

# EFFECTS OF THE KILLING RATE ON GLOBAL BIFURCATION IN AN ONCOLYTIC-VIRUS SYSTEM WITH TUMORS\*

Wenshuang Suo<sup>1</sup> and Yunfeng Jia<sup>1,†</sup>

**Abstract** Oncologists and virologist are quite concerned about many kinds of issues related to tumor-virus dynamics in different virus models. Since the virus invasive behavior emerges from combined effects of tumor cell proliferation, migration and cell-microenvironment interactions, it has been recognized as a complex process and usually simulated by nonlinear differential systems. In this paper, a nonlinear differential model for tumor-virus dynamics is investigated mathematically. We first give a priori estimates for positive steady-states and analyze the stability of the positive constant solution. And then, based on these, we mainly discuss effects of the rate of killing infected cells on the bifurcation solution emanating from the positive constant solution by taking the killing rate as the bifurcation parameter.

**Keywords** Tumor-virus system, bifurcation, positive solution, stability, Leray-Schauder degree.

**MSC(2010)** 35K57, 58J55.

## 1. Introduction

Mathematical modeling research of virus-cell interaction has a long history. Equally, extensive efforts have been dedicated to the mathematical modeling of cancer development by oncologists over many years. In this paper, we analyze a complex process that involves both virus-cell interaction and tumor growth, which is the interaction of the so called oncolytic viruses with tumors. The interaction between oncolytic virus and tumor cells is amenable to mathematical modeling using adaptations of techniques employed previously for modeling other types of virus-cell interaction. The corresponding model considers two types of cells growing in logistic fashion, which has the following form:

$$\begin{cases} u_t = r_1 u(1 - (u + v)/k) - buv, & t > 0, \\ v_t = r_2 v(1 - (u + v)/k) + buv - av, & t > 0, \end{cases} \quad (1.1)$$

where  $u$  and  $v$  are the sizes of uninfected and infected cells populations. The coefficients  $r_1, r_2, k, b, a$  are positive constants.  $r_1, r_2$  are the maximum per capita

<sup>†</sup>the corresponding author. Email address: [jiayf@snnu.edu.cn](mailto:jiayf@snnu.edu.cn) (Y. Jia)

<sup>1</sup>School of Mathematics and Information Science, Shaanxi Normal University, Xi'an, Shaanxi 710062, China

\*The authors were supported in part by the National Science Foundations of China (11271236), the Program of New Century Excellent Talents in University of Ministry of Education of China (NCET-12-0894), by the Shaanxi New-star Plan of Science and Technology (2015KJXX-21), and also by the Natural Science Basic Research Plan in Shaanxi Province of China (2015JQ1023).

growth rates of uninfected and infected cells,  $k$  is the carrying capacity,  $b$  is the transmission rate, and  $a$  is the rate of infected cells killed by the virus. Model (1.1) is a version of the classical predator-prey model of a biological community first developed by Lotka [14] and Volterra [20]. The term  $buv$  describes the simplest correspondence between prey consumption and predator production similar to the law of mass action. The main result of the analysis of a more general model with respect to (1.1) in [22] consists in defining conditions required for maximum reduction of the tumor load, where whether the tumor cells would become extinct has not been stated clearly. In [16], a complete parametric analysis of dynamic regimes of a conceptual model (which contains model (1.1)) of anti-tumor virus therapy is presented. The authors described deterministic elimination of the tumor cells. Moreover, for different parameter values, they analyzed the asymptotic state to the system.

As most solid tumors have distinct spatial structure, tumor-virus dynamics is usually described by systems of partial differential equations (such as [4–7, 10, 18, 24]), which is an obvious and necessary extension of ordinary differential equation models. In general, these partial differential equation systems are basically divided into two types: (I) The different populations of cells are continuously presented everywhere in the tumor at all times (see [6]); (II) The different populations of cells are separated by interfaces (see [7]).

In larger-scale of tumor-virus dynamical systems, where the models described by partial differential equations, the governing equations are typically of reaction-diffusion type since the distribution of the cells are spatially inhomogeneous. In recent decades, reaction-diffusion equations have been successfully used to model the dynamics of tumors, see [1, 3, 9, 23] for examples. For a similar consideration, instead of (1.1), we are led to investigating the following reaction-diffusion system

$$\begin{cases} u_t - \Delta u = r_1 u(1 - (u + v)/k) - buv, & x \in \Omega, t > 0, \\ v_t - \Delta v = r_2 v(1 - (u + v)/k) + buv - av, & x \in \Omega, t > 0, \\ u(x, t) \geq 0, \neq 0, v(x, t) \geq 0, \neq 0, & x \in \Omega, t = 0, \\ \partial_\nu u = \partial_\nu v = 0, & x \in \partial\Omega, t > 0, \end{cases} \quad (1.2)$$

in a bounded domain  $\Omega \subset R^N$  with smooth boundary  $\partial\Omega$ . Where  $\nu$  is the outward unit normal vector on  $\partial\Omega$ . With an appropriate change of variables, the model (1.2) can be simplified to the following system

$$\begin{cases} u_t - \Delta u = u(1 - (u + v)) - \beta uv, & x \in \Omega, t > 0, \\ v_t - \Delta v = \alpha v(1 - (u + v)) + \beta uv - mv, & x \in \Omega, t > 0, \\ u(x, 0) \geq 0, \neq 0, v(x, 0) \geq 0, \neq 0, & x \in \Omega, t = 0, \\ \partial_\nu u = \partial_\nu v = 0, & x \in \partial\Omega, t > 0, \end{cases} \quad (1.3)$$

where  $\alpha = \frac{r_2}{r_1}$ ,  $\beta = \frac{bk}{r_1}$ ,  $m = \frac{a}{r_1}$ . Then  $m$  will be regarded as the rate of infected cells killed by the virus.

Bifurcation solution of partial differential equation systems is one of the principal concerns of many researchers, and many valuable results were obtained. For example, a diffusive predator-prey system with Holling-type functional response and

homogenous Neumann boundary condition was considered in [8], where the authors considered the bifurcation solution emanating from a positive constant solution by taking the growth rate as a bifurcation parameter, and performed a detailed local and global bifurcation analysis to the diffusive system. In [17], the author surveyed some basic bifurcation results for equation in a setting of infinite dimensional Banach spaces. For a reaction-diffusion system, he found the bifurcating points and obtained a general bifurcation result by taking the diffusion coefficient as a bifurcation parameter. In [19], a semi-linear elliptic problem with nonlinear boundary conditions was studied. The author used the bifurcation results to investigate the set of positive solutions bifurcating from the trivial line. A generic Turing type reaction-diffusion system derived from the Taylor expansion near a constant equilibrium was considered in [11], where the authors studied the existence of Hopf bifurcations and steady-state bifurcations, analyzed the bifurcation direction and the stability of the bifurcating periodic orbits. Moreover, numerical simulations were included to show the spatiotemporal dynamics. Regarded the growth rate of prey as the bifurcation parameter, a delayed predator-prey system with diffusion and Dirichlet boundary conditions was investigated in [12]. The authors showed that Hopf bifurcation occurs when the parameter varies. Furthermore, the explicit algorithm for determining the direction of the Hopf bifurcations and stability of the bifurcating periodic solutions were derived.

For a biological depletion model, the authors, in [21], discussed the stability of the positive constant steady-states and made a detailed description for the global bifurcation structure. Where they took the diffusion coefficient as the bifurcation parameter to investigate the bifurcation solution emanating from positive constant solutions for the model. It is worth noting that the bifurcation parameter sequence is non-monotonic (which means that the extra condition is needed) and the positive constant solutions both have no relationship with the bifurcation parameter.

Motivated by the techniques in [21], in this paper, we mainly study the effects of  $m$  on positive steady-states of (1.3), specifically, we consider the effects of  $m$  on bifurcations of (1.3), and our aim is to make a better description for the structure of non-constant steady-states. Different from [21], here, we will take  $m$  as the bifurcation parameter to discuss the bifurcation solution which emanates from the positive constant solution. The result shows that the local bifurcation emanating from the positive constant solution may be extended to global bifurcation if  $m$  is restricted in a suitable value range. Compared with [21], we find that the positive constant solution depends on the bifurcation parameter  $m$ . What's more, influenced by the model itself, in order to ensure the existence of the positive constant in our model, we must claim that  $m$  is in a bounded interval. So, the bifurcation points are in a bounded domain. Moreover, we see that the bifurcation points come in pairs, say,  $m_i^-$  and  $m_i^+$ . Besides that,  $\{m_i^-\}$  and  $\{m_i^+\}$  can be arranged orderly. Just for these reasons, it needs no extra conditions when we discuss the bifurcation solutions (While in [21], it does, see Remark 2.3 in Subsection 2.3). Our result shows that if the bifurcation curve  $\Gamma_j^-$  eventually meets some bifurcation points, and  $k$  is the biggest footnote of all these points at which  $\Gamma_j^-$  meets, then  $\Gamma_j^-$  must meet both  $(m_k^-, 0)$  and  $(m_k^+, 0)$ .

## 2. Main results

### 2.1. A priori estimates of non-constant positive solutions

As a preparation for bifurcation analysis, in this subsection, we give a priori upper bounds for non-constant positive solutions of the elliptic system

$$\begin{cases} -\Delta u = u(1 - (u + v)) - \beta uv, & x \in \Omega, \\ -\Delta v = \alpha v(1 - (u + v)) + \beta uv - mv, & x \in \Omega, \\ \partial_\nu u = \partial_\nu v = 0, & x \in \partial\Omega. \end{cases} \quad (2.1)$$

Here, to give a simple and direct proof for the a priori upper bounds, we prefer an elliptic maximum principle due to Lou and Ni.

**Lemma 2.1** (Proposition 2.2, [15]). *Suppose that  $F(x, \omega) \in C(\overline{\Omega} \times \mathbb{R})$ . If  $\omega \in C^2(\Omega) \cap C^1(\overline{\Omega})$  satisfies*

$$\Delta\omega(x) + F(x, \omega(x)) \geq 0 \quad \text{in } \Omega; \quad \partial_\nu\omega \leq 0, \quad \text{on } \partial\Omega,$$

and  $\omega(x_0) = \max_{\overline{\Omega}} \omega$ , then  $F(x_0, \omega(x_0)) \geq 0$ . Similarly, if the two inequalities are reversed and  $\omega(x_0) = \min_{\overline{\Omega}} \omega$ , then  $F(x_0, \omega(x_0)) \leq 0$ .

**Theorem 2.1** (A priori estimates). *Suppose  $m < \alpha + \beta$ . If  $(u, v) = (u(x), v(x))$  is a non-constant positive solution to the elliptic system (2.1), then*

$$u < 1 \quad \text{and} \quad v < \frac{\alpha + \beta - m}{\alpha}.$$

**Proof.** It is clear that  $u < 1$  is an immediate result of Lemma 2.1. We only need to show the upper bound for  $v$ . If  $v$  attains its maximum at some  $x_0 \in \overline{\Omega}$ , then by the second equation of (2.1) and Lemma 2.1 we get

$$\alpha v(x_0)(1 - (u(x_0) + v(x_0))) + \beta u(x_0)v(x_0) - mv(x_0) \geq 0.$$

The positivity of  $v$  implies that

$$\alpha(1 - (u(x_0) + v(x_0))) + \beta u(x_0) - m \geq 0.$$

And then

$$v \leq v(x_0) \leq \frac{\alpha(1 - u(x_0)) + \beta u(x_0) - m}{\alpha} < \frac{\alpha + \beta - m}{\alpha}$$

since  $u < 1$ . This completes the proof.  $\square$

**Remark 2.1.** In Subsection 2.3, we discuss bifurcation solution under condition (H1) (see Subsection 2.3). We see (H1) insures  $m < \alpha + \beta$ .

### 2.2. Stability of the constant positive solution

It is easy to verify that the system (2.1) has a unique positive constant solution  $(u^*, v^*)$  with

$$u^* = \frac{\alpha\beta - (\beta + 1)m}{\beta(\alpha - \beta - 1)}, \quad v^* = \frac{m - \beta}{\beta(\alpha - \beta - 1)}$$

if and only if one of the following two conditions is satisfied:

- (H1)  $\beta < m < \frac{\alpha\beta}{\beta+1}, \alpha > \beta + 1;$
- (H2)  $\frac{\alpha\beta}{\beta+1} < m < \beta, \alpha < \beta + 1.$

We next prove the local stability of  $(u^*, v^*)$ . Let  $0 = \lambda_0 < \lambda_1 < \lambda_2 < \dots$  be the sequence of eigenvalues for the elliptic operator  $-\Delta$  subject to the Neumann boundary condition on  $\Omega$ , where each  $\lambda_i$  has multiplicity  $s_i \geq 1$ . Let  $\phi_{ij}, 1 \leq j \leq s_i$ , be the normalized eigenfunctions corresponding to  $\lambda_i$ . Then the set  $\{\phi_{ij}\}, i \geq 0, 1 \leq j \leq s_i$ , forms a complete orthogonal basis in  $L^2(\Omega)$ . The local stability of  $(u^*, v^*)$  is as follows.

**Theorem 2.2.** *The constant steady-state  $(u^*, v^*)$  of (2.1) is asymptotically stable if (H2) holds, and is unstable if (H1) holds.*

**Proof.** Consider the linearized operator of (2.1) at  $(u^*, v^*)$

$$L \triangleq \begin{pmatrix} \Delta + f_0 & f_1 \\ g_0 & \Delta + g_1 \end{pmatrix},$$

where

$$\begin{aligned} f_0 &= \frac{(\beta + 1)m - \alpha\beta}{\beta(\alpha - \beta - 1)} < 0, & f_1 &= \frac{(\beta + 1)((\beta + 1)m - \alpha\beta)}{\beta(\alpha - \beta - 1)} < 0, \\ g_0 &= \frac{(\beta - \alpha)(m - \beta)}{\beta(\alpha - \beta - 1)}, & g_1 &= \frac{\alpha(\beta - m)}{\beta(\alpha - \beta - 1)} < 0. \end{aligned}$$

Suppose  $(\phi, \psi)^T$  is an eigenfunction of  $L$  corresponding to eigenvalue  $\mu$ . Then we have

$$\begin{cases} \Delta\phi + (f_0 - \mu)\phi + f_1\psi = 0, \\ \Delta\psi + (g_1 - \mu)\psi + g_0\phi = 0. \end{cases}$$

Let

$$\phi = \sum_{0 \leq i \leq \infty, 1 \leq j \leq s_i} a_{ij}\phi_{ij}, \quad \text{and} \quad \psi = \sum_{0 \leq i \leq \infty, 1 \leq j \leq s_i} b_{ij}\phi_{ij},$$

where  $a_{ij}, b_{ij}$  are constants. We find that

$$\sum_{0 \leq i \leq \infty, 1 \leq j \leq s_i} \begin{pmatrix} f_0 - \lambda_i - \mu & f_1 \\ g_0 & g_1 - \lambda_i - \mu \end{pmatrix} \begin{pmatrix} a_{ij} \\ b_{ij} \end{pmatrix} \phi_{ij} = 0.$$

It follows that  $\mu$  is an eigenvalue of  $L$  if and only if for some  $i \geq 0$  the determinant of the corresponding matrix is zero, that is,

$$\mu^2 - P_i\mu + Q_i = 0$$

with

$$\begin{aligned} P_i &= -2\lambda_i + f_0 + g_1 < 0, \\ Q_i &= (f_0 - \lambda_i)(g_1 - \lambda_i) - f_1 + g_0 = \frac{\beta(1 + \beta - \alpha)}{\alpha} f_0 g_1 + \lambda_i^2 - (f_0 + g_1)\lambda_i. \end{aligned} \quad (2.2)$$

If  $\alpha < \beta + 1$ , then by (2.2),  $Q_i > 0$  for all  $i \geq 0$ . This implies that the real parts  $\operatorname{Re} \mu$  of  $\mu$  are negative for all eigenvalues  $\mu$ , and so the steady-state  $(u^*, v^*)$  is asymptotically stable.

If  $\alpha > \beta + 1$ , then from (2.2) we have at least  $Q_0 = \frac{\beta(1+\beta-\alpha)f_0g_1}{\alpha} < 0$ , and so the instability of  $(u^*, v^*)$  follows. And the proof is finished.  $\square$

When  $(u^*, v^*)$  is unstable, we may expect the existence of non-constant steady-states near  $(u^*, v^*)$ . In the following, we will discuss the bifurcation under (H1).

### 2.3. Local bifurcation and global bifurcation

In this subsection, under the condition (H1), we fix  $\alpha$  and  $\beta$ , and take  $m$  as a bifurcation parameter to analyze the bifurcating solution of (2.1), which bifurcates from  $(u^*, v^*)$ . By using the local bifurcation theory, we give a precise description for the structure of positive solutions near the bifurcation points. Then we prolong the bifurcation curves by the global bifurcation theory.

With the condition (H1), we suppose

$$\alpha = 4\beta^2 + 5\beta + 1, \quad \lambda_1 \leq \frac{\beta^2}{2\beta + 1}, \quad (2.3)$$

or

$$\alpha \neq 4\beta^2 + 5\beta + 1, \quad (2.4)$$

$$\lambda_1 \leq \frac{\beta(\alpha + \beta + 1) - 2\beta(1 + \beta)\sqrt{\alpha - \beta}}{\alpha - 4\beta^2 - 5\beta - 1} \triangleq \lambda^* \quad (2.5)$$

holds. Moreover, we define  $i_\alpha = i_\alpha(\alpha, \beta, \Omega)$  the largest positive integer such that

$$\lambda_i \leq \frac{\beta^2}{2\beta + 1} \quad \text{or} \quad \lambda_i \leq \lambda^*, \quad \text{for } i \leq i_\alpha.$$

Clearly, if (2.3) or (2.4)–(2.5) is satisfied, then  $1 \leq i_\alpha < \infty$ . In this case, we let

$$m_i^- = \frac{\beta(\alpha + \beta + 1) - (\alpha - \beta - 1)\lambda_i - \sqrt{(\alpha - \beta - 1)[(\alpha - 4\beta^2 - 5\beta - 1)\lambda_i^2 - 2\beta(\alpha + \beta + 1)\lambda_i + \beta^2(\alpha - \beta - 1)]}}{2(\beta + 1)},$$

$$m_i^+ = \frac{\beta(\alpha + \beta + 1) - (\alpha - \beta - 1)\lambda_i + \sqrt{(\alpha - \beta - 1)[(\alpha - 4\beta^2 - 5\beta - 1)\lambda_i^2 - 2\beta(\alpha + \beta + 1)\lambda_i + \beta^2(\alpha - \beta - 1)]}}{2(\beta + 1)}.$$

It is easy to see that these points satisfy

$$\beta < m_1^- < m_2^- < \cdots < m_{i_\alpha}^- < m_{i_\alpha}^+ < \cdots < m_2^+ < m_1^+ < \frac{\beta\alpha}{\beta + 1}. \quad (2.6)$$

**Remark 2.2.**  $\lambda^*$  is the larger root of the equation  $(\alpha - 4\beta^2 - 5\beta - 1)\lambda^2 - 2\beta(\alpha + \beta + 1)\lambda + \beta^2(\alpha - \beta - 1) = 0$ . It is easy to show that whether  $\alpha - 4\beta^2 - 5\beta - 1$  is larger than 0 or smaller than 0,  $\lambda^*$  is always positive.

**Remark 2.3.** In [21], the bifurcation parameter sequence  $\{d_i\}$  is non-monotonic, so there needs the extra condition  $d_i \neq d_j$  for  $i \neq j$ . Here  $\{m_i^-\}$  and  $\{m_i^+\}$  are monotonic, and we do not need such additional conditions.

Now, let  $Y = L^2(\Omega) \times L^2(\Omega)$  be the Hilbert space with the inner product  $(U_1, U_2)_Y = (u_1, u_2)_{L^2(\Omega)} + (v_1, v_2)_{L^2(\Omega)}$  for  $U_1 = (u_1, v_1), U_2 = (u_2, v_2) \in Y$ , and

$$E = \{(u, v) : u, v \in C^2(\bar{\Omega}), \quad \partial_\nu u = \partial_\nu v = 0, \quad x \in \partial\Omega\}.$$

Then  $E$  is a Banach space with usual  $C^2$  norm. Define operator  $F : (\beta, \frac{\beta\alpha}{\beta+1}) \times E \rightarrow Y$  as

$$F(m, U) = \begin{pmatrix} \Delta u + u(1 - (u + v)) - \beta uv \\ \Delta v + \alpha v(1 - (u + v)) + \beta uv - mv \end{pmatrix},$$

where  $U = (u, v)$ . Thus  $U$  is the solution of (2.1) if and only if  $U$  satisfies  $F(m, U) = 0$ . With  $U^* = (u^*, v^*)$ , we have

$$F(m, U^*) = 0$$

for all  $\beta < m < \frac{\beta\alpha}{\beta+1}$ .

**Theorem 2.3.** *Suppose (H1) holds. If*

$$\alpha = 4\beta^2 + 5\beta + 1, \quad \lambda_j \leq \frac{\beta^2}{2\beta + 1}, \quad (2.7)$$

or

$$\alpha \neq 4\beta^2 + 5\beta + 1, \quad \lambda_j \leq \lambda^*, \quad (2.8)$$

holds and  $\lambda_j$  is simple for some  $j$ . Then  $(m_j^-, U^*)$  and  $(m_j^+, U^*)$  are both bifurcation points of  $F(m, U) = 0$  with respect to the curve  $(m, U^*)$ .

**Proof.** Note that the Fréchet derivative of  $F$  at  $U^*$  is

$$F_U(m, U^*) = \begin{pmatrix} \Delta + f_0 & f_1 \\ g_0 & \Delta + g_1 \end{pmatrix} = L.$$

Let  $\Phi = (\phi, \psi)^T \in \ker L$  with  $\ker L$  being the kernel space of  $L$ . And write

$$\phi = \sum_{0 \leq i \leq \infty, 1 \leq j \leq s_i} a_{ij} \phi_{ij}, \quad \psi = \sum_{0 \leq i \leq \infty, 1 \leq j \leq s_i} b_{ij} \phi_{ij}$$

as in the proof of Theorem 2.2. Then

$$\sum_{0 \leq i \leq \infty, 1 \leq j \leq s_i} B_i \begin{pmatrix} a_{ij} \\ b_{ij} \end{pmatrix} \phi_{ij} = 0$$

with

$$B_i = \begin{pmatrix} f_0 - \lambda_i & f_1 \\ g_0 & g_1 - \lambda_i \end{pmatrix}.$$

Since

$$\det B_i = 0 \quad \text{if and only if} \quad m = m_i^- \quad \text{or} \quad m = m_i^+,$$

taking  $m = m_j^-$ , by (2.6) we know that  $m_j^- \neq m_i^-$  and  $m_j^- \neq m_i^+$  for  $i \neq j$ . So, there only holds  $\det B_j = 0$ . Moreover, the eigenfunction corresponding to  $\lambda_j$  is  $\phi_{j1}$  in view of the multiplicity of  $\lambda_j$  is 1. Then

$$\ker L = \text{span}\{\Phi\}, \quad \Phi = \begin{pmatrix} 1 \\ b_{j1} \end{pmatrix} \phi_{j1}$$

with  $b_{j1} = \frac{\lambda_j - f_0}{f_1} < 0$ . Considering the adjoint operator  $L^*$  of  $L$

$$L^* = \begin{pmatrix} \Delta + f_0 & g_0 \\ f_1 & \Delta + g_1 \end{pmatrix},$$

we obtain

$$\ker L^* = \text{span}\{\Phi^*\}, \quad \Phi^* = \begin{pmatrix} 1 \\ b_{j1}^* \end{pmatrix} \phi_{j1}$$

with  $b_{j1}^* = \frac{\lambda_j - f_0}{g_0} < 0$ . Here we note that  $g_0 < 0$ , under the assumption (H1). Denote by  $R(L)$  the range space of  $L$ . Then  $\text{codim}R(L) = \dim \ker(L^*) = 1$  in view of  $R(L) = (\ker L^*)^\perp$ .

Finally, since

$$F_{U_m}(m_j^-, U^*)\Phi = \begin{pmatrix} 0 & 0 \\ 0 & -1 \end{pmatrix} \Phi = \begin{pmatrix} 0 \\ -b_{j1}\phi_{j1} \end{pmatrix},$$

and

$$(F_{U_m}(m_j^-, U^*)\Phi, \Phi^*)_Y = (-b_{j1}\phi_{j1}, b_{j1}^*\phi_{j1}) = -b_{j1}b_{j1}^* < 0,$$

then we obtain  $F_{U_m}(m_j^-, U^*)\Phi \notin R(L)$ . Then the conditions of the local bifurcation theorem [2] are satisfied, and it follows that  $(m_j^-, U^*)$  is a bifurcation point. This completes the proof.  $\square$

According to the local bifurcation theorem, there is a one-parameter family of non-trivial solutions  $\Gamma_j^-(s) = (m(s), u(s), v(s))$  of the problem (2.1) for  $|s|$  sufficiently small, where  $m(s), u(s), v(s)$  are continuous functions satisfying  $m(0) = m_j^-$  and

$$u(s) = u^* + s\phi_{j1} + o(s), \quad v(s) = v^* + sb_{j1}\phi_{j1} + o(s), \quad m(s) = m_j^- + o(s).$$

The zero set of  $F$  consists of two curves  $(m, U^*)$  and  $\Gamma_j^-(s)$  in a neighborhood of the bifurcation point  $(m_j^-, U^*)$ . What's more, in the same way as above we can verify that  $(m_j^+, U^*)$  is also a bifurcation point and we have the similar conclusion for the bifurcation point  $(m_j^+, U^*)$ .

**Remark 2.4.** Theorem 2.3 assumes that  $\lambda_j$  is simple for some  $j \geq 1$ . In one dimensional case, it is well known that all eigenvalues of  $-\Delta$  are simple. However, in multi-dimensional case, in general, it is hard to know the multiplicity of  $\lambda_j, j \geq 1$ . Sometimes,  $\lambda_j, j \geq 1$  may be simple for special  $\Omega$ . For example, if  $\Omega$  is a rectangle region, say,  $\Omega = (0, a) \times (0, b)$ , then the set of eigenvalues of  $-\Delta$  is  $\{\lambda_{m,n} = (\frac{m\pi}{a})^2 + (\frac{n\pi}{b})^2\}_{m,n=0}^\infty$ , and  $\varphi_{m,n}(x, y) = \cos \frac{m\pi}{a}x \cos \frac{n\pi}{b}y, (x, y) \in (0, a) \times (0, b)$ , is the eigenfunction corresponding to  $\lambda_{m,n}$ . For  $m = n$ , it is easy to verify that the corresponding eigenvalues have multiplicity one indeed.

The above local bifurcation result gives a relatively precise description for the structure of positive solutions near bifurcation points, but it provides no information on the bifurcation curve far from the equilibrium. Therefore, a further study is necessary in order to understand the bifurcation curve when it is far away from the



bifurcation point. In the following, we investigate the coexistence of the steady-state solution by considering the global bifurcation. For simplicity, we suppose that  $\Omega$  is one dimensional, say  $\Omega = (0, l)$ . By applying the global bifurcation theory and the Leray-Schauder degree theory to the compact linear operator, we can obtain the following global result.

**Theorem 2.4.** *Let  $\Omega = (0, l)$  and (H1) be satisfied. If (2.7) or (2.8) holds for some  $j$ . Then the bifurcation curve  $\Gamma_j^-$  satisfies either situation (i) or situation (ii).*

- (i) *The projection of the bifurcation curve  $\Gamma_j^-$  on the  $m$ -axis contains  $(\beta, m_j^-)$  or  $(m_j^-, \frac{\beta\alpha}{\beta+1})$ . If  $m > m_1^-$ ,  $m \neq m_k^-$  and  $m \neq m_k^+$  for any integer  $k > 0$ , then the system (2.1) possesses at least one non-constant positive solution;*
- (ii)  *$\Gamma_j^-$  meets some bifurcation points, which are in  $\{(m_i^-, 0)\}_1^{i_\alpha} \setminus \{(m_j^-, 0)\}$  or  $\{(m_i^+, 0)\}_1^{i_\alpha}$ . If  $\Gamma_j^-$  meets  $(m_k^-, 0)$ , but not  $(m_i^-, 0)$  and  $(m_i^+, 0)$  for any  $i > k$ . Then it must meet  $(m_k^+, 0)$ .*

**Proof.** We rewrite the system (2.1) in a new form. Let  $\tilde{u} = u - u^*$ ,  $\tilde{v} = v - v^*$ . Then (2.1) is transformed into

$$\begin{aligned} -\tilde{u}'' &= f_0\tilde{u} + f_1\tilde{v} + \tilde{f}(\tilde{u}, \tilde{v}), \\ -\tilde{v}'' &= g_0\tilde{u} + g_1\tilde{v} + \tilde{g}(\tilde{u}, \tilde{v}), \end{aligned}$$

where  $\tilde{f}$  and  $\tilde{g}$  are higher-order terms of  $\tilde{u}$  and  $\tilde{v}$ . The constant steady-state  $(u^*, v^*)$  of (2.1) is converted to  $(0, 0)$  of this new system.

Let  $G : h \rightarrow \omega$  be the Green operator for the boundary value problem

$$-\omega'' - f_0\omega = h \quad \text{in } (0, l); \quad \omega' = 0 \quad \text{at } x = 0, l,$$

and  $G' : h \rightarrow \omega$  be the Green operator for

$$-\omega'' - g_1\omega = h \quad \text{in } (0, l); \quad \omega' = 0 \quad \text{at } x = 0, l$$

with  $f_0 < 0$  and  $g_1 < 0$ . Put  $\tilde{U} = (\tilde{u}, \tilde{v})$ ,

$$K(m)\tilde{U} = (f_1G(\tilde{v}), g_0G'(\tilde{u})),$$

and

$$H(\tilde{U}) = (G(\tilde{f}(\tilde{u}, \tilde{v})), G'(\tilde{g}(\tilde{u}, \tilde{v}))).$$

Then system (2.1) can be interpreted as the equation

$$\tilde{U} = K(m)\tilde{U} + H(\tilde{U}). \tag{2.9}$$

For each  $m \in (\beta, \frac{\beta\alpha}{\beta+1})$ ,  $K(m)$  and  $H$  ( $H(\tilde{U}) = o(|\tilde{U}|)$ ) are compact linear operators on  $E$ .

In order to apply the global bifurcation theory in [13], firstly, we need to verify that 1 is an eigenvalue of  $K(m_j^-)$  with algebraic multiplicity one. By the proof of Theorem 2.3, it is clear that  $\ker(K(m_j^-) - I) = \ker L = \text{span}\{\Phi\}$ , so 1 is an eigenvalue of  $K(m_j^-)$  and  $\dim\ker(K(m_j^-) - I) = 1$ . Because the algebraic multiplicity of eigenvalue 1 is the dimension of the generalized null space  $\bigcup_{i=1}^\infty \ker(K(m_j^-) - I)^i$ , then we need to verify that  $\ker(K(m_j^-) - I) \cap R(K(m_j^-) - I) = \{0\}$ .

We now compute  $\ker(K^*(m_j^-) - I)$ , where  $K^*(m_j^-)$  is the adjoint of  $K(m_j^-)$ . Let  $(\phi, \psi)^T \in \ker(K^*(m_j^-) - I)$ . Then

$$g_0 G'(\psi) = \phi, \quad f_1 G(\phi) = \psi.$$

By the definition of  $G$  and  $G'$  we obtain

$$\phi'' + g_1 \phi + g_0 \psi = 0, \quad \psi'' + f_0 \psi + f_1 \phi = 0.$$

In the one dimensional case, let  $\{\phi_i\}$  be a complete orthogonal basis in  $L^2((0, l))$ . Write  $\phi = \sum a_i \phi_i$ ,  $\psi = \sum b_i \phi_i$ , where  $a_i, b_i$  are constants. Then

$$\sum_{i=0}^{\infty} A_i \begin{pmatrix} a_i \\ b_i \end{pmatrix} \phi_i = 0,$$

where

$$A_i = \begin{pmatrix} g_1 - \lambda_i & g_0 \\ f_1 & f_0 - \lambda_i \end{pmatrix}.$$

By calculation we know that  $\det A_i = \det B_i$ , then  $\det A_i = 0$  only for  $i = j$ , and  $\ker(K^*(m_j^-) - I)$  is spanned by  $(1, \frac{f_1}{\lambda_j - f_0})\phi_j$  (In the case of one dimensional, we denote  $\phi_{j1}$  by  $\phi_j$ ).

Since

$$(\Phi, (1, \frac{f_1}{\lambda_j - f_0})\phi_j) = ((1, \frac{\lambda_j - f_0}{f_1})\phi_j, (1, \frac{f_1}{\lambda_j - f_0})\phi_j) = 2,$$

this means that  $\Phi \notin (\ker(K^*(m_j^-) - I))^\perp = R(K(m_j^-) - I)$ . Further,

$$\ker(K(m_j^-) - I) \cap R(K(m_j^-) - I) = \{0\},$$

which shows that the eigenvalue 1 has algebraic multiplicity one indeed.

Secondly, we need to verify that the  $\text{index}(I - K(m_j^-) - H, (m_j^-, 0))$  changes when  $m$  crosses  $m_j^-$ . That is, for  $\epsilon > 0$  sufficient small, we should show that the index inequality

$$\text{index}(I - K(m_j^- - \epsilon) - H, (m_j^- - \epsilon, 0)) \neq \text{index}(I - K(m_j^- + \epsilon) - H, (m_j^- + \epsilon, 0))$$

holds. Suppose  $N(m_j^-)$  is a small neighborhood of  $m_j^-$ . If  $m \in N(m_j^-)$ ,  $m \neq m_j^-$ , then the linear operator  $I - K(m) : E \rightarrow E$  is a bijection and 0 is an isolated solution of (2.9) for fixed  $m$ . The index of this isolated zero of  $I - K(m) - H$  is given by

$$\text{index}(I - K(m) - H, (m, 0)) = \deg(I - K(m), B, 0) = (-1)^p,$$

where  $B$  is a sufficiently small ball centering at 0, and  $p$  is the sum of the algebraic multiplicities of eigenvalues of  $K(m)$  that are larger than 1.

Suppose that  $\mu$  is an eigenvalue of  $K(m)$  and  $(\phi, \psi)^T$  is the corresponding eigenfunction. Then

$$-\mu \phi'' - \mu f_0 \phi = f_1 \psi, \quad -\mu \psi'' - \mu g_1 \psi = g_0 \phi.$$

Let  $\phi = \sum a_i \phi_i, \psi = \sum b_i \phi_i$ . Then

$$\sum_{i=0}^{\infty} \begin{pmatrix} \mu(-\lambda_i + f_0) & f_1 \\ g_0 & \mu(-\lambda_i + g_1) \end{pmatrix} \begin{pmatrix} a_i \\ b_i \end{pmatrix} \phi_i = 0.$$

Thus  $\mu$  satisfies

$$\mu^2(-\lambda_i + f_0)(-\lambda_i + g_1) = f_1 g_0 \tag{2.10}$$

for  $0 \leq i \leq \infty$ .

Let  $\mu(m), \tilde{\mu}(m)$  be the roots of the equation (2.10). Then

$$\mu(m) = \sqrt{\frac{f_1 g_0}{(-\lambda_i + f_0)(-\lambda_i + g_1)}}, \quad \tilde{\mu}(m) = -\sqrt{\frac{f_1 g_0}{(-\lambda_i + f_0)(-\lambda_i + g_1)}}.$$

Take  $m = m_j^-$ . Then  $\mu = 1$  is a root of (2.10) if and only if  $i = j$ . And in this case

$$\mu(m_j^-) = 1 \quad \text{and} \quad \tilde{\mu}(m_j^-) < 1$$

since  $\mu(m)$  is increasing in  $(\beta, m_j^*)$  and decreasing in  $(m_j^*, \frac{\beta\alpha}{\beta+1})$ , where

$$m_j^* = \frac{\beta \sqrt{(\beta + 1)^2 \lambda_j^2 + (\beta + 1)(\alpha + \lambda_j(\alpha + \beta + 1)) - \beta(\beta + 1)\lambda_j}}{(\beta + 1)}.$$

These points satisfy  $m_j^- \in (\beta, m_j^*), m_j^+ \in (m_j^*, \frac{\beta\alpha}{\beta+1})$ . For  $\epsilon > 0$  sufficiently small, there results

$$\mu(m_j^- + \epsilon) > 1, \quad \text{and} \quad \mu(m_j^- - \epsilon) < 1.$$

Hence  $K(m_j^- + \epsilon)$  has exactly one more eigenvalues that are larger than 1 than  $K(m_j^- - \epsilon)$  dose. In the same way as above we can verify that this eigenvalue has algebraic multiplicity one, so the desired index inequality holds.

By the global bifurcation theorem, we know that either  $\Gamma_j^-$  is noncompact in  $(\beta, \frac{\beta\alpha}{\beta+1}) \times E$  or  $\Gamma_j^-$  meets  $m_k^+$  and  $m_k^-$  where  $m_k^- \neq m_j^-$  for  $k \neq j$ . Then, we verify if the second alternative occurs, it must be the situation (ii) in Theorem 2.4. If  $\Gamma_j^-$  meets some other bifurcation points, say,  $\Gamma_j^-$  meets  $(m_k^-, 0)$ , but dose not meet  $(m_i^-, 0)$  and  $(m_i^+, 0)$  for any  $i > k$ . Consider the system (2.1) on the interval  $(0, l/k)$

$$\begin{cases} -u'' = u(1 - (u + v)) - \beta uv, \\ -v'' = \alpha v(1 - (u + v)) + \beta uv - mv, \\ u' = v' = 0, \quad x = 0, l/k, \end{cases} \tag{2.11}$$

with  $x \in (0, l/k)$  in equations. If  $\bar{U}$  is a solution of (2.11), then we construct a solution  $U$  to (2.1) by a reflective and periodic extension. Let  $x_n = nl/k, n = 0, 1, \dots, k$ , and

$$U(x) = \begin{cases} \bar{U}(x - x_{2n}), & x_{2n} \leq x \leq x_{2n+1}, \\ \bar{U}(x_{2n+2} - x), & x_{2n+1} \leq x \leq x_{2n+2}. \end{cases}$$

Define  $\hat{m}_i^+$  and  $\hat{m}_i^-$  as

$$\hat{m}_i^+ = \frac{\beta(\alpha+\beta+1) - (\alpha-\beta-1)\bar{\lambda}_i + \sqrt{(\alpha-\beta-1)[(\alpha-4\beta^2-5\beta-1)\bar{\lambda}_i^2 - 2\beta(\alpha+\beta+1)\bar{\lambda}_i + \beta^2(\alpha-\beta-1)]}}{2(\beta+1)},$$

$$\hat{m}_i^- = \frac{\beta(\alpha+\beta+1) - (\alpha-\beta-1)\bar{\lambda}_i - \sqrt{(\alpha-\beta-1)[(\alpha-4\beta^2-5\beta-1)\bar{\lambda}_i^2 - 2\beta(\alpha+\beta+1)\bar{\lambda}_i + \beta^2(\alpha-\beta-1)]}}{2(\beta+1)},$$

where  $\bar{\lambda}_i = (k\pi i/l)^2$ . Then  $\bar{\lambda}_i = \lambda_{ik}$  ( $\lambda_{ik}$  is the  $ik$ -th eigenvalue for the elliptic operator  $-\Delta$  under the one dimensional case). We obtain that  $\hat{m}_1^- = m_k^-$  is a bifurcation point of (2.1). Let  $\bar{\Gamma}_1^-$  be the bifurcation branch of (2.11) that meets  $(\hat{m}_1^-, 0)$ . Then by the global bifurcation theorem, either it is noncompact in  $(\beta, \frac{\beta\alpha}{\beta+1}) \times E$  or it meets

- case (1):  $(\hat{m}_s^-, 0)$  or  $(\hat{m}_s^+, 0)$  with  $s > 1$ ;
- case (2):  $(\hat{m}_1^+, 0)$ .

If case (1) occurs, then by the extension we know that  $\Gamma_j^-$  meets  $(m_{sk}^-, 0)$  or  $(m_{sk}^+, 0)$ , where  $sk > k$ . This violates the definition of  $k$ . So, case (1) will not occur. Suppose that case (2) also will not occur. Since we consider the bifurcation from positive constant solution  $(u^*, v^*)$ , the situation  $\frac{\alpha\beta}{\beta+1} = m = \beta$  will not be considered. Otherwise,  $(u^*, v^*) \equiv (0, 0)$ . For  $m < \beta$  and  $m > \frac{\alpha\beta}{\beta+1}$ , we know that  $(u^*, v^*)$  is stable in light of Theorem 2.2, so there has no nonconstant positive solution bifurcating from  $(u^*, v^*)$  indeed. And then,  $\bar{\Gamma}_1^-$  is noncompact in  $(\beta, \frac{\beta\alpha}{\beta+1}) \times E$ , and by the extension,  $\Gamma_j^-$  is noncompact in  $(\beta, \frac{\beta\alpha}{\beta+1}) \times E$  (More precisely,  $\bar{\Gamma}_1^-$  and  $\Gamma_j^-$  are noncompact in a maximal connected subset of  $(\beta, \frac{\beta\alpha}{\beta+1}) \times E$  in view of the boundedness of positive solutions), which means that the projection of the bifurcation curve  $\Gamma_j^-$  on the  $m$ -axis contains  $(\beta, m_j^-)$  or  $(m_j^-, \frac{\beta\alpha}{\beta+1})$ , which is the situation (i) in Theorem 2.4; If case (2) occurs, by extension we know that  $\Gamma_j^-$  meets  $(m_k^+, 0)$ , which is the situation (ii) in Theorem 2.4.

If  $\Gamma_j^-$  meets some other bifurcation points, say,  $\Gamma_j^-$  meets  $(m_k^+, 0)$ , but does not meet  $(m_i^-, 0)$  and  $(m_i^+, 0)$  for any  $i > k$ . By the same argument, we can get the same conclusion.

Using the same way as above, we can obtain that the bifurcation curve  $\Gamma_j^+$  has similar properties with  $\Gamma_j^-$ . The proof is accomplished.  $\square$

### 3. Discussion and conclusion

For tumor-virus models, from valuable results that the scholars have obtained, we know that the size of the tumor may be reduced in a short time if the injected viral density is suitable. This means that both infected and uninfected tumors can be eliminated with time, and complete recovery is possible. We investigate a mathematical model for cancer treatment by using oncolytic viruses. The viruses specifically infect and kill cancer cells. We establish the existence of the non-constant positive solution and we know the rate of killing the infected cell has effects on the global bifurcation.

In order to make good use of oncolytic virus, there is still much to be learned and discovered about oncolytic viruses and virus therapy. Because of possible adverse side effects, it is important to achieve reduction of the tumor cells with small dosage, which remains a problem. Searching for optimal schedules of injections is also a

promising area for future research. The role of the immune reaction in controlling the extent of infection is still unclear. One may try to explore these problems and results established in this paper, although they are based on a number of simplifying assumptions, they still can be used as a rigorous tool. As more information becomes available, our model can be refined and expanded to incorporate more of the known biology. To this end, the development of biologically realistic mathematical models is an important tool to explore these problems.

## Acknowledgements

The authors are grateful to the referees for their suggestions and comments which improved the presentation of this manuscript.

## References

- [1] W. Allegretto, G. Cao, G. Li and Y. Lin, *Numerical analysis of tumor model in steady state*, *Comput. Math. Appl.*, 52(2006)(5), 593–606.
- [2] M. G. Crandall and P. H. Rabinowitz, *Bifurcation from simple eigenvalues*, *J. Funct. Anal.*, 8(1971)(2), 321–340.
- [3] V. Cristini, X. Li, J. S. Lowengrub and S. M. Wise, *Nonlinear simulations of solid tumor growth using a mixture model: invasion and branching*, *J. Math. Biol.*, 58(2009)(4–5), 723–763.
- [4] V. Cristini, J. S. Lowengrub and Q. Nie, *Nonlinear simulation of tumor growth*, *J. Math. Biol.*, 46(2003)(3), 191–224.
- [5] J. Escher and A.V. Matioc, *Bifurcation analysis for a free boundary problem modeling tumor growth*, *Arch. Math.*, 97(2011)(1), 79–90.
- [6] A. Friedman and B. Hu, *Stability and instability of Liapunov-Schmidt and Hopf bifurcation for a free boundary problem arising in a tumor model*, *Trans. Am. Math. Soc.*, 360(2008)(10), 5291–5342.
- [7] H. Hao, J. D. Hauenstein, B. Hu, Y. Liu, A. J. Sommesse and Y. Zhang, *Bifurcation of steady-state solutions for a tumor model with a necrotic core*, *Nonlinear Anal. RWA*, 13(2012), 694–709.
- [8] Y. Jia, J. Wu and H. -K. Xu, *Positive solutions for a predator-prey interaction model with Holling-type functional response and diffusion*, *Taiwanese J. Math.*, 15(2011)(5), 2013–2034.
- [9] E. Khain and L. M. Sander, *Dynamics and pattern formation in invasive tumor growth*, *Phys. Rev. Lett.*, 96(2006)(18), 188103–1–4.
- [10] D. A. Knopoff, D. R. Fernandez, G. A. Torres and C. V. Turner, *Adjoint method for a tumor growth PDE-constrained optimization problem*, *Comput. Math. Appl.*, 66(2013)(6), 1104–1119.
- [11] P. Liu, J. Shi, R. Wang and Y. Wang, *Bifurcation analysis of a generic reaction-diffusion Turing model*, *Int. J. Bifurcation Chaos*, 24(2014)(4), 1450042–1–12.
- [12] J. Liu and J. Wei, *On Hopf bifurcation of a delayed predator-prey system with diffusion*, *Int. J. Bifurcation Chaos*, 23(2013)(2), 1350023–1–13.

- [13] J. López-Gómez and M. Molina-Meyer, *Bounded components of positive solutions of abstract fixed point equations: mushrooms, loops and isolas*, J. Differential Equations, 209(2005)(2), 416–441.
- [14] A. J. Lotka, *Elements of Physical Biology*, Williams & Wilkins Company, New York, 1925.
- [15] Y. Lou and W. -M. Ni, *Diffusion, self-diffusion and cross-diffusion*, J. Differential Equations, 131(1996)(1), 79–131.
- [16] A. S. Novozhilov, F. S. Berezovskaya, E. V. Koonin and G. P. Karev, *Mathematical modeling of tumor therapy with oncolytic viruses: regimes with complete tumor elimination within the framework of deterministic model*, Biol. Direct, 1(2006)(1), 231–276.
- [17] J. Shi, *Bifurcation in infinite dimensional spaces and applications in spatiotemporal biological and chemical models*, Front Math. China, 4(2009)(3), 407–424.
- [18] Y. Tao and Q. Guo, *The competitive dynamics between tumor cells, a replication-competent virus and an immune response*, J. Math. Biol., 51(2005)(1), 37–74.
- [19] K. Umezū, *Global structure of supercritical bifurcation with turning points for the logistic elliptic equation with nonlinear boundary conditions*, Nonlinear Anal., 89(2013)(3), 250–266.
- [20] V. Volterra, *Variazioni e fluttuazioni del numero d'individui in specie animali conviventi*, Mem. R. Accad. Naz. dei Lincei, 2(1926)(2), 31–113.
- [21] Y. Wang and J. Wu, *Stability of positive constant steady states and their bifurcation in a biological depletion model*, Discrete Contin. Dyn. Syst. Ser. B, 15(2011)(3), 849–865.
- [22] D. Wodarz, *Viruses as antitumor weapons: defining conditions for tumor remission*, Cancer Res., 61(2001)(8), 3501–3507.
- [23] J. Wu and S. Cui, *Bifurcation analysis of a mathematical model for the growth of solid tumors in the presence of external inhibitors*, Math. Method Appl. Sci., 38(2014)(9), 1813–1823.
- [24] D. Yang, J. P. Tian and J. Wang, *A solvable hyperbolic free boundary problem modelling tumour regrowth*, Appl. Anal., 92(2013)(7), 1541–1558.