Bifurcation analysis of a tumour-immune model with nonlinear killing rate as state-dependent feedback control

Likun Guan, Jin Yang*, Yuanshun Tan and Zijian Liu
College of Mathematics and Statistics
Chongqing Jiaotong University
Chongqing 400074, P. R. China
yseehom@126.com

Robert A. Cheke
Natural Resources Institute, University of Greenwich at Medway
Central Avenue, Chatham Maritime, Chatham
Kent, ME4 4TB, UK

Impulsive control strategies have been widely used in cancer treatment and linear impulsive control has always been considered in previous studies. We propose a novel tumour-immune model with nonlinear killing rate as state-dependent feedback control, which can better reflect the saturation effects of the tumour and immune cell mortalities due to chemotherapy, and its dynamic behaviors are investigated. The paper aims to discuss the transcritical and subcritical bifurcations of the model. To begin with, the threshold conditions for tumour eradication and tumour persistence in the model without pulse interventions are provided. We define the Poincare map of the proposed model and then address the existence and orbital asymptotically stability of the model' s tumour-free periodic solution. Furthermore, by using the bifurcation theory of the discrete one-parameter family of maps, which is determined by the Poincare mapping, we investigate the model's transcritical and subcritical pitchfork bifurcations with respect to the key parameter.

Keywords: Tumour-immune model; Nonlinear feedback control; Poincare map; Bifurcations

1. Introduction

Cancer is a malignant tumour caused by several gene mutations in normal cells, and it is generally thought to be one of the most serious diseases in the world. It kills over 10 million people each year, accounting for almost one-sixth of all fatalities worldwide [Wild et al., 2020]. Traditional treatment approaches for curing cancer mostly involved surgery, chemotherapy, radiation, and etc. However, these treatments usually failed to entirely clear tumour cells and sometimes induced a series of negative side e_ects for the patients. Due to this, a novel cancer treatment named immunotherapy was developed, which not only strengthened the efficacy of the traditional treatment, but also reduced the corresponding side e_ects [Gubin et al., 2014; Powles et al., 2014; Ribas et al., 2003; L_opez et al., 2017]. Two immunotherapies were proposed, including adoptive immunotherapy and active immunotherapy, where adoptive immunotherapy was carried out by means of injecting the cultured e_ector cells directly into patient's cancer regions, and active immunotherapy was implemented by infusing tumour vaccines to induce specifc immune responses or

_Corresponding author: Jin Yang
yCorresponding author's email address: yseehom@126.com

injecting immunomodulators to activate non-specific immune function [Couzin Frankel, 2013; Norman, 2004; Shiao *et al.*, 2011].

In order to study the pathogenesis of cancers, many mathematical models have been constructed to describe the interactions between tumour cells and immune systems [De Angelis *et al.*, 2003; Foryś & Bodnar, 2003; Rozova & Bratus, 2016]. In 1994, Kuznetsov initially established a tumour-immune dynamical model, in which the tumour cells played the role of predator and the immune cells acted as the role of prey [Kuznetsov *et al.*, 1994]. Magda then simplified the model by using the Lotka-Volterra form to characterize the interactions between tumour and immune cells instead of the Michaelis-Menten type [Gałach, 2003], which can be described by the following two equations:

$$\begin{cases} \dfrac{dE}{dt} = s + \alpha ET - dE, \\ \dfrac{dT}{dt} = aT\left(1 - \dfrac{T}{K}\right) - nET, \end{cases} \tag{1}$$

where E and T represent effector cells (such as cytotoxic T lymphocytes, natural killer cells, and etc) and tumour cells, respectively. s denotes the natural constant flowing rate of adult effector cells into tumour site (non-increased by the existence of tumour cells), the accumulation rate of effector cells caused by tumours is denoted by α, d denotes the death rate of effector cells. a represents the tumour cell growth rate, which includes both multiplication and death. K is the tumour cells environment capacity, the rate at which tumour cells are lethally hit by the existence of effector cells is denoted by n.

In practice, immunotherapy and chemotherapy play a significant role in the treatment of cancer, which are carried out in the form of impulses, as confirmed by experiments and clinical practice [Yamaguchi *et al.*, 2006; Hegmans *et al.*, 2005; Samanta *et al.*, 2017]. Then many tumour-immune mathematical models concerning pulsed treatments have been developed and analysed. In fact, Steve found that when the average tumour size is around $50mm^2$, surgical excision followed by adjuvant immunotherapy revealed that this approach has the potential to cure cancers in the long term [Broomfield *et al.*, 2005]. Driven by this, Tang et al. used the impulsive semi-dynamic system to describe this treatment which depends on the tumour size, and established a tumour-immune mathematical model with state dependent feedback control. They studied the existence and stability of the order-1 and order-2 periodic solutions [Yang *et al.*, 2015, 2019; Wei & Lin, 2013; Tang *et al.*, 2016]. Yang et al. developed a novel impulsive tumour-immune system with drug responses, they studied the effects of drug dosages on the evolution of tumours and proposed a more effective method to maintain a high tumour cell depletion rate [Yang *et al.*, 2020]. Actually, the methods of state-dependent feedback control have been used in a variety of fields, including integrated pest management [Tang & Cheke, 2008, 2005], infectious disease control [Cheng *et al.*, 2019; Zhang *et al.*, 2020], the neurological system [Touboul & Brette, 2009], and etc.

In the above studies, the tumour size was selected as a threshold to implement the treatment strategy [Tang *et al.*, 2016; Yang *et al.*, 2020]. But the Staccato study has designed a new therapeutic method to treat tumours, which therapy was initiated guided by $CD4^+$ T cell counts [Anaworanich *et al.*, 2006]. Subsequently, Tang et al. utilized piecewise functions to describe this novel therapy, then proposed a piecewise mathematical model using effector cell counts as a threshold at which structural therapeutic interruption (STI) strategies of antiretroviral therapy was applied [Tang *et al.*, 2012]. Tang and co-authors also developed a piecewise tumour-immune models which based on the effector cell-guided treatments, complex dynamics were observed including coexistence of multiple attractors and an infinite number of possible topologies of attractors [Tang *et al.*, 2017]. This suggests that although it is very important to select effector cells as the threshold to implement therapeutic strategies, there are few theoretical studies in this field. In this paper, we make use of semi-dynamical system to depict this novel threshold control strategy instead of piecewise system. Notice that in the presence of toxicological effects of drugs and drug resistance, the mortality of tumours and immune cells caused by chemotherapy must not be linear, but a nonlinear function with saturation effects. Driven by these facts, we developed a novel state-dependent feedback control tumour-immune dynamical model with nonlinear killing rates concerning immunotherapy,

which can be described by the following equations,

$$\begin{cases} \left.\begin{aligned} \frac{dE}{dt} &= s + \alpha ET - dE, \\ \frac{dT}{dt} &= aT\left(1 - \frac{T}{K}\right) - nET, \end{aligned}\right\} E > EL, \\ \left.\begin{aligned} E\left(t^+\right) &= \left(1 - \frac{\delta_1 E}{E + h_1}\right) E + \tau, \\ T\left(t^+\right) &= \left(1 - \frac{\delta_2 T}{T + h_2}\right) T, \end{aligned}\right\} \quad E = EL, \end{cases} \tag{2}$$

where $h_1, h_2 > 0$ denote the half saturation constants of effector cells and tumour cells, respectively. $\tau > 0$ represents the number of injections of effector cells, $\delta_1, \delta_2 \in [0, 1]$ denote the maximum killing rate of effector cells and tumour cells. For simplicity, we denote functions $A_1(E) = -\delta_1 E^2/(E + h_1), A_2(T) = -\delta_2 T^2/(T + h_2), f(T) = T + A_2(T)$ throughout the paper. It is found that a comprehensive therapy is initiated only if the number of effector cells is reduced to the critical size EL. Although the dynamics of model (1) without impulsive effects are simple, it depicts the interaction between tumour cells and immune cells. In order to emphasize the impact of nonlinear feedback control, integrated treatment strategy is considered in model (1).

This paper is arranged as follows. Some important definitions and lemmas about the impulsive semi-dynamical systems are introduced in section 2. In section 3, we first define the Poincare map and then study the existence and stability of tumour-free periodic solution. In section 4, the transcritical bifurcation and pitchfork bifurcation are investigated. Finally, biological implications are discussed and conclusions are presented.

2. Preliminaries

The planar impulsive dynamical systems can be defined as follows

$$\begin{cases} \left.\begin{aligned} \frac{dx}{dt} &= P(x, y) \\ \frac{dy}{dt} &= Q(x, y) \end{aligned}\right\} (x, y) \notin \mathcal{D}, \\ \left.\begin{aligned} x\left(t^+\right) &= x + \alpha(x, y) \\ y\left(t^+\right) &= y + \beta(x, y) \end{aligned}\right\} \quad (x, y) \in \mathcal{D}, \end{cases} \tag{3}$$

where $(x, y) \in R^2$,P,Q,α,β are continuous maps from R^2 to R, $\mathcal{D} \subset R^2$ is the impulsive set. and set $x^+ = x(t^+)$ and $y^+ = y(t^+)$. For every $z(x, y) \in \mathcal{D}$, the map $F : R^2 \to R^2$ is defined

$$z^+ = F(z) = (x + \alpha(x, y), y + \beta(x, y)) = (x^+, y^+) \in R^2,$$

where z^+ is the impulsive point of z.

Set $\mathcal{P} = F(\mathcal{D})$, for any $z \in \mathcal{D}, one yields F(z) = z^+ \in \mathcal{P}$ and $\mathcal{P} \cap \mathcal{D} = \varnothing$. In the following, some definitions of generalized semi-dynamic systems are introduced.

Let (X, Π, R_+) or (X, Π) to be the impulsive dynamical system [Simeonov & Bainov, 1988; Bainov & Simeonov, 1993], here X is a metric space and R_+ is a set of non-negative reals. let $\Pi_z(t) = \Pi(z, t)$, the map $\Pi_z : R \to X$ is continuous such that $\Pi(z, 0) = z$ for all $z \in X$, and $\Pi(\Pi(z, t), s) = \Pi(x, t + s)$ for all $z \in X$ and $t, s \in R_+$. Assume $H^+(z) = \{\Pi(z, t) | t \in R\}$ to be the non-negative trajectory passing through z. Let $\mathcal{D}^+(z) = C^+(z) \cap \mathcal{D} - \{z\}$ and $\mathcal{D}^-(z) = G(z) \cap \mathcal{D} - \{z\}$, where $G(z) = \cup\{G(z, t) | t \in R\}$ and $G(z, t) = \{\omega \in X | \Pi(\omega, t) = z\}$ is the attainable set of z at $t \in R_+$. Finally, Let $\mathcal{D} = \mathcal{D}^+(z) \cup \mathcal{D}^-(z)$. We now intruduce the following useful definitions and lemmas [Kaul, 1990; Ciesielski, 2004; Bonotto & Federson, 2008].

Definition 2.1. An impulsive semi-dynamical system $(X, \Pi; \mathcal{D}, F)$ contains three parts: a continuous semi-dynamical system (X, Φ), a nonempty closed subset $\mathcal{D}$ of X and a continuous map $F : \mathcal{D} \to X$. It also satisfies: limit point of $\mathcal{D}(z)$ is not any $z \in X$; $\{t | G(z, t) \cap \mathcal{D} \neq \varnothing\}$ is a closed subset of R.

Pulsed point of Π_z is denoted by $\{z_n^+\}$, then map $\mathcal{I}$ is defined from X to the positive reals $R \cup \{\infty\}$ as: let $z \in X$, if $\mathcal{D}^+(z) = \varnothing$, then $\mathcal{I}(z) = \infty$, othrwise $\mathcal{D}^+(z) \neq \varnothing$ and let $\mathcal{I}(z) = s$, where $\Pi(x,t) \notin \mathcal{D}$ for $0 < t < s$ but $\Pi(z,s) \in \mathcal{D}$.

Definition 2.2. A solution Π_z of $(X, \Pi; \mathcal{D}, F)$ is called an order k period solution with period T_k if there are nonnegative integers $m \geqslant 0$ and $k \geqslant 1$ such that k is the smallest integer for which $z_m^+ = z_{m+k}^+$ and $T_k = \sum_{i=m}^{m+k-1} \mathcal{I}(z_i) = \sum_{i=m}^{m+k-1} s_i$.

Lemma 1. *([Simeonov & Bainov, 1988; Bainov & Simeonov, 1993])The T-periodic solution* $(x, y) = (\xi(t), \eta(t))$ *of the system*

$$\begin{cases} \dfrac{dx(t)}{dt} = P(x,y), & \dfrac{dy(t)}{dt} = Q(x,y), \qquad if\ \psi(x,y) \neq 0, \\ \Delta x = \beta_1(x,y), & \Delta y = \beta_2(x,y), \qquad if\ \psi(x,y) = 0, \end{cases}$$

is orbitally asymptotically stable if the Floque multiplier μ_2 *satisfies the condition* $|\mu_2| < 1$*, where*

$$\mu_2 = \prod_{k=1}^{q} \Delta_k \exp\left[\int_0^T \left(\frac{\partial P}{\partial x}(\xi(t),\eta(t)) + \frac{\partial Q}{\partial y}(\xi(t),\eta(t))\right) dt\right],$$

with

$$\Delta_k = \frac{P_+\left(\dfrac{\partial \beta_2}{\partial y}\dfrac{\partial \psi}{\partial x} - \dfrac{\partial \beta_2}{\partial x}\dfrac{\partial \psi}{\partial y} + \dfrac{\partial \psi}{\partial x}\right) + Q_+\left(\dfrac{\partial \beta_1}{\partial x}\dfrac{\partial \psi}{\partial y} - \dfrac{\partial \beta_1}{\partial y}\dfrac{\partial \psi}{\partial x} + \dfrac{\partial \psi}{\partial y}\right)}{P\dfrac{\partial \psi}{\partial x} + Q\dfrac{\partial \psi}{\partial y}},$$

P, Q, $\partial\beta_1/\partial x$, $\partial\beta_1/\partial y$, $\partial\beta_2/\partial x$, $\partial\beta_2/\partial y$, $\partial\psi/\partial x$, $\partial\psi/\partial y$ *are calculated at the point* $(\xi(t), \eta(t))$*.* $P_+ = P(\xi(t_k^+), \eta(t_k^+))$ *and* $Q_+ = Q(\xi(t_k^+), \eta(t_k^+))$*. Here* $\psi(x,y)$ *is a sufficiently smooth function such that grad* $\psi(x,y) \neq 0$ *,and* t_k *is the time of the kth jump.*

Lemma 2. *(Transcritical bifurcation) Let* $G : U \times I \to R$*,* G *is* C^r *with* $r \leqslant 2$*,* U *and* I *are open intervals of the real line containing* 0*. If*

$$(1) G(0,\alpha) = 0 \ for\ all\ \alpha; \qquad (2) \frac{\partial G}{\partial x}(0,0) = 1;$$

$$(3) \frac{\partial^2 G}{\partial x \partial \alpha}(0,0) > 0; \qquad (4) \frac{\partial^2 G}{\partial x^2}(0,0) > 0.$$

then, there are $\alpha_1 < 0 < \alpha_2$ *and* $\epsilon > 0$ *such that*
(i) if $\alpha_1 < \alpha < 0$*, then* $G_\alpha = G(\cdot, \alpha)$ *has two fixed points, 0 and* $x_{1\alpha} > 0$ *in* $(-\epsilon, \epsilon)$ *with the origin being asymptotically stable and the other fixed point being unstable.*
(ii) if $0 < \alpha < \alpha_2$*, then* G_α *has two fixed points, 0 and* $x_{1\alpha} < 0$ *in* $(-\epsilon, \epsilon)$ *with the origin being unstable and the other fixed point being asymptotically stable.*

It is revealed that case $\partial^2 G/\partial x \partial \alpha(0,0) < 0$ *can be analyzed by changing* $\alpha \to -\alpha$*.*

Lemma 3. *(Supercritical pitchfork bifurcation) Let* $G : U \times I \to R$*,* G *is* C^r *with* $r \geqslant 3$*,* U *and* I *are open intervals of the real line containing* 0*. If* $\partial^2 G/\partial x \partial \alpha(0,0) > 0$*,* $\partial^2 G/\partial x^2(0,0) = 0$ *and* $\partial^3 G/\partial x^3(0,0) < 0$*, then there exist with* $\alpha_1 < 0 < \alpha_2$ *and* $\epsilon > 0$ *such that*
(i) if $\alpha_1 < \alpha \leqslant 0$*, then* $G_\alpha = G(\cdot, \alpha)$ *exists a unique fixed point in* $(-\epsilon, \epsilon)$*, which is asymptotically stable.*
(ii) if $0 < \alpha < \alpha_2$*, then* G_α *has three fixed points in* $(-\epsilon, \epsilon)$ *with the origin being unstable and the others* $x_{1\alpha} < 0 < x_{2\alpha}$ *being asymptotically stable.*

The case $\partial^2 G/\partial x \partial \alpha(0,0) < 0$ *can be discussed by changing* $\alpha \to -\alpha$*. And if* $\partial^3 G/\partial x^3(0,0) > 0$*, it is undergoes a subcritical pitchfork bifurcation.*

Solving $s + \alpha ET - dE = 0$ and $aT(1 - T/K) - nET = 0$, we have two isolines,

$$L_1 : T = \frac{1}{\alpha}\left(d - \frac{s}{E}\right) \doteq k_0(E), \qquad L_2 : E = \frac{a}{n}\left(1 - \frac{T}{K}\right),$$

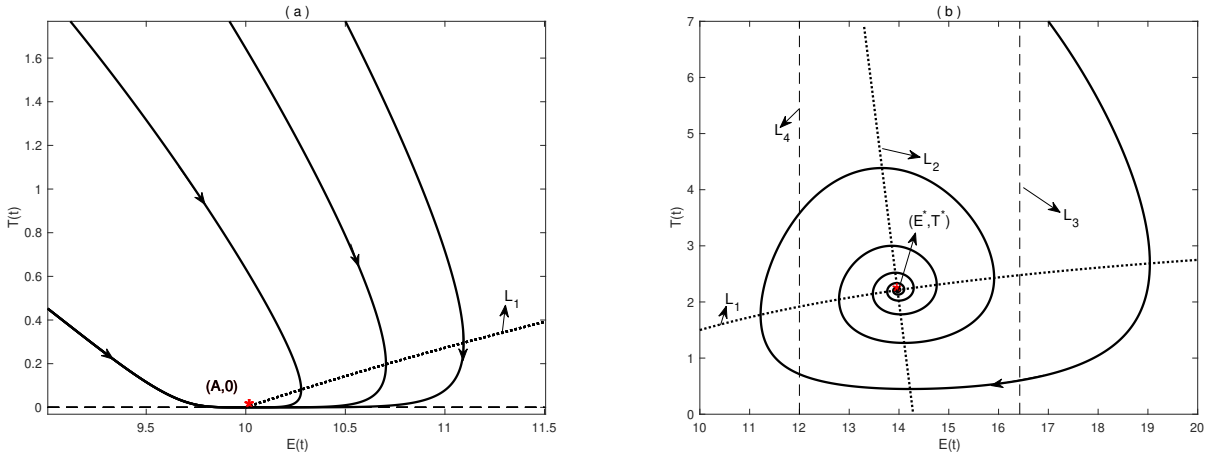

Fig. 1. Phase traits of system (1). (a)$\bar{E} < A$; (b) $\bar{E} > A$

denote $A \doteq s/d$ and $\bar{E} \doteq a/n$, we have the following results for model (1) [Gałach, 2003].

Lemma 4. *If $\bar{E} < A$, then model (1) has a boundary equilibrium $P_0(A, 0)$, which is stable; if $\bar{E} > A$, then there exists a positive interior equilibrium $P^*(E^*, T^*)$, which is asymptotically stable, and the boundary equilibrium $(A, 0)$ is unstable. Where*

$$E^* = \frac{a\left(\alpha K - d + \sqrt{\Delta}\right)}{2nK\alpha}, \quad T^* = \frac{\alpha K + d - \sqrt{\Delta}}{2\alpha}, \Delta = (\alpha k - d)^2 + 4\left(\frac{\alpha k n}{a}\right) s.$$

3. Poincaré Map and Tumour-free Periodic Solution of Model (2)

3.1. *The Definition of the Poincaré Map*

Define

$$L_3 : E = EP, \qquad L_4 : E = EL,$$

and let $EP \doteq (1 - \delta_1 EL/(EL + h_1))\, EL + \tau$. Denoted by $E_{EP} = \{(E, T)|E = EP, T \geq 0\}$; $E_{EL} = \{(E, T)|E = EL, T \geq 0\}$, the segment E_{EP} is defined as the poincaré section. Point $P_k^+ = (EP, T_k^+) \in E_{EP}$ will meet section E_{EL} at point $P_{k+1} = (EL, T_{k+1})$ in a finite time, where T_{k+1} is determined by T_k^+ and let $T_{k+1} \doteq g(T_k^+)$. Then a single-pulse is occured at P_{k+1} such that it jumps to point $P_{k+1}^+ = (EP, T_{k+1}^+)$ with $T_{k+1}^+ = T_{k+1} + A_2(T_{k+1})$. Thus, we can define the poincaré map as

$$\mathcal{P}(T_k^+) \doteq T_{k+1}^+ = g(T_k^+) + A_2(T_{k+1}),$$

and the impulsive set $\mathcal{M}$ is defined by

$$\mathcal{M} = \{(E, T) \in R_+^2 | E = EL, 0 \leq T \leq T_M\},$$

where $T_M = \mathcal{P}(T_{EP})$. Set the continuous function $F : (EL, T) \to (E^+, T^+) = (EP, f(T)) \in R_+^2$, where $f(t) \in [0, T_M]$, then the phase set is defined as follows:

$$\mathcal{N} = F(\mathcal{M}) = \{(E^+, T^+) \in R_+^2 | T^+ = EP, 0 \leq T^+ \leq f(T_M)\}.$$

Scalar differential equation of system (2) in phase space is as follows,

$$\begin{cases} \dfrac{dT}{dE} = \dfrac{T\left(a - \dfrac{aT}{K} - nE\right)}{s + \alpha ET - dE} \doteq h(E, T), \\ T(EP) = T_0^+, \end{cases} \tag{4}$$

set

$$\Omega = \left\{(E,T)|E>0, T>0, T<\frac{1}{\alpha}\left(d-\frac{s}{E}\right)\right\}$$

then the function $h(E,T)$ is continuously differentiable. Denote $T_0^+ = T_0, E_0 = EP$. Then

$$T(E) = T(E;EP,T_0) = T(E,T_0), \quad EP < E < EL,$$

and

$$T(E,T_0) = T_0 + \int_{EP}^{E} h(E,T(E,T_0))dE.$$

From the above, the expression of the Poincaré Map can be obtained,

$$\mathcal{P}(T_k^+) = T_{k+1}^+ = T(EL,T_k^+) + A_2(T(EL,T_k^+)),$$

$$\mathcal{P}(T_0) = T(EL,T_0) + A_2(T(EL,T_0)) = f(T(EL,T_0)),$$

For simplicity, by using the methods in [K.Hale, 1969], we have the following results which are very useful in the rest of the paper.

$$\left.\frac{\partial h(E,T)}{\partial T}\right|_{T=0} = \frac{a-nE}{s-dE},$$
$$\left.\frac{\partial^2 h(E,T)}{\partial T^2}\right|_{T=0} = \frac{-\frac{2a}{K}(s-dE) - 2\alpha E(a-nE)}{(s-dE)^2}.$$

And

$$\frac{\partial T(E,T_0)}{\partial T_0} = \exp\left(\int_{EP}^{E}\frac{\partial h(E,T(E,T_0))}{\partial T}dE\right),$$
$$\frac{\partial^2 T(E,T_0)}{\partial T_0^2} = \frac{\partial T(E,T_0)}{\partial T_0}\int_{EP}^{E}\frac{\partial^2 h(E,T(E,T_0))}{\partial T^2}\frac{\partial T(E,T_0)}{\partial T_0}dE.$$

It follows from $\mathcal{P}(T_0) = f(T(EL,T_0))$, $T = T(EL,T_0)$ that

$$\begin{aligned}\frac{\partial \mathcal{P}(T_0)}{\partial T_0} &= \left(1-\frac{\delta_2 T(EL,T_0)(T(EL,T_0)+2h_2)}{(T(EL,T_0)+h_2)^2}\right)\frac{\partial T(E,T_0)}{\partial T_0}\\ &= \left(1-\frac{\delta_2 T(EL,T_0)(T(EL,T_0)+2h_2)}{(T(EL,T_0)+h_2)^2}\right)\exp\left(\int_{EP}^{EL}\frac{\partial h(E,T(E,T_0))}{\partial T}dE\right)\\ &= f'(T(EL,T_0))\exp\left(\int_{EP}^{EL}\frac{\partial h(E,T(E,T_0))}{\partial T}dE\right),\end{aligned} \tag{5}$$

$$\begin{aligned}\frac{\partial^2 \mathcal{P}(T_0)}{\partial T_0^2} &= \frac{\partial^2 T(EL,T_0)}{\partial T_0^2} + \frac{\partial^2 T(EL,T_0)}{\partial T_0^2}\frac{\partial A_2(T)}{\partial T} + \frac{\partial T(EL,T_0)}{\partial T_0}\left(\frac{\partial \partial A_2(T)}{\partial T_0 \quad \partial T}\right)\\ &= (A_2'(T(EL,T_0))+1)\frac{\partial^2 T(EL,T_0)}{\partial T_0^2} + \left(\frac{\partial T(EL,T_0)}{\partial T_0}\right)^2 A_2''(T(EL,T_0))\\ &= f'(T(EL,T_0))\frac{\partial^2 T(EL,T_0)}{\partial T_0^2} - \left(\frac{\partial T(EL,T_0)}{\partial T_0}\right)^2\frac{2\delta_2 h_2^2}{(T(EL,T_0)+h_2)^3}.\end{aligned} \tag{6}$$

3.2. *Existence and Stability of Tumour-free Periodic Solution (TFPS)*

Let $T(t) = 0$, system (2) can be reduced as

$$\begin{cases} \dfrac{dE}{dt} = s - dE, \\ E\left(t^{+}\right) = \left(1 - \dfrac{\delta_1 E}{E + h_1}\right) E + \tau. \end{cases} \tag{7}$$

Solving system (7) with the initial conditon $E(0) = EP$ yields

$$E^T(t) = A - (A - EP)\exp(-dt)$$

with period T

$$T = \int_{EP}^{EL} \frac{1}{s - dE} dE = -\frac{1}{d} \ln\left(\frac{EL - A}{EP - A}\right). \tag{8}$$

Therefore, system (2) has a TFPS $(E^T(t), 0)$ with period T.

Theorem 1. *If $A < \bar{E} < EL < EP$, then the TFPS $(E^T(t), 0)$ of system (2) is orbitally asymptotically stable.*

Proof. It follows from Lemma 1,

$$P(E,T) = s + \alpha ET - dE, \quad Q(E,T) = aT\left(1 - \frac{T}{K}\right) - nET,$$

$$\beta_1(E,T) = -\frac{\delta_1 E^2}{E + h_1} + \tau, \quad \beta_2(E,T) = -\frac{\delta_2 T^2}{T + h_2}, \quad \psi(E,T) = E - EL.$$

By calculation,

$$\frac{\partial P}{\partial E} = \alpha T - d, \quad \frac{\partial Q}{\partial T} = a - \frac{2a}{K}T - nE, \quad \frac{\partial \beta_1}{\partial E} = -\frac{\delta_1 E(E + 2h_1)}{(E + h_1)^2},$$

$$\frac{\partial \beta_2}{\partial T} = -\frac{\delta_2 T(T + 2h_2)}{(T + h_2)^2}, \quad \frac{\partial \psi}{\partial E} = 1 - L, \quad \frac{\partial \beta_1}{\partial T} = \frac{\partial \beta_2}{\partial E} = \frac{\partial \psi}{\partial T} = 0,$$

and $(\xi(T), \eta(T)) = (EL, 0), \quad (\xi(T^+), \eta(T^+)) = (EP, 0)$, $P_+ = s - dEP$.

$$\begin{aligned} \Delta_1 &= \frac{P_+\left(\dfrac{\partial \beta_2}{\partial T}\dfrac{\partial \psi}{\partial E} - \dfrac{\partial \beta_2}{\partial E}\dfrac{\partial \psi}{\partial T} + \dfrac{\partial \psi}{\partial E}\right) + Q_+\left(\dfrac{\partial \beta_1}{\partial E}\dfrac{\partial \psi}{\partial T} - \dfrac{\partial \beta_1}{\partial T}\dfrac{\partial \psi}{\partial E} + \dfrac{\partial \psi}{\partial T}\right)}{P\dfrac{\partial \psi}{\partial E} + Q\dfrac{\partial \psi}{\partial T}} \\ &= \frac{P_+\left(1 - \dfrac{\delta_2 T(T + 2h_2)}{(T + h_2)^2}\right)}{P} \\ &= \left(1 - \frac{\delta_2 T(T + 2h_2)}{(T + h_2)^2}\right)\frac{EP - A}{EL - A}, \end{aligned} \tag{9}$$

and

$$\begin{aligned}
&\exp\left(\int_0^T \left(\frac{\partial P}{\partial E}(\xi(t),\eta(t)) + \frac{\partial Q}{\partial T}(\xi(t),\eta(t))\right) dt\right) \\
&= \exp\left(\int_0^T (-d + a - nE)\right) \\
&= \exp\left(\int_0^T (-d + a - n(A - (A - EP)\exp(-dt)))\right) \\
&= \exp(-dT)\exp(aT)\exp\left(\int_0^T -n(A - (A - EP)\exp(-dt))dt\right).
\end{aligned} \tag{10}$$

Denote

$$M_1 \doteq -dT = \ln\left(\frac{EL - A}{EP - A}\right), \quad M_2 \doteq aT = -\frac{a}{d}\ln\left(\frac{EL - A}{EP - A}\right),$$

$$\begin{aligned}
M_3 &\doteq \int_0^T -n(A - (A - EP)\exp(-dt))dt \\
&= \frac{n}{d}\left[A\ln\left(\frac{EL - A}{EP - A}\right) + EL - EP\right].
\end{aligned}$$

For the expression of Δ_1, there are two cases needed to be considered: $h_2 = 0$ and $h_2 \neq 0$. If $h_2 = 0$, then $\Delta_1 = (1 - \delta_2)(EP - A)/(EL - A)$; if $h_2 \neq 0$, then $\Delta_1 = (EP - A)/(EL - A)$, thus,

$$\mu_2 = \begin{cases} \exp(M_2 + M_3), & h_2 \neq 0, \\ (1 - \delta_2)\exp(M_2 + M_3), & h_2 = 0. \end{cases} \tag{11}$$

In the light of $A < EL < EP$, it follows from the monotonictiy of $k_1(x) \doteq ln(1 - x) + x$ that $M_2 > 0$ and $M_3 < 0$, then

$$\begin{aligned}
M_2 + M_3 &= -\frac{a}{d}\ln\left(\frac{EL - A}{EP - A}\right) + \frac{n}{d}\left[A\ln\left(\frac{EL - A}{EP - A}\right) + EL - EP\right] \\
&= \frac{n}{d}\left[\ln\left(\frac{EP - A}{EL - A}\right)(\bar{E} - A) + EL - EP\right] \\
&< \frac{n}{d}\left[\left(\frac{EP - EL}{\sqrt{(EP - A)(EL - A)}}\right)(\bar{E} - A) + EL - EP\right] \\
&= \frac{n}{d}(EP - EL)\left(\frac{(\bar{E} - A) - \sqrt{(EP - A)(EL - A)}}{\sqrt{(EP - A)(EL - A)}}\right) \\
&< \frac{n}{d}(EP - EL)\left(\frac{\bar{E} - EL}{\sqrt{(EP - A)(EL - A)}}\right),
\end{aligned}$$

which means if $EL > \bar{E}$, then $M_2 + M_3 < 0$, i.e., $\mu_2 < 1$. From Lemma 1, the TFPS $(E^T(t), 0)$ of system (2) is orbitally asymptotically stable. This completes the proof. ■

4. Bifurcation

It follows from Theorem 1 that the TFPS is orbitally asymptotically stable provided $EL > \bar{E}$. If $EL < \bar{E}$, then the TFPS becomes unstable. Since δ_1 and δ_2 are important indexes that can reflect the therapeutic effects, EL is the threshold for treatment implementation and τ denotes the intensity of immunotherapy. Therefore, in this section, we mainly focus on the bifurcation near the TFPS of model (2) with respect to these key parameters.

4.1. *Transcritical Bifurcations for δ_1*

Notice that the expression of Δ_1 differs for $h_2 \neq 0$ and $h_2 = 0$. When $h_2 \neq 0$, we choose δ_1 as the bifurcation parameter and consider $M_2 + M_3$ as a function of δ_1,

$$M_{12}(\delta_1) \doteq M_2 + M_3 = \frac{n}{d}(EL - EP) + \frac{a}{d}\ln\left(\frac{EL - A}{EP - A}\right)\left(\frac{ns}{da} - 1\right),$$
$$\mu_2(\delta_1) = \exp(M_{12}(\delta_1)),$$

and $EP = EL + A_1(EL, \delta_1) + \tau$. By calculations,

$$\frac{\partial EP}{\partial \delta_1} = \frac{\partial A_1(EL, \delta_1)}{\partial \delta_1} = -\frac{EL^2}{EL + h_1} < 0,$$

and

$$\frac{d\mu_2(\delta_1)}{d\delta_1} = \exp(M_{12})\frac{dM_{12}(\delta_1)}{d\delta_1}$$
$$= \exp(M_{12})\frac{\partial A_1(EL, \delta_1)}{\partial \delta_1}\left(\frac{nEP - a}{s - dEP}\right).$$

Solving $d\mu_2(\delta_1)/d\delta_1 = 0$ with respect to δ_1 and denoting the unique root as $\overline{\delta}_1$, we get

$$\overline{\delta}_1 = \left(1 + \frac{h_1}{EL}\right)\left(1 - \frac{\bar{E} - \tau}{EL}\right). \tag{12}$$

To make sure that $0 < \overline{\delta}_1 \leq 1$, it needs inequality $h_1 EL/(EL + h_1) \leq \bar{E} - \tau < EL$ holds true. If $\delta_1 \in (0, \overline{\delta}_1)$, then $EP > \bar{E}$ and $d\mu_2(\delta_1)/d\delta_1 > 0$. If $\delta_1 \in (\overline{\delta}_1, 1)$, then $EP < \bar{E}$ and $d\mu_2(\delta_1))/d\delta_1 < 0$. It follows from $\mu_2(0) < 1$ and $d\mu_2(\delta_1)/d\delta_1 > 0$, there exists with a unique $\delta_1^* \in (0, \overline{\delta}_1)$ with $\mu_2(\delta_1^*) = 1$. That is, if $0 < \delta_1 < \delta_1^*$, then the periodic solution $(E^T(t), 0)$ is stable, if $\delta_1^* < \delta_1 < \overline{\delta}_1$, then the periodic solution $(E^T(t), 0)$ is unstable, which means the transcritical bifurcation occurs at $\delta_1 = \delta_1^*$.

Furthermore, if $\delta_1 = 1$, then $EP = h_1 EL/(h_1 + EL) + \tau$. It follows from $A < EL < EP$ that

$$\ln\left(\frac{EP - A}{EL - A}\right) > \frac{2(EP - EL)}{EP + EL - 2A}. \tag{13}$$

Then

$$M_{12}(1) = \frac{n}{d}(EL - EP) + \frac{n}{d}\ln\left(\frac{EL - A}{EP - A}\right)(A - \bar{E})$$
$$= \frac{n}{d}(EL - EP) + \frac{n}{d}\ln\left(\frac{EP - A}{EL - A}\right)(\bar{E} - A) \tag{14}$$
$$> \frac{n}{d}(EP - EL)\left[\frac{2(\bar{E} - A)}{EP + EL - 2A} - 1\right],$$

according to the monotonicity of $EP(\delta)$, $\delta = 1$ implies $EP < \bar{E}$. Thus, the positive $M_{12}(1)$ reveals $\mu_2(1) > 1$. Therefore, the TFPS is unstable and transcritical bifurcation does not occur due to $\mu_2(1) > 1$ and $d\mu_2(\delta_1))/d\delta_1 < 0$ for $\delta_1 \in (\overline{\delta}_1, 1)$. Based on the above discussions, we have the following results.

Theorem 2. *If $A < EL < \bar{E} < EP$, $\mu_2(0) < 1$ and $W < 2\delta_2/h_2$, then the $\mathcal{P}(T_0, \delta_1)$ exists with a stable positive fixed point when δ_1 changes through δ_1^* from left to right, which implies that the system(2) exists a stable positive periodic solution when $\delta_1 \in (\delta_1^*, \delta_1^* + \epsilon)$ with $\epsilon > 0$ small enough. However, if $W > 2\delta_2/h_2$, then the $\mathcal{P}(T_0, \delta_1)$ exists with an unstable positive fixed point when δ_1 changes through δ_1^* from right to left, which is just an unstable positive periodic solution of the system(2) for $\delta_1 \in (\delta_1^* - \epsilon, \delta_1^*)$ with $\epsilon > 0$ small enough.*

Proof. Theorem 2 can be proved by verifying four conditions of Lemma 2 for the Poincar'e map $\mathcal{P}$. To this end, denote $T(E; EP, T_0) = T(E, T_0)$, we have $\mathcal{P}(0, \delta_1) = f(T(EL, 0)) = 0$ and $\mathcal{P}(T_0, \delta_1) = f(T(EL, T_0))$. It indicates that the first condition of Lemma 2 holds. From equation(5),

$$\frac{\partial \mathcal{P}(0, \delta_1)}{\partial T_0} = \exp\left(\int_{EP}^{EL} \frac{a - nE}{s - dE} dE\right) = \mu_2(\delta_1),$$

so

$$\frac{\partial \mathcal{P}(0, \delta_1^*)}{\partial T_0} = \mu_2(\delta_1^*) = 1,$$

which implies the second condition of Lemma 2 holds. Furthere,

$$\begin{aligned}\frac{\partial^2 \mathcal{P}(0, \delta_1)}{\partial T \partial \delta_1} &= \frac{\partial}{\partial EP}\left(\frac{\partial \mathcal{P}(0, \delta_1)}{\partial T_0}\right) \cdot \frac{\partial EP}{\partial \delta_1} \\ &= \frac{\partial T(EL, T_0)}{\partial T_0} \cdot \frac{\partial}{\partial EP}\left(\int_{EP}^{EL} \frac{\partial h(E, T(E, 0))}{\partial T} dE\right) \cdot \frac{\partial EP}{\partial \delta_1} \\ &= \frac{d\mu_2(\delta_1)}{d\delta_1},\end{aligned}$$

thus,

$$\frac{\partial^2 \mathcal{P}(0, \delta_1^*)}{\partial T \partial \delta_1} = \frac{d\mu_2(\delta_1^*)}{d\delta_1} > 0,$$

and the third condition of Lemma 2 holds.

Finally, according to equation(6),

$$\begin{aligned}\frac{\partial^2 \mathcal{P}(0, \delta_1)}{\partial T_0^2} &= \frac{\partial T(EL, T_0)}{\partial T_0} \cdot \int_{EP}^{EL} \frac{\partial^2 h(E, T(E, 0))}{\partial T_0^2} \cdot \frac{\partial T(E, 0)}{\partial T_0} dE \\ &\quad - \left(\frac{\partial T(EL, 0)}{\partial T_0}\right)^2 \cdot \frac{2\delta_2}{h_2} \\ &= \exp(M_{12}) \cdot \int_{EP}^{EL} \frac{\partial^2 h(E, T(E, 0))}{\partial T_0^2} \cdot \frac{\partial T(E, 0)}{\partial T_0} dE - \frac{2\delta_2}{h_2} \exp(2M_{12}).\end{aligned}$$

Denote

$$\begin{aligned}z_1(E) &= \int_{EP}^{E} \frac{a - nE}{s - dE} dE, \\ r_1(E) &= \frac{\partial T(E, 0)}{\partial T_0} = \exp\left(\int_{EP}^{E} \frac{a - nE}{s - dE} dE\right) = \exp(z_1(E)),\end{aligned}$$

and $r_1(EP) = 1, r_1(EL) = \mu_2(\delta_1)$. The derivative of $z_1(E)$ about E leads to

$$z_1'(E) = \frac{a - nE}{s - dE},$$

let

$$\begin{aligned}z_2(E) &= \frac{\partial^2 h(E, T(E, 0))}{\partial T_0^2} = \frac{-\frac{2a}{K}(s - dE) - 2\alpha E(a - nE)}{(s - dE)^2}, \\ r_2(E) &= \frac{z_2(E)}{z_1'(E)} = \frac{-\frac{2a}{K}}{a - nE} - \frac{2\alpha E}{s - dE},\end{aligned}$$

the derivative of $r_2(E)$ about E yields

$$r_2'(E) = -\left(\frac{1}{K} \cdot \frac{2na}{(a - nE)^2} + \frac{2\alpha E}{(s - dE)^2}\right),$$

then

$$\frac{\partial^2 \mathcal{P}\left(0,\delta_1^*\right)}{\partial T_0^2} = \frac{\partial^2 T(EL,0)}{\partial T_0^2} - \frac{2\delta_2}{h_2}, \tag{15}$$

where

$$\begin{aligned} W \doteq \frac{\partial^2 T(EL,0)}{\partial T_0^2} &= \int_{EP_{\delta_1^*}}^{EL} \frac{\partial^2 h\left(E,T(E,0)\right)}{\partial T_0^2} \cdot \frac{\partial T(E,0)}{\partial T_0} dE \\ &= \int_{EP_{\delta_1^*}}^{EL} z_2(E) r_1(E) dE \\ &= \int_{EP_{\delta_1^*}}^{EL} z_2(E) \exp(z_1(E)) dE \\ &= \int_{EP_{\delta_1^*}}^{EL} \frac{z_2(E)}{z_1'(E)} z_1'(E) \exp(z_1(E)) dE \\ &= \int_{EP_{\delta_1^*}}^{EL} r_2(E) d(r_1(E)), \end{aligned}$$

on $[EL, \bar{E}]$, the function $r_1(E)$ is monotonically increasing. Thus, there exists $\delta_1 = \delta_1^*$ such that $r_1(EP_{\delta_1^*}) = \mu_2(\delta_1^*) = 1$ $(EP_{\delta_1^*} = (1 - \delta_1^* EL/(EL + h_1))\, EL + \tau)$. Therefore, $r_1(\bar{E}) < r_1(E) \leq 1$ for $E \in [EL, EP_{\delta_1^*}]$.

For any $E \in [EL, EP_{\delta_1^*}]$, we get $r_2'(E) < 0$ and $r_2(E)$ is a monotonically decreasing function. Then

$$\begin{aligned} \int_{EP_{\delta_1^*}}^{EL} r_2(E) d(r_1(E)) &= r_1(E) r_2(E)|_{EP_{\delta_1^*}}^{EL} - \int_{EP_{\delta_1^*}}^{EL} r_2'(E) r_1(E) dE \\ &= r_2(EL) - r_2(EP_{\delta_1^*}) - \int_{EP_{\delta_1^*}}^{EL} r_2'(E) r_1(E) dE \\ &= \int_{EP_{\delta_1^*}}^{EL} (1 - r_1(E)) r_2'(E) dE, \end{aligned} \tag{16}$$

thus,

$$0 < W < \left(1 - r_1(\bar{E})\right) \left(r_2(EL) - r_2(EP_{\delta_1^*})\right). \tag{17}$$

If $A < EL < \bar{E} < EP$, $\mu_2(0) < 1$ and $W \neq 2\delta_2/h_2$, then the forth condition of Lemma 2 holds, which means that the transcritical bifurcation occurs at $\delta_1 = \delta_1^*$. Furtheremore, if $W > 2\delta_2/h_2$, then the $\mathcal{P}(T_0, \delta_1)$ has an unstable positive fixed point when δ_1 changes through δ_1^* from right to left. However, if $W < 2\delta_2/h_2$, then the $\mathcal{P}(T_0, \delta_1)$ has a stable positive fixed point when δ_1 changes through δ_1^* from left to right. This completes the proof. ■

For the case $W = 2\delta_2/h_2$, we get $\partial^2 G/\partial x^2(0,0) = 0$ and show that the $\mathcal{P}(T_0, \delta_1)$ undergoes pithfork bifurcation. From equation 6,

$$\begin{aligned} \frac{\partial^3 \mathcal{P}\left(0,\delta_1^*\right)}{\partial T_0^3} &= \frac{\partial^3 T(EL,0)}{\partial T_0^3} + 3A_2''(T(EL,0)) \cdot \frac{\partial T(EL,0)}{\partial T_0} \cdot \frac{\partial^2 T(EL,0)}{\partial T_0^2} \\ &\quad + A_2'''(T(EL,0)) \cdot \left(\frac{\partial T(EL,0)}{\partial T_0}\right)^3 \\ &= \frac{\partial^3 T(EL,0)}{\partial T_0^3} + 3A_2''(T(EL,0)) \cdot W + A_2'''(T(EL,0)) \\ &= \frac{\partial^3 T(EL,0)}{\partial T_0^3} - \frac{12\delta_2^2}{h_2^2} + \frac{6\delta_2}{h_2^2}, \end{aligned} \tag{18}$$

where

$$\begin{aligned}\frac{\partial^3 T(EL,0)}{\partial {T_0}^3} &= \frac{\partial^2 T(EL,0)}{\partial {T_0}^2}\cdot\int_{EP_{\delta_1^*}}^{EL}\frac{\partial^2 h(E,T(E,0))}{\partial {T_0}^2}\cdot\frac{\partial T(E,0)}{\partial T_0}dE\\ &+\frac{\partial T(EL,0)}{\partial T_0}\cdot\frac{\partial}{\partial T_0}\left(\int_{EP_{\delta_1^*}}^{EL}\frac{\partial^2 h(E,T(E,0))}{\partial {T_0}^2}\cdot\frac{\partial T(E,0)}{\partial T_0}dE\right)\\ &= W^2+\frac{\partial}{\partial T_0}\left(\int_{EP_{\delta_1^*}}^{EL}\frac{\partial^2 h(E,T(E,0))}{\partial {T_0}^2}\cdot\frac{\partial T(E,0)}{\partial T}dE\right)\\ &= \frac{4{\delta_2}^2}{h_2^2}+\frac{\partial}{\partial T_0}\left(\int_{EP_{\delta_1^*}}^{EL}\frac{\partial^2 h(E,T(E,0))}{\partial {T_0}^2}\cdot\frac{\partial T(E,0)}{\partial T_0}dE\right),\end{aligned} \tag{19}$$

and

$$\begin{aligned}&\frac{\partial}{\partial T_0}\left(\int_{EP_{\delta_1^*}}^{EL}\frac{\partial^2 h\left(E,T\left(E,0\right)\right)}{\partial T_0^2}\cdot\frac{\partial T\left(E,0\right)}{\partial T_0}dE\right)\\ &\quad=\int_{EP_{\delta_1^*}}^{EL} r_1(E)z_2(E)\Big(3k_0(E)\cdot r_1(E)-z_1(E)\Big)dE.\end{aligned} \tag{20}$$

From Lemma 3, the following results hold true.

Theorem 3. *If $A<EL<\bar{E}<EP$, $\mu_2(0)<1$, $W=2\delta_2/h_2$ and $\partial^3\mathcal{P}\left(0,\delta_1^*\right)/\partial T_0^3\neq 0$, then $\mathcal{P}(T_0,\delta_1)$ undergoes a pitchfork bifurcation at δ_1^*. Furthermore, if $\partial^3\mathcal{P}\left(0,\delta_1^*\right)/\partial T_0^3>0$, then the $\mathcal{P}(T_0,\delta_1)$ undergoes a subcritical pithfork bifurcation, which generates an unstable positive fixed point; if $\partial^3\mathcal{P}\left(0,\delta_1^*\right)/\partial T_0^3<0$, then the $\mathcal{P}(T_0,\delta_1)$ also undergoes a supercritical pithfork bifurcation, which generates a stable positive fixed point.*

If $h_2=0$, then

$$\mu_2\left(\delta_1\right)=\left(1-\delta_2\right)\exp\left(M_2+M_3\right).$$

The monotonicity of $M_{12}(\delta_1)$ suggests that μ_2 is increasing on $[0,\bar{\delta}_1)$ and decresing on $(\bar{\delta}_1,1]$. Because of $\mu_2(0)<1$ and $\mu_2(\bar{\delta}_1)>1$, there is a $\delta_1^*\in[0,\bar{\delta}_1)$ such that $\mu_2(\delta_1^*)=1$. If $\mu_2(1)<1$, then a $\delta_1^{**}\in(\bar{\delta}_1,1]$ exists and $\mu_2(\delta_1^{**})=1$ holds. Similarly, we get

$$\begin{aligned}\frac{\partial^2\mathcal{P}\left(0,\delta_1^*\right)}{\partial T\partial\delta_1}&=\frac{d\mu_2(\delta_1^*)}{d\delta_1}>0,\quad \frac{\partial^2\mathcal{P}\left(0,\delta_1^*\right)}{\partial T_0^2}=W>0,\\ \frac{\partial^2\mathcal{P}\left(0,\delta_1^{**}\right)}{\partial T\partial\delta_1}&=\frac{d\mu_2(\delta_1^{**})}{d\delta_1}<0,\quad \frac{\partial^2\mathcal{P}\left(0,\delta_1^{**}\right)}{\partial T_0^2}=W>0.\end{aligned}$$

Thus, the following results hold.

Corollary 4.1. *If $h_2=0$, $A<EL<\bar{E}<EP$, $\mu_2(0)<1$ and $\mu_2(1)<1$, then $\mathcal{P}(T_0,\delta_1)$ undergoes transcritical bifurcation at both $\delta_1=\delta_1^*$ and $\delta_1=\delta_1^{**}$. That is, the $\mathcal{P}(T_0,\delta_1)$ exists with a stable positive fixed point when δ_1 changes through δ_1^* from right to left or through δ_1^{**} from left to right, which means that there is a stable positive periodic solution for system(2) if $\delta_1\in(\delta_1^*-\epsilon,\delta_1^*)$ or $\delta_1\in(\delta_1^{**},\delta_1^{**}+\epsilon)$ with $\epsilon>0$ small enough.*

The $\mathcal{P}(T_0,\delta_1)$ could also undergoes transcritical bifurcation for δ_2 when $h_2=0$. Similarly,

$$\mu_2(\delta_2)=(1-\delta_2)\exp(M_2+M_3).$$

Solving $\mu_2(\delta_2) = 1$, there is a $\delta_2^* = 1 - \exp(-M_2 - M_3)$ satisfying $\mu_2(\delta_2^*) = 1$. The inequality $0 < \delta_2 \leq 1$ holds provided $M_2 + M_3 > 0$. The inequality (13) leads to

$$\begin{aligned} M_2 + M_3 &= \frac{n}{d}(EL - EP) + \frac{n}{d}\ln\left(\frac{EP - A}{EL - A}\right)\left(\bar{E} - A\right) \\ &> \frac{n}{d}(EP - EL)\left[\frac{2(\bar{E} - A)}{EP + EL - 2A} - 1\right] \\ &> \frac{n}{d}(EP - EL)\left[\frac{2(\bar{E} - EP)}{EP + EL - 2A}\right], \end{aligned}$$

if $EP < \bar{E}$, then $M_2 + M_3 > 0$. By using the same methods in Theorem 2, one has

$$\frac{\partial \mathcal{P}\left(0, \delta_2\right)}{\partial T_0} = \mu_2(\delta_2), \quad \frac{\partial^2 \mathcal{P}\left(0, \delta_2^*\right)}{\partial T \partial \delta_2} = \frac{d\mu_2(\delta_2^*)}{d\delta_2} = -\exp(M_2 + M_3) < 0,$$

$$\frac{\partial^2 \mathcal{P}\left(0, \delta_2^*\right)}{\partial T_0^2} = W > 0.$$

By verifying four conditions of Lemma 2, we have the following results.

Corollary 4.2. *If $h_2 = 0$ and $A < EL < EP < \bar{E}$, then $\mathcal{P}(T_0, \delta_2)$ undergoes transcritical bifurcation at $\delta_2 = \delta_2^*$, i.e., the $\mathcal{P}(T_0, \delta_2)$ has a stable positive fixed point when δ_2 changes through δ_2^* from left to right, which is just a stable positive periodic solution of system(2) if $\delta_1 \in (\delta_2^*, \delta_2^* + \epsilon)$ with $\epsilon > 0$ small enough.*

4.2. *Transcritical Bifurcations for EL*

Similarly, when $h_2 \neq 0$, parameter EL is chosen as a bifurcation parameter. μ_2 is assumed to be a function of EL,

$$\mu_2(EL) = \exp\left(M_{12}(EL)\right),$$

where

$$M_{12}(EL) = \int_{EP}^{EL} \frac{a - nE}{s - dE} dE = \frac{n}{d}\ln\left(\frac{A - EL}{A - EP}\right)\left(A - \bar{E}\right) + \frac{n}{d}(EL - EP),$$

with $EP = EL + A_1(EL) + \tau$. Direct calculations lead to

$$\frac{d\mu_2(EL)}{dEL} = \exp\left(M_{12}(EL)\right) \cdot \frac{dM_{12}(EL)}{dEL},$$

$$\frac{dM_2(EL)}{dEL} = \frac{\partial}{\partial EL}\left(\int_{EP}^{EL} \frac{a - nE}{s - dE} dE\right),$$

and denote $k_3(x) \doteq (a - nx)/(s - dx)$, Thus,

$$\frac{dM_{12}(EL)}{dEL} = k_3(EL) - \left(1 + A_1'(EL)\right) k_3(EP).$$

If $A < EL < \bar{E} < EP$, then $k_3(EP) > 0, k_3(EL) < 0$. Thereby, $dM_{12}(EL)/dEL < 0$ and so $M_{12}(EL)$ is a monotonically decreasing function of EL. Furthermore,

$$\lim_{EL \to A} M_{12}(EL) = \lim_{EL \to A} \frac{n}{d}\ln\left(\frac{A - EL}{A - EP}\right)\left(A - \bar{E}\right) + \frac{n}{d}(EL - EP) = +\infty,$$

$$\lim_{EL \to \bar{E}} M_{12}(EL) = \lim_{EL \to \bar{E}} \int_{EP}^{EL} \frac{a - nE}{s - dE} dE < 0.$$

Therefore, there is a unique $EL^* \in (A, \overline{E})$ such that $M_{12}(EL^*) = 0$, i.e., $\mu_2(EL^*) = 1$. Moreover,

$$\frac{\partial \mathcal{P}(0, EL)}{\partial T_0} = \mu_2(EL),$$

$$\frac{\partial^2 \mathcal{P}(0, EL^*)}{\partial T_0 \partial EL} = \frac{\partial T\left(EL^*, T_0\right)}{\partial T_0} \cdot \frac{\partial}{\partial EL}\left(\int_{EP}^{EL} \frac{\partial h\left(E, T\left(E, 0\right)\right)}{\partial T_0} dE\right) = \frac{d\mu_2(EL^*)}{dEL} < 0.$$

Similarly, from Theorem 2 we can determine the signs of $\partial^2 \mathcal{P}\left(0, EL^*\right) / \partial T_0^2$ and $\partial^3 \mathcal{P}\left(0, EL^*\right) / \partial T_0^3$.

Theorem 4. *If $A < EL < \bar{E} < EP$ and $W < 2\delta_2/h_2$, then $\mathcal{P}(T_0, EL)$ undergoes transcritical bifurcation at $EL = EL^*$. Therefore, the $\mathcal{P}(T_0, EL)$ has an unstable positive fixed point when EL changes through EL^* from left to right, which means that the system(2) exists with an unstable positive periodic solution if $EL \in (EL^*, EL^* + \epsilon)$ with $\epsilon > 0$ small enough. However, if $W > 2\delta_2/h_2$, then $\mathcal{P}(T_0, EL)$ has a stable positive fixed point when EL changes through EL^* from right to left, which indicates that there is a stable positive periodic solution of the system(2) if $EL \in (EL^* - \epsilon, EL^*)$ with $\epsilon > 0$ small enough.*

Theorem 5. *If $A < EL < \bar{E} < EP$, $W = 2\delta_2/h_2$ and $\partial^3 \mathcal{P}\left(0, EL^*\right) / \partial T_0^3 \neq 0$, then $\mathcal{P}(T_0, EL)$ undergoes a pitchfork bifurcation at EL^*. Further, if $\partial^3 \mathcal{P}\left(0, EL^*\right) / \partial T_0^3 > 0$, then the $\mathcal{P}(T_0, EL)$ has an unstable positive fixed point. If $\partial^3 \mathcal{P}\left(0, EL^*\right) / \partial T_0^3 < 0$, then $\mathcal{P}(T_0, EL)$ has a stable positive fixed point.*

When $h_2 = 0$, then $\mu_2(EL) = (1 - \delta_2) \exp\left(M_{12}(EL)\right)$, the derivative of $\mu_2(EL)$ about EL yields

$$\frac{d\mu_2(EL)}{dEL} = (1 - \delta_2) \exp\left(M_{12}(EL)\right) \cdot \frac{dM_{12}(EL)}{dEL} < 0,$$

thereby, there is a unique EL^* that satisfies $M_{12}(EL^*) = \ln\left(1/(1 - \delta_2)\right)$, i.e., $\mu_2(EL^*) = 1$. In the light of $\partial^2 \mathcal{P}\left(0, EL^*\right) / \partial T_0^2 = W > 0$, from Lemma 2 we have the following results.

Corollary 4.3. *If $h_2 = 0$ and $A < EL < \bar{E} < EP$, then $\mathcal{P}(T_0, EL)$ undergoes transcritical bifurcation at $EL = EL^*$, i.e., there is a stable positive fixed point for $\mathcal{P}(T_0, EL)$ when EL changes through EL^* from right to left, which reveals that there is a stable positive periodic solution of system(2) if $EL \in (EL^* - \epsilon, EL^*)$ with $\epsilon > 0$ small enough.*

4.3. *Transcritical Bifurcations for τ*

When $h_2 \neq 0$, τ is chosen as a bifurcation parameter. To this end, let $M_2 + M_3$ be a function of τ,

$$\mu_2(\tau) = \exp(M_{12}(\tau)),$$

$$M_{12}(\tau) = \int_{EP}^{EL} \frac{a - nE}{s - dE} dE = \frac{n}{d} \ln\left(\frac{A - EL}{A - EP}\right)\left(A - \bar{E}\right) + \frac{n}{d}(EL - EP),$$

where $EP = EL - \delta_1 EL^2/(EL + h_1) + \tau$. By calculations,

$$\frac{d\mu_2(\tau)}{d\tau} = \exp\left(M_{12}(\tau)\right) \cdot \frac{dM_{12}(\tau)}{d\tau}, \quad \frac{\partial EP(\tau)}{\partial \tau} = 1,$$

$$\frac{dM_{12}(\tau)}{d\tau} = \frac{\partial}{\partial \tau}\left(\int_{EP}^{E} \frac{a - nE}{s - dE} dE\right) = \left(\frac{nEP - a}{s - dEP}\right),$$

solving $d\mu_2(\tau)/d\tau = 0$ with respect to τ and Denoting $\overline{\tau}$ the unique root of as $EP = \bar{E}$, then

$$\overline{\tau} = \bar{E} - EL + \frac{\delta_1 EL^2}{EL + h_1}.$$

If $\tau \in (0, \overline{\tau})$, then $EP < \bar{E}$ and $d\mu_2(\tau)/d\tau > 0$, so $\mu_2(\tau) > 1$ for all $\tau \in (0, \overline{\tau})$. Thereby, the TFPS is unstable when $\tau \in (0, \overline{\tau})$. If $\tau > \overline{\tau}$, then $EP > \bar{E}$ and $d\mu_2(\tau)/d\tau < 0$. It indicates that there is a unique τ^* that satisfies $M_{12}(\tau^*) = 0$, i.e., $\mu_2(\tau^*) = 1$. By calculations,

$$\frac{\partial \mathcal{P}(0, \tau)}{\partial T_0} = \mu_2(\tau), \quad \frac{\partial^2 \mathcal{P}\left(0, \tau^*\right)}{\partial T_0^2} = W - \frac{2\delta_2}{h_2},$$

$$\frac{\partial^2 \mathcal{P}(0,\tau)}{\partial T_0 \partial \tau} = \frac{\partial T(\tau, T_0)}{\partial T_0} \cdot \frac{\partial}{\partial \tau}\left(\int_{EP}^{EL} \frac{\partial h(E, T(E,0))}{\partial T_0} dE\right) = \frac{d\mu_2(\tau)}{d\tau} < 0.$$

Theorem 6. *If $A < EL < \bar{E} < EP$ and $W < 2\delta_2/h_2$, then $\mathcal{P}(T_0, \tau)$ undergoes transcritical bifurcation at $\tau = \tau^*$. Thus, the $\mathcal{P}(T_0, \tau)$ has an unstable positive fixed point when τ changes through τ^* from left to right, which means there is an unstable positive periodic solution of the system(2) if $EL \in (\tau^*, \tau^* + \epsilon)$ with $\epsilon > 0$ small enough. However if $W > 2\delta_2/h_2$, the $\mathcal{P}(T_0, \tau)$ has a stable positive fixed point when τ changes through τ^* from right to left, which implies there is a stable positive periodic solution of the system(2) if $\tau \in (\tau^* - \epsilon, \tau^*)$ with $\epsilon > 0$ small enough.*

If $h_2 = 0$, then $\mu_2(\tau) = (1-\delta_2)\exp(M_{12}(\tau))$. The monotonically of M_{12} implies that $\mu_2(\tau)$ is decreasing when $\tau > \overline{\tau}$. i.e., there is a unique τ^* such that $M_{12}(\tau^*) = 0$, i.e., $\mu_2(\tau^*) = 1$, which reveals that the bifurcation could occur at $\tau = \tau^*$. Moreover, if $(1 - \delta_2)$ small enough, it is observed that there is a $\hat{\tau}$ so that $\mu_2(\hat{\tau}) < 0$. Because on $(0, \overline{\tau})$, $\mu_2(\tau)$ is monotonic, there exists with a unique τ^{**} such that $\mu_2(\tau^{**}) = 1$. Similarly,

$$\frac{\partial^2 \mathcal{P}(0,\tau^*)}{\partial T_0 \partial \tau} = \frac{d\mu_2(\tau^*)}{d\tau} < 0, \quad \frac{\partial^2 \mathcal{P}(0,\tau^*)}{\partial T_0^2} = W > 0,$$
$$\frac{\partial^2 \mathcal{P}(0,\tau^{**})}{\partial T_0 \partial \tau} = \frac{d\mu_2(\tau^{**})}{d\tau} > 0, \quad \frac{\partial^2 \mathcal{P}(0,\tau^{**})}{\partial T_0^2} = W > 0,$$

the following results hold.

Corollary 4.4. *If $h_2 = 0$, $A < EL < \bar{E} < EP$, then $\mathcal{P}(T_0, \tau)$ undergoes transcritical bifurcation at $\tau = \tau^*$, i.e., the $\mathcal{P}(T_0, \tau)$ has an unstable positive fixed point when τ changes through τ^* from left to right, which means there exists with an unstable positive periodic solution of the system(2) if $\tau \in (\tau*, \tau^* + \epsilon)$ with $\epsilon > 0$ small enough. However, if $A < EL < EP < \bar{E}$ and $(1 - \delta_2)$ samll enough, then $\mathcal{P}(T_0, \tau)$ undergoes transcritical bifurcation at $\tau = \tau^{**}$. i.e., the $\mathcal{P}(T_0, \tau)$ has an unstable positive fixed point when τ changes through τ^{**} from right to left, which indicates that there isan unstable positive periodic solution of the system(2) if $\tau \in (\tau^{**} - \epsilon, \tau^{**})$ with $\epsilon > 0$ small enough.*

5. Numerical Experiment

In section 4, bifurcation analysis has been carried out for model (2), this part mainly deals with numerical studies and adresses biological implications of the results.

In Theorem 2, the bifurcations of the tumour-free periodic solution have been studied when parameter δ_1 changes. For example, fix parameter values as $\delta_2 = 0.3$, $h_2 = 3 \neq 0$, $\tau = 9$ and $EL = 12$, we consider μ_2 as a function of δ_1 and then change the value of δ_1 in the interval $(0, 1)$ (Fig. 2(a)). It is observed that there is a extreme point $\overline{\delta}_1$ and the function $\mu_2(\delta_1)$ is monotonically increasing in the interval $[0, \overline{\delta}_1]$ and decreasing on the interval $[\overline{\delta}_1, 1]$ (Fig. 2(a)). Further, it is found that function $\mu_2(\delta_1)$ has a value greater than one on the interval $[\delta_1^*, 1]$. Therefore, $\mu_2(\delta_1) = 1$ has a unique zero point δ_1^*, which means that the TFPS of model (2) undergoes a transcritical bifurcation at $\delta_1 = \delta_1^* = 0.486$. In particylarly, if $h_2 = 0$, then $\mu_2(\delta_1) = (1 - \delta_2)\exp(M_2 + M_3)$. The monotonicity of the function $\mu_2(\delta_1)$ is the same as shown in Fig. 2(a) (Fig. 2(b)). However, as δ_1 exceeds the extreme point $\overline{\delta}_1$, then $\mu_2(\delta_1)$ will keep decreasing and eventually be less than one (Fig. 2(b)). Thus, the TFPS of model(2) undergoes transcritical bifurcations at $\delta_1^* = 0.696$ and $\delta_2^{**} = 0.97$, which is consistent with the results of Corollary 4.1. Biologically, it is worth pointing out that δ_1 denotes the maximum killing rate of the effector cells, which can reflect the efficacy of the therapy. For the case $h_2 \neq 0$ (Fig. 2(a)), the TFPS of system (2) is asymptotically stable if δ_1 is less than a certain constant. It means that in the case of saturation effect, the killing rate of effector cells should be controlled at a low level so that the eventual elimination of the tumours can be reached. However, when $h_2 = 0$, there is no saturation for the killing rate of tumour cells, even if δ_1 reaches a high level, it is still guaranteed the stablility of the TFPS (Fig. 2(b)). This suggests that two different strategies can be adopted, maintaining a low level of δ_1 or initially treating at a high level of δ_1. Therefore, it is noted that μ_2 is very sensitive to the killing rate δ_1 and the saturation constant h_2. In reality, the saturation effect should not be ignored.

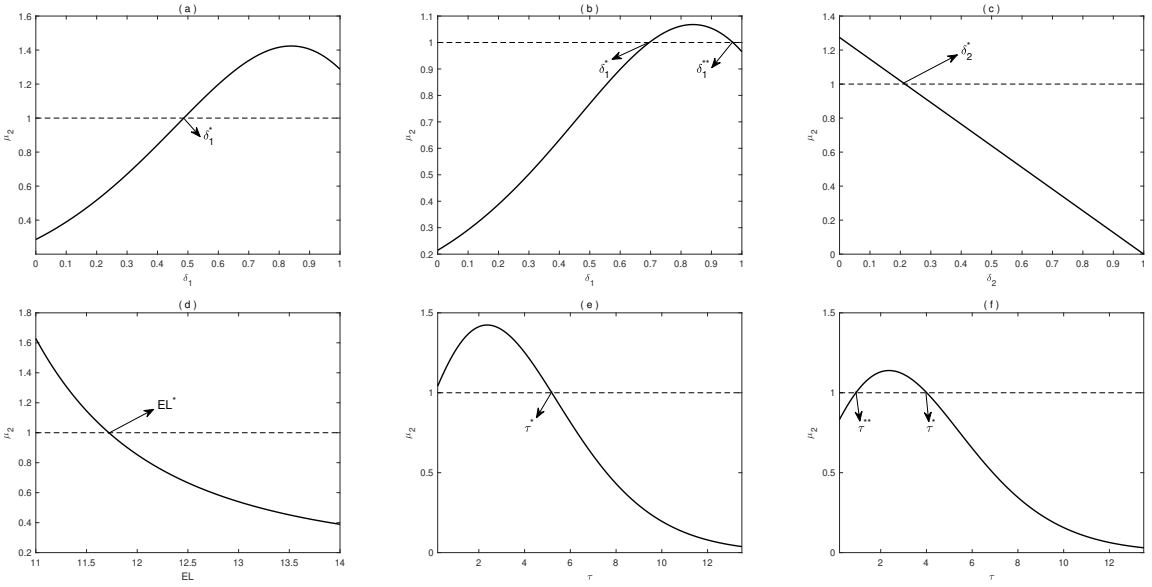

Fig. 2. The function μ_2 with respect to δ_1, δ_2, EL and τ. (a) $\delta_2 = 0.3, h_2 = 3, \tau = 9, EL = 12$; (b) $\delta_2 = 0.25, h_2 = 0, \tau = 9, EL = 12$; (c) $\delta_1 = 0.4, h_2 = 0, \tau = 7, EL = 12$; (d) $\delta_1 = 0.4, \delta_2 = 0.3, h_2 = 3, \tau = 9$; (e) $\delta_1 = 0.01, \delta_2 = 0.3, h_2 = 3, EL = 12$; (f) $\delta_1 = 0.01, \delta_2 = 0.2, h_2 = 3, EL = 12$. The other parameter values are as follows: $s = 5, \alpha = 0.2, d = 0.8, a = 10, n = 0.7, K = 100, h_1 = 6$

From Corollary 4.2, the $\mathcal{P}(T_0, \delta_1)$ could also undergoes transcritical bifurcation for δ_2 when $h_2 = 0$. Considering μ_2 as a function of δ_2, it is shown that $\mu_2(\delta_2)$ is a linear decreasing function about δ_2 on the interval $[0, 1]$ (Fig. 2(c)). It is revealed that the TFPS of model (2) undergoes a transcritical bifurcation at $\delta_2 = \delta_2^*$. Note that δ_2 represents the maximum killing rate of tumour cells, a large level of δ_2 is needed to maintain the stability of the TFPS (Fig. 2(c)). From Fig. 2(d), we know that the function $\mu_2(EL)$ is also monotonically decreasing wih respect to the effector cell threshold EL. Therefore, there is a unique EL^* such that $\mu_2(EL^*) = 1$. That is, the TFPS of model (2) undergoes a transcritical bifurcation at EL^*. It is advised that the larger the effector threshold EL, the more benefit to treating cancers.

As shown in Fig. 2(e) and Fig. 2(f), there exists a $\overline{\tau}$ such that the function $\mu_2(\tau)$ is monotonically increasing on the interval $[0, \overline{\tau}]$ and decreasing on the interval $[\overline{\tau}, +\infty]$. If $h_2 \neq 0$, according to Theorem 6, the TFPS of model (2) only undergoes a transcritical bifurcation at τ^* (Fig. 2(e)). Further, if $h_2 = 0$, then there exists another τ^{**} on $[0, \overline{\tau}]$ such that $\mu_2(\tau^{**}) = 1$ (Fig. 2(f)). In this case, the TFPS of model (2) undergoes transcritical bifurcations at τ^* and τ^{**}. It is pointed out that the larger the injection numbers of effector cells τ, the more useful for curing cancers.

Moreover, it follows from the Fig. 2(a) that the transcritical bifurcation occurs at $\delta_1^* = 0.486$. Correspondingly, when we choose $\delta_1 = 0.4$ and fix the other parameter values as the same shown in Fig. 2(a), the TFPS of model(2) is stable with $|\mu_2| < 1$ (Fig 3(a)-(c)). If we gradually increase the value of δ_1 until it exceeds δ_1^*, and fix $\delta_1 = 0.52$, then the TFPS becomes unstable and there exists with a stable periodic solution (Fig 3(d)-(f)).

In summary, it is found that μ_2 is very sensitive to the bifurcation parameters: the killing rates δ_1 and δ_2, the saturation constant h_2, the effector cell threshold EL and the injection numbers of effector cells τ. In order to control tumours, the feasible ways including: (1) for $h_2 \neq 0$, decreasing the killing rate of effector cells δ_1 and increasing the injection numbers of effector cells τ (Fig. 2(a) and Fig. 2(e)); (2) for $h_2 = 0$, maintaining a low level of δ_1 or a high level of δ_1 (Fig. 2(b)), or keeping a low level of τ or a high level of τ (Fig. 2(f)); (3) increasing the killing rate of tumour cells δ_2 or the effector cell threshold EL (Fig. 2(c) and Fig. 2(d)).

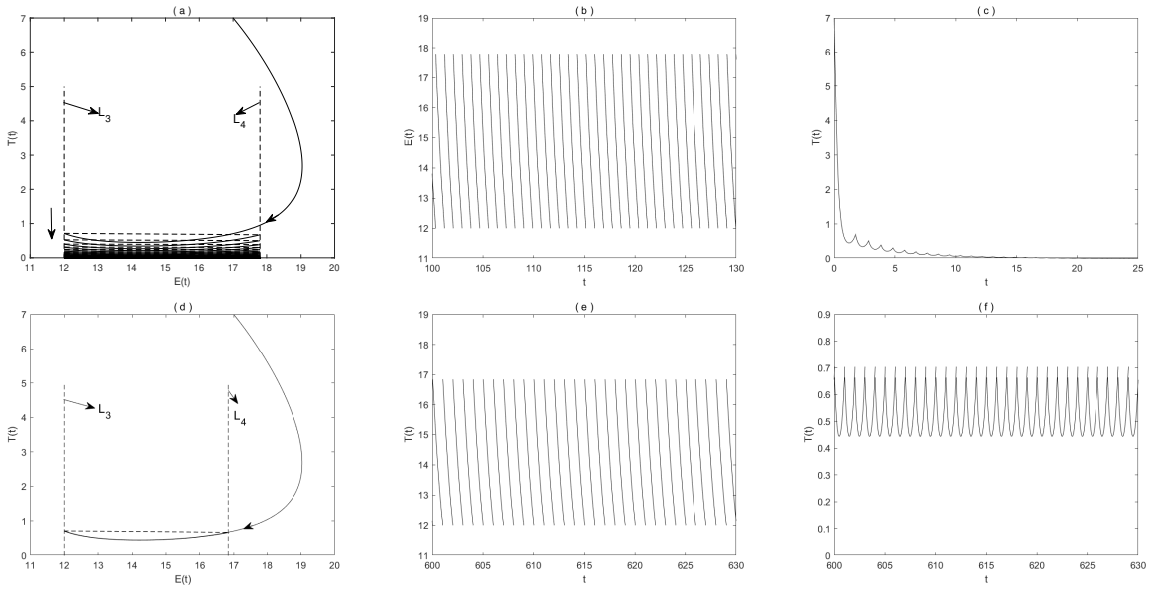

Fig. 3. the tumour-free periodic solution and it's stability. $\delta_1 = 0.4$ in(a),(b) and (c); $\delta_1 = 0.589$ in (d), (e) and (f). The other parameter values are as follows: $s = 5, \alpha = 0.2, d = 0.8, a = 10, n = 0.7, K = 100, \delta_2 = 0.3, h_1 = 6, h_2 = 3, \tau = 9, EL = 12$.

6. Conclusions

Cancer is becoming one of the most serious diseases in humankind. In recent decades, comprehensive therapy has played an important role in cancer treatment. The mathematical model of tumour immunity with pulsed control has attracted much attention [Yamaguchi *et al.*, 2006; Hegmans *et al.*, 2005; Samanta *et al.*, 2017]. However, fixed-time pulsed therapy is usually accompanied by drug resistance. While the state-dependent pulsed therapy, which is applied depending on the number or size of tumours, will not only reduce the waste of drugs, but also prevent tumour cells from acquiring drug resistance [Tang *et al.*, 2016; Wei & Lin, 2013; Yang *et al.*, 2015, 2019, 2020]. In this paper, we proposed a novel pulsed tumour-immune model with nonlinear killing rates as state-dependent feedback control. On the one hand, we will focus on the investigations of bifurcations, on the other hand, biological implications are addressed.

For model (1), some basic properties are provided: (a) if $A > \bar{E}$, then there is a stable boundary equilibrium $(A, 0)$; (b) if $A < \bar{E}$, then there exists with a stable interior equilibrium $P^*(E^*, T^*)$ and an unstable boundary equilibrium $(A, 0)$. In this paper, we only focus on the interior equilibrium P^*. Under this scenario, we first define a discrete one-parameter Poincaré map, then the existence and stability of the tumour-free periodic solution of model (2) are addressed. It is founded that if $\bar{E} < EL < EP$, then the TFPS $(E^T(t), 0)$ of model (2) is orbitally asymptotically stable. If $EL < \bar{E}$, then by employing the bifurcation theories of one-parameter discrete maps, the transcritical bifurcations or pitchfork bifurcations with respect to the maximum kill rate of effector cells δ_1, the threshold size EL and the number of injections of effector cells τ have been investigated. It is concluded that system (2) undergoes a transcritical bifurcation or pitchfork bifurcation when one of the following conditions hold:

- If $A < EL < \bar{E} < EP$, $\mu_2(0) < 1$ and $W \neq 2\delta_2/h_2$ holds, for $h_2 \neq 0$ then $\mathcal{P}(T_0, \delta_1)$ undergoes a transcritical bifurcation at $\delta_1 = \delta_1^*$; for $h_2 = 0$ and $\mu_2(1) < 1$, then $\mathcal{P}(T_0, \delta_1)$ undergoes transcritical bifurcation at both $\delta_1 = \delta_1^*$ and $\delta_1 = \delta_1^{**}$.
- $\mathcal{P}(T_0, \delta_1)$ undergoes a transcritical bifurcation at $\delta_1 = \delta_1^*$, if $A < EL < \bar{E} < EP$, $\mu_2(0) < 1$,$h_2 \neq 0$ and $W = 2\delta_2/h_2$ holds. Further, if $\partial^3 \mathcal{P}(0, \delta_1^*)/\partial T_0^3 > 0$, then the $\mathcal{P}(T_0, \delta_1)$ undergoes a subcritical pithfork bifurcationif; if $\partial^3 \mathcal{P}(0, \delta_1^*)/\partial T_0^3 < 0$, then the $\mathcal{P}(T_0, \delta_1)$ also undergoes a supercritical pithfork bifurcation.
- For parameter δ_2, if $h_2 = 0$ and $A < EL < EP < \bar{E}$ holds, then $\mathcal{P}(T_0, \delta_2)$ undergoes transcritical bifurcation at $\delta_2 = \delta_2^*$.

- If $A < EL < \bar{E} < EP$ holds, for $h_2 \neq 0$ and $W \neq 2\delta_2/h_2$, then $\mathcal{P}(T_0, EL)$ undergoes transcritical bifurcation at $EL = EL^*$; for $h_2 = 0$, then $\mathcal{P}(T_0, EL)$ also undergoes transcritical bifurcation at $EL = EL^*$. Moreover, if $W = 2\delta_2/h_2$ and $\partial^3\mathcal{P}(0, EL^*)/\partial T_0^3 \neq 0$, then $\mathcal{P}(T_0, EL)$ undergoes a pitchfork bifurcation at EL^*.
- If $h_2 \neq 0$, $A < EL < \bar{E} < EP$, and $W \neq 2\delta_2/h_2$, then $\mathcal{P}(T_0, \tau)$ undergoes transcritical bifurcation at $\tau = \tau^*$. If $h_2 = 0$ holds, for $A < EL < \bar{E} < EP$, then $\mathcal{P}(T_0, \tau)$ undergoes transcritical bifurcation at $\tau = \tau^*$; for $A < EL < EP < \bar{E}$ and $(1 - \delta_2)$ samll enough, then $\mathcal{P}(T_0, \tau)$ undergoes transcritical bifurcation at $\tau = \tau^{**}$.

Biologically, the bifurcation parameters of the killing rates δ_1 and δ_2, the saturation constant h_2, the effector cell threshold EL and the injection numbers of effector cells τ play signicant roles for condition μ_2. The results show that the feasible ways for treating tumours include: (1) for $h_2 \neq 0$, decreasing the killing rate of effector cells δ_1 and increasing the injection numbers of effector cells τ (Fig. 2(a) and Fig. 2(e)); (2) for $h_2 = 0$, maintaining a low level of δ_1 or a high level of δ_1 (Fig. 2(b)), or keeping a low level of τ or a high level of τ (Fig. 2(f)); (3) increasing the killing rate of tumour cells δ_2 or the effector cell threshold EL (Fig. 2(c) and Fig. 2(d)).

Compared to the previous studies [Tang *et al.*, 2016; Yang *et al.*, 2020], the highlights are listed as follows: (1) we propose a novel state-dependent tumour-immune model with nonlinear feedback control, which can better reflect the saturation of the tumour and immune cell mortality due to chemotherapy; (2) we mainly focus on discussing the transcritical and subcritical bifurcations.

The results enrich and improve the studies of tumour immune models. However, for simplicity, we consider a simplified model for the convenience of theoretical investigations. In future, we are looking forward to proposing more general models.

Acknowledgments

This work was supported by the National Natural Science Foundation of China under Grants (11961024(Y. Tan), 11801047(J. Yang)), and by Team Building Project for Graduate Tutors in Chongqing (JDDSTD201802 (J. Yang)), and by Joint Training Base Construction Project for Graduate Students in Chongqing (JDLHPYJD2021016), and by the Program of Chongqing Municipal Education Commission (KJQN201900707(Z. Liu)), and by the Natural Science Foundation of Chongqing under Grant (cstc2019jcyj-msxmX0755 (Z. Liu)), and by Group Building Scientific Innovation Project for universities in Chongqing (CXQT21021), and by the Graduate Research and Innovation Project of Chongqing (CYS21370(L.Chen)).

References

Anaworanich, J., Nuesch, R., Braz, M. *et al.* [2006] "Cd4 guided scheduled treatment interruption compared to continuous therapy: results of the staccato trial," *Lancet* **368**, 459–465.

Bainov, D. & Simeonov, P. [1993] "Impulsive differential equations: periodic solutions and applications," Vol. 66 (CRC Press).

Bonotto, E. & Federson, M. [2008] "Limit sets and the poincaré–bendixson theorem in impulsive semidynamical systems," *Journal of Differential Equations* **244**, 2334–2349.

Broomfield, S., Currie, A., Brown, M., Van Bruggen, I., Robinson, B. W. & Lake, R. A. [2005] "Partial, but not complete, tumor-debulking surgery promotes protective antitumor memory when combined with chemotherapy and adjuvant immunotherapy," *Cancer research* **65**, 7580–7584.

Cheng, T., Tang, S. & Cheke, R. A. [2019] "Threshold dynamics and bifurcation of a state-dependent feedback nonlinear control susceptible–infected–recovered model," *Journal of Computational and Nonlinear Dynamics* **14**, 071001.

Ciesielski, K. [2004] "On time reparametrizations and isomorphisms of impulsive dynamical systems," *Annales Polonici Mathematici* **84**, 1–25.

Couzin-Frankel, J. [2013] "Cancer immunotherapy," (American Association for the Advancement of Science Press) .

De Angelis, E., Marasco, A. & Romano, A. [2003] "Bifurcation analysis for a mean field modelling of tumor and immune system competition," *Mathematical and computer modelling* **37**, 1131–1142.

Foryś, U. & Bodnar, M. [2003] "Time delays in regulatory apoptosis for solid avascular tumour," *Mathematical and computer modelling* **37**, 1211–1220.

Gałach, M. [2003] "Dynamics of the tumor—immune system competition—the effect of time delay," *International Journal of Applied Mathematics and Computer Science* **13**, 395–406.

Gubin, M. M., Zhang, X., Schuster, H., Caron, E., Ward, J. P., Noguchi, T., Ivanova, Y., Hundal, J., Arthur, C. D., Krebber, W. J. *et al.* [2014] "Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens," *Nature* **515**, 577–581.

Hegmans, J. P., Hemmes, A., Aerts, J. G., Hoogsteden, H. C. & Lambrecht, B. N. [2005] "Immunotherapy of murine malignant mesothelioma using tumor lysate–pulsed dendritic cells," *American journal of respiratory and critical care medicine* **171**, 1168–1177.

Kaul, S. [1990] "On impulsive semidynamical systems," *Journal of Mathematical Analysis and Applications* **150**, 120–128.

K.Hale, J. [1969] *Ordinary Differential Equations* (New York Press).

Kuznetsov, V. A., Makalkin, I. A., Taylor, M. A. & Perelson, A. S. [1994] "Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis," *Bulletin of mathematical biology* **56**, 295–321.

López, Á. G., Seoane, J. M. & Sanjuán, M. A. [2017] "Bifurcation analysis and nonlinear decay of a tumor in the presence of an immune response," *International Journal of Bifurcation and Chaos* **27**, 1750223.

Norman, P. S. [2004] "Immunotherapy: 1999-2004," *Journal of allergy and clinical immunology* **113**, 1013–1023.

Powles, T., Eder, J. P., Fine, G. D., Braiteh, F. S., Loriot, Y., Cruz, C., Bellmunt, J., Burris, H. A., Petrylak, D. P., Teng, S.-l. *et al.* [2014] "Mpdl3280a (anti-pd-l1) treatment leads to clinical activity in metastatic bladder cancer," *Nature* **515**, 558–562.

Ribas, A., Butterfield, L. H., Glaspy, J. A. & Economou, J. S. [2003] "Current developments in cancer vaccines and cellular immunotherapy," *Journal of clinical oncology* **21**, 2415–2432.

Rozova, V. & Bratus, A. [2016] "Therapy strategy in tumour cells and immune system interaction mathematical model," *Applicable Analysis* **95**, 1548–1559.

Samanta, G., Aíza, R. G. & Sharma, S. [2017] "Analysis of a mathematical model of periodically pulsed chemotherapy treatment," *International Journal of Dynamics and Control* **5**, 842–857.

Shiao, S. L., Ganesan, A. P., Rugo, H. S. & Coussens, L. M. [2011] "Immune microenvironments in solid tumors: new targets for therapy," *Genes & development* **25**, 2559–2572.

Simeonov, P. S. & Bainov, D. D. [1988] "Orbital stability of periodic solutions of autonomous systems with impulse effect," *International Journal of Systems Science* .

Tang, B., Xiao, Y., Sivaloganathan, S. & Wu, J. [2017] "A piecewise model of virus-immune system with effector cell-guided therapy," *Applied Mathematical Modelling* **47**, 227–248.

Tang, B., Xiao, Y., Tang, S. & Cheke, R. A. [2016] "A feedback control model of comprehensive therapy for treating immunogenic tumours," *International Journal of Bifurcation and Chaos* **26**, 1650039.

Tang, S. & Cheke, R. A. [2005] "State-dependent impulsive models of integrated pest management (ipm) strategies and their dynamic consequences," *Journal of Mathematical Biology* **50**, 257–292.

Tang, S. & Cheke, R. A. [2008] "Models for integrated pest control and their biological implications," *Mathematical Biosciences* **215**, 115–125.

Tang, S., Xiao, Y., Wang, N. & Wu, H. [2012] "Piecewise hiv virus dynamic model with cd4+ t cell count-guided therapy: I," *Journal of theoretical biology* **308**, 123–134.

Touboul, J. & Brette, R. [2009] "Spiking dynamics of bidimensional integrate-and-fire neurons," *SIAM Journal on Applied Dynamical Systems* **8**, 1462–1506.

Wei, H.-C. & Lin, J.-T. [2013] "Periodically pulsed immunotherapy in a mathematical model of tumor-immune interaction," *International Journal of Bifurcation and Chaos* **23**, 1350068.

Wild, C., Weiderpass, E. & Stewart, B. W. [2020] *World cancer report: cancer research for cancer prevention*

(IARC Press).

Yamaguchi, S., Ogiue-Ikeda, M., Sekino, M. & Ueno, S. [2006] "Effects of pulsed magnetic stimulation on tumor development and immune functions in mice," *Bioelectromagnetics* **27**, 64–72.

Yang, J., Tan, Y. & Cheke, R. A. [2019] "Thresholds for extinction and proliferation in a stochastic tumour-immune model with pulsed comprehensive therapy," *Communications in Nonlinear Science and Numerical Simulation* **73**, 363–378.

Yang, J., Tan, Y. & Cheke, R. A. [2020] "Complexities and bifurcations induced by drug responses in a pulsed tumour-immune model," *International Journal of Bifurcation and Chaos* **30**, 2050104.

Yang, J., Tang, S. & Cheke, R. A. [2015] "Modelling pulsed immunotherapy of tumour–immune interaction," *Mathematics and Computers in Simulation* **109**, 92–112.

Zhang, Q., Tang, B., Cheng, T. & Tang, S. [2020] "Bifurcation analysis of a generalized impulsive kolmogorov model with applications to pest and disease control," *SIAM Journal on Applied Mathematics* **80**, 1796–1819.