A free boundary tumor model with time dependent nutritional supply☆

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Abstract

A non-autonomous free boundary model for tumor growth is studied. The model consists of a nonlinear reaction diffusion equation describing the distribution of vital nutrients in the tumor and a nonlinear integro-differential equation describing the evolution of the tumor size. First the global existence and uniqueness of a transient solution is established under some general conditions. Then with additional regularity assumptions on the consumption and proliferation rates, the existence and uniqueness of steady-state solutions is obtained. Furthermore the convergence of the transient solutions toward the steady-state solution is verified. Finally the long time behavior of the solutions is investigated by transforming the time-dependent domain to a fixed domain.

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1. Introduction

Over the past decades, extensive studies have been done on free boundary problems modeling the growth of tumors (see, e.g., [2, 4, 3, 6, 15, 16, 20, 21]). In this paper we consider a spherically symmetric non-necrotic tumor in $\mathbb{R}^3$ and study the concentration of a certain type of nutrient within the tumor. Let t

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be the time variable scaled by the tumor-cell doubling time and $r = |x|$ be the spatial space variable scaled by the tumor-cell radius. Denote by $u = u(r,t)$ the scaled nutrient concentration at time t and radius r from the tumor center and denote by $R(t)$ the scaled tumor radius at time t. Then $u = u(r,t)$ and $R(t)$ follow a system of coupled reaction diffusion and integro-differential equations [2, 10]:

$$\mu \frac{\partial u(r,t)}{\partial t} = \Delta_r u(r,t) - f(u(r,t)) \quad \text{for} \quad 0 < r < R(t),\ t > 0, \tag{1}$$

$$\frac{\mathrm{d}R(t)}{\mathrm{d}t} = \frac{1}{R^2(t)} \int_0^{R(t)} g(u(r,t)) r^2 \mathrm{d}r \quad \text{for} \quad t > 0, \tag{2}$$

where $f(u)$ is the scaled consumption rate of the nutrient by tumor-cells in a unit volume, $g(u)$ is the scaled proliferation rate of tumor-cells in a unit volume (i.e., the number of new-born cells minus the number of new-dying cells in a unit volume within a unit time interval), and $\mu = T_{diffusion}/T_{growth}$ is the ratio of the nutrient diffusion time scale to the tumor growth (e.g. tumor doubling) time scale. Note that typically $T_{diffusion} \approx 1\,minute$ while $T_{growth} \approx 1\,day$, so that $\mu \ll 1$ (see, e.g., [1, 5, 19]). Also note that Δ_r represents the radial Laplacian, i.e.,

$$\Delta_r u = \frac{1}{r^2} \frac{\partial}{\partial r} \big(r^2 \frac{\partial u}{\partial r} \big).$$

Assume that the scaled concentration of the nutrient supplied on the tumor surface is of level α and that the nutrient level does not change at the center of the tumor, i.e.,

$$\frac{\partial u}{\partial r}(0,t) = 0, \quad u(R(t),t) = \alpha \quad \text{for} \quad t > 0. \tag{3}$$

In addition, let the initial size of the tumor and initial nutrient level within the tumor be

$$R(0) = R_0, \qquad u(r,0) = u_0(r) \quad \text{for} \quad 0 \leqslant r \leqslant R_0. \tag{4}$$

The system (1)–(4) was proposed by Byrne and Chaplain in [2] for the growth of a tumor consisting of live cells (non-necrotic tumor) and receiving blood supply through a developed network of capillary vessels (vascularized tumor). It was analyzed mathematically by Friedman and Reitich [13] for the linear case and by Cui [12] for the nonlinear case. See, e.g., [11, 9] and references therein for other relevant literature.

We are interested in studying the above system with a time dependent nutrition supply on the tumor surface, i.e., the constant α in boundary conditions (3) becomes a function of time $\alpha(t)$, i.e.,

$$\frac{\partial u}{\partial r}(0,t) = 0, \quad u(R(t),t) = \alpha(t) \quad \text{for} \quad t \geqslant 0. \tag{5}$$

The problem then becomes non-autonomous and consequently we change the initial time to be t_0 instead of 0 and revise the initial conditions to be

$$R(t_0) = R_0 > 0, \quad u(r,t_0) = u_0(r) \quad \text{for} \quad 0 \leqslant r \leqslant R_0. \tag{6}$$

As far as we know, some relevant mathematical model has been investigated when the nutrition supply $\alpha(t)$ on the tumor surface is periodic (see, e.g. [6, 16, 21]). When a Gibbs-Thmson relation is taken into account, Wu [20] established the existence and uniqueness of solutions of the tumor model for the linear case.

In this paper, we are interested in studying system (1)-(2) with general time dependent nutritional supply $\alpha(t)$ on the tumor surface and general functions f and g. Throughout this paper it is assumed that

(**A0**) $\alpha(t)$ is continuously differentiable and bounded with

$$0 \leqslant \underline{\alpha} \leqslant \alpha(t) \leqslant \bar{\alpha} \qquad \forall\, t \geqslant t_0.$$

The aim of this work is to study the nonautonomous tumor growth system (1)–(2) with (5)–(6), referred to as (NTS) in the sequel. The paper is organized as follows. In Section 2 we introduce notation and present some preliminary results. In Section 3 we establish the global existence and uniqueness of a transient solution for (NTS) by constructing a functional metric space and a contraction mapping and then using the fixed point theorem. In Section 4 we show the existence and uniqueness of a steady-state solution and further prove the convergence of the transient solutions toward the steady-state solution by the method of comparison and maximum principle with nontrivial mathematical analysis. In Section 5 we investigate the asymptotic behavior of the solutions to (NTS) in a fixed domain in general situation. Some closing remarks will be given in Section 6.

2. Preliminaries

Denote by $|\cdot|$ the Euclidean norm. Unless otherwise specified, given a space Ω, $\overline{\Omega}$ denotes the closure of Ω. Given $T > t_0$ and $R(t) > 0$, denote

$$\mathfrak{Q}_T^R := \big\{(x,t) \in \mathbb{R}^3 \times \mathbb{R} : |x| < R(t),\, t \in (t_0, T)\big\}.$$

In particular,

$$\mathfrak{Q}_T^{R_0} = \mathcal{B}_{R_0} \times (t_0, T) \quad \text{where } \mathcal{B}_{R_0} = \big\{x \in \mathbb{R}^3 \,:\, |x| < R_0\big\}.$$

For $p \geq 1$ and $\lambda \in (0,1)$ denote

$$\begin{aligned} \mathscr{W}_p^{m,k}(\mathfrak{Q}_T^R) &= \big\{u \in \mathscr{L}^p(\mathfrak{Q}_T^R) \,:\, \partial_x^\alpha u(x,t), \partial_t^l u(x,t) \in \mathscr{L}^p(\mathfrak{Q}_T^R) \\ &\qquad \text{for } |\alpha| \leqslant m,\, l \leqslant k\big\}, \\ \mathscr{C}^{2+\lambda, 1+\frac{\lambda}{2}}(\mathfrak{Q}_T^R) &= \text{the Hölder space on the parabolic domain } \mathfrak{Q}_T^R. \end{aligned}$$

Given $p > 0$ and $\alpha(t) > 0$ define $\mathscr{D}_{p,\alpha(t)}(\mathcal{B}_{R_0})$ to be

$$\mathscr{D}_{p,\alpha(t)}(\mathcal{B}_{R_0}) := \Big\{v \ : \ \begin{aligned} &\text{there exists } V \in \mathscr{W}_p^{2,1}(\mathfrak{Q}_T^{R_0}) \cap \mathscr{C}^0(\overline{\mathfrak{Q}_T^{R_0}}) \text{ such that} \\ &V(x,t) = \alpha(t) \text{ for } |x| = R_0,\, t \in [t_0, T] \\ &\text{and } V(x,t_0) = v(x) \text{ for all } |x| \leqslant R_0\Big\}. \end{aligned}$$

Note that $v \in \mathscr{D}_{p,\alpha(t)}(\mathcal{B}_{R_0})$ implies that $v \in \mathscr{C}^0(\overline{\mathcal{B}_{R_0}})$ and $v(x) = \alpha(t)$ for all $|x| = R_0$. The norm on $\mathscr{D}_{p,\alpha(t)}(\mathcal{B}_{R_0})$ is defined to be

$$\|v\|_{\mathscr{D}_{p,\alpha(t)}(\mathcal{B}_{R_0})} := \inf\Big\{\|V\|_{\mathscr{W}_p^{2,1}(\mathfrak{Q}_T^{R_0})} : \quad V(x,t) = \alpha(t) \text{ for } |x| = R_0,\, t \in [t_0, T] \\ \text{and } V(x,t_0) = v(x) \text{ for all } |x| \leqslant R_0\Big\}.$$

Now consider the following auxiliary problem

$$\begin{cases} \mu \dfrac{\partial v}{\partial t}(x,t) = \Delta v(x,t) + h(x,t) \quad \text{in} \quad \mathfrak{Q}_T^R, \\ v(x,t) = \alpha(t) \quad \text{for} \quad |x| = R(t), \ t_0 \leqslant t \leqslant T, \\ v(x,t_0) = v_0(x) \quad \text{for} \quad |x| \leqslant R_0, \end{cases} \tag{7}$$

where μ and R_0 are positive constants, $R(\cdot) \in \mathscr{C}^1([t_0,T])$ is a positive function, $h(\cdot,\cdot) \in \mathscr{C}^0(\overline{\mathfrak{Q}_T^R})$, and $v_0 \in \mathscr{D}_{p,\alpha(t_0)}(\mathcal{B}_{R_0})$ for some $\dfrac{5}{2} < p < \infty$. Note that if $p > \dfrac{5}{2}$ then

$$\mathscr{W}_p^{2,1}(\mathfrak{Q}_T^1) \subset \mathscr{C}^{\lambda,\frac{\lambda}{2}}(\overline{\mathfrak{Q}_T^1}) \quad \text{with} \quad \lambda = 2 - \frac{5}{p};$$

if $p > 5$ then

$$\|\nabla u\|_{L^\infty(\mathfrak{Q}_T^1)} \leqslant C(p,T)\|u\|_{\mathscr{W}_p^{2,1}(\mathfrak{Q}_T^1)}.$$

The following results regarding system (7) will be used to study (NTS) later.

Lemma 2.1. *Let (**A0**) hold. Then system (7) has a unique solution $v \in \mathscr{W}_p^{2,1}(\mathfrak{Q}_T^R) \subset \mathscr{C}^0(\overline{\mathfrak{Q}_T^R})$. Moreover,*

(i) *there exists a constant $C > 0$ depending on μ, the upper bounds of $R(t)$, $\frac{1}{R(t)}$, $|\dot{R}(t)|$, $|\alpha(t)|$, $|\dot{\alpha}(t)|$, $|h(x,t)|$ and $\|v_0\|_{\mathscr{D}_{p,\alpha(0)}(\mathcal{B}_{R_0})}$, such that*

$$\|v\|_{\mathscr{W}_p^{2,1}(\mathfrak{Q}_T^R)} \leqslant C.$$

If further $p > 5$ then

$$\|\nabla v\|_{L^\infty(\mathfrak{Q}_T^R)} \leqslant C',$$

where C' is a constant similar to C.

(ii) *If $R(\cdot)$ and $\alpha(\cdot) \in \mathscr{C}^{1+\frac{\lambda}{2}}([t_0,T])$ and $h(\cdot,\cdot) \in \mathscr{C}^{\lambda,\frac{\lambda}{2}}(\mathfrak{Q}_T^R)$ for some $0 < \lambda < 1$, then $v \in \mathscr{C}^{2+\lambda,1+\frac{\lambda}{2}}(\mathfrak{Q}_T^R)$.*

(iii) *If $v_0(x)$ and $h(x,t)$ are radially symmetric in x, then $v(x,t)$ is also radially symmetric in x.*

Proof. Let $w(x,t) = v(x,t) - \alpha(t) + 1$, then problem (7) is equivalent to

$$\begin{cases} \mu \dfrac{\partial w}{\partial t}(x,t) = \Delta w(x,t) + \tilde{h}(x,t) \quad \text{in} \ \ \mathfrak{Q}_T^R, \\ w(x,t) = 1 \ \ \text{for} \ \ |x| = R(t), \ t_0 \leqslant t \leqslant T, \\ w(x,t_0) = w_0(x) \ \ \text{for} \ \ |x| \leqslant R_0, \end{cases} \tag{8}$$

where $\tilde{h}(x,t) = h(x,t) - \mu\dot{\alpha}(t)$ and $w_0(x) = v_0(x) - \alpha(t_0) + 1$. Clearly $w_0 \in \mathscr{D}_{p,1}(\mathcal{B}_{R_0})$. The proof then follows directly by applying Lemma 2.1 in [10] to the above problem (8). ☐

Lemma 2.2. *Let (**A0**) hold and in addition assume that*

(a) $h(x,t) \leqslant 0$ *for all* $(x,t) \in \mathfrak{Q}_T^R$;

(b) $v_0(x) \leqslant \overline{\alpha}$ *for all* $|x| \leqslant R_0$.

Then $v(x,t) \leqslant \overline{\alpha}$ *for all* $(x,t) \in \overline{\mathfrak{Q}_T^R}$.

Proof. Let $w(x,t) = v(x,t) - \overline{\alpha}$, then $w(x,t)$ satisfies

$$\begin{cases} \mu w_t(x,t) - \Delta w(x,t) \leqslant 0 \ \ \text{in} \ \ \mathfrak{Q}_T^R, \\ w(x,t) \leqslant 0 \ \ \text{for} \ \ |x| = R(t), \ t_0 \leqslant t \leqslant T, \\ w(x,t_0) \leqslant 0 \ \ \text{for} \ \ |x| \leqslant R_0. \end{cases}$$

By the maximum principle, it follows that $w(x,t) \leqslant 0$. Hence $v(x,t) \leqslant \overline{\alpha}$ for all $(x,t) \in \overline{\mathfrak{Q}_T^R}$, which completes the proof. ☐

Lemma 2.3. *Let (**A0**) hold and in addition assume that there exists a constant* m_v *such that*

(a) $v_0(x) \geqslant m_v$ *for all* $|x| \leqslant R_0$;

(b) $h(x,t) \geqslant 0$ *if* $v(x,t) \leqslant m_v$.

Then $v(x,t) \geqslant m_v$ *for all* $(x,t) \in \overline{\mathfrak{Q}_T^R}$.

Proof. If there is no point $(x,t) \in \overline{\mathfrak{Q}_T^R}$ such that $v(x,t) < m_v$, then the lemma holds immediately. Otherwise, let $\widehat{\mathfrak{Q}_T^R} := \left\{(x,t) \in \overline{\mathfrak{Q}_T^R} \,\middle|\, v(x,t) \leqslant m_v\right\}$ and let

$$w(x,t) = v(x,t) - m_v \qquad (x,t) \in \widehat{\mathfrak{Q}_T^R}.$$

Then by the continuity of $v(x,t)$, there exist disjoint domains $\{Q_j\} = \{\tilde{Q}_j \times \hat{Q}_j\} \subseteq \widehat{\mathfrak{Q}_T^R}$ with $x \in \tilde{Q}_j, t \in \hat{Q}_j$ and on each Q_j, $w(x,t)$ satisfies

$$\begin{cases} \mu w_t(x,t) = \Delta w(x,t) + h(x,t) \ \ \text{in} \ \ Q_j, \\ w(x,t) = 0 \ \ \text{for} \ \ x \in \partial\tilde{Q}_j, \ t_0 \leqslant t \leqslant T, \\ w(x,t_0) \leqslant 0 \ \ \text{for} \ \ x \in \tilde{Q}_j. \end{cases}$$

We next show that on each Q_j, $w(x,t)$ achieves minimum value on ∂Q_j so that $w(x,t) \equiv 0$ on Q_j.

Notice that $h(x,t) \geq 0$ on each Q_j. Below we discuss the cases $h(x,t) > 0$ and $h(x,t) = 0$, respectively.

(1) $h(x,t) > 0$ on Q_j: suppose (for contradiction) that there exists $(x_0, \tau) \in Q_j \backslash \partial Q_j$, i.e., in the interior of Q_j, such that

$$w(x_0, \tau) = \min_{(x,t)\in Q_j} w(x,t) < 0.$$

Then $w_t(x,t)|_{(x_0,\tau)} \leqslant 0$ and $\Delta w(x,t)|_{(x_0,\tau)} \geqslant 0$. As a result

$$h(x_0, \tau) = \mu w_t(x,t)|_{(x_0,\tau)} - \Delta w(x,t)|_{(x_0,\tau)} \leqslant 0,$$

which contradicts with $h(x,t) > 0$ in Q_j. Thus the minimum of $w(x,t)$ in each Q_j is achieved on the boundary of Q_j.

(2) $h(x,t) = 0$ on Q_j: for every $(x,t) \in Q_j$ with $x = (x_1, x_2, x_3)$ and $t \in [t_0, T]$, let

$$\tilde{w}(x,t) = w(x,t) - \varepsilon e^{x_1} \quad \text{for } \varepsilon > 0.$$

Then

$$\tilde{h}(x,t) := \mu \tilde{w}_t(x,t) - \Delta \tilde{w}(x,t) = h(x,t) + \varepsilon e^{x_1} = \varepsilon e^{x_1} > 0.$$

It then follows from part (1) that $\tilde{w}(x,t)$ achieves minimum on ∂Q_j. Letting $\varepsilon \to 0$ we obtain that the minimum of $w(x,t)$ in each Q_j is achieved on the boundary of Q_j.

In summary $w(x,t) \equiv 0$ in each Q_j and by the definition of Q_j, $w(x,t) \geq 0$ for all $(x,t) \in \overline{\mathfrak{Q}_T^R}$, i.e.,

$$v(x,t) \geqslant m_v \;\; \text{for all} \;\; (x,t) \in \overline{\mathfrak{Q}_T^R}.$$

The proof is complete. □

Remark 2.1. *In the present paper, we take in particular* $m_v = 0$.

3. Existence and uniqueness of solution

In this section we establish the existence and uniqueness of solutions for the problem (NTS). In addition to assumption (**A0**) throughout this section it is also assumed that

(**A1**) there exists $L_\alpha > 0$ such that $|\dot{\alpha}(t)| \leqslant L_\alpha$ for all $t \geq t_0$.

(**A2**) $u_0 \in \mathscr{W}_\infty^{2,0}(0, R_0)$ and satisfies $u_0'(0) = 0, u_0(R_0) = \alpha(t_0)$ and $0 \leqslant u_0(r) \leqslant \overline{\alpha}$ for all $r \in [0, R_0]$.

(**A3**) $f(0) = 0$ and $f : \mathbb{R} \to \mathbb{R}$ is nondecreasing and Lipschitz continuous with Lipschitz constant $L_f > 0$.

(**A4**) $g : \mathbb{R} \to \mathbb{R}$ is Lipschitz continuous with Lipschitz constant $L_g > 0$.

Theorem 3.1. *Let assumptions (**A0**)-(**A4**) hold. Then the problem (NTS) has a unique solution $(u(r,t), R(t))$. Moreover, the solution satisfies*

$$0 \leqslant u(r,t) \leqslant \overline{\alpha} \quad \text{for} \quad 0 \leqslant r \leqslant R(t),\ t \geqslant t_0, \tag{9}$$

$$\frac{1}{3} m_g \leqslant \frac{\dot{R}(t)}{R(t)} \leqslant \frac{1}{3} M_g \quad \text{for} \quad t \geqslant t_0, \tag{10}$$

$$R_0 e^{\frac{1}{3} m_g (t-t_0)} \leqslant R(t) \leqslant R_0 e^{\frac{1}{3} M_g (t-t_0)} \quad \text{for} \quad t \geqslant t_0, \tag{11}$$

where m_g and M_g are two constants defined by (14)

Proof. The proof is similar to that of Theorem 2.2 in [10] with a considerable number of modifications. For the reader's convenience we present the complete proof below in three steps.

Step I (Existence and uniqueness of a local solution).

Given any $T > t_0$ and $M > 0$ (large enough), define a metric space $(\mathfrak{S}_T, \boldsymbol{d})$ as follows:

(i) $\mathfrak{S}_T = \tilde{\mathfrak{S}}_T \times \hat{\mathfrak{S}}_T := \big\{ \big(u(\cdot,\cdot), R(\cdot)\big) \,\big|\, u(\cdot,\cdot) \in \tilde{\mathfrak{S}}_T, R(\cdot) \in \hat{\mathfrak{S}}_T \big\}$ with $R(t)$ and $u(r,t)$ satisfy, respectively:

- $R(\cdot) \in \mathscr{C}[t_0, T], R(t_0) = R_0$ and

$$R_0 e^{\frac{1}{3} m_g (t-t_0)} \leqslant R(t) \leqslant R_0 e^{\frac{1}{3} M_g (t-t_0)} \quad \text{for} \quad t_0 < t \leqslant T; \tag{12}$$

- $u(\cdot,\cdot) \in \mathscr{W}^{1,0}_{\infty}([0,\infty) \times [t_0, T]) \cap \mathscr{C}([0,\infty) \times [t_0, T])$ and

$$\begin{cases} u(r,t) \leqslant M \quad \text{for} \quad 0 \leqslant r \leqslant R(t),\ t_0 \leqslant t \leqslant T, \\ u(r,t) = \alpha(t) \quad \text{for} \quad r > R(t),\ t_0 \leqslant t \leqslant T, \\ u(r,t_0) = u_0(r) \quad \text{for} \quad 0 \leqslant r \leqslant R_0, \end{cases}$$

(ii) $\boldsymbol{d}((u_1, R_1), (u_2, R_2)) := \max\limits_{\substack{r \geqslant 0 \\ t_0 \leqslant t \leqslant T}} |u_1(r,t) - u_2(r,t)| + \max\limits_{t_0 \leqslant t \leqslant T} |R_1(t) - R_2(t)|.$

It is straightforward to check that $(\mathfrak{S}_T, \boldsymbol{d})$ is a complete metric space.

Given any $(u(r,t), R(t)) \in \mathfrak{S}_T$, let $R^*(t; R_0) = R^*(t)$ be the unique solution of the following problem

$$\begin{cases} \dfrac{\mathrm{d}R^*(t)}{\mathrm{d}t} = \dfrac{R^*(t)}{R^3(t)} \displaystyle\int_0^{R(t)} g(u(r,t)) r^2 \mathrm{d}r, \quad t_0 \leqslant t \leqslant T, \\ R^*(t_0) = R_0, \end{cases}$$

which gives, by direct computation,

$$R^*(t) = R_0 e^{\int_{t_0}^t G(\theta)\mathrm{d}\theta} \quad \text{where} \quad G(t) = \frac{1}{R^3(t)} \int_0^{R(t)} g(u(r,t)) r^2 \mathrm{d}r. \tag{13}$$

Since $(u(r,t), R(t)) \in \mathfrak{S}_T$, $u(r,t)$ is bounded, which ensures that $g(u(r,t))$ is bounded for every $r \geqslant 0$ and $t_0 \leqslant t \leqslant T$, write

$$m_g := \min_{u \in \tilde{\mathfrak{S}}_T} g(u), \quad M_g := \max_{u \in \tilde{\mathfrak{S}}_T} g(u), \tag{14}$$

and then

$$\frac{m_g}{3} \leqslant G(t) \leqslant \frac{M_g}{3} \quad \text{for} \;\; t_0 \leqslant t \leqslant T. \tag{15}$$

Consequently

$$R_0 e^{\frac{1}{3} m_g (t - t_0)} \leqslant R^*(t) \leqslant R_0 e^{\frac{1}{3} M_g (t - t_0)} \quad \text{for} \;\; t_0 \leqslant t \leqslant T. \tag{16}$$

Observing that $R^*(\cdot) \in \mathscr{C}^1([t_0, T])$ and $R^* > 0$, due to Lemma 2.1 there exists a unique solution $u^*(x,t)$ for the following problem

$$\begin{cases} \mu u_t^* = \Delta u^* - f(u(|x|,t)), & |x| < R^*(t), \quad t_0 < t \leqslant T, \\ u^*(x,t) = \alpha(t), & |x| = R^*(t), \quad t_0 < t \leqslant T, \\ u^*(x,t_0) = u_0(|x|), & |x| \leqslant R_0. \end{cases}$$

Moreover, $u^* \in \mathscr{W}_p^{2,1}(\mathfrak{Q}_T^{R^*})$ for any $\frac{5}{2} < p < \infty$ which is radially symmetric in x (so we write $u^* = u^*(r,t)$). Since $f(u(|x|,t)) \geqslant 0$, it then follows from the assumptions (**A0**), (**A2**) and Lemma 2.2 that $u^*(r,t) \leqslant \overline{\alpha}$ for all $0 \leqslant r \leqslant R^*(t)$ and $t_0 \leqslant t \leqslant T$. Note that $u^*(r,t)$ can be extended to $[0, \infty) \times [t_0, T]$ such that

$$\begin{cases} u^*(r,t) \leqslant \overline{\alpha} \quad \text{for} \quad 0 \leqslant r \leqslant R^*(t), \quad t_0 \leqslant t \leqslant T, \\ u^*(r,t) = \alpha(t) \quad \text{for} \quad r > R^*(t), \quad t_0 \leqslant t \leqslant T. \end{cases}$$

Now choose $M = \overline{\alpha}$ in (i). Then clearly $(u^*(\cdot,\cdot), R^*(\cdot)) \in \mathfrak{S}_T$. Define a mapping $\Theta : \mathfrak{S}_T \to \mathfrak{S}_T$ by

$$\Theta \, : \, (u(\cdot,\cdot), R(\cdot)) \mapsto (u^*(\cdot,\cdot), R^*(\cdot)). \tag{17}$$

We next verify that Θ is a contraction mapping for suitable small $(T - t_0)$. To this end consider $(u_i(\cdot,\cdot), R_i(\cdot)) \in \mathfrak{S}_T$ and $(u_i^*(\cdot,\cdot), R_i^*(\cdot)) = \Theta(u_i(\cdot,\cdot), R_i(\cdot))$ for $i = 1, 2$. From (13), (14) and (15) we can deduce that for any $t \in [t_0, T]$,

$$\begin{aligned} \big|R_1^*(t) - R_2^*(t)\big| &= R_0 \big| e^{\int_{t_0}^t G_1(\theta)\mathrm{d}\theta} - e^{\int_{t_0}^t G_2(\theta)\mathrm{d}\theta} \big| \\ &\leqslant R_0 (T - t_0) e^{\frac{1}{3} M_g (T - t_0)} \cdot \max_{t_0 \leqslant \theta \leqslant T} \big| G_1(\theta) - G_2(\theta) \big|, \end{aligned}$$

where $G_i(\theta) = \dfrac{1}{R_i^3(\theta)} \displaystyle\int_0^{R_i(\theta)} g(u_i(r,\theta))r^2 \mathrm{d}r$, $i = 1, 2$. Then due to the Lipschitz condition on g we have

$$
\begin{aligned}
&\big|G_1(\theta) - G_2(\theta)\big| \\
=&\Big|\int_0^1 \big[g(u_1(R_1 r,\theta)) - g(u_2(R_2 r,\theta))\big]\mathrm{d}r\Big| \\
\leqslant& L_g \int_0^1 |u_1(R_1 r,\theta) - u_2(R_2 r,\theta)|\mathrm{d}r \\
\leqslant& L_g \int_0^1 |u_1(R_1 r,\theta) - u_2(R_1 r,\theta)|\mathrm{d}r + L_g \int_0^1 |u_2(R_1 r,\theta) - u_2(R_2 r,\theta)|\mathrm{d}r \\
\leqslant& L_g \max_{r\geqslant 0} |u_1(r,\theta) - u_2(r,\theta)| \\
&+ L_g \operatorname*{ess\,sup}_{0\leqslant\xi\leqslant\max\{R_1,R_2\}} |\frac{\partial u_2}{\partial r}(\xi,\theta)| \int_0^1 |R_1(\theta) - R_2(\theta)| r \mathrm{d}r \\
\leqslant& L_g \max_{r\geqslant 0} |u_1(r,\theta) - u_2(r,\theta)| + CL_g |R_1(\theta) - R_2(\theta)|
\end{aligned}
$$

and hence

$$
\begin{aligned}
\big|R_1^*(t) - R_2^*(t)\big| &\leqslant R_0(T-t_0)e^{\frac{1}{3}M_g(T-t_0)} \cdot C(T) \cdot \boldsymbol{d}\big((u_1,R_1),(u_2,R_2)\big) \\
&=: (T-t_0)C(T)\boldsymbol{d}\big((u_1,R_1),(u_2,R_2)\big). \qquad (18)
\end{aligned}
$$

Next, we estimate $\big|u_1^*(r,t) - u_2^*(r,t)\big|$. To this end, define

$$
\begin{aligned}
R_m^*(t) :=& \min\{R_1^*(t), R_2^*(t)\}, \quad R_M^*(t) := \max\{R_1^*(t), R_2^*(t)\}, \\
w(x,t) =& u_1^*(|x|,t) - u_2^*(|x|,t), \quad |x| \leqslant R_m^*(t),\ t_0 \leqslant t \leqslant T, \\
h(x,t) =& f(u_1(|x|,t)) - f(u_2(|x|,t)), \quad x \in \mathbb{R}^3,\ t_0 \leqslant t \leqslant T.
\end{aligned}
$$

Then, $w(x,t)$ satisfies

$$
\begin{cases}
\mu w_t = \Delta w - h(x,t) \ \text{ in } \ \mathfrak{Q}_T^{R_m^*}, \\
w(x,t) = w(x,t) \ \text{ for } \ |x| = R_m^*(t),\ t_0 < t \leqslant T, \\
w(x,t_0) = 0 \ \text{ for } \ |x| \leqslant R_0.
\end{cases} \qquad (19)
$$

Let $\tilde{w} = \tilde{w}(x,t)$, $x \in \mathbb{R}^3$, $t \in [t_0,T]$ be the solution of the following initial value problem

$$
\begin{cases}
\mu \tilde{w}_t = \Delta \tilde{w} - h(x,t) \ \text{ in } \ R^3 \times [t_0,T], \\
\tilde{w}(x,t_0) = 0 \ \text{ for } \ x \in \mathbb{R}^3,
\end{cases} \qquad (20)
$$

and let $w^* = w^*(x,t) = w(x,t) - \tilde{w}(x,t)$, $|x| \leqslant R_m^*(t)$, $t \in [t_0, T]$. Then w^* satisfies

$$\begin{cases} \mu w_t^* = \Delta w^* \ \text{ in } \ \mathfrak{Q}_T^{R_m^*}, \\ w^*(x,t_0) = w(x,t) - \tilde{w}(x,t) \ \text{ for } \ |x| = R_m^*(t), \ t_0 < t \leqslant T, \\ w^*(x,t_0) = 0 \ \text{ for } \ |x| \leqslant R_0. \end{cases}$$

Applying the maximum principle to w^* on $\overline{\mathfrak{Q}_T^{R_m^*}}$, we obtain

$$\begin{aligned} \max_{\overline{\mathfrak{Q}_T^{R_m^*}}} |w^*(x,t)| \leqslant & \max_{\substack{|x| = R_m^*(t), \\ t_0 \leqslant t \leqslant T}} |w(x,t) - \tilde{w}(x,t)| \\ & \leqslant \max_{t_0 \leqslant t \leqslant T} |u_1^*(R_m^*(t),t) - u_2^*(R_m^*(t),t)| + \sup_{\mathbb{R}^3 \times [t_0,T]} |\tilde{w}(x,t)|. \end{aligned}$$

Observe that

$$\begin{aligned} & \max_{\substack{0 \leqslant r \leqslant R_m^*(t) \\ t_0 \leqslant t \leqslant T}} |u_1^*(r,t) - u_2^*(r,t)| = \max_{\overline{\mathfrak{Q}_T^{R_m^*}}} |w| \leqslant \max_{\overline{\mathfrak{Q}_T^{R_m^*}}} |\tilde{w}| + \max_{\overline{\mathfrak{Q}_T^{R_m^*}}} |w^*| \\ \leqslant & 2 \sup_{\mathbb{R}^3 \times [t_0,T]} |\tilde{w}| + \max_{t_0 \leqslant t \leqslant T} |u_1^*(R_m^*(t),t) - u_2^*(R_m^*(t),t)|. \end{aligned}$$

Therefore,

$$\max_{\substack{r \geqslant 0 \\ t_0 \leqslant t \leqslant T}} |u_1^*(r,t) - u_2^*(r,t)| \leqslant 2 \sup_{\substack{x \in \mathbb{R}^3 \\ t_0 \leqslant t \leqslant T}} |\tilde{w}(x,t)| + \max_{\substack{R_m^*(t) \leqslant r \leqslant R_M^*(t) \\ t_0 \leqslant t \leqslant T}} |u_1^*(r,t) - u_2^*(r,t)|. \tag{21}$$

It follows from (20) and assumption (**A3**) that

$$\begin{aligned} \sup_{\substack{x \in \mathbb{R}^3 \\ t_0 \leqslant t \leqslant T}} |\tilde{w}(x,t)| \leqslant & \frac{1}{\mu}(T - t_0) \sup_{\substack{x \in \mathbb{R}^3 \\ t_0 \leqslant t \leqslant T}} |h(x,t)| && (22) \\ & \leqslant \frac{L_f}{\mu}(T - t_0) \max_{\substack{0 \leqslant r \\ t_0 \leqslant t \leqslant T}} |u_1(r,t) - u_2(r,t)| \\ & \leqslant \frac{L_f}{\mu}(T - t_0) \boldsymbol{d}\big((u_1, R_1), (u_2, R_2)\big). && (23) \end{aligned}$$

For the second term on the right-hand side of (21), based on Lemma 2.1, Lemma 2.2 and the Sobolev spatial embedding relationship

$$\mathscr{W}_p^{2,1}(\mathfrak{Q}_T^R) \hookrightarrow \mathscr{C}^{q,\frac{q}{2}}(\mathfrak{Q}_T^R) \quad \text{for} \ \ 0 \leqslant q < 2 - \frac{5}{p},$$

we obtain that for every $t \in [t_0, T]$ and $r \in [R_m^*(t), R_M^*(t)]$ it holds

$$
\begin{aligned}
&|u_1^*(r,t) - u_2^*(r,t)| \leqslant |u_1^*(r,t) - \alpha(t)| + |u_2^*(r,t) - \alpha(t)| \\
=&|u_1^*(r,t) - u_1^*(R_1^*(t),t)| + |u_2^*(r,t) - u_2^*(R_2^*(t),t)| \\
\leqslant &\left(\sup_{0 \leqslant \xi \leqslant R_1^*(t)} \left| \frac{\partial u_1^*}{\partial r}(\xi,t) \right| + \sup_{0 \leqslant \xi \leqslant R_2^*(t)} \left| \frac{\partial u_2^*}{\partial r}(\xi,t) \right| \right) \cdot \left| R_1^*(t) - R_2^*(t) \right| \\
\leqslant &C \left| R_1^*(t) - R_2^*(t) \right|
\end{aligned}
$$

for some $C > 0$. Therefore

$$
\max_{\substack{R_m^*(t) \leqslant r \leqslant R_M^*(t), \\ t_0 \leqslant t \leqslant T}} |u_1^*(r,t) - u_2^*(r,t)| \leqslant C(T) \cdot \max_{t_0 \leqslant t \leqslant T} |R_1^*(t) - R_2^*(t)|, \tag{24}
$$

where $C(T)$ depends on μ and the upper bounds of $R^*(t), \dfrac{1}{R^*(t)}, |\dot{R}^*(t)|, |\alpha(t)|,$ $|\dot{\alpha}(t)|$, but not on the choice of (u_1, R_1) and (u_2, R_2). Substituting (23) and (24) into (21) and using (18), we obtain

$$
\max_{\substack{0 \leqslant r, \\ t_0 \leqslant t \leqslant T}} |u_1^*(r,t) - u_2^*(r,t)| \leqslant (T - t_0) C(T) \boldsymbol{d}((u_1, R_1), (u_2, R_2)),
$$

which together with (18) implies that

$$
\boldsymbol{d}((u_1^*, R_1^*), (u_2^*, R_2^*)) \leqslant (T - t_0) C(T) \boldsymbol{d}((u_1, R_1), (u_2, R_2)).
$$

Therefore, Θ defined in (17) is a contraction mapping for suitable small $(T - t_0)$ satisfying $(T - t_0)C(T) < 1$. According to Banach fixed point theorem, we conclude that there exists a fixed point $(u(r,t), R(t))$ which is the local unique solution of the problem (NTS) with $t \in [t_0, T]$.

Step II (*A priori* estimates of the solution $(u(r,t), R(t))$)

Based on comparison results Lemma 2.2 and Lemma 2.3, it is not difficult to check that 0 and $\overline{\alpha}$ are respectively a lower and an upper solution of the system (1), (5) and (6). Consequently, we have the estimate (9). Furthermore, (10) and (11) follow from (13), (15) and (16).

Step III (The global existence of solution)

Suppose (for contradiction) that the maximal existence time interval $[t_0, T_1)$ is finite, i.e. $T_1 < +\infty$. From (10) and (11), we see that $R(t), \dfrac{1}{R(t)}$ and $\dot{R}(t)$ are bounded in $[t_0, T_1]$. Evidently, $|\alpha(t)|, |\dot{\alpha}(t)|$ and $\|u_0\|_{\mathscr{D}_{p,\alpha(0)}(\mathcal{B}_{R_0})}$ are also bounded in $[t_0, T_1]$. In addition, from (9), it follows that

$$
|f(u(r,t))| = |f(u(r,t)) - f(0)| \leqslant L_f |u(r,t) - 0| \leqslant 2\overline{\alpha} L_f, \quad t \in [t_0, T_1].
$$

Therefore, based on Lemma 2.1, we can deduce that

$$
\|u\|_{\mathscr{W}_p^{2,1}(\mathfrak{Q}_{T_1}^R)} < \infty \ \text{ for } \ \frac{5}{2} < p < \infty.
$$

Moreover, from the arguments in **Step I**, for any $\tau \in [t_0, T_1)$, we can deduce that there exists a time $T_2 > 0$ such that a solution of the problem (NTS) exists in the time interval $[\tau, \tau + T_2]$. By the uniqueness of the solution, we can conclude the existence time interval can be extended to $[t_0, T_1 + T_2)$, which is in contradiction to the assumption. Thus the the solution exists globally in time. The proof is complete. $\square$

4. Steady-state solutions

In this section, we consider the case that the nutritional supply $\alpha(t)$ on the tumor surface eventually becomes stable. The purpose of this section is to study the asymptotic behavior of the transient solutions $(u(r,t), R(t))$ obtained in Theorem 3.1 as $\alpha(t) \to \alpha_s$ (a constant and, clearly, $\alpha_s \in [\underline{\alpha}, \overline{\alpha}]$). To this end, we first prove the existence and uniqueness, then investigate its asymptotic stability of the steady-state solution of (NTS) with nutritional supply $\alpha(t) \equiv \alpha_s$ on the tumor surface.

4.1. Existence and uniqueness of a steady-state solution

This subsection is devoted to the existence and uniqueness of a solution $(u_s(r), R_s)$ for the following steady-state form of (NTS):

$$\begin{cases} \Delta_r u_s = f(u_s(r)), \quad 0 < r < R_s, \\ u_s'(0) = 0, \quad u_s(R_s) = \alpha_s, \\ \dfrac{1}{R_s^2} \displaystyle\int_0^{R_s} g(u_s(r)) r^2 \mathrm{d}r = 0, \end{cases} \tag{25}$$

where α_s is a constant in the interval $[\underline{\alpha}, \bar{\alpha}]$. To this end, the following additional regularity conditions on f and g are needed:

(**A5**) $f \in \mathscr{C}^1(\mathbb{R})$, $f(0) = 0$ and $f'(u) > 0$ for all $u \in \mathbb{R}$;

(**A6**) $g \in \mathscr{C}^1[0, +\infty)$, $g'(u) \in [0, L_g]$ for all $u \geqslant 0$; and there exists a unique $\alpha^* > 0$ such that $g(\alpha^*) = 0$ but g does not identically equal zero on any interval.

Remark 4.1. *Note that the quantity α^* is critical to the analysis in the sequel. It plays the role as a threshold for different types of behavior of the solutions.*

First consider the following auxiliary problem

$$\begin{cases} \Delta_r U(r, \lambda) = \lambda f(U(r, \lambda)), \quad 0 < r < 1, \\ \dfrac{\partial U}{\partial r}(0, \lambda) = 0, \quad U(1, \lambda) = \alpha_s, \end{cases} \tag{26}$$

where λ is a nonnegative parameter.

The lemma below is similar to Lemma 3.1 in [10], with slight improvements. But for the reader's convenience we still provide full proof.

Lemma 4.1. *Assume (***A5***) hold. Then for any $\lambda \geqslant 0$, there exists a unique solution $U = U(r,\lambda)$ for problem* (26)*. Moreover,*

(i) *the solution satisfies*

$$0 \leqslant U(r,\lambda) \leqslant \alpha_s \quad \textit{for} \;\; 0 \leqslant r \leqslant 1,\, \lambda \geqslant 0, \tag{27}$$

$$0 \leqslant \frac{\partial U}{\partial r}(r,\lambda) \leqslant \frac{\lambda}{3} r f(\alpha_s) \quad \textit{for} \;\; 0 \leqslant r < 1, \;\; \lambda \geqslant 0. \tag{28}$$

(ii) *$U(r,\lambda)$ is continuously differentiable with respect to λ for all $0 \leqslant r \leqslant 1$, $\lambda \geqslant 0$, and*

$$-\frac{1}{6} f(\alpha_s) \leqslant \frac{\partial U}{\partial \lambda}(r,\lambda) < 0 \quad \textit{for} \;\; 0 < r < 1, \;\; \lambda \geqslant 0. \tag{29}$$

(iii) *$U(r,0) = \alpha_s$ for $0 \leqslant r \leqslant 1$, and*

$$\lim_{\lambda\to\infty} U(r,\lambda) = \begin{cases} 0, & \textit{for} \;\; 0 \leqslant r < 1, \\ \alpha_s, & \textit{for} \;\; r = 1. \end{cases} \tag{30}$$

Proof. First, it is clear that 0 and α_s are a pair of lower and upper solutions for system (26), from which the existence of a solution U satisfying (27) follows by using the upper and lower solution method. In addition, the uniqueness of the solution U is a consequence of the monotonicity of f. Since $\Delta_r U = \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 \frac{\partial U}{\partial r})$, integrating the first equation in (26) with respect to r leads to

$$\frac{\partial U}{\partial r}(r,\lambda) = \frac{\lambda}{r^2}\int_0^r f(U(\rho,\lambda))\rho^2 \mathrm{d}\rho, \tag{31}$$

which together with (27) and the nonnegativity and monotonicity of the function f yield (28). Thus, the assertion (i) holds.

Next, differentiating (26) with respect to λ and writing $W(r,\lambda) = \frac{\partial U}{\partial \lambda}(r,\lambda)$, we obtain

$$\begin{cases} \Delta_r W = \lambda f'(U) W + f(U), \quad 0 < r < 1, \\ \dfrac{\partial W}{\partial r}(0,\lambda) = 0, \quad W(1,\lambda) = 0. \end{cases}$$

Thanks to $f(U) \geqslant 0$, $\lambda f'(U) \geqslant 0$, and it follows from the maximum principle (see [14]) that $W(r,\lambda) < 0$ for all $0 \leqslant r < 1$ and all $\lambda \geqslant 0$. Therefore,

$$\Delta_r W \leqslant f(U) \leqslant f(\alpha_s) \quad \text{for} \;\; 0 < r < 1.$$

Integrating the above inequality gives

$$W(r,\lambda) \geqslant -\frac{f(\alpha_s)}{6} + \frac{f(\alpha_s)}{6} r^2 \geqslant -\frac{f(\alpha_s)}{6} \quad \text{for} \;\; 0 < r < 1,$$

i.e., the assertion (ii) follows.

Finally, we verify the assertion (iii). Integrating (31) with respect to r over $[r,1]$ gives

$$\begin{aligned}&\int_r^1 \frac{\partial U}{\partial\theta}\mathrm{d}\theta = U(1,\lambda)-U(r,\lambda)=\alpha_s - U(r,\lambda)\\ =&\lambda\int_r^1\frac{1}{\theta^2}\int_0^\theta f(U(\rho,\lambda))\rho^2\mathrm{d}\rho\mathrm{d}\theta = -\lambda\left[\int_r^1\int_0^\theta f(U(\rho,\lambda))\rho^2\mathrm{d}\rho\mathrm{d}(\frac{1}{\theta})\right]\\ =&-\lambda\left[\int_0^1 f(U(\rho,\lambda))\rho^2\mathrm{d}\rho-\frac{1}{r}\int_0^r f(U(\rho,\lambda))\rho^2\mathrm{d}\rho-\int_r^1\theta\cdot f(U(\theta,\lambda))\mathrm{d}\theta\right].\end{aligned}$$

Hence,

$$\begin{aligned}U(r,\lambda)=&\alpha_s+\lambda\int_0^1 f(U(\rho,\lambda))\rho^2\mathrm{d}\rho-\frac{\lambda}{r}\int_0^r f(U(\rho,\lambda))\rho^2\mathrm{d}\rho-\lambda\int_r^1 f(U(\rho,\lambda))\rho\mathrm{d}\rho\\ =&\alpha_s-\lambda(\frac{1}{r}-1)\int_0^r f(U(\rho,\lambda))\rho^2\mathrm{d}\rho-\lambda\int_r^1 f(U(\rho,\lambda))\rho(1-\rho)\mathrm{d}\rho.\end{aligned}\tag{32}$$

In particular, $U(r,0)=\alpha_s$. From the boundedness and monotonicity of $U(r,\lambda)$ with respect to λ, we can conclude that $\lim_{\lambda\to\infty}U(r,\lambda)$ exists point-wise.

For each $r\geqslant 0$, denote

$$U^*(r)=\lim_{\lambda\to\infty}U(r,\lambda).$$

Now, dividing (32) by λ and letting $\lambda\to\infty$, we get

$$\big(\frac{1}{r}-1\big)\int_0^r f(U^*(\rho))\rho^2\mathrm{d}\rho+\int_r^1 f(U^*(\rho))\rho(1-\rho)\mathrm{d}\rho=0,\quad 0<r<1,$$

which implies that $f(U^*(r))=0$ a.e. on $[0,1]$. Further, $U^*(r)=0$ a.e. on $[0,1]$. Since $U^*(r)$ is a monotonically nondecreasing function on $(0,1)$, (30) holds. The proof is complete. $\square$

Now we introduce a function $F(R)$ as follows

$$F(R):=\int_0^1 g(U(r,R^2))r^2\mathrm{d}r\quad\text{for}\quad R\geqslant 0.\tag{33}$$

Then we have the following two lemmas, which can be proved in the same way as Lemma 3.2 and Lemma 3.3 in [10], so we omit the proof here.

Lemma 4.2. *Under the assumption (**A5**), problem (25) has a solution $(u_s(r),R_s)$ with $R_s>0$ if and only if the function $F(R)$ has a positive root R_s. Moreover the solution $u_s(r)$ of (25) is given by*

$$u_s(r)=U\big(\frac{r}{R_s},R_s^2\big)\quad\text{for}\quad 0\leqslant r\leqslant R_s.\tag{34}$$

Lemma 4.3. *Suppose that the assumptions (**A5**) – (**A6**) hold. Then*

(i) $F'(R) < 0$ *for all* $R > 0$.

(ii) $F(0) = \dfrac{1}{3}g(\alpha_s)$ *and* $\lim\limits_{R\to\infty} F(R) = \dfrac{1}{3}g(0)$.

Furthermore, as a consequence of Lemma 4.2 and Lemma 4.3 and recalling that α^* is defined such that $g(\alpha^*) = 0$, we have

Theorem 4.1. *Under the assumptions (**A5**) – (**A6**), the following assertions hold:*

(i) *If* $\alpha_s \leqslant \alpha^*$, *then the problem* (1)-(2)-(5) *has no steady-state solution satisfying* (25).

(ii) *If* $\alpha_s > \alpha^*$, *then the problem* (1)-(2)-(5) *has a unique steady-state solution* $(u_s(r), R_s)$ *satisfying* (25), *where* R_s *is the unique positive root of the function* $F(R)$, *and* $u_s(r)$ *is given by* (34).

4.2. The asymptotic stability of steady-state solutions

The main purpose of this subsection is to show the asymptotic stability of steady-state solutions in the sense of the transient solution $(u(r,t), R(t))$ obtained in Theorem 3.1 toward the steady-state solution $(u_s(r), R_s)$ with $R_s > 0$ obtained in Theorem 4.1 under the assumption that $\alpha_s > \alpha^*$. Thus throughout this subsection it is assumed that $\alpha_s > \alpha^*$. In addition, we assume that

(**A7**) given $\alpha_s > \alpha^*$, there exist a continuous function $M_\alpha(t)$ satisfying $M_\alpha(t) \to 0$ over time such that
$$|\alpha(t) - \alpha_s| \leqslant \mu M_\alpha(t)$$

Throughout this subsection denote by $(u(r,t), R(t))$ the solution of system (NTS) and let

$$v(r,t) := U\Big(\frac{r}{R(t)}, R^2(t)\Big), \quad 0 \leqslant r \leqslant R(t),\ t \geqslant t_0, \tag{35}$$

where $U(r,\lambda)$ is the solution of system (26).

Lemma 4.4. *Let (**A5**) and (**A7**) hold and in addition assume that given any* $T > t_0$, *there exist* $L_R > 0$, $m_{_R} > 0$ *and* $M_R > 0$ *such that*

$$|\dot{R}(t)| \leqslant L_R \quad \text{and} \quad m_{_R} \leqslant R(t) \leqslant M_R, \qquad \text{for} \quad t_0 \leqslant t < T. \tag{36}$$

Then exist $\mu_1 > 0$ *and* $C := C(m_R, M_R, \alpha_s)$ *such that*

$$|u(r,t) - v(r,t)| \leqslant C, \quad \forall\ r \in [0, R(t)],\ t \in [t_0, T] \text{ and } \mu \in (0, \mu_1].$$

Proof. First according to the definition of v, it satisfies

$$\begin{cases} \Delta_r v(r,t) = f(v(r,t)) \quad \text{for} \quad 0<r<R(t),\ t\geqslant t_0, \\ \dfrac{\partial v}{\partial r}(0,t)=0, \quad v(R(t),t)=\alpha_s \quad \text{for} \quad t\geqslant t_0. \end{cases} \tag{37}$$

Observe that

$$\frac{\partial v}{\partial t} = \left(2\frac{\partial U}{\partial \lambda} - \frac{\partial U}{\partial r}\cdot\frac{r}{R^3(t)}\right)\cdot R(t)\cdot \dot{R}(t),$$

from Lemma 4.1 and (36), it follows that

$$\left|\frac{\partial v}{\partial t}\right| \leqslant CL_R \quad \text{for} \quad 0<r<R(t),\ t\geqslant t_0, \tag{38}$$

where the constant C depends on m_R, M_R and α_s.

Now for any $\varepsilon>0$ arbitrarily small, define $\ell_f := \frac{1}{2}\inf_{u\in\mathbb{R}} f'(u)+\varepsilon$ and let

$$u_{\pm}(r,t) = v(r,t) \pm CL_R\ell_f^{-1}\mu \pm \overline{\alpha}e^{-\frac{\ell_f(t-t_0)}{\mu}}.$$

Notice that by assumption (**A5**), $\ell_f>0$. Then by (37)-(38), it follows that if

$$\begin{aligned} &\mu(u_-)_t - \Delta_r u_- + f(u_-) \\ =&\mu v_t + \ell_f\overline{\alpha}e^{-\frac{\ell_f(t-t_0)}{\mu}} - \Delta_r v + f\big(v(r,t) - CL_R\ell_f^{-1}\mu - \overline{\alpha}e^{-\frac{\ell_f(t-t_0)}{\mu}}\big) \\ \leqslant&\mu CL_R + \ell_f\overline{\alpha}e^{-\frac{\ell_f(t-t_0)}{\mu}} - f(v) + f\big(v(r,t) - CL_R\ell_f^{-1}\mu - \overline{\alpha}e^{-\frac{\ell_f(t-t_0)}{\mu}}\big). \end{aligned}$$

Notice that due to the boundedness of v, $f'(u)>0$ for all u lies in between $v(r,t)$ and $v(r,t) - CL_R\ell_f^{-1}\mu - \overline{\alpha}e^{-\frac{\ell_f(t-t_0)}{\mu}}$. Pick $\varepsilon>0$ small enough such that $f'(u)\geq \ell_f$, then

$$\begin{aligned} \mu(u_-)_t - \Delta_r u_- + f(u_-) &\leqslant \mu CL_R + \ell_f\overline{\alpha}e^{-\frac{\ell_f(t-t_0)}{\mu}} - \ell_f(CL_R\ell_f^{-1}\mu + \overline{\alpha}e^{-\frac{\ell_f(t-t_0)}{\mu}}) \\ &= 0 \quad \text{for} \quad 0<r<R(t),\ t\geqslant t_0. \end{aligned}$$

Since $|u_0(r)-v(r,t_0)|\leqslant\overline{\alpha}$ for $0\leqslant r\leqslant R_0$ and by assumption (**A7**) we have

$$\begin{aligned} u_-(R(t),t) &= v(R(t),t) - CL_R\ell_f^{-1}\mu - \overline{\alpha}e^{-\frac{\ell_f(t-t_0)}{\mu}} \\ &= \alpha_s - CL_R\ell_f^{-1}\mu - \overline{\alpha}e^{-\frac{\ell_f(t-t_0)}{\mu}} \\ &\leqslant \alpha(t) + \mu M_\alpha(t) - CL_R\ell_f^{-1}\mu. \end{aligned}$$

Then taking C such that $C > \dfrac{\ell_f}{L_R}\cdot\max\limits_{t\in[t_0,\infty)} M_\alpha(t)$ gives immediately

$$\begin{cases} \dfrac{\partial u_-}{\partial r}(0,t)=0, \quad u_-(R(t),t)\leqslant\alpha(t), \quad t\geqslant t_0, \\ u_-(r,t_0)\leqslant u_0(r), \quad 0\leqslant r\leqslant R_0. \end{cases}$$

Therefore, by comparison, we conclude that

$$u_-(r,t) \leqslant u(r,t) \quad \text{for} \ \ 0 \leqslant r \leqslant R(t),\ t_0 \leqslant t \leqslant T.$$

Similarly, we have

$$u_+(r,t) \geqslant u(r,t) \quad \text{for} \ \ 0 \leqslant r \leqslant R(t),\ t_0 \leqslant t \leqslant T.$$

Then, for any $0 \leqslant r \leqslant R(t)$, $t_0 \leqslant t \leqslant T$, it follows from the above two inequalities that

$$-CL_R\ell_f^{-1}\mu - \bar{\alpha}e^{-\frac{\ell_f(t-t_0)}{\mu}} \leqslant u(r,t) - v(r,t) \leqslant CL_R\ell_f^{-1}\mu + \bar{\alpha}e^{-\frac{\ell_f(t-t_0)}{\mu}},$$

which yields the desired assertion. □

Lemma 4.5. *Let assumptions (***A5***)–(***A7***) hold. Then given any $R_0 > 0$ there exists a constant $\mu_2 > 0$ such that*

$$\frac{1}{2}\min\{R_0, R_s\} < R(t) < 2\max\{R_0, R_s\} \tag{39}$$

for all $t \geqslant t_0$ and $\mu \in (0, \mu_2]$.

Proof. First note that since $R_0 > 0$, $\frac{1}{2}R_0 < R_0 < 2R_0$ and by continuity of $R(t)$, (39) holds for a certain period of time. Suppose (for contradiction) that there exists $T > t_0$ such that (39) holds for $t_0 \leqslant t < T$, but fails at $t = T$, i.e.,

$$\text{either} \quad R(T) = 2\max\{R_0, R_s\} \quad \text{or} \quad R(T) = \frac{1}{2}\min\{R_0, R_s\}.$$

Without loss of generality, we assume that $R(T) = 2\max\{R_0, R_s\} := K_T$. Clearly, we have

$$\dot{R}(T) \geqslant 0. \tag{40}$$

Moreover, it follows from (10) that there exists a constant L_R (the same as that in Lemma 4.4) satisfying

$$|\dot{R}(t)| \leqslant \frac{R(t)}{3}\max\{|m_g|, |M_g|\} \leqslant L_R, \quad \forall\, t_0 \leqslant t \leqslant T. \tag{41}$$

Now we can use Lemma 4.4 to conclude that there exists a positive constant C_0 (independent of μ) such that, for all $0 < \mu \leqslant \mu_1$,

$$|u(r,t) - v(r,t)| \leqslant C_0\big(\mu + e^{-\frac{\ell_f(t-t_0)}{\mu}}\big) \quad \text{for} \quad 0 \leqslant r \leqslant R(t),\ t_0 \leqslant t \leqslant T. \tag{42}$$

Let $\tilde{L}_g = \max\limits_{0 \leqslant u \leqslant \overline{\alpha}} g'(u) > 0$, then it follows from the above inequality that

$$g(u(r,t)) - g(v(r,t)) \leqslant \tilde{L}_g C_0\big(\mu + e^{-\frac{\ell_f(t-t_0)}{\mu}}\big)$$

for all $0 \leqslant r \leqslant R(t)$, $t_0 \leqslant t \leqslant T$ and $0 < \mu \leqslant \mu_1$. Consequently,

$$\begin{aligned}\dot{R}(t) =& \frac{1}{R^2(t)} \int_0^{R(t)} g(u(r,t))r^2 \mathrm{d}r \\ \leqslant& \frac{1}{R^2(t)} \int_0^{R(t)} g(v(r,t))r^2 \mathrm{d}r + \frac{1}{3}\tilde{L}_g C_0 (\mu + e^{-\frac{\ell_f (t-t_0)}{\mu}}) \cdot R(t) \\ =& R(t)F(R(t)) + \frac{1}{3}\tilde{L}_g C_0 (\mu + e^{-\frac{\ell_f (t-t_0)}{\mu}}) \cdot R(t) \quad \text{for} \quad t_0 \leqslant t \leqslant T. \end{aligned} \tag{43}$$

In particular,

$$\begin{aligned}\dot{R}(T) \leqslant& R(T) \left(F(R(T)) + \frac{1}{3}\tilde{L}_g C_0 (\mu + e^{-\frac{\ell_f (T-t_0)}{\mu}}) \right) \\ =& K_T \left(F(K_T) + \frac{1}{3}\tilde{L}_g C_0 (\mu + e^{-\frac{\ell_f (T-t_0)}{\mu}}) \right). \end{aligned}$$

From (11), we see that

$$K_T = R(T) \leqslant R_0 e^{\frac{1}{3}M_g (T-t_0)},$$

which gives

$$T - t_0 \geqslant \frac{3}{M_g} \log(\frac{K_T}{R_0}) \geqslant \frac{3\log 2}{M_g}.$$

Hence

$$\begin{aligned}\dot{R}(T) \leqslant& K_T \left(F(K_T) + \frac{1}{3}\tilde{L}_g C_0 \big(\mu + e^{-\frac{\ell_f}{\mu} \cdot \frac{3\log 2}{M_g}} \big) \right) \\ =& K_T \left(F(K_T) + \frac{1}{3}\tilde{L}_g C_0 \big(\mu + 2^{-\frac{3\ell_f}{\mu M_g}} \big) \right). \end{aligned} \tag{44}$$

Further, we can deduce that there exists a constant $\tilde{\mu}_1 > 0$ such that

$$\frac{1}{3}\tilde{L}_g C_0 \big(\mu + 2^{-\frac{3\ell_f}{\mu M_g}} \big) \leqslant \frac{1}{2}|F(K_T)| \quad \text{for all} \quad \mu \leqslant \tilde{\mu}_1. \tag{45}$$

On the other hand, by Lemmata 4.2 and 4.3, we see that $F(R_s) = 0$ and $F(\cdot)$ is a monotone decreasing function. Since $K_T \geqslant 2R_s > R_s$, so we can obtain

$$F(K_T) < 0,$$

which together with (44) and (45) implies

$$\dot{R}(T) < 0 \quad \text{for all} \quad \mu \leqslant \tilde{\mu}_1.$$

Therefore, taking $\mu_2 = \min\{\mu_1, \tilde{\mu}_1\}$, we get a contradiction to (40) for all $\mu \in (0, \mu_2]$. The proof is complete. □

With the above lemmata and Lemma 4.4 in [10] we can state the main result of this subsection.

Theorem 4.2. *Let assumptions (*$\mathbf{A0}$*)–(*$\mathbf{A2}$*) and (*$\mathbf{A5}$*)–(*$\mathbf{A7}$*) hold. Then given any* $R_0 > 0$ *there exist corresponding positive constants* C, γ *and* M_μ *such that*

$$|R(t) - R_s| < Ce^{-\gamma(t-t_0)}, \quad |\dot{R}(t)| < Ce^{-\gamma(t-t_0)}, \quad |u(r,t) - u_s(r)| < Ce^{-\gamma(t-t_0)}.$$

for every $\mu \in (0, M_\mu]$, $t \geqslant t_0$ *and* $0 \leqslant r \leqslant R(t)$.

Proof. First due to Lemma 4.5, there exists a constant $\mu_2 > 0$ such that

$$\min\{\frac{1}{2}R_0 - R_s, -\frac{1}{2}R_s\} < R(t) - R_s < \max\{2R_0 - R_s, R_s\},$$

for every $\mu \in (0, \mu_2]$, which implies that

$$|R(t) - R_s| \leqslant 2R_0 + R_s := \beta_1, \quad |R(t)| \leqslant 2R_0 + 2R_s, \quad \forall\ t \geqslant t_0. \tag{46}$$

Then it follows from (10) that

$$|\dot{R}(t)| \leqslant \frac{2}{3}(R_0 + R_s)\max\{|m_g|, |M_g|\} := \beta_2, \quad \text{for} \quad t \geqslant t_0.$$

Moreover,

$$|u(r,t) - u_s(r)| \leqslant 2\overline{\alpha} := \beta_3, \quad \forall\ 0 \leqslant r \leqslant R(t),\ t \geqslant t_0$$

.

Let $\beta := \max\{\beta_1, \beta_2, \beta_3\}$ and $\mu \leq \min\{\mu_1, \mu_2, \mu_3\}$. It then follows directly from Lemma 4.4 in [10] that there exist constants $\widehat{C} > 0$, $\theta > 0$ and $T_0 > 0$ such that

$$|R(t) - R_s| \leqslant \widehat{C}\beta(\mu + e^{-\theta(t-t_0)}) \leqslant 2\widehat{C}\beta\mu \quad \text{for} \quad t \geqslant T_0 + t_0.$$

Similar estimates also hold for $|\dot{R}(t)|$ and $|u(r,t) - u_s(r)|$ for $t \geqslant T_0 + t_0$. Then, by successively applying Lemma 4.4 in [10] over $[nT_0 + t_0, \infty)$, we can obtain

$$|R(t) - R_s| \leqslant \widehat{C}(2\widehat{C}\mu)^{n-1}\beta\big(\mu + e^{-\theta[t-(n-1)T_0-t_0]}\big) \leqslant (2\widehat{C}\mu)^n\beta, \quad t \geqslant nT_0 + t_0.$$

Define $\gamma > 0$ by $2\widehat{C}\mu = e^{-\gamma T_0}(< 1)$. For any $t > t_0$ let n be the largest integer such that $nT_0 + t_0 \leqslant t < (n+1)T_0 + t_0$, and set

$$M_\mu := \min\big\{\mu_1, \mu_2, \mu_3, \frac{1}{2\widehat{C}\beta}\big\}, \quad C := \max\big\{\beta e^{\gamma T_0}, \widehat{C}(M_\mu + 1)\beta\big\}.$$

We then conclude that for every $\mu \in (0, M_\mu]$,

$$\begin{aligned} |R(t) - R_s| \leqslant& (2\widehat{C}\mu)^n\beta = \beta \cdot e^{-\gamma nT_0} = \beta e^{-\gamma t}e^{-\gamma(nT_0 - t)} \\ <& \beta e^{-\gamma t}e^{-\gamma[nT_0-(n+1)T_0-t_0]} = \beta e^{\gamma(T_0+t_0)}e^{-\gamma t} \\ =& \beta e^{\gamma T_0}e^{-\gamma(t-t_0)} \leqslant Ce^{-\gamma(t-t_0)}, \quad \forall t \geqslant t_0. \end{aligned}$$

Similarly $|\dot{R}(t)| < Ce^{-\gamma(t-t_0)}$ and $|u(r,t) - u_s| < Ce^{-\gamma(t-t_0)}$ also hold. The proof is complete. □

Remark 4.2. *Theorem 4.2 implies the nutrient concentration and tumor size will evolve toward a dormant state if the nutritional supply $\alpha(t)$ becomes stable as time goes on. Moreover, the exponential rate of convergence of the transient solution (u(r,t),R(t)) to the steady-state solution $(u_s(r), R_s)$ is obtained under assumption (**A7**) with suitable $M_\alpha(t)$. In particular, we note that the convergence rate of the transient solution $(u(r,t), R(t))$ to the steady-state solution $(u_s(r), R_s)$ is restricted by the convergence rate of $\alpha(t)$ to α_s over time.*

5. Long time behavior of solutions: general case

In this section, we investigate the long term behavior of solutions to the (NTS) system in other situations. To facilitate computations in the sequel, we first transform the time-dependent domain $\mathfrak{Q}_T^R$ into a fixed domain. In particular, let $y = \dfrac{R_0}{R(t)}x$ where $R_0 = R(t_0)$, and denote

$$\tilde{u}(y,t) = u\left(\frac{R(t)}{R_0}y, t\right), \quad \tilde{u}_0(y) = u_0(y).$$

Then the problem (NTS) can be transformed to the following problem in the fixed spatial domain $\Omega_0 := \mathcal{B}_{R_0} = \{y \in \mathbb{R}^3 : |y| \leqslant R_0\}$:

$$\begin{cases} \mu\dfrac{\partial \tilde{u}}{\partial t}(y,t) = \dfrac{R_0^2}{R^2(t)}\Delta\tilde{u}(y,t) + \mu\dfrac{\dot{R}(t)}{R(t)}(y\cdot\nabla\tilde{u}) - f(\tilde{u}(y,t)) \text{ for } |y| < R_0, \\ \tilde{u}(y,t) = \alpha(t) \text{ for } |y| = R_0, \ t_0 \leqslant t, \\ \dfrac{\mathrm{d}R(t)}{\mathrm{d}t} = \dfrac{R(t)}{R_0^3}\displaystyle\int_0^{R_0} g(\tilde{u}(r))r^2\mathrm{d}r \\ R(t_0) = R_0, \quad \tilde{u}(y,t_0) = \tilde{u}_0(y) \text{ for } |y| \leqslant R_0, \end{cases} \tag{47}$$

Note that based on the arguments in previous sections, the solution of problem (47) exists and satisfies the same estimates as those of the solution of problem (NTS). Moreover, the solution $\tilde{u}(y,t)$ is radially symmetric in y, so throughout this section we write $\tilde{u}(y,t) = \tilde{u}(|y|,t) = \tilde{u}(r,t)$ and set

$$m_g := \min_{s\in[0,\overline{\alpha}]} g(s) \quad \text{and} \quad M_g := \max_{s\in[0,\overline{\alpha}]} g(s). \tag{48}$$

Throughout the rest of this section, denote $\mathfrak{X} := \mathscr{L}^2[\Omega_0]$ and the norms in $\mathfrak{X}$ and $H^1[\Omega_0]$ are, respectively,

$$\|\cdot\| := \|\cdot\|_{\mathscr{L}^2[\Omega_0]} \quad \text{and} \quad \|\cdot\|_{H^1} := \|\cdot\|_{H^1[\Omega_0]}.$$

We will next investigate long term behavior of solutions $(\tilde{u}(y,t), R(t))$ of the problem (47) in the domain $\mathfrak{X}\times\mathbb{R}$. In particular we first show that all solutions of problem (47) with the same boundary conditions but different initial conditions will converge to a singleton trajectory $(\hat{u}(y,t), \hat{R}(t))$ as $t \to \infty$ (see Theorem 5.1 below). We then investigate the special case when $M_g < 0$, for which all solutions converges to $(\alpha(t), 0)$ as $t \to \infty$ (see Theorem 5.2 below).

To that end, we first recall a Poincaré inequality

$$\lambda \|\varphi(t)\|^2 \leqslant \|\nabla\varphi(t)\|^2, \quad \forall \varphi(y,t) \in H_0^1[\Omega_0], \tag{49}$$

for some constant $\lambda > 0$. The following Lemma will be used in the proof of Theorem 5.1.

Lemma 5.1. *Assume (**A5**) hold. Then the function $F(u) := -f(u)$ satisfies a local one-sided dissipative Lipschitz condition, i.e., there exists a positive constant $\widetilde{L}_f$ such that*

$$(u_1 - u_2) \cdot (F(u_1) - F(u_2)) \leqslant -\widetilde{L}_f |u_1 - u_2|^2 \quad \text{for all} \quad u_1,\, u_2 \in [0, \overline{\alpha}].$$

Proof. Due to assumption (**A5**), $\widetilde{L}_f := \min\limits_{u \in [0,\overline{\alpha}]} f'(u) > 0$ exists. Moreover, for any u_1, $u_2 \in [0, \overline{\alpha}]$, we see that $(u_1 - u_2) \cdot (f(u_1) - f(u_2)) \geqslant 0$ and further

$$(u_1 - u_2) \cdot (f(u_1) - f(u_2)) = \frac{f(u_1) - f(u_2)}{u_1 - u_2}(u_1 - u_2)^2 \geqslant \widetilde{L}_f (u_1 - u_2)^2.$$

The proof is complete. □

Given any continuous function $R(t) > 0$, consider the following initial-boundary value problem:

$$\begin{cases} \mu \dfrac{\partial \hat{u}}{\partial t} = \dfrac{R_0^2}{R^2(t)} \Delta \hat{u} + \mu \dfrac{\dot{R}(t)}{R(t)} (y \cdot \nabla \hat{u}) - f(\hat{u}) \ \text{ for } 0 < |y| < R_0,\ t > t_0, \\ \hat{u}(R_0, t) = \alpha(t) \quad \text{for} \quad t > t_0, \\ \hat{u}(y, t_0) = \hat{u}_0(y) \quad \text{for} \quad 0 \leqslant |y| \leqslant R_0. \end{cases} \tag{50}$$

Using the same arguments in Section 3, we conclude that the problem (50) admits a unique solution $\hat{u}_R(y,t;t_0,\hat{u}_0)$. Given two initial conditions $\hat{u}_0^{(1)}(y)$ and $\hat{u}_0^{(2)}(y)$ define the difference

$$w(y,t) := \hat{u}_R(y,t;t_0,\hat{u}_0^{(1)}) - \hat{u}_R(y,t;t_0,\hat{u}_0^{(2)}).$$

Then w satisfies the initial-boundary value problem

$$\begin{cases} \mu \dfrac{\partial w}{\partial t} = \dfrac{R_0^2}{R^2(t)} \Delta w + \mu \dfrac{\dot{R}(t)}{R(t)} (y \cdot \nabla w) - h \quad \text{for} \ \ 0 < |y| < R_0,\ t > t_0, \\ w(R_0, t) = 0 \quad \text{for} \quad t > t_0, \\ w(y, t_0) = w_0(y) \quad \text{for} \quad 0 \leqslant |y| \leqslant R_0, \end{cases} \tag{51}$$

where $h(y,t) = f(\hat{u}_R^{(1)}) - f(\hat{u}_R^{(2)})$ and $w_0(y) = \hat{u}_0^{(1)}(y) - \hat{u}_0^{(2)}(y)$ for $0 \leqslant |y| \leqslant R_0$.

Multiplying (51) by $w(y,t)$, integrating the resultant equality over Ω_0 and using Lemma 5.1, (10) and (49) yields

$$\begin{aligned}\frac{\mu}{2}\frac{\mathrm{d}}{\mathrm{d}t}\|w(t)\|^2 &= -\frac{R_0^2}{R^2(t)}\|\nabla w\|^2 - \frac{3\mu}{2}\frac{\dot{R}(t)}{R(t)}\|w\|^2 - \int_{\Omega_0} h\cdot w\mathrm{d}y \\ &\leqslant -\frac{\lambda R_0^2}{R^2(t)}\|w\|^2 - \frac{1}{2}\mu m_g\|w\|^2 - \widetilde{L}_f\|w\|^2.\end{aligned}$$

Hence, under the condition $-\mu m_g < 2\widetilde{L}_f$, there exists a positive constant ν such that

$$\|w(t)\|^2 \leqslant \|w_0\|^2 e^{-\nu(t-t_0)}. \tag{52}$$

In addition, from Theorem 3.1, it is not difficult to conclude that there exists a pullback absorbing set of nonempty closed and bounded subsets $\{B_t : t\in\mathbb{R}\}$ of $\mathscr{L}^2[\Omega]$, which pullback absorbs all solutions $\hat{u}_R(t)$ of system (50). Thus the system (50) has a pullback attractor, [7]. It follows then by inequality (52) that there is a single function $\hat{u}(y,t)$ for all $t\in\mathbb{R}$, which solves the problem (50). Moreover it attracts all other solutions $\hat{u}_R(t)$ of (50) as $t\to\infty$.

In particular, let $R(t)$ be the solution of system (47) and $\hat{u}_R(y,t)$ be the unique solution to the problem (50) obtained above. We next show that the singleton $\hat{u}(y,t)$ attracts all solutions of (47) as $t\to\infty$.

Theorem 5.1. *Let assumptions (*$\mathbf{A0}$*)–(*$\mathbf{A2}$*), (*$\mathbf{A5}$*) and (*$\mathbf{A6}$*) hold. Then, there exists constant* $\mu_0>0$ *and* $\nu:=\nu(\nu_0)$ *such that every solution* $(\tilde{u}(y,t),R(t))$ *of problem* (47) *approaches* $(\hat{u}(y,t),R(t))$ *in the sense that*

$$\|\tilde{u}(\cdot,t)-\hat{u}(\cdot,t)\|^2 \leqslant \|\tilde{u}_0(\cdot)-\hat{u}_0(\cdot)\|^2 e^{-\nu(t-t_0)}, \quad \forall\mu\in(0,\mu_0]. \tag{53}$$

Moreover, if in addition $\alpha(t)\to\alpha_s$ *as* $t\to\infty$*, then*

(a) $R(t)\to R_s$ *as* $t\to\infty$ *if* $\alpha_s>\alpha^*$*;*

(b) $R(t)\to 0$ *as* $t\to\infty$ *if* $\alpha_s<\alpha^*$.

Proof. The equality (53) follows directly from a comparison of equations in (50) and (47), and the inequality (52). The assertion (a) is a consequence of Theorem 4.2.

It remains to prove the assertion (b). Since $\alpha(t)\to\alpha_s$ as $t\to\infty$, so there exist constants $\mu_0>0$ and $\tilde{t}_0\geqslant t_0$ such that

$$\alpha(t)<\alpha^* \ \text{ for all } \ t\geqslant\tilde{t}_0,\ \mu\leqslant\mu_0,$$

which together with ($\mathbf{A6}$) implies

$$\tilde{M}_g := \max_{0\leqslant u\leqslant \max\limits_{t\geqslant\tilde{t}_0}\alpha(t)} g(u) < g(\alpha^*) = 0.$$

By the same arguments as those used in section 3, we obtain

$$R(t)\leqslant R(\tilde{t}_0)\cdot e^{\frac{1}{3}\tilde{M}_g(t-t_0)} \to 0 \ \text{ as } \ t\to\infty.$$

Thus the assertion (b) holds. The proof is complete. □

The $\hat{u}_R(t)$ constructed above can be regarded as a "limiting" trajectory that attracts all solutions of (47) as time evolves. However, we did not have more details of $\hat{u}_R(t)$ in addition to its existence and uniqueness. In what below we will discuss the special case when $M_g < 0$, for which the "limiting" trajectory can be constructed explicitly.

The last main result reads:

Theorem 5.2. *Let assumptions (**A0**)–(**A4**) hold and in addition assume that $M_g < 0$. Then given any $u_0(\cdot) \in \mathfrak{X}$ there exist positive constants $C_1, C_2, \tilde{M}_1$ and $\tilde{M}_2$ such that for all $t \geqslant t_0$ and $\mu < \frac{6\lambda}{\tilde{M}_1}$, the solution $(\tilde{u}(y,t), R(t))$ of problem (47) satisfies*

$$R_0 e^{-\frac{1}{3}\tilde{M}_1(t-t_0)} \leqslant R(t) \leqslant R_0 e^{-\frac{1}{3}\tilde{M}_2(t-t_0)}, \tag{54}$$

$$\begin{aligned}\|\tilde{u}(t)-\alpha(t)\|^2 \leqslant &\|\tilde{u}_0-\alpha(t_0)\|^2 e^{-\frac{\beta_0}{\mu}(t-t_0)} \\ &+ \frac{6C_1R_0^2}{3\beta_0 - 2\mu\tilde{M}_2}\big(e^{-\frac{2}{3}\tilde{M}_2(t-t_0)} - e^{-\frac{\beta_0}{\mu}(t-t_0)}\big),\end{aligned} \tag{55}$$

where $\beta_0 = \lambda - \dfrac{\mu\tilde{M}_1}{6} > 0.$

Proof. Since $M_g < 0$, it holds that $m_g < M_g < 0$. Writing $\tilde{M}_1 := -m_g > 0$ and $\tilde{M}_2 := -M_g > 0$, then clearly $\tilde{M}_1 > \tilde{M}_2$, and (54) follows directly from (11).

Now let $v(y,t) = \tilde{u}(y,t) - \alpha(t)$. It is straightforward to see that $v(y,t)$ satisfies

$$\begin{cases} \mu\dfrac{\partial v}{\partial t} = \dfrac{R_0^2}{R^2(t)}\Delta v + \mu\dfrac{\dot{R}(t)}{R(t)}(y\cdot\nabla v) - f(v+\alpha(t)) + \mu\dot{\alpha}(t) \\ \qquad\qquad\qquad\qquad \text{for } \ 0<|y|<R_0, \ t>t_0, \\ v(R_0,t) = 0 \ \text{ for } \ t>t_0, \\ v(r,t_0) = v_0(r) \ \text{ for } \ 0\leqslant r\leqslant R_0, \end{cases} \tag{56}$$

where $v_0(r) = \tilde{u}_0(r) - \alpha(t_0) \in \mathfrak{X}$. Multiplying (56) by $v(y,t)$, integrating the resultant equality over Ω_0 and using assumptions (**A1**), (**A3**), (10) and (49), we obtain

$$\begin{aligned}\frac{\mu}{2}\frac{\mathrm{d}}{\mathrm{d}t}\|v(t)\|^2 &= -\frac{R_0^2}{R^2(t)}\|\nabla v\|^2 - \frac{\mu}{2}\frac{\dot{R}(t)}{R(t)}\|v(t)\|^2 - \int_{\Omega_0}(f(v+\alpha(t)) - \mu\dot{\alpha}(t))v\mathrm{d}y \\ &\leqslant -\frac{\lambda R_0^2}{R^2(t)}\|v\|^2 + \frac{\mu\tilde{M}_1}{6}\|v\|^2 + \frac{\beta(t)}{2}\|v\|^2 + C_1R^2(t) \\ &\leqslant -\frac{\beta(t)}{2}\|v\|^2 + C_1R^2(t),\end{aligned}$$

where C_1 is a positive constant and $\beta(t) := \dfrac{\lambda R_0^2}{R^2(t)} - \dfrac{\mu \tilde{M}_1}{6} > 0$, which together with (54) gives

$$\frac{\mathrm{d}}{\mathrm{d}t}\|v(t)\|^2 + \frac{\beta_0}{\mu}\|v(t)\|^2 \leqslant \frac{2C_1 R_0^2}{\mu} e^{-\frac{2}{3}\tilde{M}_2(t-t_0)}, \tag{57}$$

where $\beta_0 := \dfrac{2\lambda}{3} - \dfrac{\mu \tilde{M}_1}{3} > 0$. The inequality (55) then follows directly from the above inequality. The proof is complete. □

Remark 5.1. *The assumption $\mu < \frac{6\lambda}{\tilde{M}_1}$ was imposed to ensure that $\beta(t) = \lambda \frac{R_0^2}{R(t)} - \mu \frac{\tilde{M}_1}{6}$ is positive. This assumption can be largely weakened or even removed as $R(t) \to 0$ as $t \to \infty$. Moreover, μ is naturally small from modeling perspective.*

6. Closing remarks

The system (1)-(2) proposed by Byrne and Chaplain [2] for tumor growth has drawn extensive attention from both researchers and practitioners in cancer research. However to the best of our knowledge most of the existing works assumed that the nutrient supply rate at the tumor surface was constant or periodic. One natural question would then arise, what if the nutrient is supplied at a non-constant rate, and how would that affect the effectiveness of cancer treatment. This motivates our work of studying system (1)-(2) with time dependent nutritional supply $\alpha(t)$ on the tumor surface and general functions f and g.

Not surprisingly, through this work fundamental differences are discovered to exist between the model (1)-(2) with time dependent nutrient supply $\alpha(t)$ and with constant nutrient supply α. In particular, as presented in Subsection 4.2 and Section 5, the long time behavior of the solutions of problem (NTS) is highly dependent on $\alpha(t)$. In addition to the consideration of time-dependent nutrient supply, another novelty of our work lies in that the functions f and g are not required to be linear or almost linear, which largely extends existing results on linear cases.

The highlights of this work are summarized as follows. The global existence and uniqueness of a transient solution for the problem (NTS) is established first by using fixed point theorem. Then, under additional regularity conditions on f and g (i.e., assumptions (**A5**) and (**A6**)), we verify that with a certain fixed nutrition supply $\alpha_s(> \alpha^*)$ on the tumor surface, the problem (NTS) has a unique steady-state solution. Moreover, the nutrient concentration and the tumor size will evolve toward a dormant state eventually if the time dependent nutritional supply $\alpha(t)$ becomes stable as time goes on. To be exact, if $\alpha(t)$ converges exponentially to α_s, then the transient solution will approach the steady-state solution exponentially fast. In the last section we present more comprehensive analysis for evolution of the nutrient concentration and tumor size under different conditions. More precisely under some general conditions about the nutritional supply $\alpha(t)$ rate and functions f and g, we mainly verify that

(i) provided μ suitable small, the nutrient concentration will exponentially converge together over time. Moreover, the changes of radius of the tumor cell over time is given under different situations between α^* and α_s.

(ii) if $\max_{0\leqslant s\leqslant\overline{\alpha}} g(s) < 0$, then the tumor size tends to 0 and the nutrient concentration within the tumor tends to the nutrient supply $\alpha(t)$ on the tumor surface, i.e., the tumor will disappear as $t \to \infty$.

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