GLOBAL DYNAMICS IN A TUMOR-IMMUNE MODEL WITH AN IMMUNE CHECKPOINT INHIBITOR

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Abstract. In this paper, we fill several key gaps in the study of the global dynamics of a highly nonlinear tumor-immune model with an immune checkpoint inhibitor proposed by Nikolopoulou et al. (Letters in Biomathematics, 5 (2018), S137-S159). For this tumour-immune interaction model, it is known that the model has a unique tumour-free equilibrium and at most two tumorous equilibria. We present sufficient and necessary conditions for the global stability of the tumour-free equilibrium or the unique tumorous equilibrium. The global dynamics is obtained by employing a new Dulac function to establish the nonexistence of nontrivial positive periodic orbits. Our analysis shows that we can almost completely classify the global dynamics of the model with two critical values \( C_{K0}, C_{K1}(C_{K0} > C_{K1}) \) for the carrying capacity \( C_K \) of tumour cells and one critical value \( d_{T0} \) for the death rate \( d_T \) of T cells. Specifically, the following are true. (i) When no tumorous equilibrium exists, the tumour-free equilibrium is globally asymptotically stable. (ii) When \( C_K \leq C_{K1} \) and \( d_T > d_{T0} \), the unique tumorous equilibrium is globally asymptotically stable. (iii) When \( C_K > C_{K1} \), the model exhibits saddle-node bifurcation of tumorous equilibria. In this case, we show that when a unique tumorous equilibrium exists, tumor cells can persist for all positive initial densities, or can be eliminated for some initial densities and persist for other initial densities. When two distinct tumorous equilibria exist, we show that the model exhibits bistable phenomenon, and tumor cells have alternative fates depending on the positive initial densities. (iv) When \( C_K > C_{K0} \) and \( d_T = d_{T0} \), or \( d_T > d_{T0} \), tumor cells will persist for all positive initial densities.

1. Introduction. Nonlinear dynamics represents a natural and powerful lens to view the ubiquitous complexity observed in biological processes. Indeed, nonlinear dynamics continuously plays an indispensable role in the development and advancement of many areas of mathematical biology and medicine. In particular, the

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mathematically tractable two dimensional nonlinear autonomous ordinary differential equation models enable researchers to gain deep and significant insights into biological complexities. Many well-known examples can be found in the study of predator-prey interaction ([4, 5, 6], [8], [19]), theory of chemostat ([20]), epidemiology ([11], [7], [11], [25]), neuroscience ([2]) and mathematical oncology ([9]).

The immune system can distinguish healthy cells and tumor cells, and immune cells, such as T cells, identify and eliminate tumor cells. Tumor cells often evolve strategies to dysregulate, co-opt, or suppress the immune system. For example, the programmed cell death protein 1 (PD-1), a checkpoint protein expressed by activated T cells, when it is bound to another protein called PD-L1, it helps keep T cells from killing other cells, including cancer cells. The ligand PD-L1 is often expressed on cancer cells, leading to immune evasion ([16],[18],[21],[23]). Therapies that block such immune evasion mechanisms, using antibodies that target immune checkpoints, such as PD-1, have been introduced to enhance activated T cell responses by inhibiting immune regulatory functions ([12], [15], [21]). The efficacy of PD-1 inhibitor has been confirmed in overall survival of patients in a 2012 clinical trial [22]. Therapy involving immune checkpoint inhibitor has led to a durable response in some patients, although only a part of patients responded, possibly due to other immune evasion mechanisms ([16],[18]). Based on the clinical trial data analysis results, the use of PD-1 inhibitor alone is not very effective and it is expensive. Therefore, therapies involving the combination of immune checkpoint inhibitors treatment with chemotherapy, radiotherapies and/or other types of immunotherapies are being actively pursued ([3], [15], [24], [13]).

To consider the combination effect of anti-PD-1 and a tumour vaccine, Lai and Friedman [10] first developed a mathematical model, which composed of 13 partial differential equations, they explored the synergy of the combination of two drugs, suggesting that the tumour vaccine and the anti-PD-1 work better to reduce tumor size in combination than individually. However, the complexity of their model prevents a more in-depth understanding of its rich qualitative properties and biological implications.

Motivated by and based on the model of Lai and Friedman [10], Nikolopoulou et al. [14] proposed a dramatically simplified model of three highly nonlinear ordinary differential equations by focusing on only one treatment (i.e., anti-PD-1). Their treatment free model, which models the natural tumour-immune interaction, takes the following form:

\[
\begin{align*}
\frac{dC}{dt} & = \lambda_C C \left(1 - \frac{C}{C_K}\right) - \eta C T, \\
\frac{dT}{dt} & = (M + NT) F(C, T) - d_T T,
\end{align*}
\]

(1)

where \(C(t)\) and \(T(t)\) represent the population densities of the tumor and activated T cell at time \(t\), respectively. \(\lambda_C > 0\) is the tumor cell growth rate, \(C_K > 0\) is the carrying capacity of tumor cells, \(\eta > 0\) is the kill rate of tumor cells by T cells. \(M > 0\) and \(N > 0\) represent the activation rate of naive T cells by IL-12 and the proliferation rate of T cells activated by IL-2, respectively. \(d_T > 0\) is the death rate of T cells. The function

\[
F(C, T) = \left(1 + \frac{\beta T (T + \epsilon_C C)}{K_{TQ}}\right)^{-1}
\]

where \(\epsilon_C > 0\) is the cost of killing tumor cells by T cells, \(\beta > 0\) is the rate of kill, \(K_{TQ}\) is the half-saturation constant for inhibition of T cell proliferation.
represents the suppression of T-cell activation and proliferation by the PD-1-PD-L1 complex, where $\epsilon > 1$ is the ratio of expressions of PD-L1 in tumor cells and T cells, $1/KTQ > 0$ measures the inhibition level of the function of T cells by PD-1-PD-L1 complex, $\beta > 0$ is the expression level of PD-1 on T cells.

Nikolopoulou et al. gained an in-depth understanding of model (1) by a systematic study of its qualitative dynamics [14]. In a subsequent paper, Nikolopoulou et al. studied the dynamics of a similar mathematical model of the effect of combined therapies involving an immune checkpoint inhibitor and an immunostimulant [15]. In [14], the authors established some sufficient but not necessary conditions for global stability of the tumorous and tumour-free equilibria. Specifically, they were able to show the following. (i) When $\lambda_C < \eta T^*_0$ ($T^*_0$ is the T-coordinate of the tumour-free equilibrium) and no tumorous equilibrium exists, they proved that the tumour-free equilibrium of model (1) is globally asymptotically stable under the additional restriction

$$d_T > N.$$  (2)

(ii) When $C_K < \frac{\lambda_C}{\eta \epsilon C}$, they proved that the unique tumorous equilibrium of model (1) is globally asymptotically stable under the same restriction (2). The condition (2) can be interpreted as the death rate of T cells being greater than the stimulation rate of T cells by IL-2, thus, their mathematical analysis suggested that even patients with weakened immune systems, and thereby shorter lifetimes of T cells, can see tumour elimination for slow-growing tumours ($\lambda_C < \eta T^*_0$). It is natural to think that patients with stronger immune systems ($d_T \leq N$), and thereby longer lifetimes of T cells, should also see tumour elimination for slow-growing tumours ($\lambda_C < \eta T^*_0$). Moreover, Their bifurcation diagram suggested their mathematical results still have room for improvement. Their condition proves to be sufficient but not necessary for determining the stability of the tumour-free and tumorous equilibria. Further exploration is required to determine necessary conditions [14]. Nikolopoulou et al. focused their analysis of the tumorous equilibrium for the case of $C_K < \frac{\lambda_C}{\eta \epsilon C}$ [14]. In this paper, we will see that model (1) has more interesting and complex dynamics for the complementing case of $C_K \geq \frac{\lambda_C}{\eta \epsilon C}$.

In this paper, we will remove the additional restriction (2), and explore the sufficient and necessary conditions for global stability of the tumorous and tumour-free equilibria. Moreover, we will consider the more complex case: $C_K \geq \frac{\lambda_C}{\eta \epsilon C}$. Our qualitative analysis shows that the model dynamics can be classified by two critical values $C_{K0}, C_{K1} = \frac{\lambda_C}{\eta \epsilon C}, (C_{K0} > C_{K1})$ of the carrying capacity $C_K$ of tumour cells, and one critical value $d_{T0}$ of the death rate $d_T$ of T cells. We will establish the following results. (i) When no tumorous equilibrium exists, the tumour-free equilibrium is globally asymptotically stable, i.e., tumor cells will be eliminated for all positive initial densities. (ii) When $C_K \leq C_{K1}$ and $d_T > d_{T0}$, the unique tumorous equilibrium is globally asymptotically stable. (iii) When $C_K > C_{K1}$, the model exhibits saddle-node bifurcation of tumorous equilibria: In this case, the unique tumour-free equilibrium is globally asymptotically stable when no tumorous equilibrium exists. When a unique tumorous equilibrium exists, tumor cells can persist for all positive initial densities, or exhibit alternative fates of extinction and persistence. When two distinct tumorous equilibria exist, the model exhibits bistable phenomenon, and tumor cells have alternative fates depending on the positive initial densities. (iv) When $C_K > C_{K0}$ and $d_T = d_{T0}$, or $d_T > d_{T0}$, tumor cells will persist for all positive initial densities. Numerical simulations about phase portraits
are also given to illustrate these theoretical results. Our results can be seen as an almost complete complement to the work by Nikolopoulou et al. [14].

The rest of the paper is organized as follows. In section 2, we discuss the types and stability of equilibria. The saddle-node bifurcation for positive equilibria is given in section 3. In section 4, we explore the global dynamics of model (1). A brief discussion is presented in section 5.

2. Types and stability of equilibria. In this chapter, we consider the types and stability of equilibria in model (1).

We first make the following scaling

\[ C = xC_K, \quad T = \frac{\lambda_C}{\eta} y, \quad t = \frac{1}{\lambda_C} \tau, \]

then model (1) becomes (for simplicity we still denote \( \tau \) by \( t \))

\[
\begin{align*}
\frac{dx}{dt} &= x(1 - x - y) := f_1(x, y), \\
\frac{dy}{dt} &= \frac{a + by}{1 + cy^2 + dxy} - ey := f_2(x, y),
\end{align*}
\]

(3)

where

\[
\begin{align*}
a &= \frac{\eta M}{\lambda_C}, \quad b = \frac{N}{\lambda_C}, \quad c = \frac{\beta \lambda_C^2 \epsilon C_K}{\eta^2 K_T Q}, \quad d = \frac{\beta \lambda_C \epsilon C_K}{\eta K_T Q}, \quad e = \frac{d_T}{\lambda_C},
\end{align*}
\]

(4)

and \( a, b, c, d, e \) are all positive. Moreover, we can denote \( \lambda_C, \eta, \beta, M, N \) by \( a, b, c, d, e \) and \( C_K, \epsilon_C, K_T Q, d_T \) as

\[
\lambda_C = \frac{d_T}{e}, \quad \eta = \frac{dd_T}{ce C_K \epsilon_C}, \quad \beta = \frac{K_T Q d^2}{c C_K^2 \epsilon_C}, \quad M = \frac{acd_T C_K \epsilon_C}{ed}, \quad N = \frac{bd_T}{e}.
\]

To study the dynamics of model (3), we first recall a Lemma in [14].

**Lemma 2.1.** Solutions of system (1) that start positive remain positive and bounded.

Due to Lemma 2.1 and its biological implication, we consider only the dynamics of system (3) in the closed first quadrant in the \((x, y)\) plane. The equilibria of system (3) satisfy

\[ x(1 - x - y) = 0, \quad \frac{a + by}{1 + cy^2 + dxy} - ey = 0, \]

(5)

which yield

\[ cey^3 - (b - e)y - a = 0 \quad \text{if } x = 0; \]

(6)

or

\[ e(d - c)y^3 - dey^2 + (b - e)y + a = 0 \quad \text{if } x = 1 - y (0 < y < 1). \]

(7)

Let

\[
\begin{align*}
G_1(y) &= cey^3 - (b - e)y - a, \\
g_1(y) &= G_1'(y) = 3cey^2 - (b - e),
\end{align*}
\]

(8)

and

\[
\begin{align*}
G_2(y) &= e(d - c)y^3 - dey^2 + (b - e)y + a, \\
g_2(y) &= G_2'(y) = 3e(d - c)y^2 - 2dey + (b - e).
\end{align*}
\]

(9)

These functions will be used to study the existence and local stability of equilibria in system (3).
The Jacobian matrix of system (3) at any equilibria $E(x, y)$ is

$$J(E) = \begin{pmatrix}
1 - 2x - y & -x \\
\frac{(a + by)dy}{(1 + cy^2 + dxy)^2} & \frac{-bcy^2 + 2acy + adx - b}{(1 + cy^2 + dxy)^2} - e
\end{pmatrix}. $$

The determinant of $J(E)$ is

$$\text{Det}(J(E)) = -(1 - 2x - y) \left[ \frac{bcy^2 + 2acy + adx - b}{(1 + cy^2 + dxy)^2} + e \right] - \frac{(a + by)dy}{(1 + cy^2 + dxy)^2},$$

and the trace of $J(E)$ is

$$\text{Tr}(J(E)) = 1 - 2x - y - e - \frac{bcy^2 + 2acy + adx - b}{(1 + cy^2 + dxy)^2}.$$

$E(x, y)$ is an elementary equilibrium if $\text{Det}(J(E)) \neq 0$. It is a hyperbolic saddle if $\text{Det}(J(E)) < 0$, or a degenerate equilibrium if $\text{Det}(J(E)) = 0$, respectively.

We first discuss the boundary equilibrium of system (3).

2.1. Tumor-free equilibria. If $E_0(0, y_0)$ is a boundary equilibrium of system (3), then $y_0$ is a positive root of $G_1(y) = 0$. According to the relations of roots and coefficients of the third-order algebraic equation $G_1(y) = 0$, if $y_0, (i = 1, 2, 3)$ are the roots of $G_1(y) = 0$, then we have

$$y_0_1 + y_0_2 + y_0_3 = 0, \quad y_0_1y_0_2y_0_3 = \frac{a}{ce} > 0,$$

from which we know that $G_1(y) = 0$ has a unique positive root, which is simple (see Figure 1), denoted by $y_0$. Correspondingly, system (3) has a unique boundary equilibrium $E_0(0, y_0)$.

![Figure 1. A unique positive root $y_0$ of $G_1(y) = 0$.](image)

**Theorem 2.2.** System (3) always has a unique boundary equilibrium $E_0(0, y_0)$. Moreover,

(1) if $b < (c+1)e - a$, then $E_0(0, y_0)$ is a hyperbolic saddle;

(II) if $b > (c+1)e - a$, then $E_0(0, y_0)$ is a stable hyperbolic node;

(III) if $b = (c+1)e - a$, then $y_0 = 1$ and $E_0(0, 1)$ is a degenerate equilibrium. Moreover,
(i) if $d \neq 2c + \frac{a}{e}$, then $E_0(0,1)$ is a saddle-node, which includes a stable parabolic sector in the right (or left) half plane of $\mathbb{R}^2$ if $d < 2c + \frac{a}{e}$ (or $d > 2c + \frac{a}{e}$);

(ii) if $d = 2c + \frac{a}{e}$, then $E_0(0,1)$ is a stable degenerate node.

The phase portraits are shown in Figure 2.

Proof. (I)-(II) The Jacobian matrix at $E_0(0,y_0)$ is

$$
J(E_0) = \begin{pmatrix}
1 - y_0 & 0 \\
\frac{a + by_0}{(1 + cy_0^2)^2} & -\frac{bcy_0^2 + 2acy_0 - b}{(1 + cy_0^2)^2} - e
\end{pmatrix},
$$

which has two eigenvalues

$$
\lambda_1 = 1 - y_0, \quad \lambda_2 = -\frac{bcy_0^2 + 2acy_0 - b}{(1 + cy_0^2)^2} - e,
$$

and the determinant of $J(E_0)$ is

$$
\text{Det}(J(E_0)) = \lambda_1 \lambda_2 = (1 - y_0) \left[-\frac{bcy_0^2 + 2acy_0 - b}{(1 + cy_0^2)^2} - e\right].
$$

From $G_1(y_0) = 0$ in (8), we have

$$
b = \frac{cey_0^3 + ey_0 - a}{y_0},
$$

substituting (11) into $\text{Det}(J(E_0))$, we have

$$
\text{Det}(J(E_0)) = \lambda_1 \lambda_2 = \frac{(y_0 - 1)(a + 2cey_0^3)}{y_0(1 + cy_0^2)}
$$

$$
= \frac{(y_0 - 1)}{y_0(1 + cy_0^2)} [y_0 g_1(y_0) - G_1(y_0)]
$$

$$
= \frac{y_0 - 1}{(1 + cy_0^2)} g_1(y_0).
$$

On one hand, from Figure 1, we have $g_1(y_0) > 0$. On the other hand, we have $b < (c + 1)e - a \iff G_1(1) > 0 \iff y_0 < 1$. Thus, it is easy to see that the equilibrium $E_0(0, y_0)$ is a hyperbolic saddle if $b < (c+1)e - a$, and a stable hyperbolic node if $b > (c + 1)e - a$.

(III)(i) If $b = (c + 1)e - a$, then we have $y_0 = 1$, and the Jacobian matrix at $E_0(0,1)$ is

$$
J(E_0) = \begin{pmatrix}
0 & 0 \\
-\frac{ed}{1 + c} & -\frac{2ce + a}{1 + c}
\end{pmatrix},
$$

which has two eigenvalues

$$
\lambda_1 = 0, \quad \lambda_2 = -\frac{2ce + a}{1 + c} < 0.
$$

Then $E_0(0,1)$ is a degenerate equilibrium. To discuss the exact type of $E_0(0,1)$, we first translate it into the origin by letting $X = x$, $Y = y - 1$, system (3) can be
Figure 2. A unique boundary equilibrium $E_0$ which is (a) hyperbolic saddle if $b < (c + 1)e - a$; (b) stable hyperbolic node if $b > (c + 1)e - a$; (c) saddle-node with a stable parabolic sector in the right half plane if $b = (c + 1)e - a$ and $d < 2c + \frac{a}{e}$; (d) saddle-node with a stable parabolic sector in the left half plane if $b = (c + 1)e - a$ and $d > 2c + \frac{a}{e}$; (e) stable degenerate node if $b = (c + 1)e - a$ and $d = 2c + \frac{a}{e}$. 
rewritten as
\[
\begin{align*}
\frac{dX}{dt} &= -X(X + Y), \\
\frac{dY}{dt} &= \frac{e(c + 1)(Y + 1) - aY}{1 + c(Y + 1)^2 + 2X(Y + 1)} - e(Y + 1).
\end{align*}
\tag{14}
\]

Next, we let
\[
X = -\frac{a + 2ce}{1 + c}u, \quad Y = \frac{de}{1 + c}u + v, \quad t = -\frac{1 + c}{a + 2ce}\tau,
\]
then system (14) becomes (still denote \(\tau\) by \(t\))
\[
\begin{align*}
\frac{du}{dt} &= \frac{1 + c}{a + 2ce} \left[ \frac{de - a - 2ce}{1 + c} u + v \right], \\
\frac{dv}{dt} &= -\frac{1 + c}{a + 2ce} \left[ \frac{de - a - 2ce}{1 + c} u + v \right] + \\
&\quad \frac{(e(c + 1) - a)(de u + v) + e(c + 1)}{1 + c(\frac{de}{1 + c} u + v + 1)^2 - \frac{a + 2ce}{1 + c}(\frac{de}{1 + c} u + v + 1)du} - e \left( \frac{de}{1 + c} u + v + 1 \right),
\end{align*}
\tag{15}
\]
from which and using Taylor expansions, we have
\[
\dot{u} = a_{11}u^2 + a_{12}uv, \\
\dot{v} = v + a_{21}v^2 + a_{22}uv + a_{23}u^2 + O(|u, v|^3),
\tag{16}
\]
where
\[
a_{11} = -\frac{a + 2ce - de}{a + 2ce}, \quad a_{12} = \frac{1 + c}{a + 2ce}, \quad a_{21} = -\frac{c(c + 2a - 3e)}{(2ce + a)(c + 1)}, \\
a_{22} = \frac{d[2ce^2(c + 1) - (c^2 + 2c + 1 + 2a)ecd^2]}{(c + 1)^2(2ce + a)}, \\
a_{23} = \frac{de[a(c + 1) - cde^2 + (2e^2 + 2c - cd - d - 2ad)e]}{(c + 1)^2(2ce + a)}.
\]
According to the center manifold method \[17\], and noticing that \(a_{11} \neq 0\) in (16) if \(d \neq 2c + \frac{a}{e}\), we can approximate the equation near the center manifold as follows
\[
\frac{du}{dt} = -\frac{a + 2ce - de}{a + 2ce}u^2 + O(|u|^3).
\tag{17}
\]
By Theorem 7.1 in Zhang et al. \[26\], \(E_0(0, 1)\) is a saddle-node, which includes a stable parabolic sector in the right (or left) half plane \(\mathbb{R}^2\) if \(d < 2c + \frac{a}{e}\) (or \(d > 2c + \frac{a}{e}\)).

(III)(ii) If \(d = 2c + \frac{a}{e}\), then \(a_{11} = 0\) in (16). Supposing \(v = m_1u^2 + m_2u^3 + O(|u|^3)\) and substituting it to the second equation of system (16), we have
\[
m_1 = \frac{(ce + 2a)(2ce + a)}{(c + 1)^2}, \\
m_2 = -\frac{(ce + 2a)(2ce + a)[(2c^2 + 2c)e^2 - ((c + 1)^2 + 2a)e + a^2]}{e(c + 1)^4}. 
\]
According to the center manifold theorem, we next substitute \( v = m_1 u^2 + m_2 u^3 + o(|u|^3) \) into the first equation of system (16), then the reduced equation restricted to the center manifold takes the following form

\[
\frac{du}{dt} = \frac{ce + 2a}{c + 1} u^3 + O(|u|^4). \tag{18}
\]

Referring to Theorem 7.1 in Zhang et al. [26], we obtain that \( E_0(0,1) \) is a stable degenerate node.

**Remark 1.** From the scaling of system (3), we can see that condition \( b < (c+1)e - a \) is equivalent to \( d_T > d_{T0} \), where

\[
d_{T0} = \frac{\eta^2 K_{TQ}(N\lambda C + M\eta)}{\beta \lambda^3 C + \eta^2 K_{TQ} \lambda C}, \tag{19}
\]

and \( d > 2e + \frac{a}{c} \) is equivalent to \( C_K > C_{K0} \), where

\[
C_{K0} = \frac{2\lambda C}{\eta \varepsilon C} + \frac{\eta^2 M K_{TQ}}{\beta \lambda^2 d_T \varepsilon C}. \tag{20}
\]

(i) From Theorem 2.2 and Figure 2(a) and (d), we can see that tumor cells always persist in spite of being killed by T cells if the death rate \( d_T \) of T cells is larger than a critical value \( d_{T0} \), or if the death rate \( d_T \) of T cells is equal to the critical value \( d_{T0} \) and the carrying capacity \( C_K \) of tumor cells is larger than the critical value \( C_{K0} \). (ii) From Theorem 2.2 and Figure 2(b), (c) and (e), we can see that tumor cells can be eradicated because of the killing by T cells if the death rate \( d_T \) of T cells is smaller than the critical value \( d_{T0} \), or if the death rate \( d_T \) of T cells is equal to the critical value \( d_{T0} \) and the carrying capacity \( C_K \) of tumor cells is equal to or smaller than \( C_{K0} \). In both cases, T cells always persist.

Now we consider the positive equilibria of system (3). The positive equilibria \((x, y)\) satisfy (7), and \( y \) is the root of \( G_2(y) = 0 \) in the interval \((0,1)\). Since the maximum number of positive roots of \( G_2(y) = 0 \) is determined by the cubic term coefficient of \( G_2(y) \), we will classify the number and types of positive equilibria of system (3) into two cases: \( d - c > 0 \) (i.e., \( C_K > C_{K1} \)) and \( d - c \leq 0 \) (i.e., \( C_K \leq C_{K1} \)), where

\[
C_{K1} = \frac{\lambda C}{\eta \varepsilon C}. \tag{21}
\]

2.2. **Tumorous equilibria: Case \( d > c \) (i.e., \( C_K > C_{K1} \)).** In this case, by the relations of roots and coefficients of the third-order algebraic equation, \( G_2(y) = 0 \) has a unique negative root and at most two positive roots (see Figure 3). Denote the positive roots by \( y_2 \) and \( y_3 \) \((y_2 < y_3)\), if they exist. Correspondingly, system (3) has at most two positive equilibria \( E_2(x_2, y_2) \) and \( E_3(x_3, y_3) \), which may coalesce into a unique positive equilibrium \( E_1(x_1, y_1) \). Obviously, we have \( y_2 < y_1 < y_3 \).

According to the root formula of the third-order algebraic equation \( G_2(y) = 0 \) in the interval \((0,1)\), we define

\[
A = d^2 e^2 - 3e(d-c)(b-e), \quad \Delta = -4A^3 + [27ae^2(d-c)^2 + 9e^2 d(d-c)(b-e) - 2d^3 e^3]^2,
\]

and have the following results.

**Theorem 2.3.** When \( d > c \) (i.e., \( C_K > C_{K1} \)), system (3) has a unique boundary equilibrium \( E_0(0,y_0) \) and at most two positive equilibria. Moreover, the following are true.
Figure 3. The positive roots of $G_2(y) = 0$ when $d > c$: (a) no positive root; (b) one double positive root $y_1$; (c) two simple positive roots $y_2$ and $y_3$.

(I) If $\Delta > 0$, or $y_2 \geq 1$, then system (3) has no positive equilibrium. The phase portraits are given in Figures 2(e) and 4;

(II) If $\Delta = 0$ and $y_1 < 1$ (or $\Delta < 0$ and $y_2 < 1 \leq y_3$), then system (3) has a unique positive equilibrium $E_1(x_1, y_1)$ (or $E_2(x_2, y_2)$), where $E_1$ is a saddle-node including a stable parabolic sector, and $E_2$ is a stable hyperbolic node. The phase portrait is given in Figure 5 (or Figure 2(d));

(III) If $\Delta < 0$ and $y_3 < 1$, then system (3) has two distinct positive equilibria $E_2(x_2, y_2)$ and $E_3(x_3, y_3)$, both are elementary equilibria, where $E_2$ is a stable hyperbolic node and $E_3$ is a hyperbolic saddle. The phase portrait is given in Figure 6.

Proof. The Jacobian matrix of system (3) at $E_i(x_i, y_i)$ ($i = 1, 2, 3$) is given by

$$J(E_i) = \left( \begin{array}{cc}
\frac{y_i - 1}{(a + by_i)dy_i} & \frac{y_i - 1}{bcy_i^2 + 2acy_i - ady_i + ad - b} \\
-\frac{1}{[1 + cy_i^2 + d(1 - y_i)y_i]^2} & -\frac{1}{[1 + cy_i^2 + d(1 - y_i)y_i]^2}
\end{array} \right).$$
The determinant of $J(E_i)$ is
\[
\text{Det}(J(E_i)) = (y_i - 1) \left[ -\frac{bcy_i^2 + 2acy_i - ady_i + ad - b}{1 + cy_i^2 + d(1 - y_i)y_i} \right] - e + \frac{(a + by_i)dy_i}{1 + cy_i^2 + d(1 - y_i)y_i},
\]
and the trace of $J(E_i)$ is
\[
\text{Tr}(J(E_i)) = y_i - 1 - e - \frac{bcy_i^2 + 2acy_i - ady_i + ad - b}{1 + cy_i^2 + d(1 - y_i)y_i}. \tag{23}
\]
From $G_2(y_i) = 0$ in (9), we have
\[
e = \frac{a + by_i}{y_i[cy_i^2 + dy_i(1 - y_i) + 1]}, \tag{24}
\]
Substituting (24) into (22) and \( g_2(y) \) in (9), we have
\[
\text{Det}(J(E_i)) = -(y_i - 1) \frac{2bcy_i^3 - 2bdy_i^3 + 3acy_i^2 - 3ady_i^2 + bdy_i^2 + 2ady_i + a}{y_i[1 + dy_i(1 - y_i) + cy_i^2]} ,
\tag{25}
\]
and
\[
g_2(y_i) = \frac{2bcy_i^3 - 2bdy_i^3 + 3acy_i^2 - 3ady_i^2 + bdy_i^2 + 2ady_i + a}{y_i[1 + dy_i(1 - y_i) + cy_i^2]} .
\tag{26}
\]
From (25) and (26), we obtain
\[
\text{Det}(J(E_i)) = -\frac{1 - y_i}{1 + dy_i(1 - y_i) + cy_i^2} g_2(y_i).
\tag{27}
\]

**I**f \( d > c \) and \( \Delta > 0 \), or if \( d > c \) and \( y_2 \geq 1 \), then system (3) has no positive equilibrium. By Lemma 2.1 and Theorem 2.2, the unique boundary equilibrium \( E_0 \) must be a stable hyperbolic node, or a stable degenerate node, or a saddle-node with a stable parabolic sector in the right half plane.

**II**f \( d > c \), \( \Delta = 0 \) and \( y_1 < 1 \), we next show that the unique positive equilibrium \( E_1(x_1, y_1) \) is a saddle-node including a stable parabolic sector. From Figure 3(b), we see that \( G_2(y) = 0 \) has a double root \( y_1, g_2(y_1) = 0 \) and \( \text{Det}(J(E_1)) = 0 \). Hence, we have
\[
a = \frac{1}{3} \frac{e dy_1^2 - 2b y_1 + 3ely_1}{3ely_1^2} ,
\tag{28}

c = \frac{3de y_1^2 - 2de y_1 + b - e}{3eya^2} .
\]
Substituting (28) into \( \text{Tr}(J(E_1)) \), we have
\[
\text{Tr}(J(E_1)) = -\frac{3de^2 y_1^2 + (dy_1 + 2)(1 - y_1)e + b(1 - y_1)}{de y_1 + b + 2e}.
\tag{29}
\]
It is easy to see that \( \text{Tr}(J(E_1)) < 0 \) since \( 0 < y_1 < 1 \).
We first let \( \xi = x - x_1, \eta = y - y_1 \), and use (28), then system (3) becomes
\[
\dot{\xi} = -(\xi + \eta)(\xi + 1 - y_1),
\]
\[
\dot{\eta} = \frac{e y_1^2[cdy_1^2 - 2by_1 + 2ey_1 + 3b(\eta + y_1)]}{3ey_1^2[1 + d(\xi + x_1)(\eta + y_1)] + [3de y_1^2 - 2de y_1 + b - e](\eta + y_1)^2} - e(\eta + y_1).
\tag{30}
\]
Next, we make the following transformations
\[
\xi = u + Av, \eta = -u + Bv, t = \tau/(A + B),
\]
where \( A = y_1 - 1 < 0, B = -\frac{3de^2 y_1^2}{de y_1 + b + 2e} < 0 \). Then system (30) can be rewritten as
\[
\dot{u} = b_{11}u^2 + b_{12}uv + b_{13}v^2 + O(|u, v|^3),
\dot{v} = v + b_{21}u^2 + b_{22}uv + b_{23}v^2 + O(|u, v|^3),
\tag{31}
\]
where
\[ b_{11} = \frac{3(-dey_1 + b - e)Ae}{y_1(dy_1 + b + 2e)(A + B)^2}, \quad b_{21} = \frac{-3e(-dey_1 + b - e)}{(dy_1 + b + 2e)y_1(A + B)^2}, \]
\[ b_{12} = -\frac{1}{y_1(A + B)^2(dy_1 + b + 2e)^2}(9A^2d^2e^3y_1^3 + 9ABd^2e^3y_1^3 - 6ABd^2e^3y_1^2 + 4Ad^2e^2y_1^3 + B^2d^2e^2y_1^3 + 18A^2de^3y_1^2 + 18ABde^3y_1^2 + 2ABdey_1^2 - 18ABde^3y_1 + 4ABde^2y_1^2 + 4B^2de^2y_1^2 + 6AB^2e + AB^2y_1 + 6ABe^2 + 4ABe^2y_1 - 12ABe^3 + 4AB^2e^2y_1 + B^2b^2y_1 + 4B^2be^2y_1 + 4B^2e^2y_1), \]
\[ b_{13} = \frac{-A}{y_1(A + B)^2(dy_1 + b + 2e)^2}(9A^2d^2e^3y_1^4 + 18ABd^2e^3y_1^4 + 9B^2d^2e^3y_1^4 - 9ABd^2e^3y_1^3 - 9B^2d^2e^3y_1^3 + ABd^2e^2y_1^3 + 3B^2d^2e^2y_1^3 + B^2d^2e^2y_1^3 - 18ABde^3y_1^2 - 18B^2de^3y_1^2 + 2ABdey_1^2 + 9B^2de^3y_1 + 4B^2de^2y_1^2 + 4AB^2e^2y_1 + 4ABe^2y_1 + 12B^2e^3 + 4B^2e^2y_1), \]
\[ b_{22} = \frac{-1}{y_1(A + B)^2(dy_1 + b + 2e)^2}(9A^2d^2e^3y_1^3 - 9B^2d^2e^3y_1^3 + Ad^2e^2y_1^3 + 6Bd^2e^2y_1^3 + B^2d^2e^2y_1^3 + 18Ad^2e^3y_1^2 - 18Bd^2e^3y_1^2 + 2Abdey_1^2 + 4Ad^2e^2y_1^2 + 2Bd^2e^2y_1^2 + 18Bd^2e^3y_1^2 + 4Bd^2e^2y_1^2 + 4B^2e^3y_1 + 4B^2e^2y_1 + 6B^2e^3 + 12B^2e^3 + 4B^2e^2y_1), \]
\[ b_{23} = \frac{-1}{y_1(A + B)^2(dy_1 + b + 2e)^2}(9A^2d^2e^3y_1^4 - 18ABd^2e^3y_1^4 + 9B^2d^2e^3y_1^4 + 9ABd^2e^3y_1^3 + 9B^2d^2e^3y_1^3 + A^2d^2e^2y_1^3 + 3B^2d^2e^2y_1^3 + B^2d^2e^2y_1^3 + 18Abde^3y_1^2 + 18B^2de^3y_1^2 + 2Abdey_1^2 + 4Abde^2y_1^2 + 9Bd^2e^3y_1 + 3B^2d^2e^2y_1 + 4B^2e^3y_1 + 4B^2e^2y_1 + 3B^2d^2e^2y_1 + 6B^2e^3), \]

We next prove \( b_{11} \neq 0 \), i.e., \( b \neq e(1 + dy_1) \), by contradiction. Suppose \( b = e(1 + dy_1) \), then from the conditions \( \Delta = 0 \) and \( G_2(y_1) = 0 \), we have
\[ a = dey_1^2, \quad b = e(1 + dy_1), \quad c = d\left(1 + \frac{1}{y_1}\right). \quad (32) \]
or
\[ a = -\frac{1}{3}dey_1^2, \quad b = e(1 + dy_1), \quad c = d\left(1 - \frac{1}{3y_1}\right). \quad (33) \]
It is easy to see that \( d < c \) from (32) and \( a < 0 \) from (33), which are in contradiction with the conditions.

Similarly, according to the center manifold method [17], we can restrict the equation on the center manifold directly as follows
\[ \frac{du}{dt} = b_{11}u^2 + O(|u|^3). \quad (34) \]

Referring to Theorem 7.1 in Zhang et al. [26], we obtain that \( E_1(x_1, y_1) \) is a saddle-node with a stable parabolic sector when \( d > c, \Delta = 0 \) and \( y_1 < 1 \).
If $d > c$, $\Delta < 0$ and $y_2 < 1 \leq y_3$, then system (3) has a unique positive equilibrium $E_2(x_2, y_2)$ which is a stable hyperbolic node (see the following case (III)), and a unique boundary equilibrium $E_0$ which is a hyperbolic saddle if $y_3 > 1$, and a saddle-node including a stable parabolic sector in the left half plane if $y_3 = 1$ by Theorem 2.2.

(III) If $d > c$, $\Delta < 0$ and $y_3 < 1$, we consider the types of $E_2$ and $E_3$. From (27) and Figure 3(c), we have $\text{Det}(J(E_3)) < 0$ and $\text{Det}(J(E_2)) > 0$, which implies that $E_3$ is a hyperbolic saddle. Moreover, from

$$\text{Det}(J(E_2)) = -(y_2 - 1)[(p_1 + c) - q_1] > 0,$$

we have $(p_1 + e) - q_1 > 0$ since $0 < y_2 < 1$, where

$$p_1 = \frac{becy_2^2 + 2acy_2 - ady_2 + ad - b}{1 + cy_2^2 + d(1 - y_2)y_2^2}, \quad q_1 = \frac{(a + by_2)dy_2}{1 + cy_2^2 + d(1 - y_2)y_2^2}.$$

Thus,

$$\text{Tr}(J(E_2)) = y_2 - 1 - p_1 - e < 0$$

since $(p_1 + e) > q_1 > 0$. On the other hand,

$$(\text{Tr}(J(E_2)))^2 - 4\text{Det}(J(E_2)) = (y_2 - 1 - p_1 - e)^2 + 4(y_2 - 1)[(p_1 + e) - q_1]$$

$$= (y_2 - 1 + p_1 + e)^2 + 4(1 - y_2)q_1$$

$$> 0.$$  

Hence, $E_2$ is a stable hyperbolic node.

In addition, since $\Delta < 0$ and $y_3 < 1$, we have $G_2(1) > 0$, i.e., $b > (c + 1)e - a$, which implies that the unique boundary equilibrium $E_0$ is a stable hyperbolic node by Theorem 2.2.

Remark 2. From Theorem 2.3, when the carrying capacity $C_K$ of tumor cells is larger than a smaller critical value $C_{K1}$ (see (21)), i.e., $C_K > C_{K1}$, we have the following results: (I) From Figures 2(e) and 4, we can see that tumor cells can be eradicated for all positive initial populations if $\Delta > 0$, or $y_2 \geq 1$; (II) Tumor cells will persist in the form of a positive coexistent steady state for all positive initial densities if $\Delta < 0$ and $y_2 < 1 \leq y_3$ (see Figure 2(d)); (III) Tumor cells have alternative fates, i.e., tumor cells will persist in the form of multiple positive coexistent steady states for some positive initial populations, and will be eradicated for another positive initial populations if $\Delta = 0$ and $y_1 < 1$, or $\Delta < 0$ and $y_3 < 1$ (see Figures 5 and 6); (IV) Figure 6 exhibits bistable phenomenon for system (3) if $\Delta < 0$ and $y_3 < 1$.

2.3. Tumorous equilibria: Case $d \leq c$ (i.e., $C_K \leq C_{K1}$). In this case, $G_2(y) = 0$ has a unique positive root $y^*$, which is simple (see Figure 7). Correspondingly, system (3) has exactly a unique positive equilibrium $E^*(x^*, y^*)$ if $y^* < 1$. In fact, when $d < c$, by the relations of roots and coefficients of the third-order algebraic equation, we know that $G_2(y) = 0$ has a unique positive root $y^*$; when $d = c$, $G_2(y) = 0$ becomes

$$-dey^2 + (b - e)y + a = 0.$$  

(35)

It is easy to see that equation (35) has a unique positive root $y^*$. Moreover, from Figure 7, we know that $y^* < 1$ if and only if $G_2(1) < 0$, and $G_2(1) < 0$ if and only if $b < (c + 1)e - a$ by straightforward analysis. We have

$$y^* < 1 \iff b < (c + 1)e - a.$$
In conclusion, we have the following results.

**Theorem 2.4.** If \( d \leq c \) (i.e., \( C_K \leq C_{K_1} \)), then system (3) has a unique boundary equilibrium \( E_0 \) and at most one positive equilibrium \( E^*(x^*,y^*) \), moreover,

(I) if \( b < (c+1)e-a \), then system (3) has a unique positive equilibrium \( E^* \), which is a stable hyperbolic node, and \( E_0 \) is a hyperbolic saddle. The phase portrait is given in Figure 2(a);

(II) if \( b = (c+1)e-a \), then system (3) has no positive equilibrium, and \( E_0 \) is a saddle-node, which includes a stable parabolic sector in the right half plane. The phase portrait is given in Figure 2(c);

(III) if \( b > (c+1)e-a \), then system (3) has no positive equilibrium, and \( E_0 \) is a stable hyperbolic node. The phase portrait is given in Figure 2(b).

**Proof.**

(I) If \( d \leq c \) and \( b < (c+1)e-a \), then we have \( y^* < 1 \) and \( g_2(y^*) < 0 \), which implies that

\[
\text{Det}(J(E^*)) = -\frac{1 - y^*}{[1 + dy^*(1 - y^*) + cy^*]y^*}g_2(y^*) = -(y^* - 1)[(p_2 + e) - q_2] > 0,
\]

where

\[
p_2 = \frac{bcy^*2 + 2acy^* - ady^* + ad - b}{[1 + cy^*2 + d(1 - y^*)y^*]^2}, \quad q_2 = \frac{(a + by^*)dy^*}{[1 + cy^*2 + d(1 - y^*)y^*]^2}.
\]

Thus, we have \((p_2 + e) > q_2 > 0\), and

\[
\text{Tr}(J(E^*)) = y^* - 1 - p_2 - e < 0.
\]

On the other hand,

\[
(\text{Tr}(J(E^*)))^2 - 4\text{Det}(J(E^*)) = (y^* - 1 - p_2 - e)^2 + 4(y^* - 1)[(p_2 + e) - q_2]
\]

\[
= (y^* - 1 + p_2 + e)^2 + 4(1 - y^*)q_2 > 0.
\]
Hence, $E^*$ is a stable hyperbolic node if $d \leq c$ and $b < (c + 1)e - a$.

In addition, by Theorem 2.2, the unique boundary equilibrium $E_0$ is a saddle if $b < (c + 1)e - a$.

(II) If $b = (c + 1)e - a$, then $y^* = 1$ and $x^* = 0$. Hence, $E_0$ and $E^*$ coalesce into a unique boundary equilibrium $E_0$, which is a saddle-node with a stable parabolic sector in the right half plane.

(III) If $b > (c + 1)e - a$, then $y^* > 1$ and $x^* < 0$. Hence, system (3) has no positive equilibrium, and the unique boundary equilibrium $E_0$ is a stable hyperbolic node by Theorem 2.2.

Remark 3. By Remarks 1 and 2, we have $d \leq c \iff C_K \leq C_{K1}$, and $b < (c + 1)e - a \iff d_T > d_{T0}$. When the carrying capacity $C_K$ of tumour cells is equal to or smaller than a smaller critical value $C_{K1}$, we have the following results: (i) From Figure 2(a), we can see that tumor cells always persist in spite of being killed by T cells if the death rate $d_T$ of T cells is larger than a critical value $d_{T0}$, i.e., T cells can not stop the invasion of tumor cells; (ii) From Figure 2(b) and (c), we can see that tumor cells can be eradicated because of the killing by T cells if $d_T \leq d_{T0}$, i.e., T cells can stop the invasion of tumor cells.

3. Saddle-node bifurcation. From Theorem 2.3, we know that the surface $SN = \{(a, b, c, d, e) : \Delta = 0, 0 < y_1 < 1, a, b, c, d, e > 0\}$ is a saddle-node bifurcation surface. When the parameters pass through the surface from one side to the other side, the number of positive equilibria of system (3) changes from zero to two, the saddle-node bifurcation yields two positive equilibria, which means that tumor cells can persist in the form of multiple positive steady states.

4. Global dynamics of system (3). In this section, we will study the global dynamics of system (3).

Lemma 4.1. System (3) has no nontrivial positive periodic solutions.

Proof. We employ a new Dulac function to show the nonexistence of nontrivial positive periodic solutions. Letting $h(x, y) = \frac{1}{xy}$, we have

$$\frac{\partial (h(x, y)f_1(x, y))}{\partial x} + \frac{\partial (h(x, y)f_2(x, y))}{\partial y} = \frac{\partial}{\partial x} \left\{ \frac{1}{xy} [x(1 - x - y)] \right\} + \frac{\partial}{\partial y} \left\{ \frac{1}{xy} \left[ \frac{a + by}{1 + cy^2 + dxy} - e \right] \right\}$$

$$= \frac{\partial}{\partial x} \left\{ \frac{1}{xy} [1 - x - y] \right\} + \frac{\partial}{\partial y} \left[ \frac{a + by}{xy(1 + cy^2 + dxy)} - \frac{e}{x} \right]$$

$$= -\frac{1}{y} \left( ax(1 + cy^2 + dxy) + xy(a + by)(2cy + dx) \right)$$

$$< 0. \quad (36)$$

Thus, the Dulac criterion ensures that there will be no nontrivial positive periodic solutions for system (3). \qed

Now combining Theorems 2.3 and 2.4 with Lemma 4.1, we arrive at the global dynamics for system (3) as follows.
Theorem 4.2. \textbf{(I)} If \( d \leq c \) (i.e., \( C_K \leq C_{K1} \)), then system (3) has a unique boundary equilibrium \( E_0(0, y_0) \) and at most one positive equilibrium \( E^*(x^*, y^*) \). Moreover, we have the following.

\begin{enumerate}[(i)]
  \item If \( b < (c + 1)e - a \), then system (3) has a unique positive equilibrium \( E^* \), which is globally asymptotically stable. The global phase portrait is given in Figure 2(a).
  \item If \( b \geq (c + 1)e - a \), then system (3) has no positive equilibrium, and \( E_0 \) is globally asymptotically stable. The global phase portraits are given in Figure 2(b) and (c).
\end{enumerate}

\textbf{(II)} When \( d > c \) (i.e., \( C_K > C_{K1} \)), system (3) has a unique boundary equilibrium \( E_0(0, y_0) \) and at most two positive equilibria. Moreover, we have the following.

\begin{enumerate}[(i)]
  \item If \( \Delta > 0 \), or \( y_2 \geq 1 \), then system (3) has no positive equilibrium, and \( E_0 \) is globally asymptotically stable. The global phase portraits are given in Figures 2(c) and 4.
  \item If \( \Delta = 0 \) and \( y_1 < 1 \) (or \( \Delta < 0 \) and \( y_2 < 1 \leq y_3 \)), then system (3) has a unique positive equilibrium \( E_1(x_1, y_1) \) (or \( E_2(x_2, y_2) \)). Moreover, \( E_1 \) is a saddle-node, which means that tumor cells have alternative fates: \( E_2 \) is a stable hyperbolic node, which is globally asymptotically stable. The global phase portraits are given in Figure 5 (or Figure 2(d)).
  \item If \( \Delta < 0 \) and \( y_3 < 1 \), then system (3) has two distinct positive equilibria \( E_2(x_2, y_2) \) (stable hyperbolic node) and \( E_3(x_3, y_3) \) (hyperbolic saddle), which shows the existence of bistable phenomenon and alternative fates for tumor cells. The global phase portrait is given in Figure 6.
\end{enumerate}

Remark 4. \textbf{(I)} From cases (I)(ii) and (II)(i) in Theorem 4.2, it is easy to see that the unique tumour-free equilibrium \( E_0(0, y_0) \) is globally asymptotically stable if and only if system (3) has no tumorous equilibrium, while in Theorem 3.7 in [14], Nikolopoulos et al. showed that the tumour-free equilibrium of model (1) is globally asymptotically stable when \( d_T > N \), \( \lambda_c < \eta T^*_x \), and no tumorous equilibrium exists, where \( \lambda_c < \eta T^*_x \) \( \iff b > (c + 1)e - a \). Our results show that the conditions \( d_T > N \) and \( \lambda_c < \eta T^*_x \) are unnecessary: \textbf{(II)} From cases (I)(i) and (II)(ii) in Theorem 4.2, it is easy to see that the unique tumorous equilibrium \( E^* \) (or \( E_2 \)) is globally asymptotically stable if and only if \( d \leq c \) and \( b < (c + 1)e - a \) (or \( d > c \), \( \Delta < 0 \), and \( y_2 < 1 \leq y_3 \)), while in Theorem 3.7 in [14], Nikolopoulos et al. only showed that the tumorous equilibrium \( E^* \) of model (1) is globally asymptotically stable when \( C_K < \frac{\lambda_c}{\eta T^*_x} \), \( f(\frac{\lambda c}{\eta}) < 0 \), and \( d_T > N \), where \( C_K < \frac{\lambda c}{\eta T^*_x} \) \( \iff d < c \) and \( f(\frac{\lambda c}{\eta}) < 0 \) \( \iff b < (c+1)e-a \). Our results show that not only the condition \( d_T > N \) is unnecessary, but also for another case \( C_K \geq \frac{\lambda c}{\eta T^*_x} \), the unique positive tumorous \( E^* \) (or \( E_2 \)) can also be globally asymptotically stable with some conditions.

5. Numerical simulations. In this chapter, we will use the experimental parameter values in [14] to illustrate our theoretical results.

We first list the parameter values or ranges of model (1) in Table 2 of [14] as follows:

\begin{itemize}
  \item \( \lambda_C : 0.18 - 0.67 \text{ day}^{-1} \), \( C_K : 0.8 - 0.945 \text{ g/cm}^3 \), \( d_T : 0.0 - 0.05 \text{ day}^{-1} \),
  \item \( \varepsilon_C : 1 - 100 \), \( \eta = 57.5 \text{ day}^{-1} \cdot \text{cm}^3/\text{g} \), \( \beta : 1.136 \cdot 10^{-13} - 1.67 \cdot 10^{-12} \),
  \item \( M = 2.643 \cdot 10^{-3} \text{day}^{-1} \cdot \text{g/cm}^3 \), \( N = 0.25 \text{ day}^{-1} \), \( K_{TQ} = 1.365 \cdot 10^{-18} \text{ g/cm}^3 \).
\end{itemize}
From (37) and (4), by simple calculation, we can obtain the parameter values or ranges of system (3) and the critical values $C_{K0}, C_{K1}, d_{T0}$ as follows:

\[ a : 0.339 - 4.691, \quad b : 0.373 - 1.389, \quad c : 0.816 - 166.2, \quad d : 2.08 \cdot 10^2 - 1.36 \cdot 10^6, \]
\[ e : 0 - 0.278, \quad C_{K0} : 1.05 \cdot 10^{-4} - \infty \ g/cm^3, \quad d_{T0} : 2.85 \cdot 10^{-3} - 0.603 \ day^{-1}, \]
\[ C_{K1} : 3.13 \cdot 10^{-5} - 1.165 \cdot 10^{-2} g/cm^3. \]

From the above parameter values, it is easy to see that $C_K > C_{K1}$ (i.e., $d > c$) always holds.

In (37), we let $\lambda_C = 0.18 \ day^{-1}, \varepsilon_C = 1, C_K = 0.8 \ g/cm^3, d_T = 0.027 \ day^{-1}$ and $\beta = 1.136 \cdot 10^{-13}$. Then, from (37) and (4), we have $a = 4.691, b = 1.389, c = 0.815, d = 208.4$ and $e = 0.15$. It is easy to check that this set of parameter values satisfies the condition: $\Delta > 0$ in Theorem 4.2(ii). Thus, system (3) has no tumorous equilibrium, and the unique tumour-free equilibrium is globally asymptotically stable. The phase portrait is given in Figure 8.

Letting $\lambda_C = 0.67 \ day^{-1}, \varepsilon_C = 1, C_K = 0.8 \ g/cm^3, d_T = 0.05 \ day^{-1}$ and $\beta = 6.27 \cdot 10^{-13}$, we have $a = 0.339, b = 0.373, c = 62.4, d = 4285$ and $e = 0.075$ from (37) and (4). This set of parameter values satisfies the conditions: $\Delta < 0$ and $y_2 < 1 < y_3$ in Theorem 4.2(ii). Thus, system (3) has a stable hyperbolic node, which is globally asymptotically stable, which implies that tumor cells will persist for all positive initial densities. The phase portrait is given in Figure 9.

Finally, letting $\lambda_C = 0.18 \ day^{-1}, \varepsilon_C = 1, C_K = 0.8 \ g/cm^3, d_T = 0.04 \ day^{-1}$ and $\beta = 1.136 \cdot 10^{-13}$, we have $a = 4.691, b = 1.389, c = 0.815, d = 208.4$ and $e = 0.222$ from (4). This set of parameter values satisfies the conditions in Theorem 4.2(iii). Thus, system (3) has two distinct positive equilibria, which indicates that the model exhibits bistable phenomenon, and tumor cells have alternative fates depending on the positive initial densities. The phase portrait is given in Figure 10.

6. Conclusions. In this paper, we revisited a tumor-immune model with an immune checkpoint inhibitor, which was proposed by Nikolopoulou et al. [14]. For
the natural tumour-immune interaction model, we removed the additional restriction conditions in [14] and obtained the global dynamics by employing a new Dulac function to prove the nonexistence of nontrivial positive periodic orbits, our qualitative analysis revealed the sufficient and necessary conditions to assure the global stability of the tumorous or tumour-free equilibrium, while the conditions in [14] are sufficient but not necessary. Moreover, we explored the global dynamics for the more interesting and complex case: $C_K > \frac{\lambda C}{\eta C}$, which has not been discussed in [14]. In details, our results showed that there exist two critical values $C_{K0}, C_{K1} (= \frac{\lambda C}{\eta C})$ ($C_{K0} > C_{K1}$, see (20), (21)) for the carrying capacity $C_K$ of tumour cells, and one critical value $d_{T0}$ (see (19)) for the death rate $d_T$ of T cells such that: (i) when no tumorous equilibrium exists, the tumour-free equilibrium is globally asymptotically stable, i.e., tumor cells will be eliminated for all positive initial densities; (ii) when $C_K \leq C_{K1}$ and $d_T > d_{T0}$, the unique tumorous equilibrium is globally asymptotically stable; (iii) when $C_K > C_{K1}$, the model exhibits
saddle-node bifurcation of tumorous equilibria: The unique tumour-free equilibrium is globally asymptotically stable when no tumorous equilibrium exists; when a unique tumorous equilibrium exists, tumor cells can persist for all positive initial densities, or exhibit alternative fates: It can be eliminated for some positive initial densities and persist for another positive initial densities; when two distinct tumorous equilibria exist, the model exhibits bistable phenomenon, and tumor cells have alternative fates depending on the positive initial densities; (iv) when $C_K > C_{K0}$ and $d_T = d_{T0}$, or $d_T > d_{T0}$, tumor cells will persist for all positive initial densities. Our results can be seen as a complement to the work by Nikolopoulou et al. [14].

From cases (I)(ii) and (II)(i) in Theorem 4.2, it is easy to see that the unique tumorous equilibrium $E^*$ (or $E_2$) is globally asymptotically stable if and only if system (3) has no tumorous equilibrium, while in Theorem 3.7 in [14], Nikolopoulou et al. showed that the tumour-free equilibrium of model (1) is globally asymptotically stable when $d_T > N$, $\lambda_c < \eta T^*_0$ and no tumorous equilibrium exists, where $\lambda_c < \eta T^*_0 \iff b > (c+1)e - a$. Our results showed that the conditions $d_T > N$ and $\lambda_c < \eta T^*_0$ are unnecessary; Furthermore, from cases (I)(i) and (II)(ii) in Theorem 4.2, it is easy to see that the unique tumorous equilibrium $E^*$ (or $E_2$) is globally asymptotically stable if and only if $d \leq c$ and $b < (c+1)e - a$ (or $d > c$, $\Delta < 0$ and $y_1 < 1 \leq y_2$), while in Theorem 3.7 in [14], Nikolopoulou et al. only showed that the tumorous equilibrium $E^*$ of model (1) is globally asymptotically stable when $C_K < \frac{\lambda c}{\eta c^2}$, $f(\frac{\lambda c}{\eta}) < 0$ and $d_T > N$, where $C_K < \frac{\lambda c}{\eta c^2} \iff d < c$, and $f(\frac{\lambda c}{\eta}) < 0 \iff b < (c+1)e - a$. Our results show that not only the condition $d_T > N$ is unnecessary, but also for another case $C_K \geq \frac{\lambda c}{\eta c^2}$ the unique tumorous equilibrium $E^*$ (or $E_2$) may be globally asymptotically stable for some conditions.

From Lemma 2.1 and Theorem 2.2, our results showed that tumor cells will persist for all positive initial densities if and only if $b < (c+1)e - a$, or $b = (c+1)e - a$ and $d > 2c + \frac{\alpha}{e}$, which are equivalent to $d_T > d_{T0}$, or $C_K > C_{K0}$ and $d_T = d_{T0}$, respectively, i.e., if the death rate $d_T$ of T cells is larger than a critical value $d_{T0}$, or if the death rate $d_T$ of T cells is equal to the critical value $d_{T0}$ but the carrying capacity $C_K$ of tumour cells is larger than a critical value $C_{K0}$, then the T cells cannot stop the invasion of tumor cells for all positive initial densities.

On the other hand, our results revealed that tumor cells will be eliminated for all positive initial densities when no tumorous equilibrium exists, which means that the tumour-free equilibrium is globally asymptotically stable. From Theorem 4.2, the sufficient and necessary conditions to assure the global stability of tumour-free equilibrium are: $d \leq c$ and $b \geq (c+1)e - a$, or $d > c$ and $\Delta > 0$, or $d > c$ and $y_2 \geq 1$. Back to the original parameters, we have $d \leq c$ and $b \geq (c+1)e - a \iff C_K \leq C_{K1}$ and $d_T \leq d_{T0}$, i.e., if the carrying capacity $C_K$ of tumour cells is smaller than or equal to a smaller critical value $C_{K1}$ and the death rate $d_T$ of T cells is smaller than or equal to $d_{T0}$, then T cells can control the invasion of tumor cells.

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