AIMS Mathematics, 8(8): 19699–19718.
DOI: 10.3934/math.20231004
Received: 27 March 2023
Revised: 08 May 2023
Accepted: 19 May 2023
Published: 12 June 2023

http://www.aimspress.com/journal/Math

Research article

A Filippov tumor-immune system with antigenicity

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Abstract: A threshold strategy model is proposed to demonstrate the extinction of tumor load and the mobilization of immune cells. Using Filippov system theory, we consider global dynamics and sliding bifurcation analysis. It was found that an effective model of cell targeted therapy captures more complex kinetics and that the kinetic behavior of the Filippov system changes as the threshold is altered, including limit cycle and some of the previously described sliding bifurcations. The analysis showed that abnormal changes in patients' tumor cells could be detected in time by using tumor cell-directed therapy appropriately. Under certain initial conditions, exceeding a certain level of tumor load (depending on the patient) leads to different tumor cell changes, that is, different post-treatment effects. Therefore, the optimal control policy for tumor cell-directed therapy should be individualized by considering individual patient data.

Keywords: Filippov system; tumor-immune model; threshold strategy; global dynamic; sliding bifurcation
Mathematics Subject Classification: 34C25, 34D20

1. Introduction

A tumor is a new organism formed when local tissue cells lose the normal regulation of their growth under the action of various carcinogenic factors, resulting in their abnormal proliferation. Tumors can be divided into benign tumors and malignant tumors according to the degree of harm to the human body. At present, cancer refers to all malignant tumors. In the modern era of rapid development of science and technology and advanced medical technology, it has not been completely solved and has been plaguing human beings, and curing tumors is still an elusive subject [1–3]. There are two main reasons why tumors are difficult to cure. On the one hand, tumor cells cannot be completely killed. It is well known that genetic mutations are beyond our prediction and control, and tumors are diseases caused by genetic mutations in human cells and the continuous growth of tumor cells as well as their multiplication. This also results in no way to fully monitor and control the growth of

tumor cell load, but for the therapeutic aspect of tumors, we need to understand their growth pattern. Therefore, during exploration, many mathematics scholars have provided various mathematical models to accommodate and interpret tumor growth data as a way to predict patient survival and to make treatment recommendations. Several of these scholars' models suppose that the tumor load grows exponentially, but most consider their growth to be decelerating [3,4]. Although these models describe equations with a single relationship between cells, i.e., only the growth status of the tumor cells is considered, it is possible to distinguish between different types of tumors in terms of their rate of proliferation and thus to consider the association between them and the patient's age [5]. On the other hand, tumors are constantly changing. That is, the tumor load is indeterminate and cannot be fully known with certainty in terms number and other characteristics; it is always changing under the pressure of drugs, the immune system and internal competition, not at the will of man. In the case of autoimmunity, tumor cells appear partially dead, but some of them masquerade as normal cells, and others mutate, thus deceiving the immune system and avoiding the attack of immune cells [6, 7]. Apparently tumor cells are not "dull and fixed" but "smart and changing."

During the treatment process, the relationship between tumor cells and immune cells is complex. On the one hand, the number of immune cells increases in response to tumor cell stimulation, as with natural killer (NK) cells and T cells [8]. On the contrary, tumor cell load was reduced under the influence of with immune cells, a connection similar to "predator-prey" [9–13]. On the other hand, the amount of environmental capacity is unchanged, and there is also a "competitive" relationship between immune cells and tumor cells [9, 14]. The relationship between them is complicated by the existence of these two kinds of relationships simultaneously, which has attracted many scholars to propose conceptual models to explore their interrelationships and explain experimental phenomena [15–19].

In addition to the single equations describing tumor growth in terms of ordinary differential equations (ODE), scholars need to consider more immunological details about the tumor-immune relationship. Then to combine more biological details, we add some other components that may be different types of cells to one of the two equations (such as killer cells, healthy tissue cells) and cytokines.

The classical tumor-immune model was first proposed by Kuznetsov et al. [17]. This model is

$$\begin{cases} \frac{dx}{dt} = s + \frac{cxy}{\varepsilon+y} - \beta xy - \mu x, \\ \frac{dy}{dt} = ry(1 - \frac{y}{K}) - \alpha xy, \end{cases} \tag{1.1}$$

where x denotes the load of immune cells and y denotes the load of tumor cells. s is the emergence rate of immune cells into the tumor region from outside, which is not related to the presence or absence of tumor cells. β is the rate at which immune cells are killed or deactivated in the presence of tumor cells. μ is the death rate of the immune cells. r is their intrinsic growth rate, and K is the carrying capacity of tumor cells. In addition, α is the killing rate of tumor cells by immune cells through the law of mass action. Many phenomena visible in the body can be demonstrated by this model, such as immune stimulation of tumor growth, "sneaking through" of the tumor, and formation of a tumor "dormant state." Nevertheless, some complex kinetic models in (1.1) may not be available, such as periodic solutions and Hopf bifurcation.

Combining the model in [17] and the parameter c represents the antigenic nature of the tumor in the equation in [18]. Li et al. [20] developed another model considering the response of immune cells to

tumor cell growth and regression, which is hypothesized to lead to an increase in the concentration of tumor cells as the immune cells increase, described as

$$\begin{cases} \frac{dx}{dt} = s + cy - \beta xy - \mu x, \\ \frac{dy}{dt} = ry(1 - \frac{y}{K}) - \frac{\alpha xy}{1+\varepsilon y}. \end{cases} \tag{1.2}$$

That is, when having tumor antigenicity, the immune cell load is increased with the level of tumor cells, with all parameters being positive. The model (1.2) can have at most three positive equilibria (i.e., equilibria in the presence of tumor) and a larger range of more complex dynamic behavior than the model (1.1). The obtained results suggest that antigenicity has a role in the control of tumor cell growth.

Model (1.2) contemplates tumor cells and immune cells and is concerned with antigenic effects. Under its assumptions, the model (1.2) is extended and deepened to consider the threshold model of tumor cell load, in which the tumor cell load is constantly changing, The initial state of the tumor load can affect the physician's judgment and treatment, and the size of the threshold is the key to decide the treatment for the patient. A model is obtained showing the complex relationship between tumor cells and immune cells.

The aim of this study was to develop a new Filippov tumor-immune model with a threshold strategy to characterize the effect of tumor cell load on patient stress and enhanced immune cell load to suppress tumor cell load. The remaining parts are as follows: In Section 2, we present a mathematical model of tumor-immunity-antigenicity interactions and introduce some of the relevant basics. The basic preliminary and analysis of the equilibrium point of the model and its stability conditions are given in Section 3. In Section 4, we investigate the sliding model and its dynamical properties. In Section 5, we discuss the range of values for the nonexistence of nonconstant periodic solutions of the system. In Section 6, we analyze the global dynamics of the proposed system and analyze the effect of the threshold T_c. In Section 7, we analyze the equilibria and sliding bifurcation, including the boundary focus bifurcation and grazing (or touching) bifurcation. This can be used to demonstrate clinical phenomena and explain their biological significance. A short summary and some ideas are presented at the end of this paper.

2. Models and preliminaries

In this paper, we extend model (1.2) under the assumption of Li [20] and obtain the following conceptual model:

$$\begin{cases} \left.\begin{array}{l} \frac{dx}{dt} = cy - \beta xy - \mu x, \\ \frac{dy}{dt} = ry(1 - \frac{y}{K}) - \frac{\alpha xy}{1+\varepsilon y}, \end{array}\right\} & y < T_c, \\ \left.\begin{array}{l} \frac{dx}{dt} = cy - \beta xy - \mu x + s, \\ \frac{dy}{dt} = ry(1 - \frac{y}{K}) - \frac{\alpha xy}{1+\varepsilon y} - qy. \end{array}\right\} & y > T_c. \end{cases} \tag{2.1}$$

For simplicity and to retain the parameters needed to reflect the biological background, the system (2.1) is invariantly steeled such that

$$\overline{y} = \frac{y}{K}, \overline{t} = \mu t, \overline{s} = \frac{s}{\mu}, \overline{c} = \frac{cK}{\mu}, \overline{\beta} = \frac{\beta K}{\mu}, \overline{r} = \frac{r}{\mu}, \overline{\alpha} = \frac{\alpha}{r}, \overline{\varepsilon} = \varepsilon K, \overline{q} = \frac{q}{\mu},$$

we get

$$\begin{cases} \frac{dx}{dt} = cy - \beta xy - x + \tau s, \\ \frac{dy}{dt} = ry(1 - y - \frac{\alpha x}{1+\varepsilon y}) - \tau qy, \end{cases} \tag{2.2}$$

with

$$\tau = \begin{cases} 0 & y < T_c, \\ 1 & y > T_c. \end{cases} \tag{2.3}$$

Define $X = (x, y)^T$, $H(X) = y - T_c$, where $H(X)$ is a smooth scale function. The discontinuity boundary $\sum$ can be described as $\sum = \left\{X \in R_+^2 | H(X) = 0\right\}$. Let

$$F_{S_1}(X) = \begin{pmatrix} F_{11} \\ F_{12} \end{pmatrix} = \begin{pmatrix} cy - \beta xy - x \\ ry(1 - y - \frac{\alpha x}{1+\varepsilon y}) \end{pmatrix},$$

$$F_{S_2}(X) = \begin{pmatrix} F_{21} \\ F_{22} \end{pmatrix} = \begin{pmatrix} cy - \beta xy - x + s \\ ry(1 - y - \frac{\alpha x}{1+\varepsilon y}) - qy \end{pmatrix}.$$

It is not difficult to find out that $R_+^2 = S_1 \bigcup \sum \bigcup S_2$. Thus, the system (2.2) is rewritten as:

$$\dot{X}(t) = F(X) = \begin{cases} F_{S_1}(X), \mathrm{X} \in S_1, \\ F_{S_2}(X), \mathrm{X} \in S_2, \end{cases} \tag{2.4}$$

where $S_1 = \{X \in R_+^2 | H(X) < 0\}$, and $S_2 = \{X \in R_+^2 | H(X) > 0\}$. In the system (2.4), when $y < T_c$, the tumor cells are mainly suppressed by the immune system. When $y > T_c$, the tumor cells are suppressed or eliminated using biological means. The general case of planar Filippov system to be studied theoretically with dynamical system tools, but this requires excellent mathematical techniques under the consideration of factors such as cytokine storms [21] and time delays [22, 23]. The equilibrium point (2.2) in Filippov system (2.4) has the following definition [24].

Definition 2.1. *An equilibrium X^* is denoted as a real equilibrium if $F_{S_1}(X^*) = 0$, $H(X^*) < 0$ or $F_{S_2}(X^*) = 0$, $H(X^*) > 0$. Similarly, X^* is denoted as a virtual equilibrium if $F_{S_1}(X^*) = 0$, $H(X^*) > 0$ or $F_{S_2}(X^*) = 0$, $H(X^*) < 0$.*

Definition 2.2. *An equilibrium X^* is denoted as a pseudo-equilibrium if it is an equilibrium of the sliding mode of system* (2.2)*, i.e., $\lambda F_{S_1}(X^*) + 1 - \lambda F_{S_2}(X^*) = 0$, $H(X^*) = 0$ and $0 < \lambda < 1$ with $\lambda = \frac{\langle H_X(X), F_{S_2}(X^*) \rangle}{\langle H_X(X), F_{S_2}(X^*) - F_{S_1}(X^*) \rangle}$.*

Definition 2.3. *An equilibrium X^* is denoted as a boundary equilibrium of Filippov system* (2.2) *if $F_{S_1}(X^*) = 0$ or $F_{S_2}(X^*) = 0$ with $X^* \in \sum$.*

Definition 2.4. *An equilibrium X^* is denoted as a tangent point of Filippov system* (2.2) *if $\langle H_X(X), F_{S_1}(X^*) \rangle = 0$ or $\langle H_X(X), F_{S_2}(X^*) \rangle = 0$ with $X^* \in \sum$.*

3. Dynamics of two subsystems

3.1. Dynamics of subsystem S_1

If $y < T_c$, an endemic equilibrium satisfies the subsystem S_1 of system (2.2), we easily obtain the boundary equilibrium $E_0^1 = (0, 0)$, and in addition. We have

$$cy - \beta xy - x = 0,$$

$$1 - y - \frac{\alpha x}{1 + \varepsilon y} = 0.$$

Substituting $x = \frac{cy}{1+\beta y}$ into the above second equation,

$$f_1(y) = 1 - n_1 y + m_1 y^2 - \beta\varepsilon y^3, \tag{3.1}$$

where $n_1 = 1 + \alpha c - \beta - \varepsilon$ and $m_1 = \beta\varepsilon - \beta - \varepsilon$.

Note $f_1'(y) = -n_1 + 2m_1 y - 3\beta\varepsilon y^2$. Using Descartes' Rule of Signs combined with derivatives for cubic equations,three positive roots exist if the following conditions are satisfied:

$$\begin{cases} n_1 = 1 + \alpha c - \beta - \varepsilon > 0, \\ m_1 = \beta\varepsilon - \beta - \varepsilon > 0, \\ m_1 \geq \sqrt{3\beta\varepsilon n_1}. \end{cases}$$

By calculation, the above three equations cannot be satisfied simultaneously, so there is no case of three positive roots. Also consider that $f_1(0) = 1, f_1(1) = -\alpha c$, so there must be a positive root in $[0, 1]$. That is, there is only one positive equilibrium in system S_1. Consider the positive equilibrium $E_1 = (x_1, y_1)$ of subsystem S_1, whose Jacobian matrix is

$$J(E_1) = \begin{pmatrix} -\beta y_1 - 1 & c - \beta x_1 \\ -\frac{\alpha r y_1}{1+\varepsilon y_1} & r[1 - 2y_1 - \frac{\alpha\varepsilon x_1}{(1+\varepsilon y_1)^2}] \end{pmatrix}.$$

Substituting $x_1 = \frac{cy_1}{1+\beta y_1}$ into $c - \beta x_1$ and $x_1 = \frac{(1-y_1)(1+\varepsilon y_1)}{\alpha}$ into $r[1 - 2y_1 - \frac{\alpha\varepsilon x_1}{(1+\varepsilon y_1)^2}]$, we can rewrite

$$J(E_1) = \begin{pmatrix} -\beta y_1 - 1 & \frac{c}{1+\beta y_1} \\ -\frac{\alpha r y_1}{1+\varepsilon y_1} & \frac{r y_1(\varepsilon - 1 - 2\varepsilon y_1)}{1+\varepsilon y_1} \end{pmatrix}.$$

Then the characteristic equation about the endemic equilibrium $E_1 = (x_1, y_1)$ is given by the following equation:

$$\overline{\lambda}^2 - trJ(E_1)\overline{\lambda} + detJ(E_1) = 0,$$

where

$$trJ(E_1) = \frac{-1 - 4(2r + \beta)\varepsilon y_1^2 + ((r-1)\varepsilon - r - \beta)y_1}{1 + \varepsilon y_1},$$

$$detJ(E_1) = \frac{r(2\beta\varepsilon^2 {y_1}^4 + ((2-\beta)\varepsilon^2 + 3\beta\varepsilon){y_1}^3 + (-\beta\varepsilon - \varepsilon^2 + \beta + 3\varepsilon){y_1}^2 + (c\alpha - \varepsilon + 1)y_1)}{(1 + \varepsilon y_1)^2}.$$

If $trJ(E_1) < 0$, and $detJ(E_1) > 0$, the endemic equilibrium E_1 is locally asymptotically stable.

3.2. Dynamics of subsystem S_2

If $y > T_c$, an endemic equilibrium satisfies the subsystem S_2 of system (2.2). We easily obtain the disease-free equilibrium $E_0^2 = (S, 0)$, in addition to having [20]

$$cy - \beta xy - x + s = 0,$$
$$r(1 - y - \frac{\alpha x}{1 + \varepsilon y}) - q = 0.$$

Substituting $x = \frac{cy+s}{1+\beta y}$ into the above second equation,

$$f_2(y) = L - n_2 y + m_2 y^2 - \beta r \varepsilon y^3, \tag{3.2}$$

where $L = r - \alpha r s - q$, $n_2 = (c\alpha - \beta - \varepsilon + 1)r + q(\beta + r)$, $m_2 = ((\beta - 1)\varepsilon - \beta)r - q\beta\varepsilon$.

Equation (3.2) has only one positive root, and the endemic equilibrium $E_2 = (x_2, y_2)$ of subsystem S_2 has a Jacobian matrix of

$$J(E_2) = \begin{pmatrix} -\beta y_2 - 1 & c - \beta x_1 \\ -\frac{\alpha r y_2}{1+\varepsilon y_2} & r[1 - 2y_2 - \frac{\alpha\varepsilon x_2}{(1+\varepsilon y_2)^2}] - q \end{pmatrix}.$$

Substituting $x_2 = \frac{s+cy_1}{1+\beta y_1}$ into $c - \beta x_1$ and $x_2 = \frac{(1-y_1-\frac{q}{r})(1+\varepsilon y_1)}{\alpha}$ into $r[1 - 2y_2 - \frac{\alpha\varepsilon x_2}{(1+\varepsilon y_2)^2}] - q$, we can rewrite

$$J(E_2) = \begin{pmatrix} -\beta y_2 - 1 & \frac{c-\beta s}{1+\varepsilon y_2} \\ -\frac{\alpha r y_2}{1+\varepsilon y_2} & \frac{r y_2(\varepsilon - 1 - 2\varepsilon y_2)}{1+\varepsilon y_2} \end{pmatrix}.$$

Then the characteristic equation about the endemic equilibrium $E_2 = (x_2, y_2)$ is given by the following equation:

$$\overline{\lambda}^2 - trJ(E_2)\overline{\lambda} + detJ(E_2) = 0,$$

where

$$trJ(E_2) = \frac{-1 - 4(2r + \beta)\varepsilon y_2^2 + ((r-1)\varepsilon - r - \beta)y_2}{1 + \varepsilon y_2},$$

$$detJ(E_2) = \frac{r(2\beta\varepsilon^2 {y_2}^4 + ((2-\beta)\varepsilon^2 + 3\beta\varepsilon){y_2}^3 + (-\beta\varepsilon - \varepsilon^2 + \beta + 3\varepsilon){y_2}^2 + ((c - \beta s)\alpha - \varepsilon + 1)y_2)}{(1 + \varepsilon y_2)^2}.$$

If $trJ(E_2) < 0$, and $detJ(E_2) > 0$, the endemic equilibrium E_2 is locally asymptotically stable.

4. Sliding dynamics

4.1. Sliding segment and region

First, we discuss the existence of a sliding segment and region. If there are regions near the manifold of the flow $\sum$ in which the two different structures of the system (2.4) have vectors pointing to each other, there is a "sliding mode" [25]. By means of the Utkin' equivalent control method in [26], we receive the definition of the sliding domain correlation.

Let $h(X) = \langle H_X(X), F_{S_1}(X)\rangle \langle H_X(X), F_{S_2}(X)\rangle$. Then, the sliding domain satisfies

$$\begin{aligned} \sum{}_S &= \{x \in \sum | h(X) \le 0\} \\ &= \left\{(x, y) \in R^2 | \tfrac{(r(1-T_c)-q)(1+\varepsilon T_c)}{\alpha r} \le x \le \tfrac{(1-T_c)(1+\varepsilon T_c)}{\alpha}\right\}. \end{aligned}$$

Note: The Filippov system (2.2) does not involve the escape region, because these two inequalities are not satisfied simultaneously.

4.2. Pseudo-equilibrium

Due to the fact that $H(X) = 0$ and the first equation of model (2.2) holds, it is possible to derive

$$\frac{\partial H}{\partial t} = ry(t)(1 - y(t) - \frac{\alpha x(t)}{1 + \varepsilon y(t)}) - \tau q y(t) = 0,$$

with $y(t) = T_c$.

Solving the above equation yields

$$\tau = \frac{r}{q}(1 - T_c - \frac{\alpha E}{1 + \varepsilon T_c}).$$

Substituting the first equation of system (2.2),

$$\frac{dx(t)}{dt} = \frac{-\varepsilon((\beta x - c)q + rs){T_c}^2 + ((-\beta x - x\varepsilon + c)q + rs(\varepsilon - 1))T_c - xq - rs(\alpha x - 1)}{(\varepsilon T_c + 1)q} \doteq \phi(x). \quad (4.1)$$

Then the pseudo-equilibrium point can be expressed as $E_p = (x^*, T_c)$, where

$$x^* = \frac{((cq - rs)T_c + rs)(\varepsilon T_c + 1)}{{T_c}^2\beta q\varepsilon + q(\beta + \varepsilon)T_c + \alpha rs + q},$$

and $x^* \in \sum_S$. The pseudo-equilibrium E_p is viable with $\frac{(r(1-T_c)-q)(1+\varepsilon T_c)}{\alpha r} < x^* < \frac{(1-T_c)(1+\varepsilon T_c)}{\alpha}$ [25]. By arranging this inequality, there is an easy way to provide pseudo-equilibrium E_p only when $y_2 < T_c < y_1$. At this point, it is worthwhile to analyze the stabilization of the pseudo-equilibrium of the Filippov system (2.2). Following the ODE theory of stabilization, it is possible to derive y on both sides of Eq (4.1).

$$\phi'(x) = \frac{-1}{q\varepsilon T_c + q}(\beta q\varepsilon {T_c}^2 + \beta q T_c + \varepsilon q T_c + \alpha rs + q).$$

It is easy to see that $\phi'(x) < 0$, which shows that the pseudo-equilibrium $E_p = (x^*, T_c)$ of the Filippov system with the sliding part $\sum_S$ is locally asymptotically stable [27].

4.3. Boundary equilibrium

Let E_B be the boundary equilibrium, i.e., E_B satisfies the following:

$$\begin{cases} cy - \beta xy - x + \tau s = 0, \\ ry(1 - y - \frac{\alpha x}{1+\varepsilon y}) - \tau q y = 0, \\ y - T_c = 0. \end{cases} \quad (4.2)$$

So, one can get two different boundary equilibrium points through the solution of (4.2):

$$E_B^1 = (\frac{cT_c}{1 + \beta T_c}, T_c), E_B^2 = (\frac{cT_c + s}{1 + \beta T_c}, T_c),$$

corresponding to $\tau = 0$, $\tau = 1$. Here, T_c satisfies $f_1(T_c) = 0$ or $f_2(T_c) = 0$, so for $f_1(T_c) = 0$, we have $T_c = y_1$, and for $f_2(T_c) = 0$, we have $T_c = y_2$. We then obtain the possible boundary equilibria:

$$E_B^1 = (\frac{1}{\alpha}(1 - T_c)(1 + \varepsilon T_c), y_1), \quad E_B^2 = (\frac{1}{\alpha r}(r(1 - T_c) - q)(1 + \varepsilon T_c), y_2).$$

4.4. Tangent point

By letting T be the tangent point, according to the definition, the next equation can be obtained.

$$\begin{cases} ry(1-y-\frac{\alpha x}{1+\varepsilon y})-\tau qy=0, \\ y-T_c=0. \end{cases} \tag{4.3}$$

Therefore, the possible tangent points are

$$T_1=(\frac{1}{\alpha}(1-T_c)(1+\varepsilon T_c),T_c), \quad T_2=(\frac{1}{\alpha r}(r(1-T_c)-q)(1+\varepsilon T_c),T_c),$$

which are the solutions to (4.3) corresponding to $\tau=0$, $\tau=1$. When T_c is a threshold value y_1 or y_2, the boundary equilibrium points E_B^1 and E_B^2 collide with the tangent points T_1 and T_2, respectively.

5. The absence of non-continuous periodical solutions

In the before two sections, it was discussed the dynamics of system (2.2) and sliding dynamics. The absence of non-continuous periodical solutions is also an essential characteristic of the system (2.2) [20].

For the subsystem S_1, denote:

$$P(x,y)=cy-\beta xy-x \quad and \quad Q(x,y)=ry(1-y-\frac{\alpha x}{1+\varepsilon y}).$$

Use the Dulac function $B(x,y)=\frac{1+\varepsilon y}{ry}$, we have

$$\frac{\partial(BP)}{\partial x}+\frac{\partial(BQ)}{\partial y}=-\frac{(1+\beta y)(1+\varepsilon y)}{ry}+[(\varepsilon-1)-2\varepsilon y]=-\frac{\varepsilon(\beta+2r)y^2+(\beta+\varepsilon+r-\varepsilon r)y+1}{ry}.$$

Obviously, $\frac{\partial(BP)}{\partial x}+\frac{\partial(BQ)}{\partial y}<0$ if $\varepsilon\le 1$. By a simple calculation shows that

$$\Delta_1=(\beta+\varepsilon+r-\varepsilon r)^2-4\varepsilon(\beta+2r)=(\varepsilon-1)^2r^2-2(\beta\varepsilon+\varepsilon^2+3\varepsilon-\beta)r+(\beta-\varepsilon)^2.$$

The discrimination of the equation $\Delta_1=0$ is $16\varepsilon(\varepsilon+1)(\beta\varepsilon+2\varepsilon-\beta)$, and being more than 0 for $\varepsilon>1$. $r=r_m$ is the larger root of $\Delta_1=0$ when $\varepsilon>1$. Then $\Delta_1<0$ for $\varepsilon>1$ and $\frac{\beta+\varepsilon}{\varepsilon-1}<r<r_m$, which means that $\frac{\partial(BP)}{\partial x}+\frac{\partial(BQ)}{\partial y}<0$ in this case. In summary, by the Bendixson-Dulac Theorem, subsystem S_1 has no nonconstant periodic solutions for which a condition is true: (1) $\varepsilon\le 1$, (2) $\varepsilon>1$ and $r<r_m=\frac{(\beta\varepsilon+\varepsilon^2+3\varepsilon-\beta)+2\sqrt{\varepsilon(1+\varepsilon)(\beta\varepsilon+\varepsilon^2-\beta)}}{(\varepsilon-1)^2}$.

Similarly, for the subsystem S_2, denote:

$$P(x,y)=s+cy-\beta xy-x \quad and \quad Q(x,y)=ry(1-y-\frac{\alpha x}{1+\varepsilon y})-qy.$$

Use the Dulac function $B(x,y)=\frac{1+\varepsilon y}{ry}$, we have

$$\frac{\partial(BP)}{\partial x}+\frac{\partial(BQ)}{\partial y}=-\frac{(1+\beta y)(1+\varepsilon y)}{ry}+[(\varepsilon-1-\frac{q\varepsilon}{r})-2\varepsilon y]=-\frac{\varepsilon(\beta+2r)y^2+(\beta+\varepsilon+r-\varepsilon r-q\varepsilon)y+1}{ry}.$$

After calculating, by the Bendixson-Dulac Theorem, subsystem S_2 has no non-continuous periodical solutions for which one of the below conditions applies: (1) $r\le q$, (2) $r>q$ and $\varepsilon\le\frac{r}{r-q}$, (3) $\varepsilon>\frac{r}{r-q}$ and $r<\frac{(\beta\varepsilon+\varepsilon^2+3\varepsilon+q\varepsilon-\beta-q\varepsilon^2)+2\sqrt{2\varepsilon((1+\frac{\beta}{2}-q)\varepsilon-\frac{\beta}{2})(1+\varepsilon)+2q\varepsilon}}{(\varepsilon-1)^2}$.

6. Global dynamics of the Filippov system

In this regard, it is time to discuss the global dynamics of the Filippov system (2.4). Based on the preceding discussion, it is clear that the equilibrium state of model (2.2), the presence of the sliding region, as well as the sliding region will receive a threshold T_c size. Moreover, we remove the appearance of non-continuous periodic solutions and review that the pseudo-equilibrium is locally asymptotically stable. Moreover, the trajectory through the endpoint of the sliding domain does not touch it again when traversing the subsystem S_2.

Case (1): $y_1 < T_c$, in this case, the endemic equilibrium of the free subsystem S_1 is real, while the endemic equilibrium of the control system S_2 is virtual (Figure 1a,b). The Filippov system (2.2) solution will converge to E_p or E_1, which needs to be considered for various initial values.

Case (2): $y_2 < T_c < y_1$, in which the endemic equilibrium state E_1, E_2 of the free subsystem is virtual (Figure 1c,d). For various initial values, the solution of the system (2.2) will converge to E_p.

Case (3): $0 < T_c < y_2$, in which the endemic equilibrium of the free subsystem S_1 is virtual, while the endemic equilibrium of the control system S_2 is real (Figure 1e,f). And the solution (2.2) of the Filippov system will tend to E_p or E_2.

In general, when the selected threshold level T_c is large enough (as above the value of E_1), the control strategy is not triggered and therefore the solution approaches the free subsystem, which depends on the particular values, such as the Figure 1a,b. However, if the selected threshold T_c is small enough (as a value less than E_2), the control strategy is always triggered, so the solution of the segmented smoothing system approaches the control subsystem, depending on the individual values, as shown in Figure 1c,d. When the threshold T_c is chosen as an intermediate value, there may be a new sliding balance, as shown in Figure 1e,f. It means that the tumor cells can be destroyed or the number of tumor cells can be reduced to a certain low level. This requires the selection of appropriate threshold levels to trigger biological means to effectively control the growth of tumor cells [28].

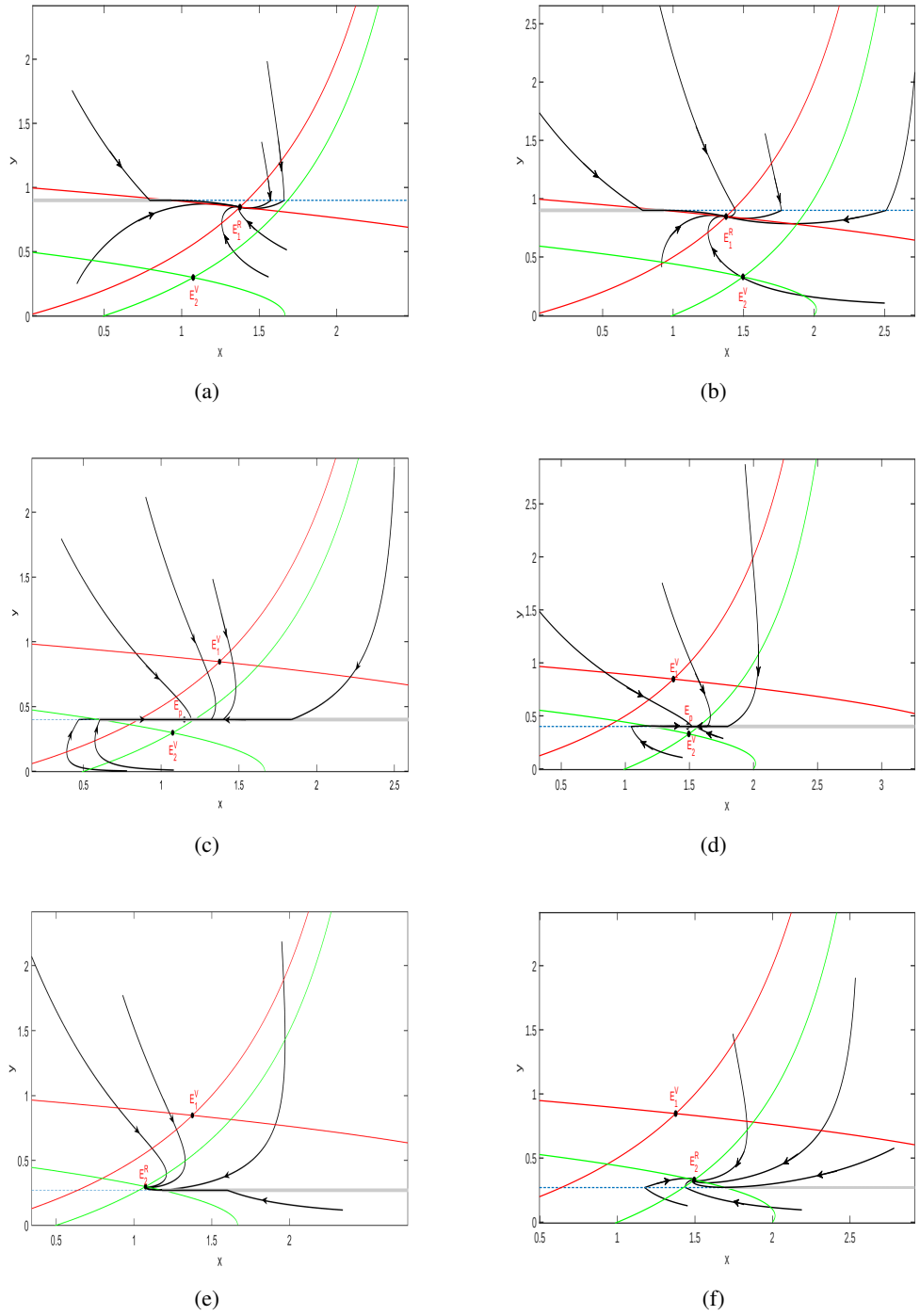


Figure 1. Trajectory plots of T_c for different thresholds. $T_c = 0.9$ in (a), (b); $T_c = 0.4$ in (c), (d); and $T_c = 0.27$ in (e), (f). The parameters are chosen as $c = 3, \beta = 1, r = 5, \alpha = 0.3$, and $\varepsilon = 2$. $s = 0.5, q = 2.5$ in (a), (c), (e); and $s = 1, q = 2$ in (b), (d), (f). The two red lines are the nullclines of system S_1, and the two green lines are the nullclines of system S_2. The gray part indicates the sliding segment.

7. Equilibria and sliding bifurcation analysis

7.1. Analysis of boundary focus bifurcation

Now, we study the boundary focus bifurcation of the Filippov system (2.4). The reader can find relevant definitions of boundary equilibrium and tangent point in the preparatory knowledge. Boundary equilibrium bifurcation may occur in the Filippov system (2.4) when an endemic equilibrium collides with a tangent point and boundary equilibrium. In this subsection, T_c is chosen to be the bifurcation parameter, and no other parameters are changed. Refer to Figure 1.

When $T_c > y_1$, from Figure 2a, the real equilibrium E_1^R exists. It can be seen that the trajectories that start from the S_1 region, staying in the S_1 region without colliding with the boundary, will converge to E_1^R. The trajectory from the S_2 region will also collide with the sliding region. The trajectories colliding with the sliding region will pass the tangent point T_2 and finally converge to E_1^R. The trajectory from the region S_2 will pass through the sliding region and finally converge to E_1^R.

When $T_c = y_1$, the real equilibrium E_1^R, tangent point T_2 and pseudo-equilibrium E_p collide together in Figure 2b. The trajectories of all impacted sliding regions will converge to $T_2(E_p)$.

When $y_2 < T_c < y_1$, it can be found that the real equilibrium E_2^R will turn into virtual equilibrium E_2^V from Figure 2c,d. In addition, the pseudo-equilibrium E_p also exists. The trajectories of all impacted sliding regions will converge to E_p.

When $T_c = y_2$, in Figure 2e, the real equilibrium E_2^R, tangent point T_1 and pseudo-equilibrium E_p collide together. The trajectories of all impacted sliding regions will converge to $T_1(E_p)$.

When $T_c < y_2$, in Figure 2f, the real equilibrium E_2^R exists, and it can be seen that the trajectory starting from region S_2 and remaining in the S_2 region without colliding with the boundary will converge to E_2^R. The trajectory from the S_2 region will also collide with the sliding region. The trajectories that collide with the sliding region will pass the tangent point T_1 and finally converge to E_2^R. The trajectory from region S_1 will cross the sliding region and eventually converge to E_2^R.

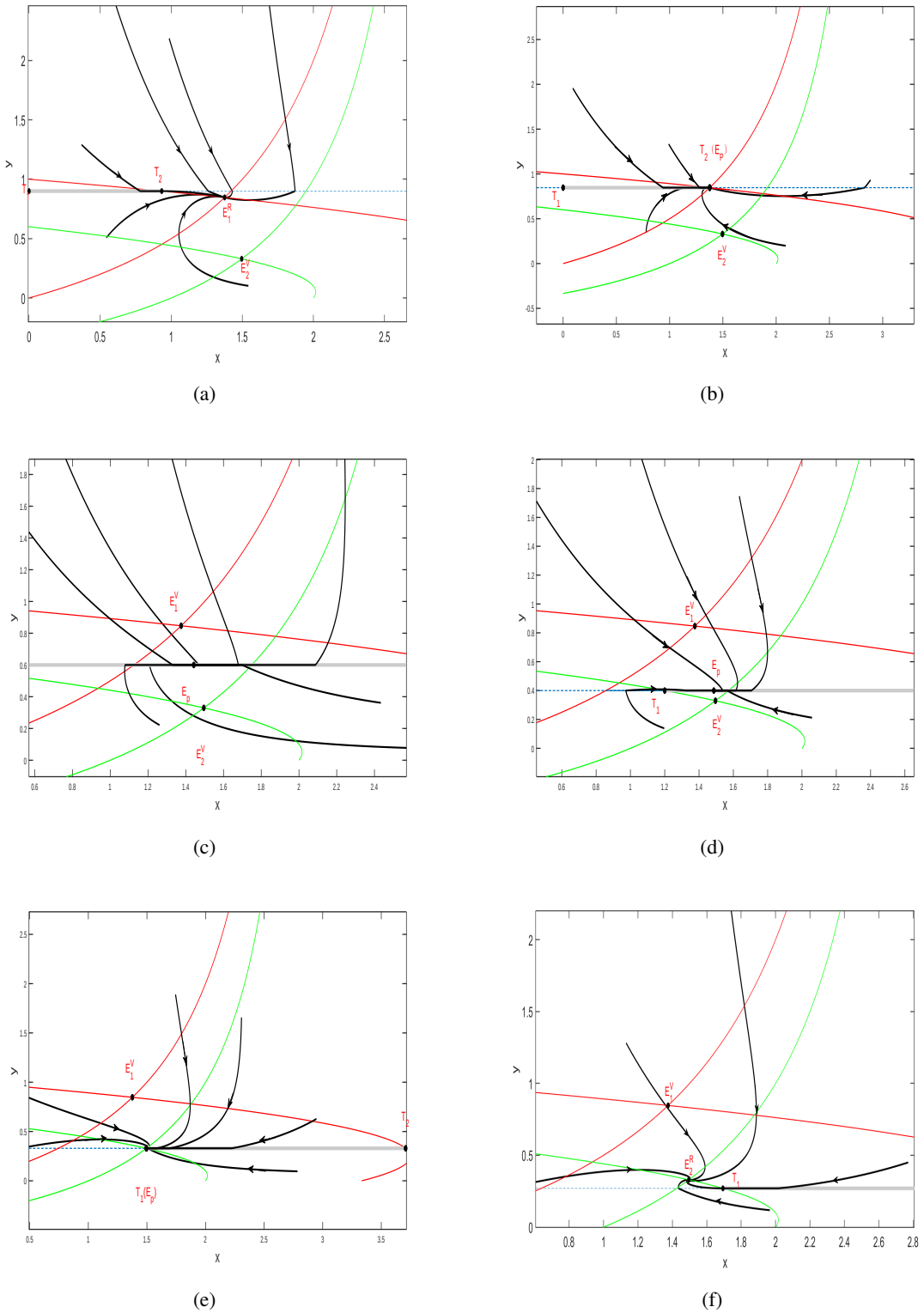


Figure 2. Boundary focus bifurcation for Filippov system (2.2). Parameter value fixed as Figure 1. (a) $T_c = 0.9$, (b) $T_c = 0.8468$, (c) $T_c = 0.6$, (d) $T_c = 0.4$, (e) $T_c = 0.32954$, (f) $T_c = 0.27$, The gray part indicates the sliding segment. The two red lines are the nullclines of system S_1, and the two green lines are the nullclines of system S_2.

7.2. Global sliding bifurcation

The global sliding bifurcation mainly includes grazing (or touching) bifurcation, buckling bifurcation and crossing bifurcation. In this study, we mainly consider the possible sliding bifurcations under different thresholds.

Grazing (or touching) bifurcation: It can be seen that when $T_c = 0.2$, the Filippov system (2.4) has a stable limit cycle inside the region G_1 (the region of system S_1), illustrated in Figure 3a. At this time there are two tangent points T_1 and T_2 located on the boundary of the sliding mode of the Filippov system (2.4), where there is an unstable real equilibrium E_1^R in the subsystem S_1 and another pseudo-equilibrium E_2^V in the subsystem S_2. When the parameter T_c gradually decreases to about 0.177, the limit cycle of the Filippov system (2.4) collides with its tangent point T_2, and a grazing (or touching) bifurcation occurs in Figure 3b. When T_c keeps decreasing, the cycle transforms into a sliding cycle when $T_c = 0.15$, where one of the sliding segments is part of the cycle in Figure 3c.

From the point of view of specific elaboration, when the bifurcation parameter T_c decreases to 0.07, the stable limit cycle disappears, and the pseudo-equilibrium E_p appears at $T_c = 0.07$. Meanwhile, the real equilibrium E_1^R becomes the virtual equilibrium E_1^V, and the real/virtual equilibrium bifurcation occurs at $T_c = 0.07$ in Figure 3d. Also Figure 3d shows that the pseudo-equilibrium of the Filippov system cannot coexist with the real equilibrium.

When the bifurcation parameter T_c is reduced to 0.03, the pseudo-equilibrium E_p disappears. At the same time, the virtual equilibrium E_2^V changes to the real equilibrium E_2^R in Figure 3e. Finally, Figure 3f takes out the sliding cycle separately and observes the change of the sliding cycle. From Figure 3f, it is observed that the length of the sliding segment decreases as the parameter T_c decreases.

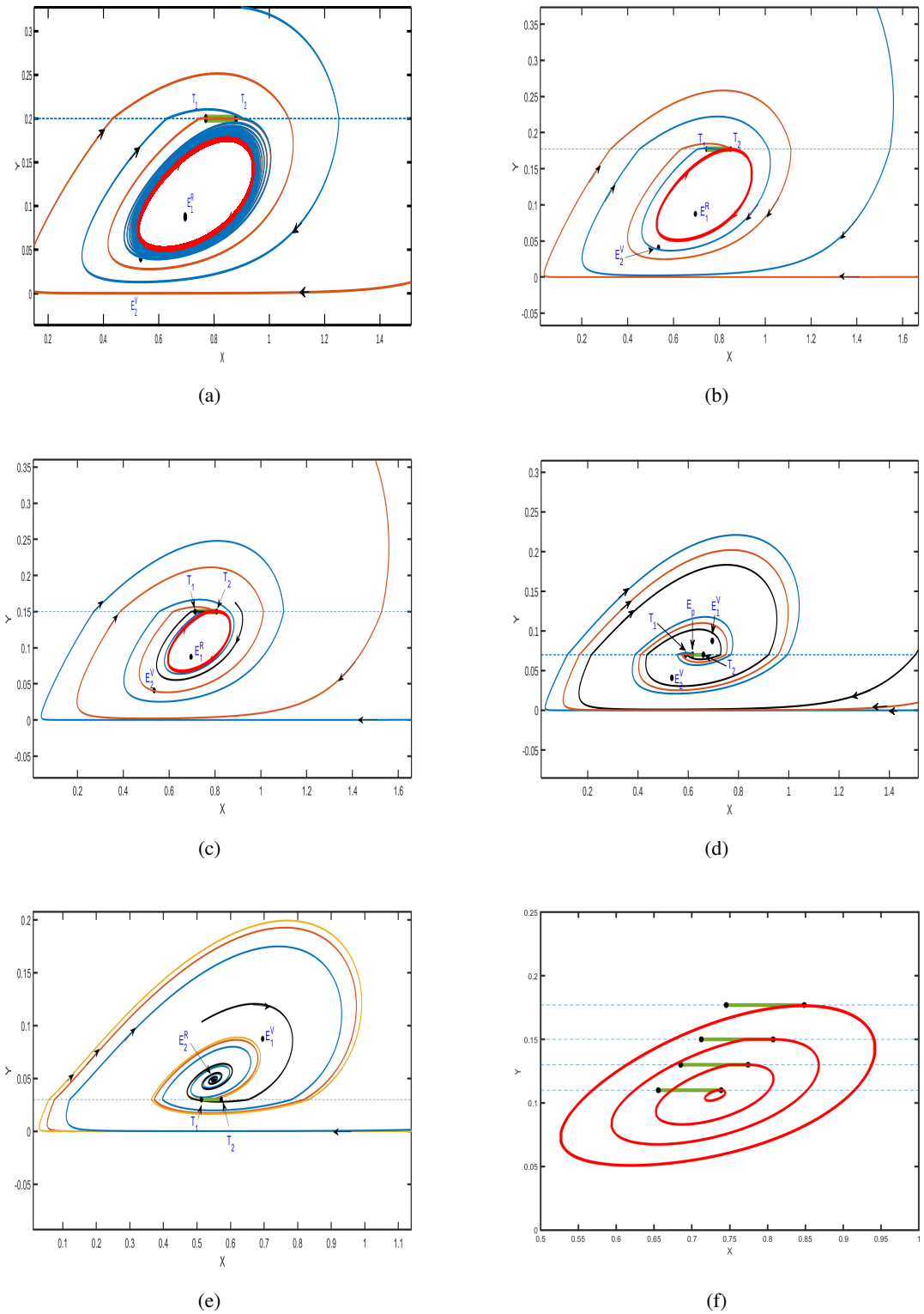
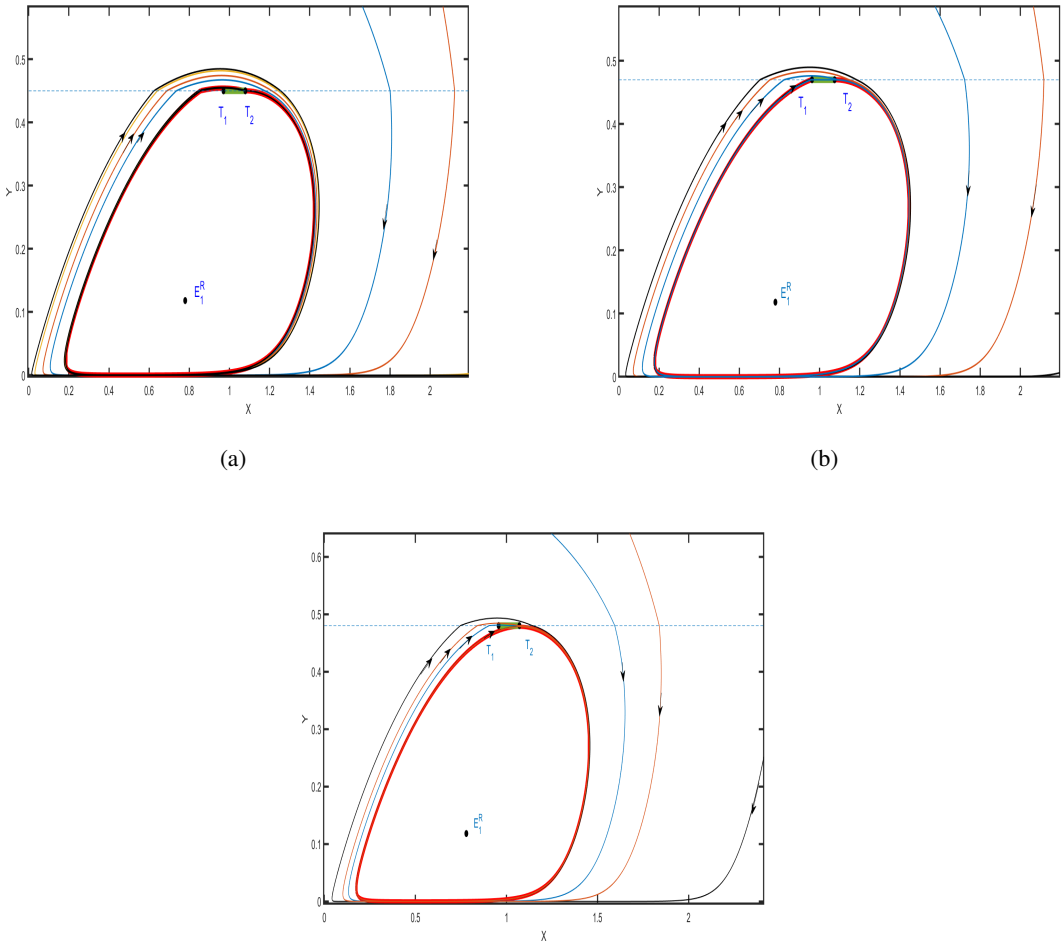


Figure 3. Grazing (or touching) bifurcation for Filippov system (2.4). Parameters are: $c = 8$, $\beta = 1.5$, $r = 5$, $\alpha = 2$, $\varepsilon = 6$, $s = 0.2$, $q = 0.5$. (a) $T_c = 0.2$, (b) $T_c = 0.177$, (c) $T_c = 0.15$, (d) $T_c = 0.07$, (e) $T_c = 0.03$.

Buckling bifurcation is defined as a standard segment of the cycle that starts passing through an invisible secondary tangent when the bifurcation parameter changes. In Figure 3a,b (see Figure 4 for a concrete representation), a sliding cycle collides with an invisible tangent point, and the new cycle contains a portion of the sliding segment. It depicts the buckling bifurcation of the Filippov system (2.4) when T_c changes. In that case, the system shows a buckling bifurcation case, but its equilibrium point and sliding segment do not change much. There is an unstable focus E_1 in subsystem S_1, and all the orbits converge to a stable periodic solution.

Figure 4 depicts the buckling bifurcation when different T_c values are chosen, which indicates that the dynamical behavior of the system is sensitive to T_c.



(a) (b)

(c)

Figure 4. Buckling bifurcation of Filippov system (2.4). Parameters are: $c = 8$, $\beta = 1.8$, $r = 9$, $\alpha = 2$, $\varepsilon = 6.5$, $s = 1$, $q = 0.5$. (a) $T_c = 0.45$, (b) $T_c = 0.47$, (c) $T_c = 0.48$.

Crossing bifurcation can be interpreted as the sliding cycle becoming a cross cycle as the bifurcation parameter changes, as shown in Figure 5. We can see that when T_c decreases from 0.48 to 0.47, the sliding cycle contains the right endpoint of sliding segment, as shown in Figure 5b,c. When T_c continues to decrease to 0.45, the sliding cycle has a great change, and it contains the whole sliding

segment in Figure 5a,b. This phenomenon is reflected as crossing bifurcation. However, it actually changes T_c when it shows crossing bifurcation in Figure 3c,d.

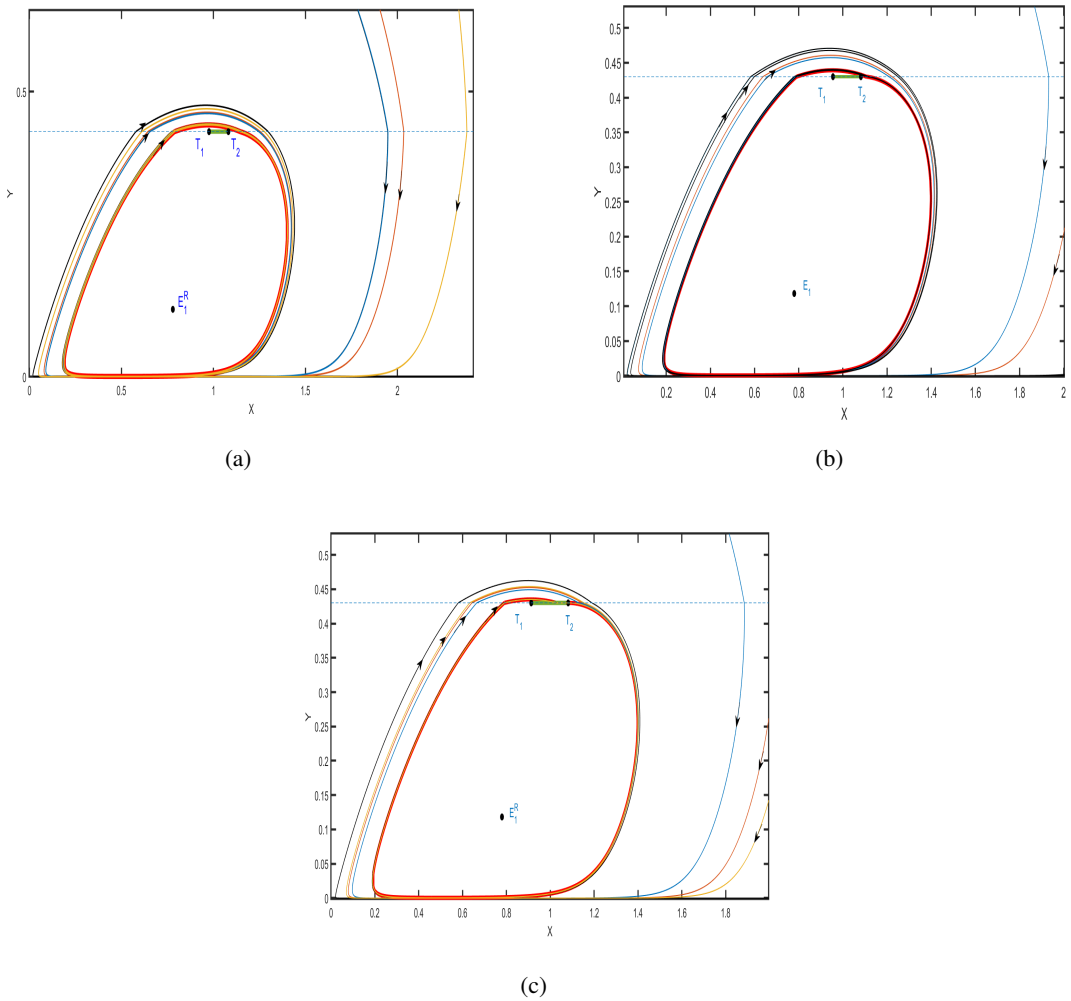


Figure 5. Crossing bifurcation of Filippov system (2.4). Parameters are: $T_c = 0.43$, $c = 8$, $\beta = 1.8$, $r = 9$, $\alpha = 2$, $\varepsilon = 6.5$, $s = 1$. (a) $q = 0.5$, (b) $q = 0.6$, (c) $q = 0.8$.

In summary, the Filippov system (2.4) occurs when the bifurcation parameter is changed : grazing (or touching) bifurcation, buckling bifurcation, crossing bifurcation. The phenomenon reflects that a change in a key parameter T_c causes a change in the dynamical behavior of the Filippov system (2.4). It also shows that T_c is an important factor in controlling tumor cell load.

8. Conclusions

In the modern era of rapid medical development, tumors remain a challenge that mankind has not been able to overcome. In considering the treatment of tumors, the tumor cell load is an obvious criterion for the effectiveness of treatment. When a patient's tumor cells increase to a certain number, physicians take some drugs or surgery in order to control rapid growth of tumor cells, so that it can be controlled within a certain range. In its biological context, we develop the model of a dynamic tumor

immunity that involves a threshold strategy guided by the tumor load, and the model we propose also incorporates the segmental elimination of tumor cells and the growth rate of immune cells to describe the treatment triggered by the threshold related to tumor cells. Throughout this paper, we have favored the study of the global dynamics of the system (2.4) and analyze the sliding bifurcation (boundary focus bifurcation and grazing (or touching) bifurcation) of the Filippov system.

When the threshold value T_c is relatively high, i.e., $T_c > y_1$, a limit cycle exists in a region of the subsystem S_1 as in Figure 3a,b,c. Our results show that there is a significant change in the dynamic in subsystem S_2. Depending on the value taken for the threshold, the presence or absence of the limit cycle changes. In the case of clinical phenomena considered, this can be interpreted as in the case of a high threshold. The number of tumor cells and immune cells can be kept under control considering the initial number of tumor cells in some patients. However, in the case of patients with a dramatic increase of tumor cells, irreparable damage can be caused to the patient's body due to the failure of the physician to perform medical measures relevant to them, accompanied by the destruction of the immune system. Based on the above, we can conclude that at high thresholds, this treatment strategy does not actually have any significant impact on the patient.

When a very low threshold is set in Figure 3e, treatment actually becomes similar to continuous treatment. Thus, relatively low or high thresholds are not good choices for treating patients with tumors. However, when the appropriate threshold is chosen, the dynamics will change as the controllable range of tumor cells is expanded. The pseudo-equilibrium E_p exists when $y_1 < T_c < y_2$ in Figure 3d. Therefore, patient treatment results may vary widely under different initial tumor loads and immune cell counts with the same treatment strategy. For some tumor patients, tumor cells can be controlled at a certain level, while other patients may experience a certain range of tumor cell fluctuations at certain times.

Indeed, several scholars have now studied multiple components of tumor-immune models, some involving the binding and association of multiple types of cells and signaling molecules [29–31], including some involving threshold models of immune cells [24]. Regarding dynamic behavior, a simple model does not imply simple dynamic behavior, and it is possible to obtain more complex results when considering different global sliding bifurcations, limit cycles, etc., with corresponding clinical implications of relevance.

Each dynamic feature in dynamic behavior corresponds to a biological or clinical situation, and we need to focus on each dynamic feature. It is worth noting that in the actual biological or clinical situation, different types of tumors, tumor load, treatment duration, treatment modality and treatment intensity, including the concentration of the drug used, can affect the therapeutic effect on the tumor. The complexity of treatment is reflected by the concentration of the drug used and the period of drug injection, as well as by the consideration of drug concentrations in drug therapy, which has not been detailed in this paper. The patient's clinical phenomena should be the tendency and load of tumor growth, removal or recurrence or transfer of the tumor, whether the tumor growth oscillates and how the oscillation period changes (not yet studied in this paper). In this sense, differences in tumor treatment conditions lead to different clinical phenomena, while influencing tumor treatment conditions precisely as described by mathematical models. Thus, a mathematical model of tumor-immune interactions needs to be explored. Threshold strategies can describe the three main elements of the complex association or "predator-prey" and "competition" among tumor cells and immune cells interactions.

Just as we saw from the model (2.2), we do not consider immune cells when implementing these strategies. Is it possible to maintain the immune cells above a certain level while considering the tumor cells? If it is possible, what therapeutic strategies should be used, i.e., what control parameters should be considered? In considering the practical aspects, it is reasonable to classify different tumor types due to the different growth characteristics of these tumors. For drug therapy, the combined use of drugs must be better than the single use of drugs in terms of effectiveness and long-term development of human health, when faced with the concentration of drugs, the way they are combined, the sensitivity of drugs, the registration period of drugs, etc. Taking into account these aspects, this will be the purpose and idea of future work.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Acknowledgments

This work was supported by The National Natural Science Foundation of China (Grant No.11961024).

Conflict of interest

The authors declare no conflict of interest.

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