to the biological meaning, all values of four state variables must be non-negative. In this section, we will discuss the well-posedness of solutions of (2.1).

Theorem 3.1. *All solutions of system (2.1) are non-negative, if the initial conditions are non-negative, for $t > 0$. Moreover, they are bounded, if $\mu - g > 0$.*

Proof. Firstly, using the method of variation of constants, for the second equation in (2.1), we have,

$$N(t) = N(0)e^{\int_0^t \left[g\frac{T(\xi)}{s+T(\xi)} - \mu - pT(\xi) - K_N(1-\eta)M(\xi)\right]d\xi}$$
$$+ \alpha_1 \int_0^t e^{\int_\theta^t \left[g\frac{T(\xi)}{s+T(\xi)} - \mu - pT(\xi) - K_N(1-\eta)M(\xi)\right]d\xi} d\theta,$$

implying $N(t) \geq 0$ for $t \geq 0$ provided that $N(0) \geq 0$.

Then, the same method to the third and fourth equation of (2.1), we have

$$C(t) = C(0)e^{\int_0^t [-\beta - K_C(1-\eta)M(\xi)]d\xi} + \alpha_2 \int_0^t e^{\int_\theta^t [-\beta - K_C(1-\eta)M(\xi)]d\xi} d\theta,$$
$$M(t) = M(0)e^{\int_0^t [-\gamma - k_T T(\xi)]d\xi} + V_M \int_0^t e^{\int_\theta^t [-\gamma - k_T T(\xi)]d\xi} d\theta,$$

implying $C(t) \geq 0$, $M(t) \geq 0$ for $t > 0$, provided that $C(0) \geq 0$, $M(0) \geq 0$.

For $T(t)$, when $T(t) = 0$, we have $\dot{T}(t) = 0$, which means hyperplane $T = 0$ is invariant, implying $T(t) \geq 0$ for $t > 0$ provided that $T(0) \geq 0$.

It remains to prove the non-negative solutions of (2.1) are all bounded, if $\mu - g > 0$. Let $(T(t), N(t), C(t), M(t))$ be a non-negative solution of model (2.1) and consider a Lyapunov function

$$V = T(t) + N(t) + C(t) + M(t).$$

Then, differentiating V along (2.1) yields

$$\dot{V}|_{(2.1)} = aT(1 - bT) - c_1 NT - K_T MT + \alpha_1 + g\frac{T}{s+T}N - \mu N - pTN$$
$$- K_N(1-\eta)MN + \alpha_2 - \beta C - K_C(1-\eta)MC - \gamma M$$
$$+ V_M - k_T TM$$
$$= -ab(T - \frac{1}{2b})^2 - c_1 NT - K_T MT - g\frac{s}{s+T}N - (\mu - g)N - pTN$$
$$- K_N(1-\eta)MN - \beta C - K_C(1-\eta)MC - \gamma M - k_T TM + \alpha_1$$
$$+ \alpha_2 + V_M + \frac{a}{4b}$$

If $\mu - g > 0$, we can obtain

$$\dot{V}|_{(2.1)} =$$
$$\begin{cases} > 0 & \text{if} \quad ab(T - \frac{1}{2b})^2 + c_1 NT + K_T MT + g\frac{s}{s+T}N + (\mu - g)N + pTN \\ & \quad + K_N(1-\eta)MN + \beta C + K_C(1-\eta)MC + \gamma M + k_T TM < \sigma, \\ < 0 & \text{if} \quad ab(T - \frac{1}{2b})^2 + c_1 NT + K_T MT + g\frac{s}{s+T}N + (\mu - g)N + pTN \\ & \quad + K_N(1-\eta)MN + \beta C + K_C(1-\eta)MC + \gamma M + k_T TM > \sigma, \end{cases}$$

where $\sigma = \alpha_1 + \alpha_2 + V_M + \frac{a}{4b}$.

This shows that any solution starting from a non-negative initial value must be bounded. By the continuation theory of ODEs, the boundedness of a solution also implies that it exists for $t > 0$. $\square$

From above result, we can have following theorem,

Theorem 3.2. $\Gamma = \{(T, N, C, M) \in \mathbb{R}_+^4 | T \geq 0, N \geq 0, C \geq 0, M \geq 0\}$ *is a positive invariant set of system (2.1) under condition $\mu - g > 0$.*

4. Equilibrium solutions and their stability

By setting $\dot{T} = \dot{N} = \dot{C} = \dot{M} = 0$ in system (2.1), we can obtain two types equilibrium solutions: the tumor free equilibrium solution

$$E_0 : (T_0, N_0, C_0, M_0)$$
$$= \left(0, \frac{\alpha_1\gamma}{\gamma\mu + K_N(1-\eta)V_M}, \frac{\alpha_2\gamma}{\beta\gamma + K_C(1-\eta)V_M}, \frac{V_M}{\gamma}\right),$$

and the coexisting equilibrium solution

$$E_1 : (T_1, N_1, C_1, M_1),$$

$$N_1 = -\frac{-a\gamma - ak_T T_1 + ab\gamma T_1 + abk_T T_1^2 + K_T V_M}{(\gamma + k_T T_1)c_1}, \quad C_1 = \frac{\alpha_2(\gamma + k_T T_1)}{\beta\gamma + \beta k_T T_1 + K_C V_M(1-\eta)}, \quad M_1 = \frac{V_M}{\gamma + k_T T_1}$$, where T_1 is determined by the equation

$$
\begin{aligned}
F(T, V_M) = \ & \alpha_1 - \frac{gT\left(-a\gamma - ak_T T + ab T\gamma + ab T^2 k_T + K_T V_M\right)}{(s+T)(\gamma + k_T T)c_1} \\
& + \frac{\mu\left(-a\gamma - ak_T T + ab T_1\gamma + ab T^2 k_T + K_T V_M\right)}{(\gamma + k_T T)c_1} \\
& + \frac{p\left(-a\gamma - ak_T T + ab T\gamma + ab T^2 k_T + K_T V_M\right)T}{(\gamma + k_T T)c_1} \\
& + \frac{K_N(1-\eta)V_M\left(-a\gamma - ak_T T + ab T\gamma + ab T^2 k_T + K_T V_M\right)}{(\gamma + k_T T)^2 c_1} = 0.
\end{aligned} \tag{4.1}
$$

4.1. Stability of the tumor free equilibrium solution E_0

In this section, we will study the tumor free equilibrium solution of (2.1) and its stability. To find the stability of the equilibrium solution E_0, we evaluate the Jacobian of system (2.1) to get

$$J(E_0) =$$
$$\begin{bmatrix} a - c_1 N_0 - K_T M_0 & 0 & 0 & 0 \\ \frac{gN_0}{s} - pN_0 & -\mu - K_N(1-\eta)M_0 & 0 & -K_N(1-\eta)N_0 \\ 0 & 0 & -\beta - K_C(1-\eta)M_0 & -K_C(1-\eta)C_0 \\ -k_T M_0 & 0 & 0 & -\gamma \end{bmatrix},$$

and then obtain the characteristic polynomial, given by

$$P(\lambda) = (\lambda - a + c_1 N_0 + K_T M_0)[\lambda + K_N M_0(1-\eta) + \mu]$$
$$\times [\lambda + K_C M_0(1-\eta) + \beta](\lambda + \gamma) = 0.$$

Hence, the eigenvalues of system (2.1) at E_0 are

$$\begin{aligned} \lambda_1 &= a - c_1 N_0 - K_T M_0, \\ \lambda_2 &= -K_N M_0(1-\eta) - \mu, \\ \lambda_3 &= -K_C M_0(1-\eta) - \beta, \\ \lambda_4 &= -\gamma. \end{aligned}$$

Since all parameters are non-negative and $0 \leq \eta \leq 1$, $\lambda_2, \lambda_3, \lambda_4$ are always negative, then the equilibrium solution E_0 is locally asymptotically stable if and only if $\lambda_1 < 0$, which is equivalent to the following inequality,

$$D_1 V_M^2 + D_2 V_M + D_3 < 0, \tag{4.2}$$

where $D_1 = -(1-\eta)K_N K_T = (1-\eta)B_1$, $D_2 = a\gamma K_N(1-\eta) - K_T\gamma\mu < B_2$ and $D_3 = a\gamma^2\mu - c_1\alpha_1\gamma^2 = B_3$ (see the expressions of B_1, B_2 and B_3 in Section 3).

From the above results, we can conclude the following theorem,

Theorem 4.1. *The tumor free equilibrium solution E_0 is locally asymptotically stable whenever $D_1 V_M^2 + D_2 V_M + D_3 < 0$.*

Furthermore, we investigate the global stability of tumor free equilibrium solution E_0 and have the following theorem.

Theorem 4.2. *The tumor free equilibrium solution E_0 is globally asymptotically stable if the condition $a - c_1 N_{\min} - K_T M_{\min} < 0$ is fulfilled, where $N_{\min}$ and $M_{\min}$ denotes the minimum effector immune cells population and the minimum chemotherapy drug concentration.*

Proof. To prove this theorem, we construct a Lyapunov function of the form $V_1(T) = T$, which is positive-definite and continuously differentiable for all positive bounded values of T, i.e., $V_1(0) = 0$ and $V_1(T) > 0$, $\forall T > 0$. Moreover, the time derivative of the Lyapunov function V_1 along (2.1) satisfies

$$
\begin{aligned}
\dot{V}_1 &= aT(1 - bT) - c_1 NT - K_T MT \\
&= T(a - abT - c_1 N - K_T M) \\
&\leq T(a - abT_{\min} - c_1 N_{\min} - K_T M_{\min}),
\end{aligned}
$$

where $T_{\min}$ denotes the minimum tumor cells population. We can easily get $T_{\min} = 0$. Hence, if imposing $a - c_1 N_{\min} - K_T M_{\min} < 0$, we have $\dot{V}_1 \leq 0$ and $\dot{V}_1 = 0$, if and only if $T = 0$. This yields $T(t) \to 0$ as $t \to \infty$, for any positive initial conditions. It follows that when $t \to \infty$, the fourth equation becomes an asymptotically autonomous equation with the limiting equation

$$\dot{M} = -\gamma M + V_M.$$

By the theory for the asymptotically autonomous systems [23], we know that the solution $M(t) \to \frac{V_M}{\gamma}$ as $t \to \infty$. Thus, with $T(t) \to 0$ and $M(t) \to \frac{V_M}{\gamma}$, the rest two equations of system (2.1) become asymptotically autonomous equations with the following limit equations:

$$\dot{N} = \alpha_1 - \mu N - K_N(1-\eta)\frac{V_M}{\gamma}N$$

$$\text{and} \quad \dot{C} = \alpha_2 - \beta C - K_C(1-\eta)\frac{V_M}{\gamma}C,$$

which, similarly, by the theory for the asymptotically autonomous systems, results in

$$\lim_{t \to \infty} N(t) = \frac{\alpha_1\gamma}{\gamma\mu + K_N(1-\eta)V_M}$$

$$\text{and} \quad \lim_{t \to \infty} C(t) = \frac{\alpha_2\gamma}{\beta\gamma + K_C(1-\eta)V_M}.$$

Therefore, under condition $a - c_1 N_{\min} - K_T M_{\min} < 0$, the tumor free equilibrium solution E_0 is globally asymptotically stable. $\square$

In order to get the expression of $N_{\min}$ and $M_{\min}$, we apply the Localization of Compact Invariant Sets (LCIS) method, which was proposed by Krishchenko in [24]. To achieve this, we firstly give some preliminaries and notations. Considering an autonomous system of the form $\dot{x} = f(x)$, where $f \in C^\infty$ is a vector function and $x \in \mathbb{R}^n$ is the state vector. Let $h(x) : \mathbb{R}^n \to \mathbb{R}$ be a $C^\infty-$ differential function. $h(x)$ is called localizing function and not the first integral of the system $\dot{x} = f(x)$. $h|_U$ is denoted the restriction of h on a set $U \subset \mathbb{R}^n$. $S(h)$ is the set $\{x \in \mathbb{R}^n | L_f h(x) = 0\}$, where $L_f h(x) = \frac{\partial h}{\partial x} f(x)$ is a Lie derivative with respect to f. We define

$$h_{\inf} = \inf\{h(x) | x \in U \cap S(h)\} \quad \text{and} \quad h_{\sup} = \sup\{h(x) | x \in U \cap S(h)\}.$$

Then all compact invariant sets are contained in the localization set $K(h) = \{h_{\inf} \leq h(x) \leq h_{\sup}\}$.

Firstly, from the first equation in (2.1), we can have

$$\dot{T} = aT(1 - bT) - c_1 NT - K_T MT \leq aT(1 - bT).$$

Based on the standard Kamke comparison theory [25], we get

$$T_{\min} = 0 \leq T(t) \leq T_{\max} = \frac{1}{b}.$$

Now we study the system in the positively invariant domain $W = \mathbb{R}^3_{+,0} \times [0, \frac{1}{b}]$. Taking the localizing function $h_1 = M$, then we have

$$L_f h_1 = -\gamma M + V_M - k_T TM,$$

from which we obtain the set

$$S(h_1) \cap W = \{(\gamma + k_T T)M = V_M\}.$$

Now we can derive the lower bound on the set $S(h_1) \cap W$ by

$$S(h_1) \cap W \subset \{(\gamma + k_T T_{\max})M \geq V_M\},$$

thus, we get the formula

$$h_1|_{S(h_1) \cap W} \geq \frac{V_M}{\gamma + k_T T_{\max}}.$$

Further, we can get the lower bound for the chemotherapy drug concentration given by

$$K_1(h_1) = \left\{ M \geq M_{\min} = \frac{V_M}{\gamma + k_T T_{\max}} = \frac{bV_M}{b\gamma + k_T} \right\}.$$

Then we determine the upper bound on the set $S(h_1) \cap W$ by

$$S(h_1) \cap W \subset \{(\gamma + k_T T_{\min})M \leq V_M\},$$

and get the upper bound for the chemotherapy drug concentration given by

$$K_2(h_1) = \left\{ M \leq M_{\max} = \frac{V_M}{\gamma + k_T T_{\min}} = \frac{V_M}{\gamma} \right\}.$$

Therefore the ultimate densities of the chemotherapy drug concentration is

$$K(h_1) = \{M_{\min} \leq M \leq M_{\max}\}. \tag{4.3}$$

To determine the upper and lower bounds for the effector immune cells, we take the function $h_2 = N$, and compute Lie derivative as follows

$$L_f h_2 = \alpha_1 + g\frac{T}{s+T}N - \mu N - pTN - K_N(1-\eta)MN,$$

from which we can obtain the following set

$$S(h_2) \cap W = \left\{ \alpha_1 + g\frac{T}{s+T}N - \mu N - pTN - K_N(1-\eta)MN = 0 \right\}.$$

To get the lower bound, we move the negative terms to the right side and obtain

$$S(h_2) \cap W = \left\{ \mu N + pTN + K_N(1-\eta)MN = \alpha_1 + g\frac{T}{s+T}N \geq \alpha_1 \right\}.$$
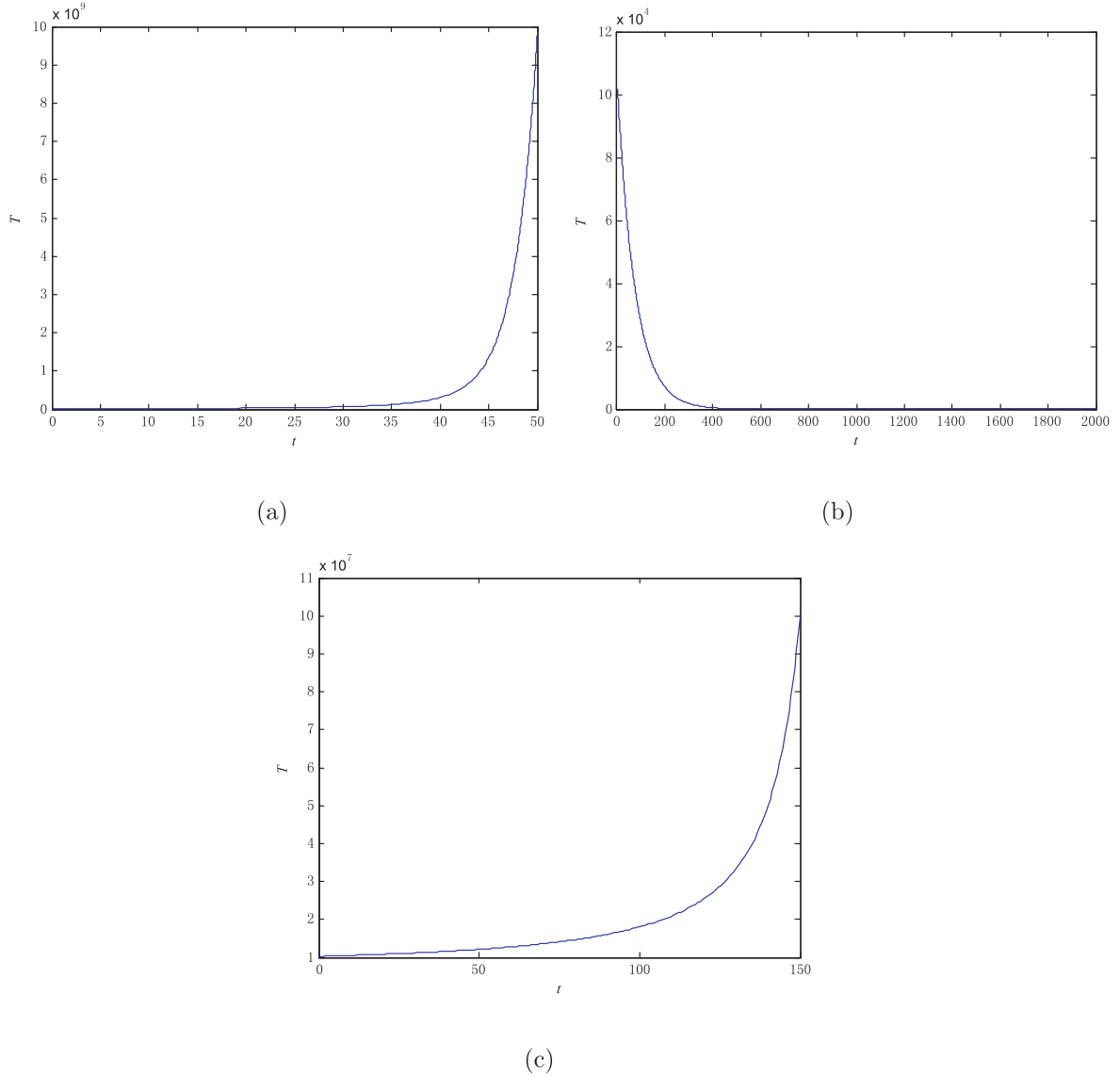
Then we have

$$S(h_2) \cap K(h_1) \cap W \subset \{[\mu + pT_{\max} + K_N(1-\eta)M_{\max}]N \geq \alpha_1\},$$

implying

$$h_2|_{S(h_2) \cap K(h_1) \cap W} \geq \frac{\alpha_1}{\mu + pT_{\max} + K_N(1-\eta)M_{\max}}.$$

Hence, we conclude the lower bound for the effector immune cells given by

$$
\begin{aligned}
K_1(h_2) &= \left\{ N \geq N_{\min} = \frac{\alpha_1}{\mu + pT_{\max} + K_N(1-\eta)M_{\max}} \right. \\
&\left. = \frac{\alpha_1\gamma b}{\mu b\gamma + p\gamma + K_N(1-\eta)bV_M} \right\}.
\end{aligned}
$$

(a)

(b)

(c)

Fig. 1. Simulation of system (2.1): (a) $V_M = 0.45$ with initial value $T(0) = 10^7$, $N(0) = 3 \times 10^5$, $C(0) = 6.25 \times 10^{10}$, $M(0) = 0.45$; and (b) $V_M = 0.50$ with initial value $T(0) = 10^5$, $N(0) = 3 \times 10^5$, $C(0) = 6.25 \times 10^{10}$, $M(0) = 0.50$; and (c) $V_M = 0.50$ with initial value $T(0) = 10^7$, $N(0) = 3 \times 10^5$, $C(0) = 6.25 \times 10^{10}$, $M(0) = 0.50$.

Continually, we make another transformation on $S(h_2) \cap W$, to get

$$S(h_2) \cap W =$$
$$\left\{ \mu N - gN + pTN + K_N(1-\eta)MN = \alpha_1 - g\frac{s}{s+T}N \le \alpha_1 \right\}.$$

Then we have

$$S(h_2) \cap K(h_1) \cap W \subset \{[\mu - g + pT_{\min} + K_N(1-\eta)M_{\min}]N \le \alpha_1\},$$

indicating

$$h_2|_{S(h_2) \cap K(h_1) \cap W} \le \frac{\alpha_1}{\mu - g + pT_{\min} + K_N(1-\eta)M_{\min}}.$$

Thus, the upper bound for the effector immune cells is given by

$$K_2(h_2) = \left\{ N \le N_{\max} = \frac{\alpha_1(b\gamma + k_T)}{(\mu - g)(b\gamma + k_T) + K_N(1-\eta)bV_M} \right\}.$$

Therefore the ultimate densities of the effector cells population is

$$K(h_2) = \{N_{\min} \le N \le N_{\max}\}. \tag{4.4}$$

Based on (4.3) and (4.4), the inequality $a - c_1 N_{\min} - K_T M_{\min} < 0$ in Theorem 4.2 becomes

$$a - \frac{\alpha_1 \gamma bc_1}{\mu b\gamma + p\gamma + K_N(1-\eta)bV_M} - \frac{bV_M K_T}{b\gamma + k_T} < 0, \tag{4.5}$$

which is equivalent to

$$G_1 V_M^2 + G_2 V_M + G_3 < 0, \tag{4.6}$$

where $G_1 = -b^2 K_N K_T(1-\eta)$, $G_2 = (ab^2 K_N \gamma + abK_N K_T)(1-\eta) - b\gamma K_T(p + b\mu)$ and $G_3 = \gamma(ab^2\gamma\mu + ab\mu k_T + abp\gamma + apk_T - \alpha_1 \gamma b^2 c_1 - \alpha_1 c_1 bk_T)$.

Here, we need to note that the condition (4.5) is a sufficient condition not necessary for global stability of equilibrium solution E_0.

At the end of this section, we check the possibility for a Hopf bifurcation arising from E_0. Since $\lambda_2, \lambda_3, \lambda_4$ are always negative, we can know that no Hopf bifurcation occurs from the tumor free equilibrium solution E_0.

4.2. Stability of the coexisting equilibrium solution E_1

In this section, we study the stability of the coexistence equilibrium solution E_1. In order to examine the stability of E_1, we evaluate the Jacobian matrix of system (2.1) at E_1, to yield the characteristic equation

$$P_1(\lambda, T, V_M) = \lambda^4 + a_1(T, V_M)\lambda^3 + a_2(T, V_M)\lambda^2$$
$$+ a_3(T, V_M)\lambda + a_4(T, V_M), \tag{4.7}$$

where the coefficients, $a_i(T, V_M)$, $i = 1, 2, 3, 4$, are expressed in terms of T and V_M, with other parameter values taken from Table 1, and T satisfies equation $F(T, V_M) = 0$ in (4.1). Here, we omit the lengthy expression for brevity.

Based on Hurwitz Criterion, the static bifurcation happens at E_1, when $a_4(T, V_M) = 0$, and all other Hurwitz arrangements are positive, that is $\Delta_1 = a_1(T, V_M) > 0$, $\Delta_2 = a_1(T, V_M)a_2(T, V_M) - a_3(T, V_M) > 0$ and $\Delta_3 = a_3(T, V_M)\Delta_2 - a_1(T, V_M)^2 a_4(T, V_M) > 0$. Combined $a_4(T, V_M) = 0$ with (4.1) and considering the biological meaning and range of V_M, we obtain one biological meaningful point: $(T_t, V_{M_t}) = (0, 0.4848095057)$, at which all other Hurwitz arrangements are positive. Here the subscript 't' stands for transcritical bifurcation. In previous section, we know that the tumor free equilibrium solution E_0 is locally stable if (4.2) is satisfied. From (4.2), we can get the critical value of V_M is $V_M = 0.4848095057$, which is exactly the same as V_{M_t}. The two equilibrium solutions E_0 and E_1 intersect and exchange their stability at this critical point. E_1 is unstable when $V_M > V_{M_t}$.

To check if any Hopf bifurcation can arise from the coexisting equilibrium solution E_1, we use the necessary and sufficient conditions for general $n-$dimensional systems to have a Hopf bifurcation in [26]. Based on the characteristic polynomial (4.7), we apply the formula in [26], that is, $\Delta_3 = a_3(T, V_M)\Delta_2 - a_1(T, V_M)^2 a_4(T, V_M) = 0$. Solving $\Delta_3 = 0$ and $F(T, V_M) = 0$ in (4.1), with other parameter values taken from Table 1, we can not get biologically meaningful point. Hence, we can conclude the following theorem.

Theorem 4.3. *The coexistence equilibrium solution E_1 of model (2.1) is unstable, when $V_M > V_{M_t}$. There is no Hopf bifurcation arising from E_1.*

4.3. Numerical simulation

In this section, we present some numerical simulations to illustrate the theoretical results obtained in the previous sections. Firstly, we will fix all parameter values as listed in Table 1, except for V_M.

For model (2.1), we take $V_M = 0.45$, which does not satisfy the condition (4.2) of Theorem 4.1. Hence, the tumor free equilibrium solution is unstable, as shown in Fig. 1(a). When choosing $V_M = 0.5$, which satisfies the condition (4.2), indicating the tumor free equilibrium solution is locally stable, as shown in Fig. 1(b) and (c). If we give a small initial tumor population, i.e., $T(0) = 10^5$, the trajectory converges to the tumor free equilibrium E_0 (see Fig. 1(b)), while if the initial tumor population is not small, i.e., $T(0) = 10^7$, the tumor cells population grow to a large tumor size, as shown in Fig. 1(c). Based on this simulation, we can conclude that using targeted chemotherapy drug can eliminate a small size tumor, but can not eliminate a large size tumor.

To verify the Theorem 4.2, we compute the inequality (4.5), and get $V_M > 1.690200926 \times 10^5$, which is out of reasonable integral of V_M ($0 \leq V_M \leq 1$), hence, we will not conduct the simulation.

5. Discussion and conclusion

In this paper, we have built a new mathematical model to describe the targeted chemotherapy tumor-immune process. We

have investigated the qualitative dynamic behavior to show that if $\mu - g > 0$, then all solutions of the model are non-negative for non-negative initial conditions, and bounded. Moreover, we have obtained two types equilibrium solutions and found that the tumor free equilibrium solution is locally asymptotically stable if condition (4.2) is satisfied, furthermore, if condition (4.6) holds, the tumor free equilibrium solution is globally stable. For the coexistence equilibrium solution, we prove that it is unstable when $V_M > 0.4848095057$. Using Hurwitz Criterion and numerical calculation, it has been shown no Hopf bifurcation can arise from the above two equilibrium solutions.

To show the advantage of targeted chemotherapy, now, we compare the results obtained in previous sections with the result summaries in Section 2. Solving the inequality (4.2), we get the bounds of the solution are

$$V_{M_0^+} = \frac{-D_2 + \sqrt{D_2^2 - D_1 D_3}}{2D_1} \quad \text{and} \quad V_{M_0^-} = \frac{-D_2 - \sqrt{D_2^2 - D_1 D_3}}{2D_1}.$$

Based on the parameter values given in Table 1, D_3 is negative, implying $V_{M^-} < 0$ and the only biologically feasible solution of (4.2) is $V_{M_0} > V_{M_0^+} = \frac{-D_2 + \sqrt{D_2^2 - D_1 D_3}}{2D_1}$. Similarly, we can obtain the biologically feasible solution of (2.2) is $V_{M_e} > V_{M_e^+} = \frac{-B_2 + \sqrt{B_2^2 - B_1 B_3}}{2B_1}$. Now comparing these two critical value, we find that $V_{M_e^+} > V_{M_0^+}$, which indicates the stable range of tumor free equilibrium solution of targeted chemotherapy is larger than that of regular chemotherapy in the same condition. This confirms that the targeted chemotherapy helps to kill tumor cells.

References

[1] Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. Ctcae v3. 0: development of a comprehensive grading system for the adverse effects of cancer treatment. In: Seminars in radiation oncology, vol. 13. Elsevier; 2003. p. 176–81.

[2] Herman SE, Gordon AL, Hertlein E, Ramanunni A, Zhang X, Jaglowski S, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by pci-32765. Blood 2011;117(23):6287–96.

[3] Zhang J, Yang PL, Gray NS. Targeting cancer with small molecule kinase inhibitors. Nat Rev Cancer 2009;9(1):28–39.

[4] Shangary S, Wang S. Small-molecule inhibitors of the MDM2-p53 protein-protein interaction to reactivate p53 function: a novel approach for cancer therapy. Annu Rev Pharmacol Toxicol 2009;49:223.

[5] Monroig PdC, Chen L, Zhang S, Calin GA. Small molecule compounds targeting mirnas for cancer therapy. Adv Drug Deliv Rev 2015;81:104–16.

[6] Huang P, Wang D, Su Y, Huang W, Zhou Y, Cui D, et al. Combination of small molecule prodrug and nanodrug delivery: amphiphilic drug–drug conjugate for cancer therapy. J Am Chem Soc 2014;136(33):11748–56.

[7] Pérez-Herrero E, Fernández-Medarde A. Advanced targeted therapies in cancer: drug nanocarriers, the future of chemotherapy. Eur J Pharm Biopharm 2015;93:52–79.

[8] Brannon-Peppas L, Blanchette JO. Nanoparticle and targeted systems for cancer therapy. Adv Drug Deliv Rev 2012;64:206–12.

[9] Glassman PM, Balthasar JP. Mechanistic considerations for the use of monoclonal antibodies for cancer therapy. Cancer Biol Med 2014;11(1):20–33.

[10] Weiner GJ. Building better monoclonal antibody-based therapeutics. Nat Rev Cancer 2015;15(6):361–70.

[11] Delalat B, Sheppard VC, Ghaemi SR, Rao S, Prestidge CA, McPhee G, et al. Targeted drug delivery using genetically engineered diatom biosilica. Nat Commun 2015;6.

[12] Kuznetsov VA, Makalkin IA, Taylor MA, Perelson AS. Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis. Bull Math Biol 1994;56(2):295–321.

[13] Kirschner D, Panetta JC. Modeling immunotherapy of the tumor–immune interaction. J Math Biol 1998;37(3):235–52.

[14] Kuznetsov VA, Knott GD. Modeling tumor regrowth and immunotherapy. Math Comput Model 2001;33(12):1275–87.

[15] de Pillis LG, Radunskaya AE, Wiseman CL. A validated mathematical model of cell-mediated immune response to tumor growth. Cancer Res 2005;65(17):7950–8.

[16] de Pillis LG, Gu W, Radunskaya AE. Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations. J Theor Biol 2006;238(4):841–62.

[17] ForyŚ U, Waniewski J, Zhivkov P. Anti-tumor immunity and tumor anti-immunity in a mathematical model of tumor immunotherapy. J Biol Syst 2006;14(01):13–30.

[18] de Pillis LG, Gu W, Fister KR, Head T, Maples K, Murugan A, et al. Chemotherapy for tumors: an analysis of the dynamics and a study of quadratic and linear optimal controls. Math Biosci 2007;209(1):292–315.

[19] López ÁG, Seoane JM, Sanjuán MA. A validated mathematical model of tumor growth including tumor–host interaction, cell-mediated immune response and chemotherapy. Bull Math Biol 2014;76(11):2884–906.

[20] Sharma S, Samanta G. Analysis of the dynamics of a tumor–immune system with chemotherapy and immunotherapy and quadratic optimal control. Differ Equ Dynam Syst 2016;24(2):149–71.

[21] Pang L, Zhao Z, Song X. Cost-effectiveness analysis of optimal strategy for tumor treatment. Chaos Solitons Fractals 2016;87:293–301.

[22] Valle PA, Starkov KE, Coria LN. Global stability and tumor clearance conditions for a cancer chemotherapy system. Commun Nonlinear Sci Numer Simul 2016;40:206–15.

[23] Castillo-Chavez C, Thieme HR. Asymptotically autonomous epidemic models. Math Popul Dynam 1995;1:33–50.

[24] Krishchenko A. Localization of invariant compact sets of dynamical systems. Differ Eq 2005;41(12):1669–76.

[25] Pinho ST, Bacelar FS, Andrade RF, Freedman H. A mathematical model for the effect of anti-angiogenic therapy in the treatment of cancer tumours by chemotherapy. Nonlinear Anal Real World Appl 2013;14(1):815–28.

[26] Yu P. Closed-form conditions of bifurcation points for general differential equations. Int J Bifurcation Chaos 2005;15(04):1467–83.