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BIFURCATION ANALYSIS IN MODELS OF TUMOR AND IMMUNE SYSTEM INTERACTIONS

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Abstract. The purpose of this paper is to present qualitative and bifurcation analysis near the degenerate equilibrium in models of interactions between lymphocyte cells and solid tumor and to understand the development of tumor growth. Theoretical analysis shows that these cancer models can exhibit Bogdanov-Takens bifurcation under sufficiently small perturbation of the system parameters whether it is vascularized or not. Periodic oscillation behavior and coexistence of the immune system and the tumor in the host are found to be influenced significantly by the choice of bifurcation parameters. It is also confirmed that bifurcations of codimension higher than 2 cannot occur at this equilibrium in both cases. The analytic bifurcation diagrams and numerical simulations are given. Some anomalous properties are discovered from comparing the vascularized case with the avascular case.

1. **Introduction.** Cancer still remains one of the most dangerous killers of humankind in the 21th century. Millions of people die from this disease every year throughout the world ([9]). The main cause of a remarkably high incidence of neoplasia clinically derives from immunological deficiency. Investigation ([19]) showed that about ten percent of patients who have spontaneous immunodeficiency diseases may develop cancer. Clinic and laboratory sources also indicate that the immune system plays an important role in controlling and eliminating tumor cells, and therefore decreasing the observed incidence of cancer. This response of immune system to the precancerous and cancerous is the so-called immunosurveillance ([17]). More detailed research about the immune surveillance can be found in [5],[13],[14], and [24].

The interactions between the immune system and tumor cells are important. Numerous effort and research have been made to explore the effects of immune system to eliminate and destroy tumor cells by stimulating the host's own immune

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response to fight cancer. But current experimental and clinic data reveal that improvement of the immune system by immunotherapy brings on not suppression but more stimulation of tumor cells growth (see [21], [23]), so the immunotherapy is still a restrained treatment modality in the clinic. Nevertheless, the promising future of effective tumor immunotherapy has been lightened by the recent breakthroughs in immunology such as the identification of immunogenic tumor-associated antigens ([25]).

In order to qualitatively estimate the function of the immune surveillance, a variety of mathematical models of the interaction between the immune system and solid tumor have been introduced. In 1977, based on some reasonable hypotheses, DeLisi and Rescigno [11] proposed the following nonvascularized model

$$\begin{aligned} \frac{dL}{dt} &= -\lambda_1 L + \alpha_1^{'} \bar{C} L (1 - \tfrac{L}{L_c}) \\ \frac{dC}{dt} &= \lambda_2 C_f - \alpha_2^{'} \bar{C} L \end{aligned} \tag{1}$$

to describe immune response to a spherical tumor, where L and C denote respectively the number of free lymphocytes and the total number of tumor cells. $\bar{C}$ and C_f are respectively the total number of free tumor cells and the number of free cells on a tumor surface. $\lambda_1,\ \lambda_2$ and $\alpha_1^{'},\ \alpha_2^{'}$ are positive constants. Free cells mean the cells that are not bound by lymphocytes. For more detailed explanation of (1) one can refer to [11].

Model (1) integrates the tumor geometrical character and renders the interactions between the immune system and a solid tumor during tumor attack, which is along the lines of but different from the earlier classical deterministic model in [6], because in system (1) only the cells on the surface of a growing tumor are susceptible to immune attack and destruction. The general directions of phase portraits for system (1) have been studied in [11] except near the degenerate equilibrium. As an application, Arrowsmith and Place [4] simply analyzed the bifurcation at the degenerate equilibrium of (1) in the case of a cusp point by their bifurcation theory. However, they did not present the explicit homoclinic bifurcation curve and the corresponding numerical simulations.

In the subsequent reviews, Swan extended the mathematical analysis of the model in [26] and studied the field of mathematical modeling in cancer research in [27]. Albert [2] set up a mathematical model of the immune system with the interaction of tumor cells in the presence of a tumor growth modulator by a set of differential equations. In [15], Kuznetsov et al. formulated a model of the cytotoxic T lymphocyte response to the growth of an immunogenic tumor and studied local and global bifurcations for some realistic values of the parameters.

In 1996, Adam [1] proposed a mathematical model describing cell populations of reactive lymphocytes and solid tumors by incorporating the effects of vascularization within a tumor or multicell spheroid to model (1), i.e., the vascularized model

$$\begin{aligned} \frac{dL}{dt} &= -\lambda_1 L + \alpha_1^{'} \bar{C} L (1 - \tfrac{L}{L_c}) - \hat{\beta}_1 C^{2/3} \\ \frac{dC}{dt} &= \lambda_2 C_f - \alpha_2^{'} \bar{C} L + \beta_2 C, \end{aligned} \tag{2}$$

where $\hat{\beta}_1$ and β_2 are nonnegative constants representing the efficiency of penetration of the tumor surface area and volume, respectively. The appearance of fractional exponent in the first equation of the vascularized model is caused by the fact that we take the tumor mass as a spherical form. From (2), Adam obtained the possibility of Hopf bifurcation near one of the nondegenerate equilibria and the existence of a limit cycle by treating any parameter in the model as a bifurcation parameter.

There are very little discussion about the properties of the possible degenerate equilibrium. Following the investigation of the models from [11] and [1], Lin [18] considered the existence of solutions and stability of steady states of the immune system on both avascular and vascularized cases, determined the regions of uncontrolled tumor growth, tumor extinction in finite time and irreversible lymphocyte decline, and proved the invariance of the systems in the plane region $(0, L_c) \times (0, +\infty)$ in both cases. But the trajectories and the dynamical properties near the degenerate equilibrium have not yet been considered completely.

In this paper we continue to follow the hypotheses in [11] and [1] and focus our attention on the study of the qualitative properties and bifurcations near the degenerate equilibrium of (1) and (2). In both models, we study possible behavior of the trajectories near the degenerate equilibrium by using methods different from [4]. One interesting result of our analysis is that it can exhibit Bogdanov-Takens bifurcation of codimension 2 at the degenerate equilibrium for the model of tumor and lymphocyte interaction just like in some predator-prey models (see [22], [29], [30]). Thus there may be a homoclinic orbit or a limit cycle bifurcated from the degenerate equilibrium when we choose the particular values of bifurcation parameters in system (2). The appearance of limit cycles implies the occurrence of the periodic oscillation behavior of these cancer models. In other words, the immune system and the solid tumor can coexist under some appropriate circumstances. Also we find that bifurcations of codimension 3 or higher cannot happen in (1) whether in nonvascularized or vascularized case, which rules out many more complicated cases on the development of the solid tumor and the lymphocytes. Our theoretical results maintain the qualitative analysis of DeLisi and Rescigno [11] and extend the results of Arrowsmith and Place [4] for the avascular case, and the results of Lin [18] for the cases prior to vascularization as well as after vascularization and of Adam [1] for the vascularized case. Numerical simulations for the nonvascularized model are presented to support the analytic conclusions on bifurcations.

2. **Bifurcations of the nonvascularized model.** If the relationship between free and bounded lymphocytes is assumed to be equilibrium controlled, K is the equilibrium for lymphocyte and tumor cell interaction, and the tumor is spherical, then DeLisi and Rescigno [11] derived that

$$C_f = C - gKLC^{2/3}/(1+KL), \quad \bar{C} = gC^{2/3}/(1+KL),$$

where $g > 0$ is a constant. Therefore, the following system of lymphocyte and tumor interaction is obtained:

$$\begin{array}{rcl} \frac{dL}{dt} & = & -\lambda_1 L + \alpha_1^{'}(\frac{gC^{2/3}}{1+KL})L(1-\frac{L}{L_c}) \\ \frac{dC}{dt} & = & \lambda_2(C - \frac{gC^{2/3}KL}{1+KL}) - \alpha_2^{'}(\frac{gC^{2/3}}{1+KL})L, \end{array} \tag{3}$$

Our main goal in this section is to investigate possible bifurcations near the degenerate positive equilibrium of (3). From the biological point of view, the domain restrictions are $0 \le L \le L_c$ and $C \ge 0$. Introducing the new variables and parameters

$$x = KL,\ y = KC,\ x_c = KL_c,\ \alpha_1 = \alpha_1^{'} gK^{-2/3},\ \alpha_2 = gK^{1/3}(\lambda_2 + \alpha_2^{'}K^{-1}),$$

we nondimensionalize system (3) in a simple expression:

$$\begin{array}{rcl} \frac{dx}{dt} & = & -\lambda_1 x + \frac{\alpha_1 x y^{2/3}}{1+x}(1-\frac{x}{x_c}) = f(x,y) \\ \frac{dy}{dt} & = & \lambda_2 y - \frac{\alpha_2 x y^{2/3}}{1+x} = g(x,y). \end{array} \tag{4}$$

Steady states appear when

$$f(x, y) = 0 = g(x, y). \tag{5}$$

It is evident to see that $(0, 0)$ is such a critical point. Adam [1] has shown that $(0, 0)$ is an unstable equilibrium of (4) by the trajectory analysis. This equilibrium is of little biological interest because it means that both lymphocyte and tumor populations are vanished. So in the following discussion we are not concerned with this trivial equilibrium any more. When x and y are nonzero, the algebraic equations (5) can be simplified into the following form which is independent on the variable y:

$$\frac{\lambda_1\lambda_2^2}{\alpha_1\alpha_2^2} = \frac{x^2(1 - x/x_c)}{(1 + x)^3} = \psi(x_c, x). \tag{6}$$

Set $k_1 = \frac{\lambda_1\lambda_2^2}{\alpha_1\alpha_2^2}$ for simplicity, then the abscissa of positive equilibrium of system (4) is equivalent to the positive solution of the equation $\psi(x_c, x) = k_1$. In Figure 1, the curve of $\psi(x_c, x)$ of x is shown, where x_m corresponds to the maximum point of $\psi(x_c, x)$ in $[0, x_c]$. From that we can find the direct results as below.

(a) If $k_1 > \psi(x_c, x_m)$, system (4) has no interior equilibrium.

(b) If $k_1 = \psi(x_c, x_m)$, system (4) has a unique interior equilibrium $S(x_m, y_m)$.

(c) If $0 < k_1 < \psi(x_c, x_m)$, system (4) has two different interior equilibria $S_1(x_1, y_1)$ and $S_2(x_2, y_2)$ satisfying $x_1 < x_m < x_2$.

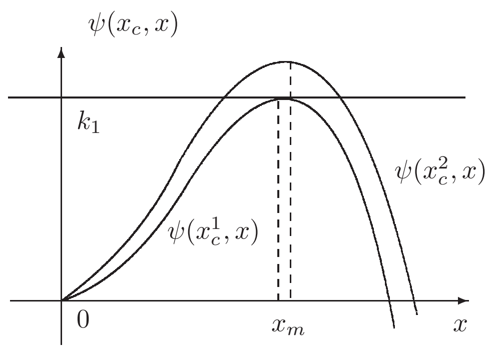


Figure 1. The curve $\psi(x_c, x)$ at different values of x_c with $x_c^1 < x_c^2$.

In case (a), $(0, 0)$ is the only equilibrium which is unstable and Adam [1] concluded that the trajectory of system (4) approaches uncontrollable tumor growth for any initial nonzero value of (x, y). For the case (b), there is another equilibrium besides the origin. DeLisi and Rescigno [11] gave a global analysis of trajectories near this positive equilibrium. But they did not discuss the property of system (4) at the point in detail. The two different equilibria in case (c) were studied successively by Adam [1] in 1996 and Lin [18] in 2004. They proved respectively that the equilibrium $S_2(x_2, y_2)$ is an unstable saddle point while $S_1(x_1, y_1)$ may be a center, focus or node and either stable or unstable. We are concerned with properties of $S(x_m, y_m)$ in case (b) in the following. Since these fixed points are far away from the origin, we can make the equivalent transformation $u = y^{1/3}$ which does not change their qualitative properties. Let us redenote respectively u, $\lambda_2/3$, and $\alpha_2/3$

as y, λ_2, and α_2, then system (4) becomes

$$\begin{aligned} \frac{dx}{dt} &= -\lambda_1 x + \frac{\alpha_1 x(1-\frac{x}{x_c})}{1+x} y^2 = F(x,y) \\ \frac{dy}{dt} &= \lambda_2 y - \frac{\alpha_2 x}{1+x} = G(x,y). \end{aligned} \tag{7}$$

By simple calculations, we know that $x_m = \frac{2x_c}{3+x_c}$ and $y_m = \frac{\alpha_2 x_m}{\lambda_2(1+x_m)}$. Substituting x_m into equation (6), the following lemma can be proved.

Lemma 2.1. *The parameter set*

$$\Sigma_{SN} = \{(\lambda_1, \lambda_2, \alpha_1, \alpha_2, x_c) | \frac{\lambda_1 \lambda_2^2}{\alpha_1 \alpha_2^2} = \frac{4x_c^2}{27(1+x_c)^2},\ x_c, \lambda_i, \alpha_i > 0,\ i = 1, 2\} \tag{8}$$

is the saddle-node bifurcation surface of system (7).

When the parameters pass through the surface Σ_{SN} from one side to the other side, the number of the interior equilibria changes from zero to two. And there is only one such point on that surface.

Now we take a mathematical analysis for system (7) near the point $S(x_m, y_m)$. To study the property at $S(x_m, y_m)$, it is necessary to make some technical transformations and use the canonical form of system (7) about this equilibrium. For the sake of simplicity, let $x_1 = x - x_m,\ y_1 = y - y_m$ so we can translate the interior equilibrium into the origin and expand system (7) in a power series about the origin, then we have

$$\begin{aligned} \frac{dx_1}{dt} &= ax_1 + by_1 + p_{11}x_1^2 + 2p_{12}x_1y_1 + p_{22}y_1^2 + P_1(x_1, y_1) \\ \frac{dy_1}{dt} &= cx_1 + dy_1 + q_{11}x_1^2 + 2q_{12}x_1y_1 + q_{22}y_1^2 + Q_1(x_1, y_1), \end{aligned} \tag{9}$$

where $P_1(x_1, y_1)$ and $Q_1(x_1, y_1)$ are C^∞ functions of (x_1, y_1) with at least the third order and the coefficients of first and second order term are the derivatives of F and G such that

$$\begin{aligned} J(x,y)|_{(x_m,y_m)} &= \begin{pmatrix} \frac{\partial F}{\partial x} & \frac{\partial F}{\partial y} \\ \frac{\partial G}{\partial x} & \frac{\partial G}{\partial y} \end{pmatrix}_{(x_m,y_m)} = \begin{pmatrix} a & b \\ c & d \end{pmatrix}, \\ P(x,y)|_{(x_m,y_m)} &= \frac{1}{2} \begin{pmatrix} \frac{\partial^2 F}{\partial x^2} & \frac{\partial^2 F}{\partial x \partial y} \\ \frac{\partial^2 F}{\partial x \partial y} & \frac{\partial^2 F}{\partial y^2} \end{pmatrix}_{(x_m,y_m)} = \begin{pmatrix} p_{11} & p_{12} \\ p_{12} & p_{22} \end{pmatrix}, \\ Q(x,y)|_{(x_m,y_m)} &= \frac{1}{2} \begin{pmatrix} \frac{\partial^2 G}{\partial x^2} & \frac{\partial^2 G}{\partial x \partial y} \\ \frac{\partial^2 G}{\partial x \partial y} & \frac{\partial^2 G}{\partial y^2} \end{pmatrix}_{(x_m,y_m)} = \begin{pmatrix} q_{11} & q_{12} \\ q_{12} & q_{22} \end{pmatrix}. \end{aligned} \tag{10}$$

As a direct observation, we obtain that $q_{12} = q_{22} = 0$ independent of the value of (x_m, y_m). Moreover, the determinant Det$J$ and the trace TrJ at $S(x_m, y_m)$ can be determined. It is easy to find that Det$J(x_m, y_m) = 0$ and Tr$J(x_m, y_m) = -\frac{2(3+xc)}{3(1+xc)}\lambda_1 + \lambda_2$ after substitution several times, which means that $S(x_m, y_m)$ is a degenerate equilibrium. We divide into two cases in order to investigate the property of this equilibrium.

2.1. **Case A:** $\lambda_2 \neq \frac{2(3+x_c)}{3(1+x_c)}\lambda_1$**.** This condition implies that the Jacobian matrix J of the linear part of system (7) at the nonhyperbolic equilibrium (x_m, y_m) is similar to the Jordan normal form $\begin{pmatrix} 0 & 0 \\ 0 & a+d \end{pmatrix}$. By a linear coordinate and time change

$X_2 = MX_1$, $\tau = (a+d)t$, system (9) is changed into

$$\begin{aligned}\frac{dx_2}{d\tau} &= (dw_1 - bw_4)x_2^2 + (dw_2 - 2bw_4)x_2y_2 + (dw_3 - bw_4)y_2^2 + P_2(x_2, y_2)\\ &= p(x_2, y_2)\\ \frac{dy_2}{d\tau} &= y_2 + (aw_1 + bw_4)x_2^2 + (aw_2 + 2bw_4)x_2y_2 + (aw_3 + bw_4)y_2^2 + Q_2(x_2, y_2)\\ &= q(x_2, y_2),\end{aligned} \tag{11}$$

where $X_i = (x_i, y_i)^T$, $i = 1, 2$, $M = \begin{pmatrix} d & -b \\ a & b \end{pmatrix}$, and w_j for j varying from 1 to 4 are defined as $w_1 = \frac{b^2p_{11}-2abp_{12}+a^2p_{22}}{b^2(a+d)^3}$, $w_2 = \frac{2(b^2p_{11}-abp_{12}+bdp_{12}-adp_{22})}{b^2(a+d)^3}$, $w_3 = \frac{b^2p_{11}+2adp_{12}+d^2p_{22}}{b^2(a+d)^3}$, $w_4 = \frac{b^2q_{11}}{b^2(a+d)^3}$, and T denotes the transposition of a matrix.

We now determine the phase portraits of system (9) near (0,0). Applying the theory in [3], we first consider the equation $q(x_2, y_2) = 0$. By the implicit function theorem, this equation has a solution $y_2 = \varphi(x_2)$ in a small neighborhood of the origin, where

$$\varphi(x_2) = -(aw_1 + bw_4)x_2^2 + (aw_1 + bw_4)(aw_2 + 2bw_4)x_2^3 + O(x_2^4)$$

is an analytic function such that $\varphi(0) = \varphi'(0) = 0$. Define a function $\psi(x_2)$ by $\psi(x_2) = p(x_2, y_2)$. Here it needs to be mentioned that the function $\psi(x_2)$ cannot vanish identically. That is because (x_m, y_m) is an isolated equilibrium of system (7) and so is the equilibrium (0,0) for (9). If $\psi(x_2) = 0$, it would deduce from the definitions of φ and ψ that all points of the curve $y_2 = \varphi(x_2)$ are steady states of system (11), which contradicts with the isolation of the equilibrium (0,0). Therefore we may expand the function $\psi(x_2)$ as the form of the power series:

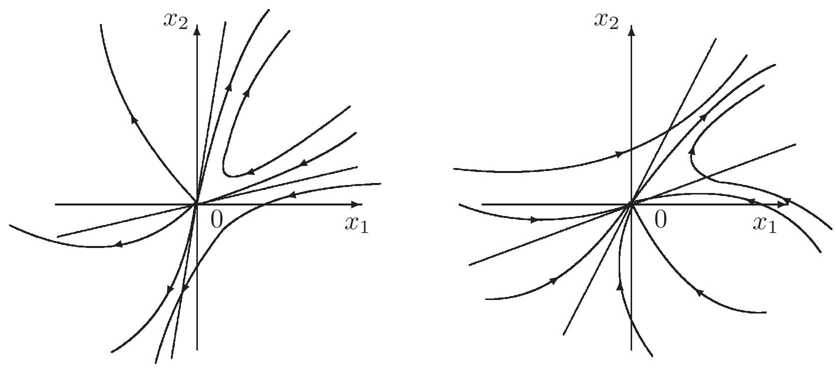
$$\begin{aligned}\psi(x_2) =&(dw_1 - bw_4)x_2^2 - (dw_2 - 2bw_4)(aw_1 + bw_4)x_2^3\\ &+ [(dw_2 - 2bw_4)(aw_1 + bw_4)(aw_2 + 2bw_4) + (dw_3 - bw_4)(aw_1 + bw_4)^2]x_2^4\\ &+ O(x_2^5),\end{aligned} \tag{12}$$

where $dw_1 - bw_4 = \frac{9(1+x_c)(3+x_c)^3\lambda_1\lambda_2}{2x_c(2(3+x_c)\lambda_1-3(1+x_c)\lambda_2)^3}$ which is actually reasonable under the condition of Case A. From the results of Andronov et al. [3], we obtain the possible topological structure of the equilibrium state (0,0) of system (9) in the following conclusion.

Theorem 2.2. *If Case A is valid, then (0,0) is a saddle-node of system (9) which consists of two hyperbolic sectors and one parabolic sector.*

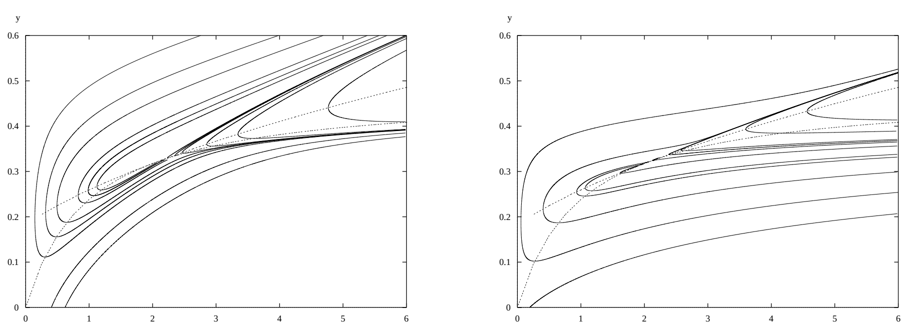
The corresponding phase portraits in the neighborhood of the origin are analyzed and drawn in Figure 2 (a) and (b).

We select the parameters $\alpha_1' = 1.5 \times 10^{-7}$, $\alpha_2' = 6.91472 \times 10^{-9}$, $g = 9.2$, $L_c = 2.5 \times 10^{11}$, $K = 10^{-8}$ in the immune system (1). When $\lambda_1 = 0.01$, $\lambda_2 = 0.01$, one gets that $\lambda_2 > \frac{2(3+x_c)}{3(1+x_c)}\lambda_1$, and the trajectories near the interior equilibrium (x_m, y_m) $= (1.9976, 0.317654)$ by numerical simulations are shown in the left picture (a) of Figure 3, where (x_m, y_m) is unstable, so almost all trajectories will head to (x_c, ∞) and the population of cancer cells will be uncontrollable as t increases to infinite. However, when $\lambda_1 = 0.01$, $\lambda_2 = 0.003333$, we find $\lambda_2 < \frac{2(3+x_c)}{3(1+x_c)}\lambda_1$ and there are trajectories originating from some regions tend to the same interior equilibrium (x_m, y_m) and the other regions bring uncontrolled growth of cancer as t goes to infinite, see Figure 3(b). In such a case, (x_m, y_m) is a semi-stable equilibrium. If the initial values are chosen suitably, cancer can coexist with the immune system because trajectories originating from such regions will close to this equilibrium as t increases.



(a) (b)

Figure 2. The outline of trajectories for system (2.5) near (x_m, y_m) where the origin denotes the equilibrium (x_m, y_m) in the plane of (x, y). (a) corresponds to the case $\lambda_2 > \frac{2(3+x_c)}{3(1+x_c)}\lambda_1$ and (b) corresponds to $\lambda_2 < \frac{2(3+x_c)}{3(1+x_c)}\lambda_1$.



(a) (b)

Figure 3. The phase portraits near the degenerate equilibrium (x_m, y_m) when $\lambda_2 \neq \frac{2(3+x_c)}{3(1+x_c)}\lambda_1$.

2.2. **Case B:** $\lambda_2 = \frac{2(3+x_c)}{3(1+x_c)}\lambda_1$**.** In this case, the Jacobian matrix J of the linear part of system (7) at the equilibrium $S(x_m, y_m)$ is similar to the Jordan block form $\begin{pmatrix} 0 & 1 \\ 0 & 0 \end{pmatrix}$. Applying the bifurcation theory in [10], [20] and [16] and taking the affine transformation $x_2 = y_1,\ y_2 = cx_1 + dy_1$, we can rewrite system (9) as follows:

$$\begin{array}{rcl} \frac{dx_2}{dt} & = & y_2 + \frac{d^2}{c^2}q_{11}x_2^2 - \frac{2d}{c^2}q_{11}x_2y_2 + \frac{1}{c^2}q_{11}y_2^2 + P_2(x_2,y_2) \\ \frac{dy_2}{dt} & = & [\frac{d^2}{c^2}(cp_{11}+dq_{11}) - 2dp_{12} + cp_{22}]x_2^2 + [-\frac{2d}{c^2}(cp_{11}+dq_{11}) + 2p_{12}]x_2y_2 \\ & & +\frac{cp_{11}+dq_{11}}{c^2}y_2^2 + Q_2(x_2,y_2), \end{array} \tag{13}$$

where $P_2(x_2,y_2)$ and $Q_2(x_2,y_2)$ are power series in (x_2,y_2) with powers at least 3. Performing the next C^∞ change of variables of system (13) in a small neighborhood of the origin:

$$\begin{array}{rcl} x_3 & = & x_2 - \frac{cp_{11}-dq_{11}}{2c^2}x_2^2 - \frac{1}{c^2}q_{11}x_2y_2 \\ y_3 & = & y_2 + \frac{d^2}{c^2}q_{11}x_2^2 - \frac{cp_{11}+dq_{11}}{c^2}x_2y_2, \end{array} \tag{14}$$

we eliminate the term y_2^2, then system (13) is C^∞ equivalent to

$$\begin{array}{rcl} \frac{dx_3}{dt} & = & y_3 + P_3(x_3,y_3) \\ \frac{dy_3}{dt} & = & [\frac{d^2}{c^2}(cp_{11}+dq_{11}) - 2dp_{12} + cp_{22}]x_3^2 + (-\frac{2d}{c}p_{11} + 2p_{12})x_3y_3 + Q_3(x_3,y_3), \end{array} \tag{15}$$

where $P_3(x_3,y_3)$ and $Q_3(x_3,y_3)$ are C^∞ functions in (x_3,y_3) at least of the third order. In order to use the results from [10] to make sure if the origin of system (15) is a cusp point, we make the transformation

$$x_4 = x_3,\ y_4 = y_3 + P_3(x_3,y_3), \tag{16}$$

which brings system (15) to the canonical normal form

$$\begin{array}{rcl} \frac{dx_4}{dt} & = & y_4 \\ \frac{dy_4}{dt} & = & [\frac{d^2}{c^2}(cp_{11}+dq_{11}) - 2dp_{12} + cp_{22}]x_4^2 + (-\frac{2d}{c}p_{11} + 2p_{12})x_4y_4 + Q_4(x_4,y_4), \end{array} \tag{17}$$

where $Q_4(x_4,y_4)$ is a C^∞ function in (x_4,y_4) at least of the third order. Mathematica works out that

$$\begin{array}{rcl} d_1 & = & \frac{d^2}{c^2}(cp_{11}+dq_{11}) - 2dp_{12} + cp_{22} = \frac{9(1+x_c)\lambda_2^3}{4\alpha_2x_c} > 0, \\ d_2 & = & -\frac{2d}{c}p_{11} + 2p_{12} = -\frac{3(1+x_c)(9+x_c)\lambda_2^2}{2x_c(3+x_c)\alpha_2} < 0, \end{array} \tag{18}$$

which means $d_1d_2 \neq 0$ for any positive values of $\lambda_2,\ \alpha_1,\ \alpha_2$, and x_c. Thus we have the following theorem by the qualitative theory of ordinary differential equations and the theory of differential manifolds.

Theorem 2.3. *For any $(\lambda_1,\lambda_2,\alpha_1,\alpha_2,x_c) \in \Sigma_{SN}$, $S(x_m,y_m)$ is a cusp-type equilibrium of codimension 2 (i.e. a Bogdanov-Takens bifurcation point) under the condition of Case B.*

The above theorem implies that system (7) cannot exhibit bifurcations of codimension greater than 2 at the degenerate equilibrium. We will prove that Bogdanov-Takens bifurcation occurs in system (7) under a small parameter perturbation by choosing suitable bifurcation parameters in the next section.

Under the hypothesis of Case B, we take λ_1 and λ_2 as bifurcation parameters to study bifurcation analysis of the versal unfolding for the codimension-2 cusp point by the results in [10] and [16].

Denote the new parameter family as $(\lambda_1-\mu_1, \lambda_2+\mu_2, \alpha_1, \alpha_2, x_c)$ after perturbing the parameter family $(\lambda_1,\lambda_2,\alpha_1,\alpha_2,x_c)$, then the perturbed system is written as

$$\begin{array}{rcl} \frac{dx}{dt} & = & (-\lambda_1+\mu_1)x + \frac{\alpha_1x(1-\frac{x}{x_c})}{1+x}y^2 \\ \frac{dy}{dt} & = & (\lambda_2+\mu_2)y - \frac{\alpha_2x}{1+x}. \end{array} \tag{19}$$

In order to simplify (19) into normal form as (17), we first make two affine translations $x_1 = x - x_m,\ y_1 = y - y_m$ and $x_2 = y_1,\ y_2 = cx_1 + \bar{d}y_1$, where $\bar{d} = d + \mu_2$. For the sake of simplification, we redenote $\bar{d}$ as d in the following discussion. Choose the C^∞ change of coordinates same as (14) and (16) in a small neighborhood of $(0,0)$, then system (19) is equivalent to

$$\begin{array}{rcl} \frac{dx_4}{dt} & = & y_4 \\ \frac{dy_4}{dt} & = & [1 + l_{12}(\mu)](cx_m\mu_1 + dy_m\mu_2) - l_{22}(\mu)y_m\mu_2 + [l_{21}(\mu) - m_{22}(\mu)y_m\mu_2]x_4 \\ & & +[l_{11}(\mu) + l_{22}(\mu)]y_4 + m_{21}(\mu)x_4^2 + m_{22}(\mu)x_4y_4 + R_1(x_4, y_4, \mu), \end{array} \tag{20}$$

where $\mu = (\mu_1, \mu_2)$, $m_{2i}(\mu) = d_i + O(|\mu|)$, d_i is expressed as (18), $l_{ij}(\mu),\ m_{1j}(\mu) = O(|\mu|)$ are C^∞ functions of μ and have the following expressions

$$l_{11}(\mu) = -(\frac{q_{11}}{c}x_m\mu_1 + \frac{p_{11}}{c}y_m\mu_2),\ l_{12}(\mu) = -\frac{1}{c^2}q_{11}y_m\mu_2,$$

$$l_{21}(\mu) = -d(\mu_1 + \mu_2) + bc + d^2 + \frac{2d^2}{c^2}q_{11}y_m\mu_2 - \frac{cp_{11} + dq_{11}}{c^2}(cx_m\mu_1 + dy_m\mu_2),$$

$$l_{22}(\mu) = \mu_1 + \mu_2 - \frac{cp_{11} + dq_{11}}{c^2}y_m\mu_2,$$

$$m_{11}(\mu) = \frac{cp_{11} - dq_{11}}{2c^2}l_{11} - \frac{d^2}{c^2}q_{11}l_{12} - \frac{1}{c^2}q_{11}[-d(\mu_1 + \mu_2) + bc + d^2],$$

$$m_{12}(\mu) = \frac{1}{c^2}q_{11}[l_{11} - (\mu_1 + \mu_2)] + \frac{cp_{11} + dq_{11}}{c^2}l_{12},$$

here p_{ij} and q_{ij} are defined as in (10), $R_1(x_4, y_4, \mu) = O(|\mu|^3|) + O(|\mu|^2|(x_4, y_4)|) + O(|\mu||(x_4, y_4)|^2) + O(|(x_4, y_4)|^3)$ is the power series of (x_4, y_4, μ) with at least degree 3 and the coefficients depend on the perturbing parameters μ, $i, j = 1, 2$.

For system (20), one can apply the Malgrange Preparation theorem to simplify the second equation in a normal form (see [10], Chapter 3, pp.194). Here we break this method and make a direct linear transformation $x_5 = x_4 + \frac{l_{21}(\mu) - m_{22}(\mu)y_m\mu_2}{2m_{21}(\mu)}$, $y_5 = y_4$ depending on the parameters. Note that for sufficiently small μ_1 and μ_2, $m_{2i}(\mu) = d_i + O(\mu) \neq 0$ for $i = 1, 2$. Thus rescaling $x_5,\ y_5,\ t$ by $x_6 = \frac{m_{22}^2}{m_{21}}x_5,\ y_6 = \frac{m_{22}^3}{m_{21}^2}y_5,\ \tau = \frac{m_{21}}{m_{22}}t$ and putting the expressions of $l_{ij},\ m_{ij},\ x_m,\ y_m$ into the new equations, we obtain that

$$\begin{aligned} \frac{dx_6}{dt} =& y_6 \\ \frac{dy_6}{dt} =& -\frac{4(9 + x_c)^4}{81(1 + x_c)(3 + x_c)^4\lambda_2^2}\{2(3 + x_c)^2\lambda_2[(3 + x_c)\mu_1 - 3(1 + x_c)\mu_2] \\ &+ (1 + x_c)(9 + x_c)^2\mu_1^2 + 2(27 + 45x_c + 29x_c^2 + 3x_c^3)\mu_1\mu_2 + 4x_c^2(1 + x_c)\mu_2^2\} \\ &+ \{\frac{2(9 + x_c)[-(9 + 18x_c + 5x_c^2)\mu_1 + 6(-3 - 2x_c + x_c^2)\mu_2]}{9(1 + x_c)(3 + x_c)^2\lambda_2} + O(|\mu|^2)\}y_6 \\ &+ x_6^2 + x_6y_6 + R_3(x_6, y_6, \mu) \\ =& \nu_1(\mu) + \nu_2(\mu)y_6 + x_6^2 + x_6y_6 + R_3(x_6, y_6, \mu), \end{aligned} \tag{21}$$

where R_3 has the same properties as R_1. Since

$$\mathrm{Det}\begin{pmatrix} \frac{\partial\nu_1}{\partial\mu_1} & \frac{\partial\nu_1}{\partial\mu_2} \\ \frac{\partial\nu_2}{\partial\mu_1} & \frac{\partial\nu_2}{\partial\mu_2} \end{pmatrix}_{(\mu_1=0,\ \mu_2=0)} = \frac{16(9 + x_c)^5}{81(1 + x_c)(3 + x_c)^4\lambda_2^2} > 0$$

for any values of the parameters x_c, $\lambda_2 > 0$, which implies that the local parameter representation transformation $\nu_1 = \nu_1(\mu)$, $\nu_2 = \nu_2(\mu)$ is nonsingular. Therefore, based on the results in [7], [8], [12] and [28], the following conclusion is valid.

Theorem 2.4. *System (21) is a universal unfolding of the cusp point of codimension 2. There is a neighborhood Ω of $(\mu_1, \mu_2) = (0, 0)$ in $\mathbb{R}^2$ such that system (19) undergoes Bogdanov-Takens bifurcation inside Ω.*

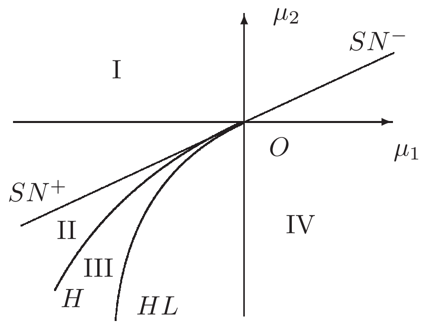
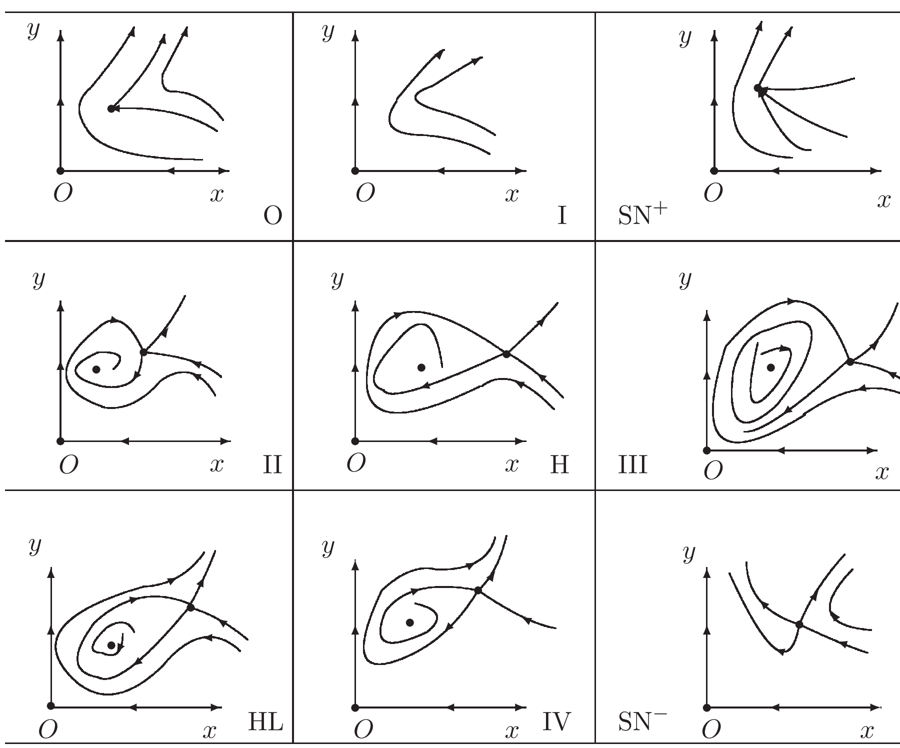


Figure 4. Bifurcation diagram at (x_m, y_m) after perturbing (λ_1, λ_2).

The local bifurcation curves in this small neighborhood Ω of the origin consist of

Table 1. The phase portraits of nonvascularized model.



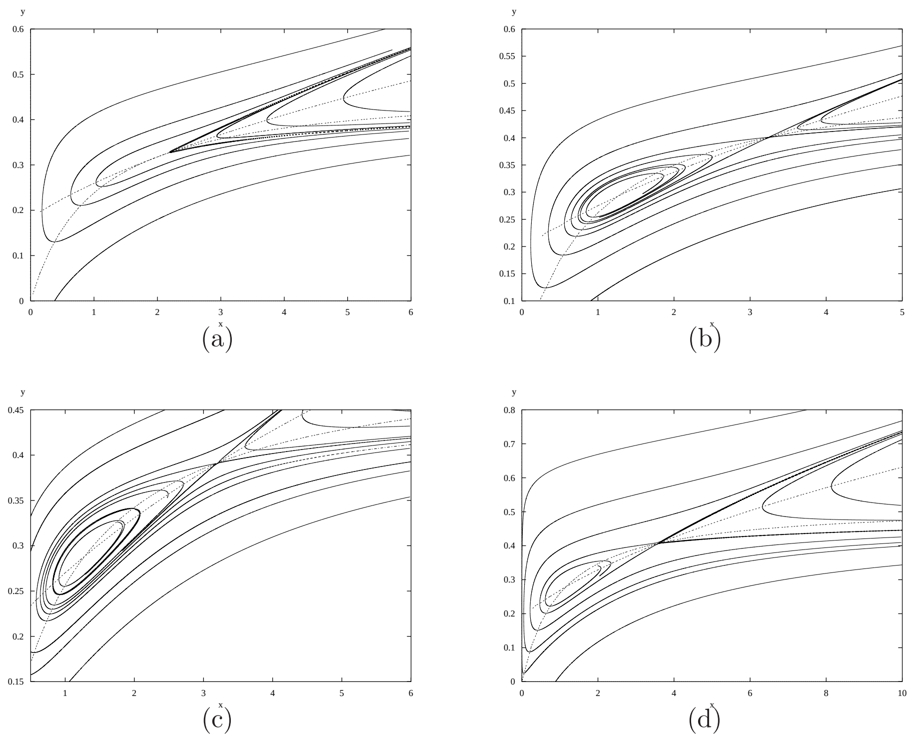


Figure 5. The phase portraits for different (μ_1, μ_2) when $\lambda_2 = \frac{2(3+x_c)}{3(1+x_c)}\lambda_1$ in the avascular case.

$\diamondsuit$ $SN = \{(\mu_1, \mu_2): \ \nu_1(\mu_1, \mu_2) = 0\}$ corresponds to the saddle-node bifurcation curve on the plane of (μ_1, μ_2). Along this curve system (21) has a unique equilibrium with a zero eigenvalue. Crossing SN from the top down implies the appearance of two equilibria, the right one is a saddle and the left one is a stable focus.

$\diamondsuit$ $H = \{(\mu_1, \mu_2): \ \nu_2(\mu_1, \mu_2) = \sqrt{-\nu_1(\mu_1, \mu_2)}\}$ corresponds to the Hopf bifurcation curve on the plane of (μ_1, μ_2). There will occur a stable periodic orbit when $(\mu_1, \mu_2) \in \Omega$ goes through H from II to III and the left equilibrium turns into an unstable focus from a stable focus.

$\diamondsuit$ $HL = \{(\mu_1, \mu_2): \ \nu_1(\mu_1, \mu_2) = -\frac{49}{25}\nu_2(\mu_1, \mu_2)^2 + O(\nu_2(\mu_1, \mu_2)^{5/2}), \ \nu_2(\mu_1, \mu_2) > 0\}$ corresponds to the homoclinic loop bifurcation curve. When $(\mu_1, \mu_2) \in HL$, there is an inner stable homoclinic orbit of system (19). But the homoclinic orbit will be broken once (μ_1, μ_2) traverses HL from III to IV.

The bifurcation diagram of system (19) for $(\mu_1, \mu_2) \in \Omega$ is displayed in Figure 4, where the regions I-IV are shaped by the above three bifurcation curves. For the perturbed system (19), the corresponding phase portraits belonging to each bifurcation region are listed in Table 1. In addition, we draw the trajectories on the phase plane (x, y) by numerical simulations shown in Figure 5 when (μ_1, μ_2) takes particular values in each bifurcation region of Ω, which is consistent with the analytic results in Table 1.

To simulate the stable singular orbits, we choose the value of the original parameters as follows: $\alpha_1^{'} = 1.5 \times 10^{-7}, \ g = 9.2, \ L_c = 2.5 \times 10^{11}, \ K = 10^{-8}, \ \alpha_2^{'} =$

4.6135×10^{-9}, $\lambda_1 = 0.01$, $\lambda_2 = 0.020016$, which followed by the values of the new parameters $\lambda_1 = 0.01$, $\lambda_2 = 0.006672$, $\alpha_1 = 0.297312$, $\alpha_2 = 0.00318$, $x_c = 2500$ in system (7) and the unique interior equilibrium $(x_m, y_m) = (1.9976, 0.317619)$.

In Figure 5, (a) corresponds to the trajectories of unperturbed system (4) near the cusp point B. The uncontrollable tumor cell population will eventually leads to death of patient. When $(\mu_1, \mu_2) = (-0.001246, -0.000609795)$ lies in the region II, the corresponding diagram of phase portrait is shown in Figure 5(b), where two interior equilibria bifurcate from the saddle-node, the left one is a stable focus and the right one is a saddle. There is a region D in the first quadrant such that any orbits originating from D will approaches to one of the equilibria. In other words, the growth of tumor cell population is under control. Figure 5(c) corresponds to the trajectories of system (19) near the steady states when $(\mu_1, \mu_2) = (-0.00083245, -0.000479525)$ lies in the region III, where a stable limit cycle encircling the left unstable focus occurs. When $(\mu_1, \mu_2) = (-0.00073, -0.00056389)$ lies on the curve HL, there is an inner stable homoclinic loop and the corresponding phase portrait is drawn in (d).

3. **Bifurcations of the vascularized model.** The qualitative features of the cancer model with neovascularization was studied by Adam [1] in 1996. Considering the vascularization to model (3), the new system is written as

$$\begin{aligned} \frac{dL}{dt} &= -\lambda_1 L + \alpha_1'\left(\frac{gC^{2/3}}{1+KL}\right)L\left(1-\frac{L}{L_c}\right) - \hat{\beta}_1 C^{2/3} \\ \frac{dC}{dt} &= \lambda_2\left(C - \frac{gC^{2/3}KL}{1+KL}\right) - \alpha_2'\left(\frac{gC^{2/3}}{1+KL}\right)L + \beta_2 C. \end{aligned} \tag{22}$$

For system (22), Adam discussed the Hopf bifurcation near the positive nondegenerate equilibrium when there is not vascularization, i.e. both $\hat{\beta}_1$ and β_2 are 0. By a fresh look at the theory of immunosurveillance, Lin [18] considered the existence, stability and behavior in the rather simple deterministic model. This section presents the qualitative analysis near the degenerate interior equilibrium for system (22) if it exists. We continue to use the notation in section 2 although there may be some differences between the vascularized and nonvascularized cases. Based on the results of the nondimensionalization in [1], system (22) can be rewritten as

$$\begin{aligned} \frac{dx}{dt} &= -\lambda_1 x + \frac{\alpha_1 x y^{2/3}}{1+x}\left(1-\frac{x}{x_c}\right) - \beta_1 y^{2/3} = f(x,y) \\ \frac{dy}{dt} &= (\lambda_2+\beta_2)y - \frac{\alpha_2 x y^{2/3}}{1+x} = g(x,y) \end{aligned} \tag{23}$$

by changes of variables and parameters $x = KL$, $y = KC$, $x_c = KL_c$, $\alpha_1 = \alpha_1' g K^{-2/3}$, $\alpha_2 = gK^{1/3}(\lambda_2 + \alpha_2' K^{-1})$, $\beta_1 = \hat{\beta}_1 K^{1/3}$. Furthermore, the interior equilibria satisfy the equation of the x-location:

$$\frac{\lambda_1(\lambda_2+\beta_2)^2}{\alpha_1\alpha_2^2} = \frac{x[x(1-x/x_c) - k_2(1+x)]}{(1+x)^3} = \psi(x_c, k_2, x), \tag{24}$$

where $k_2 = \beta_1/\alpha_1$ is a nonnegative constant not more than $1/2$ in terms of the parameters range in [18]. We need to point out that $\psi(x_c, k_2, x)$ in (24) depends on k_2 and may be zero or negative for some values of (x, k_2, x_c) in their respectively reasonable range, while this cannot happen for the nonvascularized case.

The equilibrium being far away from the origin guarantees that system (22) is equivalent to

$$\begin{aligned} \frac{dx}{dt} &= -\lambda_1 x + \left[\frac{\alpha_1 x(1-\frac{x}{x_c})}{1+x} - \beta_1\right] y^2 = F(x,y) \\ \frac{dy}{dt} &= (\lambda_2+\beta_2)y - \frac{\alpha_2 x}{1+x} = G(x,y) \end{aligned} \tag{25}$$

in terms of the transformation $y \to y^3$, $(\lambda_2+\beta_2)/3 \to \lambda_2+\beta_2$ and $\alpha_2/3 \to \alpha_2$.

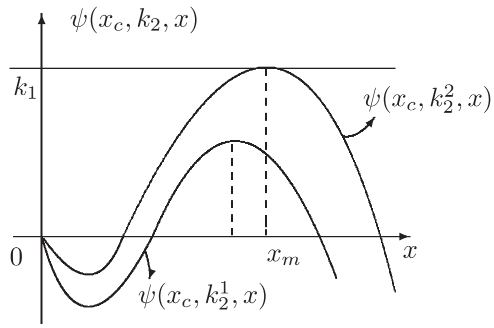


Figure 6. The curve $\psi(x_c, k_2, x)$ at different positive values of k_2 when $x_c > 4k_2/(1-k_2)^2$ with $k_2^1 < k_2^2$.

Since the solutions of (24) can be regarded as the intersection of the horizontal line $y = \frac{\lambda_1(\lambda_2+\beta_2)^2}{\alpha_1\alpha_2^2}$ with the curve of $y = \psi(x_c, k_2, x)$. The degenerate equilibrium of system (25) occurs on the extremum point of $\psi(x_c, k_2, x)$ for x (see Figure 6). The possible abscissa of this point is

$$x_m = \frac{1+\sqrt{1-k_2(1+3/x_c-k_2)}}{1+3/x_c-k_2}, \tag{26}$$

which is meaningful only when both $x_c \le \frac{3k_2}{1-k_2+k_2^2}$ and $\psi(x_c, k_2, x_m) > 0$ hold. Any one of $x_c < \frac{3k_2}{1-k_2+k_2^2}$ and $\psi(x_c, k_2, x_m) \le 0$ being valid will result in the nonexistence of degenerate equilibria for system (25). Owing to

$$x(1-x/x_c) - k_2(1+x) = -\frac{1}{x_c}[x - \frac{x_c(1-k_2)}{2}]^2 + \frac{x_c(1-k_2)^2}{4} - k_2,$$

we find that the existence of x_m requires

$$x_c > \frac{4k_2}{(1-k_2)^2} > \frac{3k_2}{1-k_2+k_2^2}.$$

Otherwise, there are also no interior equilibria for system (25). The Jacobian matrix J, Haissein matrices P and Q of system (25) at the unique interior equilibrium (x_m, y_m) are expressed in the same way as the nonvascularized case except $\hat{b} = b - 2y_m\beta_1$, $\hat{d} = d + \beta_2$ and $\hat{p}_{22} = p_{22} - \beta_1$, where b, d and p_{22} are defined as in (10), $y_m = \frac{\alpha_2 x_m}{(\lambda_2+\beta_2)(1+x_m)}$. For the sake of convenience, we drop the hat to take the uniform symbols in the vascularized case just like (10). Obviously,

$$\mathtt{Det}(J(x_m, y_m)) = \frac{\alpha_1(\lambda_2+\beta_2)y_m^2(1+x_m)^2}{3x_c}\psi_x^{'}(x_c, k_2, x_m) = 0.$$

That is why we call (x_m, y_m) a degenerate equilibrium.

On the other hand, to have the double zero eigenvalues for the matrix of the linear part of (25) at the degenerate equilibrium (x_m, y_m), namely, to have $\mathrm{Tr}(J(x_m, y_m))$

$= 0$ make sense, we should have

$$x_m^2(1+\frac{1}{x_c})-k_2(1+x_m)^2>0,$$

which means that

$$x_m > 1/[\sqrt{\frac{1}{k_2}(1+\frac{1}{x_c})}-1].$$

Using the expression of x_m, we know that the above inequality is equivalent to

$$1+k_2<\sqrt{1-k_2(1+\frac{3}{x_c}-k_2)}+\sqrt{k_2(1+\frac{1}{x_c})},$$

which can be simplified into $x_c > \frac{4k_2}{(1-k_2)^2}$. Therefore, associating with $x_c \geq \frac{3k_2}{1-k_2+k_2^2}$ deduces the following lemmas:

Lemma 3.1. *System (25) has possible interior equilibria only if $x_c > \frac{4k_2}{(1-k_2)^2}$. If the interior equilibrium exists, then its abscissa x satisfies the equation $\frac{\lambda_1(\lambda_2+\beta_2)^2}{\alpha_1\alpha_2^2} = \psi(x_c, k_2, x)$. If the degenerate equilibrium (x_m, y_m) for which the matrix of the linear part of (25) has double zero eigenvalues, then its abscissa x satisfies the equation $\alpha_1\alpha_2^2 = \frac{(\lambda_2+\beta_2)^3(1+x)^4}{x[x^2(1+\frac{1}{x_c})-k_2(1+x)^2]}$.*

Lemma 3.2. *The parameter surface*

$$\tilde{\Sigma}_{SN} = \{(\lambda_1,\lambda_2,\alpha_1,\alpha_2,\beta_1,\beta_2,x_c)|\frac{\lambda_1(\lambda_2+\beta_2)^2}{\alpha_1\alpha_2^2} = \frac{x_m^2(1-x_m/x_c)-k_2x_m(1+x_m)}{(1+x_m)^3},$$
$$\lambda_i,\alpha_i,\beta_i>0, i=1,2\}.$$

corresponds to the saddle-node bifurcation of system (25), where $k_2 = \beta_1/\alpha_1$ and $x_c > 4k_2/(1-k_2)^2$.

Next we restrict on the condition $x_c > \frac{4k_2}{(1-k_2)^2}$ to consider the degenerate interior equilibrium (x_m, y_m) of (25) where the matrix of the linear part has double zero eigenvalues. By a change of coordinates $x_1 = x - x_m,\ y_1 = y - y_m$, we simplify and expand (25) in a power series about the origin:

$$\begin{aligned} \frac{dx_1}{dt} &= -dx_1 - \frac{d^2}{c}y_1 + p_{11}x_1^2 + 2p_{12}x_1y_1 + p_{22}y_1^2 + P_1(x_1,y_1) \\ \frac{dy_1}{dt} &= cx_1 + dy_1 + q_{11}x_1^2 + Q_1(x_1,y_1). \end{aligned} \tag{27}$$

Iterating three more changes of coordinates in (13), (15) and (17), system (27) is transformed into the form of (17), where the only difference lies in

$$\begin{aligned} d_1 &= \frac{d^2}{c^2}(cp_{11}+dq_{11}) - 2dp_{12} + cp_{22} = \frac{(\lambda_2+\beta_2)^2(1+x_m)[(2+\frac{3}{x_c}-k_2)x_m-(1+k_2)]}{\alpha_2[x_m^2(1+\frac{1}{x_c})-k_2(1+x_m)^2]}, \\ d_2 &= -\frac{2d}{c}p_{11} + 2p_{12} = -\frac{2\alpha_1\alpha_2x_m^2\{[1+\frac{x_c}{k_2}(1-k_2+\frac{3}{x_c})]x_m+(3+x_c-\frac{2x_c}{k_2})\}}{(\lambda_2+\beta_2)(1+x_m)^3x_c}. \end{aligned} \tag{28}$$

According to Lemma 3.1 and Lemma 3.2, we have the following theorem for the vascularized case.

Theorem 3.3. *For any $(\lambda_1,\lambda_2,\alpha_1,\alpha_2,\beta_1,\beta_2,x_c) \in \tilde{\Sigma}_{SN}$ with $x_c > \frac{4k_2}{(1-k_2)^2}$, the possible interior equilibrium (x_m, y_m) is a nondegenerate Bogdanov-Takens bifurcation point of codimension 2 for system (25) when $\alpha_1\alpha_2^2 = \frac{(\lambda_2+\beta_2)^3(1+x_m)^4}{x_m[x_m^2(1+\frac{1}{x_c})-k_2(1+x_m)^2]}$, where x_m is defined as in (26).*

Proof. From (26), we have

$$\begin{aligned} & (2+\tfrac{3}{x_c}-k_2)x_m-(1+k_2) \\ = \; & \frac{(2+3/x_c-k_2)\sqrt{1-k_2(1+3/x_c-k_2)}+1-k_2(1+3/x_c-k_2)}{1+3/x_c-k_2}. \end{aligned}$$

Since $x_c > 4k_2/(1-k_2)^2 > 3k_2/(1-k_2+k_2^2)$ and $0 \le k_2 \le 1/2$, the numerator of the above expression is always positive, which implies that $d_1 > 0$ for any positive constants $\lambda_2,\ \beta_2,\ \alpha_1$, and α_2.

Now we need to show that d_2 is nonzero. Suppose otherwise $d_2 = 0$, it would follow from (28) that $x_m = -(3+x_c-\frac{2x_c}{k_2})/[1+\frac{x_c}{k_2}(1-k_2+\frac{3}{x_c})]$. Putting the above expression into (26), we can obtain by using Mathematica that

$$x_c = \frac{-9+12k_2-8k_2^2+(3-2k_2)\sqrt{9+16k_2^2}}{2(1-k_2)} < \frac{4k_2}{(1-k_2)^2},$$

which contradicts with the hypothesis $x_c > \frac{4k_2}{(1-k_2)^2}$.

Thus, $d_1 d_2$ cannot be vanished. As a result, (x_m, y_m) is a nondegenerate cusp-type point of codimension 2 and system (25) will exhibit nondegenerate Bogdanov-Takens bifurcation at this equilibrium. The proof is complete. □

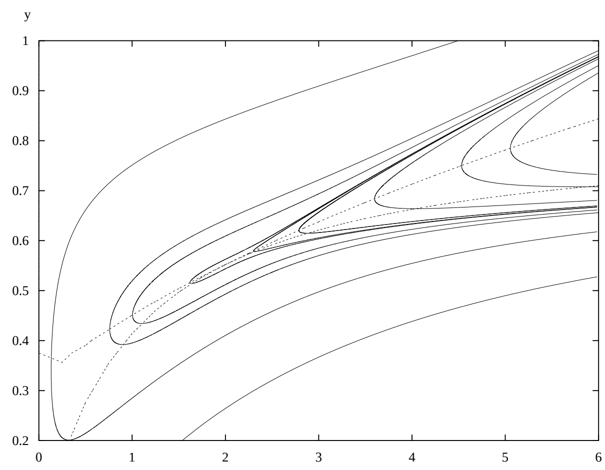


Figure 7. The phase portrait near the cusp-type equilibrium (x_m, y_m) of codimension 2 for the vascularized case.

In fact, we may choose appropriate parameters in system (25) as bifurcation parameters to have the Bogdanov-Takens bifurcation occur near the degenerate equilibrium just like the procedure in section 2. It turns out to be much more complicated to calculate the bifurcation equations and curves because of the existence of the parameters of neovascularization. Nevertheless, we are lucky to find that there are similar results at the degenerate equilibrium between the nonvascularized and vascularized models, so the discussion of the cusp-type bifurcation of codimension 2 for the second case is omitted in this section. In order to clarify the similarity to the avascular case, we select the reasonable values of the original parameters in system (22) as: $\alpha_1^{'} = 1.5 \times 10^{-7},\ g = 9.2,\ L_c = 2.5 \times 10^{11},\ K = 10^{-8},\ \alpha_2^{'} = 2.52 \times 10^{-8},\ \lambda_1 = 0.0301887,\ \lambda_2 = 0.005,\ \hat{\beta}_1 = 0.0232,\ \beta_2 = 0.0554207$, which produce the values of the new parameters $\lambda_1 = 0.0301887,\ \lambda_2 = 0.0016667,\ \alpha_1 =$

0.297312, $\alpha_2 = 0.0166825$, $x_c = 2500$, $\beta_1 = 0.0000499829$, $\beta_2 = 0.018474$ in system (25) and the interior equilibrium $(x_m, y_m) = (1.99785, 0.552014)$. Under these parameter values, the phase portrait by numerical simulations near the unique interior equilibrium for system (25) is depicted in Figure 7.

Based on Theorem 3.3, one can make the following assertion immediately.

Remark 1. Any bifurcations of codimension greater than two cannot take place near the cusp-type equilibrium for perturbed vascularized cancer model (25).

4. **Discussion.** The qualitative analysis and some bifurcation results near the degenerate equilibrium have been given for the cancer models (1) and (2) in this paper. By applying the transformation and bifurcation theory in [10] and [29], we have discovered that the degenerate equilibrium is a nondegenerate cusp of codimension two when the parameters take some critical values whether the cancer model suffers the neovascularization or not. We have also shown that the system in avascular case could exhibit Bogdanov-Takens bifurcation in the small neighborhood of the critical values of parameters. It is valuable to find out that any bifurcations with codimension greater than two cannot appear in the cancer model, which avoids more complex dynamical behavior.

In contrast with previous papers, our results sustain the qualitative analysis of Delisi and Rescigno [11] about the phase portraits in the (x, y)-plane and improve the qualitative studies of Adam [1] and Lin [18] near the degenerate equilibrium. More importantly, we present more detailed and clearer results on the dynamics of these models than Adam [1] and Lin [18], who found that tumor cell population was uncontrolled and trajectories all tended to (x_c, ∞) if $k_1 = \psi(x_m)$. As a matter of fact, the degenerate equilibrium is proved to be a codimension-2 cusp according to the realistic ranges of these parameters meeting an actual biological situation in [18]. Therefore, by choosing particular values of bifurcation parameters (μ_1, μ_2) inside Ω, limit cycles or homoclinic orbits may appear in cancer models. From the biological point of view, the special choice of parameters can lead to the occurrence of the periodic oscillation behavior or coexistence of immune system and tumor cells. The amplitude and the location of the equilibria in the phase plane determine the influence of those oscillations. When the amplitude of the corresponding oscillations is sufficiently small such that the host can put up with the maximum levels of solid tumor and lymphocyte cells, then both healthy and carcinogenic tissue can survive. On the contrary, the survival of the host may fail since the solid tumor reaches a high level when the amplitude is too large ([11]).

In the avascular case, we have obtained the interesting numerical results about the existence of a stable limit cycle and a homoclinic orbit in Figure 5(d) and (e), respectively. When the periodic or homoclinic orbit exists, it can be seen as “safe” in the interior of these closed orbits because the trajectories originating from there will never go beyond them. So the cancer cells and the immune system can coexist for a long term although the cancer is not eliminated eventually. We can interpret this situation biologically that while the immune system fights with cancer in the host, there is a balance between them because of the periodic changes in internal tissues and the external circumstances such that they coexist in a bounded region.

For the vascularized cancer model, the occurrence of Bogdanov-Takens bifurcation was predicted though we did not provide the proof. Intuitively, the presence of neovascularization enhances the possibility of tumor survival, however, the prediction of the existence of a limit cycle or a homoclinic orbit of system (2) bifurcated from the degenerate equilibrium which is similar to the avascular case has been made. Therefore, the qualitative dynamical feature near the interior degenerate equilibrium does not alter even after the cancer model incorporates the terms with respect to the neovascularization of the tumor. Periodic oscillation behavior is still able to occur after vascularization. In fact, comparison between numerical simulations in Figure 5(a) and Figure 7 has exhibited the same dynamical behavior. Such similar anomalous properties like that have also been noticed in [1] and [11].

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