Mathematical Analysis, Controllability and Numerical Simulation of a Simple Model of Avascular Tumor Growth

Jesús Ildefonso Díaz, José Ignacio Tello

Departamento de Matemática Aplicada, Universidad Complutense de Madrid, Avda Complutense, 28040 Madrid, Spain

Preface

Cancer is one of the most prevalent causes of natural death in the western world, and a high percentage of people develop some kind of this disease during their lives. For this reason medicine is one of the scientific fields which found significant interest not only within the scientific community, but also among the general population. The scientific community comprises medicine, but also other areas of research such us Biology, Chemistry, Mathematics, Pharmacy or Physics. This is evident from the huge number of research works and publications in the field and the great quantity of human and economical resources which have been devoted to cancer research in the last decades.

The development and growth of a tumor is a complicated phenomenon which involves many different aspects from the subcellular scale (gene mutation or secretion of substances) to the body scale (*metastasis*). This complexity is reflected by the different mathematical models given for each phase of the growth. The first phase is known as the *avascular* phase, previous to *vascularization*, and the second one, when *angiogenesis* occurs, is known as *vascular* phase.

The aim of this work is to present the study of the mathematical analysis, the controllability and a numerical simulation for a simple, avascular model of growth of a tumor. In Section 1, we describe the biological phenomenology of several processes which influence the growth and development of tumors. The mathematical modelling is

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presented by describing different models of partial differential equations (PDE). We focus our attention on a class of models proposed by GREENSPAN [1972] and BYRNE and CHAPLAIN [1995], BYRNE [1999a], BYRNE [1999b], BYRNE and CHAPLAIN [1996a], CHAPLAIN [1996], CHAPLAIN [1999], ORME and CHAPLAIN [1995], THOMPSON and BYRNE [1999], WARD and KING [1998], studied in FRIEDMAN and REITICH [1999], CUI and FRIEDMAN [1999], CUI and FRIEDMAN [2000], CUI and FRIEDMAN [2001], DÍAZ and TELLO [2004], DÍAZ and TELLO [2003] and by other authors. We prove the solvability of the model equations and establish uniqueness of solutions under additional conditions. In Section 6, we study the controllability of the growth of the tumor by a localized internal action of the inhibitor on a nonnecrotic tumor. It is obvious that this type of results has merely a mathematical interest and it does not suggest any special therapeutical strategy to inhibit tumor growth. Nevertheless our results show that there is not any *obstruction* to the controllability (as it appears, for instance, in some similar PDE's models: see DÍAZ and RAMOS [1995]). In a final section, we address the numerical simulation of the problem.

1. Phenomenology

A tumor originates from mutations of DNA inside cells. In order to create malignant cells, a sufficiently large number of such mutations has to occur. Factors for mutations can be external radiation, hereditary causes etc. Eventually, such gene mutations induce an uncontrolled reproduction, the onset of the formation of a malignant tumor. This process continues as long as the malignant cells find sufficient supply, and will generate a small spheroid of a few millimeters. During this time, called the *avascular* phase, nutrients (glucose and oxygen) arrive at the cells through diffusion. As the spheroid grows, the level of nutrients in the interior of the tumor decreases due to consumption by the outer cells. When the level of concentration of nutrients in the interior falls bellow a critical level, the cells cannot survive, a phenomenon called *necrosis*, and an inner region is formed in the center of the tumor by the dead cells, which decompose into simpler chemical compounds (mainly water). At this time, one can distinguish several regions in the tumor: a necrotic region in the center, an outer region, where *mitosis* (division of cells) occurs, and a region in between where the level of nutrients suffices for the cells to live, but not to proliferate. Until this moment, the tumor is a *multicell spheroid* whose radius is no more than a few millimeters.

The cells of the tumor secrete some chemical substances, known as *Tumor Angiogenesis Factors* (TAFs). These substances diffuse through the surrounding tissue. TAFs stimulate *endothelial* cells (ECs), located in neighboring blood vessels. Endothelial cells are thin cells which form the basement membrane of the blood vessels. When ECs are stimulated by TAFs, they destroy the membrane basement (by secretion of *proteases* and *collagenases*) and migrate towards the tumor forming capillary sprouts. These grow thanks to the proliferation of ECs and other substances located in the extracellular matrix (as fibronectin), forming a capillary network. Initially, the ECs move forming parallel vessels and as sprouts are closer to the tumor, the sprouts branch out and connect.

This process of formation of new vessels, known as *angiogenesis*, is one of the most decisive steps in the growth of a tumor. Angiogenesis is present in other contexts of life, as well, like in wound healing or in the formation of embryos.

The connection of the blood vessels to the tumor supplies nutrients to the malignant cells, aiding a faster proliferation of the tumor's cells. This phase of the tumor is known as *vasculature phase* and is characterized by an aggressive growth.

Finally, the cells of the tumor invade the surrounding tissue and metastasizing to other parts of the body. The circulatory and lymphatic systems are used by the malignant cells for transport to another sites. The process in which cells leave the tumor and enter into the vessels is known as *intravasation*. Cancer cells, which survive in the blood flow and escape from the circulatory system, arrive at a new site, where a new colony of cells may grow. Fortunately, less than 0.05 per cent of cells which were introduced in the circulation are able to create new colonies. Each tumor has a preference to metastasize to a specific organ.

During the growth of a tumor, the *immune system* competes with the malignant cells; it will be activated through the recognition of the cancer cells by the immune cells. *Macrophages* (Ms) are a type of white blood cells, which migrate into the tumor to the regions with low oxygen (*hypoxic* regions) in the interior of the tumor through the external layer of well nourished cells of the tumor. Ms move to the tumor (by chemotaxis) attracted by *macrophage chemoattractants*, which is secreted by the tumor. A *cytotoxic* substance is secreted into the tumor's cell which kills it. Ms may also help the growth of the tumor secreting other chemical substances which help angiogenesis.

It is the main strategy of all cancer therapies (apart from surgery) to inhibit the growth of tumors with tools adapted to the phase the tumor is in. E.g., chemotherapy or radiation therapy are intended to destroy cells of tumor, other treatments try to stimulate cells of the immune system. The first type of therapy is nonselective, destroying both, malignant cells and cells of the immune system. Another therapy based on genetic engineering is being studied. The idea is to insert a therapeutic gene into the cells of a patient and re-inject them back into the patient.

2. Mathematical modelling

Mathematical modelling of the growth of a tumor have been studied by several authors during the last thirty years in many different works.

Among the many different PDE models we can introduce (following FRIEDMAN [2002]) a rough classification into two classes: the mixed models, in which all the different population of cells are continuously present everywhere in the tumor, at all the times, and segregated models, perhaps less realistic but relevant for in vitro experiments, in which the different populations of cells are separated by unknown interfaces or free boundaries. Our analysis will be restricted to the second class of models (some references on mixed models can be found in BELLOMO and PREZIOSI [2000], DE ANGELIS and PREZIOSI [2000], CHAPLAIN and PREZIOSI [2002] and FRIEDMAN [2002]). Moreover, we shall consider spherical tumors (for other free boundary type tumors, without symmetrical shape, arising in tumoral masses growing around a blood vessel see, e.g., BERTUZZI, FASANO, GANDOLFI and MARANGI [2002] or BAZALIY and FRIEDMAN [2003]).

In this section, we describe different mathematical models for each phase. A first and simple model describing the avascular phase was presented in GREENSPAN [1972], assuming spherical symmetry in $\mathbb{R}^3$. The outer boundary delimiting the tumor is denoted by $R(t)$ and the concentration of nutrients and inhibitors by σ and β, respectively. According to principle of conservation of mass, the tumor mass is proportional to its volume $\frac{4}{3}\pi R^3(t)$, assuming the density of the cell mass is constant. The balance between the birth and death rate of cells is given as a function of the concentration of nutrients and inhibitors. Let $\widehat{S}$ be this balance, then after normalizing, we obtain the law

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{4}{3}\pi R^3(t)\right) = \int_{\{|\tilde{x}|<R(t)\}} \widehat{S}\big(\sigma(\tilde{x},t), \beta(\tilde{x},t)\big)\,\mathrm{d}\tilde{x}.$$

Depending on the author, the function $\widehat{S}$ can be written in different ways. GREENSPAN [1972] studied the problem in the presence of an inhibitor, and the possibility that this affects mitosis, when the concentration of the inhibitor is greater than a critical level $\tilde{\beta}$. He proposed $\widehat{S}(\sigma,\beta) = sH(\sigma-\tilde{\sigma})H(\tilde{\beta}-\beta)$, where $H(\cdot)$ denotes the maximal monotone graph of $\mathbb{R}^2$ associate with the Heaviside function, i.e., $H(k)=0$ if $k<0$, $H(k)=1$ if $k>0$ and $H(0)=[0,1]$. BYRNE and CHAPLAIN [1996a] study the growth when the inhibitor affects the cell proliferation and propose $\widehat{S}(\sigma,\beta) = s(\sigma-\tilde{\sigma})(\tilde{\beta}-\beta)$ (for a positive constant s). In the absence of inhibitors or in case that the inhibitor does not affect mitosis, they choose $\widehat{S}(\sigma,\beta) = s\sigma(\sigma-\tilde{\sigma})$. FRIEDMAN and REITICH [1999] and CUI and FRIEDMAN [2000] study the asymptotic behavior of the radius, $R(t)$, with the cell proliferation rate free of the action of inhibitors. They assume that $\widehat{S} = s(\sigma-\tilde{\sigma})$, where $s\sigma$ is the cell birth-rate and the death-rate is given by $s\tilde{\sigma}$ (see also the survey SLEEMAN [1996]).

We assume that the tumor is composed of an homogeneous tissue and that the distribution of the concentration of nutrients σ is governed by a PDE in the spheroid. Assuming that there is no inhibitor, that the tumor has not necrotic core and that diffusion is high, we obtain the equation

$$d_1\Delta\sigma = \lambda\sigma, \quad |x|<R,$$

where $\lambda\sigma$ represents the nutrient consumption by cells and d_1 is the diffusion coefficient.

In necrotic tumors, an inner free boundary appears, which is denoted by $\rho(t)$. It separates the necrotic core (where σ falls below σ_n) from the remaining part. A model for necrotic tumors was presented in BYRNE [1997a], who proposes the equation

$$0 = \Delta\sigma - \lambda H\big(|x|-\rho(t)\big), \quad |x|<R(t),$$

where the effect of time-delay appears in the radial growth. In addition, asymptotic techniques are used to show the effect of the delay terms.

Several authors (ADAM [1986] and BRITTON and CHAPLAIN [1993]) studied a model proposed by SHYMKO and GLASS [1976] where cell proliferation is controlled by chemical substances *Growth inhibitor factor* (GIFs) as chalones. GIFs secreted by cells reduce the mitotic activity. Two different kinds of inhibitors appear, depending on the phase of the cell cycle stage at which inhibition occurs. The inhibitor can act before DNA synthesis (as epidermal chalon in Melanoma or granulocyte chalon in Leukemia) or before mitosis (see ATTALLAH [1976]). The concentration of GIF (denoted by C) is modeled by one PDE in a bounded domain Ω of $\mathbb{R}^3$,

$$\frac{\partial C}{\partial t} = d\Delta C + f(C) + S(x), \quad x \in \Omega,\ t > 0, \tag{2.1}$$

$$D\frac{\partial C}{\partial n} + PC = 0, \quad x \in \partial\Omega,\ t > 0,\ P \geqslant 0, \tag{2.2}$$

$$C(x,t) = C_0(x), \quad x \in \Omega, \tag{2.3}$$

where $S(x)$ is a source term and $f(C)$ represents the decay of GIF (see ADAM and BELLOMO [1997]).

In 1972, GREENSPAN [1972] proposed a radially symmetric model employing the Heaviside function H for modelling the necrotic part. The avascular model considers a chemical inhibitor β, which is produced in the necrotic core. The distribution of nutrients $\hat{\sigma}$ is given by the equation

$$\frac{\partial \sigma}{\partial t} - d_1\Delta\sigma = -\lambda(\sigma_B - \sigma)H\big(|x| - \rho\big)H\big(R - |x|\big), \tag{2.4}$$

where R is the outer boundary of the tumor and ρ is the radius of the necrotic core.

The chemical substance "β" (produced within the tumor) inhibits the mitosis of cancer cells without causing their death and satisfies the diffusion equation

$$\frac{\partial \beta}{\partial t} - d_2\Delta\beta = PH\big(|x| - \rho\big)H\big(R - |x|\big) - P_d H\big(\rho - |x|\big). \tag{2.5}$$

This model, proposed by Greenspan, has been studied by several authors in the last thirty years. We shall focus on the study of a similar model and detail the modelling and some mathematical results in the next section.

When asymmetric distribution of nutrients or displacement of cells produced by nonuniform density appears in the interior of the spheroid tumor, the internal forces may break the symmetry of the outer boundary. Several authors have studied, in different models, the symmetry breaking of the boundary. GREENSPAN [1976] studied a model where the pressure p of the cancer cells satisfies

$$\Delta p = S,$$

inside the tumor, where S is the rate of volume lost per unit volume (assumed constant). The distribution of nutrients σ satisfies a elliptic equation outside of the tumor. Using Darcy's law, (the velocity v of the boundary is proportional to the gradient of p) that is $v = \mu\nabla p$, with suitable boundary conditions for p and σ, Greenspan obtains nonsymmetric explicit solutions using spherical harmonics.

Darcy's law has been used in different models in order to describe the movement of the free boundary. BYRNE [1997b], BYRNE and CHAPLAIN [1996b] and BYRNE and MATTHEWS [2002] propose similar models improving GREENSPAN [1976]; they study the stability of radially symmetric solutions via perturbations with spherical harmonics. FRIEDMAN and REITICH [2001] study the bifurcation of non-symmetric solutions from any radially symmetric steady state. Bessel functions are used in FRIEDMAN and REITICH [2001] and also in FRIEDMAN, HU and VELÁZQUEZ [2001] in a protocell model.

LEVINE, SLEEMAN and NILSEN-HAMILTON [2000] and LEVINE, PAMUK, SLEEMAN and NILSEN-HAMILTON [in press] (see also HOLMES and SLEEMAN [2000]) developed models of angiogenesis based on analysis of the relevant biochemical processes and on the methodology of the reinforced random walk of OTHMER and STEVENS [1997]. A mathematical analysis of the model proposed in LEVINE, SLEEMAN and NILSEN-HAMILTON [2000] have been performed in FONTELOS, FRIEDMAN and HU [2002]. Their model involves several diffusing populations and several chemical species. Another model of angiogenesis with one diffusing population and two non-diffusing ones, was developed in ANDERSON and CHAPLAIN [1998] and CHAPLAIN and ANDERSON [1997]. They denote the density of the endothelial cells by p, the concentration of the tumor angiogenesis factor (secreted by the tumor) by c, and w represents the density of the fibronectin cells, then

$$\frac{\partial p}{\partial t} = \operatorname{div}\left(\nabla p - p\left(\frac{\alpha}{1+c}\nabla c + \rho \nabla w\right)\right), \qquad \frac{\partial w}{\partial t} = \gamma p(1-w),$$
$$\frac{\partial c}{\partial t} = -\mu pc,$$

where α, ρ, γ and μ are positives constants. The asymptotic behavior of the solutions has been studied for some values of the parameters and special initial data in FRIEDMAN and TELLO [2002]. A computational approach is used by VALENCIANO and CHAPLAIN [2003a], VALENCIANO and CHAPLAIN [2003b] to obtain numerical solutions for similar models. LEVINE and SLEEMAN [1997] study the chemotaxis equations developed in the context of reinforced random walks. They use the classification of the second order part of a modified equation in the "Hodograph plane" and study the existence of blow up of solutions in finite time.

Recently, BERTUZZI, FASANO, GANDOLFI and MARANGI [2002] have developed a model for the phase transition in tumor cells and their migration towards the periphery.

The macrophages cells are part of the response of the immune system to cancer; their movement has been modeled by different authors (see OWEN and SHERRATT [1999]).

3. A simple mathematical model

In this section we describe a simple mathematical model which will be studied throughout the remainder of this work. It belongs to a group of first generation cancer models with Greenspan's model (2.4), (2.5) being one of the earliest ones. Similar models have been proposed and studied by several authors (BYRNE and CHAPLAIN [1996a], FRIEDMAN and REITICH [1999], CUI and FRIEDMAN [2000], CUI and FRIEDMAN [2001] and DÍAZ and TELLO [2004], DÍAZ and TELLO [2003]). We assume that the density of live cells is proportional to the concentrations of the nutrients σ. The tumor occupies a ball in $\mathbb{R}^3$ of radius $R(t)$ which is unknown (which is reason why R is usually called the free boundary of the problem).

The tumor comprised a central necrotic core of dead cells, the necrotic core is covered with a layer (of living cells) resulting in a second free boundary denoted by $\rho(t)$ in GREENSPAN [1972].

The transfer of nutrients to the tumor through the vasculature occurs below a certain level σ_B, and it is done with a rate r_1. During the development of the tumor, the immune system secretes inhibitors as a immune response to the foreign body. The structure of inhibitor absorption is similar to the transference of nutrients (for a constant r_2). If we assume that the nutrient consumption rate is proportional to the concentrations of nutrients, the nutrient consumption rate is given by $\lambda\sigma$. Both processes, consumption and transference, occur simultaneously in the exterior of the necrotic core, where cells are inhibited by $\hat{\beta}$. We assume that the host tissue is homogeneous and that the diffusion coefficient, d_1, is constant. The reaction between nutrients and inhibitors can be globally modelled by introducing the Heaviside maximal monotone graph (as function of $\hat{\sigma}$) and some continuous functions $g_i(\hat{\sigma}, \hat{\beta})$. Then $\hat{\sigma}$ satisfies

$$\frac{\partial \sigma}{\partial t} - d_1 \Delta \sigma \in \hat{r}_1\big((\sigma_B - \sigma) - \lambda_1 \sigma - \lambda \beta\big) H(\sigma - \sigma_n) + \hat{g}_1(\sigma, \beta). \tag{3.1}$$

We also assume a constant diffusion coefficient for the inhibitor concentration $\hat{\beta}$, d_2. The model considers the permanent supply of inhibitors, modeled by $\tilde{f}$ and localized on a small region ω_0 inside the tumor. This term $\tilde{f}$ was introduced in DÍAZ and TELLO [2003] to control the growth of the tumor. Then β satisfies

$$\frac{\partial \beta}{\partial t} - d_2 \Delta \beta \in -r_2(\beta - \beta_B) H(\sigma - \sigma_n) + \hat{g}_2(\sigma, \beta) + \tilde{f} \chi_{\omega_0}, \tag{3.2}$$

adding initial and boundary conditions, we obtain

$$\sigma(\tilde{x}, t) = \overline{\overline{\sigma}}, \qquad \beta(\tilde{x}, t) = \overline{\overline{\beta}}, \quad |\tilde{x}| = R(t), \tag{3.3}$$

$$\sigma(\tilde{x}, 0) = \sigma_0(\tilde{x}), \qquad \beta(\tilde{x}, 0) = \beta_0(\tilde{x}), \quad |\tilde{x}| < R_0. \tag{3.4}$$

In this formulation, the presence of the maximal monotone graph H is the reason why the symbol $\in$ appears in Eq. (3.2) instead of the equal sign (a precise notion of weak solution will be presented later). Different constants appears in the equations and boundary conditions which lead to a wide variety of special cases: σ_n is the level of concentration of nutrients above which the cells can live (below this level the cells die by *necrosis*), $\overline{\overline{\sigma}}$ and $\overline{\overline{\beta}}$ are the concentration of nutrients and inhibitors in the exterior of the tumor. The diffusion operator Δ is the Laplacian operator and χ_{ω_0} denotes the characteristic function of the set ω_0 (i.e., $\chi_{\omega_0}(\tilde{x}) = 1$, if $\tilde{x} \in \omega_0$, and $\chi_{\omega_0}(\tilde{x}) = 0$, otherwise).

Notice that the above formulation is of global nature and that the inner free boundary $\rho(t)$ is defined implicitly as the boundary of the set $\{r \in [0, R(t))\colon\ \sigma \leqslant \sigma_n\}$. So, if for instance, the initial datum σ_0 satisfies $\sigma_0(\tilde{x}) = \sigma_n$ on $[0, \rho_0]$, for some $\rho_0 > 0$ and $\hat{g}_1(\sigma_n, \beta) \in [0, r_1(\sigma_B - \sigma_n) - \lambda\sigma_n]$ for any $\beta \geqslant 0$, the above formulation leads to the associate double free boundary formulation in which $\hat{\sigma}$ satisfies

$$\begin{cases} \dfrac{\partial \sigma}{\partial t} - d_1 \Delta \sigma + \lambda_1 \sigma = \hat{r}_1(\sigma_B - \sigma) + \hat{g}_1(\sigma, \beta), & \rho(t) < |\tilde{x}| < R(t), \\ \sigma(\tilde{x}, t) = \sigma_n, & |\tilde{x}| \leqslant \rho(t), \\ \sigma(\tilde{x}, t) = \overline{\overline{\sigma}}, & |\tilde{x}| = R(t), \\ R(0) = R_0,\ \rho(0) = \rho_0,\ \sigma(\tilde{x}, 0) = \sigma_0(\tilde{x}), & \rho_0 < |\tilde{x}| < R_0. \end{cases}$$

The free boundary $R(t)$ is described by the ODE presented in Section 2,

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{4}{3}\pi R^3(t)\right) = \int_{\{|\tilde{x}|<R(t)\}} \widehat{S}\big(\sigma(\tilde{x},t), \beta(\tilde{x},t)\big)\,\mathrm{d}\tilde{x}, \quad R(0) = R_0. \tag{3.5}$$

4. Existence of solutions

In this section, we study the existence of solutions to (3.1)–(3.5) after introducing some structural assumptions on $\hat{g}_i$ and $\widehat{S}$. We also introduce some functional spaces and a useful change of variables. The existence result is presented in Theorem 4.1 and proved by using a Galerkin approximation based on a weak formulation of the problem.

We shall assume that the reaction terms $\hat{g}_i$ and the mass balance of the tumor $\widehat{S}$ satisfy:

$$\hat{g}_i \text{ are piecewise continuous,} \quad \big|\hat{g}_i(a,b)\big| \leqslant c_0 + c_1\big(|a| + |b|\big), \tag{4.1}$$

$$\widehat{S} \text{ is continuous and} \quad -\lambda_0 \leqslant \widehat{S}(a,b) \leqslant c_0 + c_1\big(|a|^2 + |b|^2\big) \tag{4.2}$$

for some positives constants λ_0, c_0, c_1.

The above assumptions ((4.1) and (4.2)) do not constitute biological restrictions, and previous models satisfy them provided σ and β are bounded. They are introduced in order to carry out the mathematical treatment, and its great generality allows us to handle all the special cases from the literature previously mentioned. They are relevant due to its generality. It is possible to show that the absence of one (or both) of the conditions implies the occurrence of very complicated mathematical pathologies, and much more sophisticated approaches would be needed for proving that the model admits a solution (in some very delicate sense).

We introduce the change of variables,

$$x = (x_1, x_2, x_3) = \frac{\tilde{x}}{R(t)}, \tag{4.3}$$

$$u(x,t) = \sigma\big(R(t)x, t\big) - \overline{\overline{\sigma}} \tag{4.4}$$

and

$$v(x,t) = \beta\big(R(t)x, t\big) - \overline{\overline{\beta}}. \tag{4.5}$$

Let the unit ball $\{x \in \mathbb{R}^3\colon |x| < 1\}$ be denoted by B and define functions from $\mathbb{R}^2$ to $2^{\mathbb{R}^2}$ by

$$\begin{cases} g_1\big(\sigma - \overline{\overline{\sigma}}, \beta - \overline{\overline{\beta}}\big) := \big(\hat{r}_1\big((\sigma_B - \sigma) - \lambda_1\sigma\big) - \lambda\beta\big)H(\sigma - \sigma_n) + \hat{g}_1(\sigma,\beta), \\ g_2\big(\sigma - \overline{\overline{\sigma}}, \beta - \overline{\overline{\beta}}\big) := -r_2(\beta - \beta_B)H(\sigma - \sigma_n) + \hat{g}_2(\sigma,\beta), \end{cases} \tag{4.6}$$

$$S\big(\sigma - \overline{\overline{\sigma}}, \beta - \overline{\overline{\beta}}\big) := \frac{4}{3\pi}\widehat{S}(\sigma,\beta) \tag{4.7}$$

and

$$f(x,t) := \tilde{f}\big(xR(t), t\big), \qquad \widetilde{\omega}_0^t = \big\{(x,t) \in B \times [0,T]\colon R(t)x \in \omega_0\big\}.$$

Problem (3.1)–(3.5) becomes

$$\begin{cases} \dfrac{\partial u}{\partial t} - \dfrac{d_1}{R(t)^2}\Delta u - \dfrac{R'(t)}{R(t)} x\cdot\nabla u \in g_1(u,v), & x\in B,\ t>0,\\ \dfrac{\partial v}{\partial t} - \dfrac{d_2}{R(t)^2}\Delta v - \dfrac{R'(t)}{R(t)} x\cdot\nabla v \in g_2(u,v) + f\chi_{\tilde\omega_0^t}, & x\in B,\ t>0,\\ R(t)^{-1}\dfrac{\mathrm{d}R(t)}{\mathrm{d}t} = \int_B S(u,v)\,\mathrm{d}x, & t>0,\\ u(x,t) = v(x,t) = 0, & x\in\partial B,\ t>0,\\ R(0)=R_0,\ u(x,0)=u_0(x),\ v(x,0)=v_0(x), & x\in B. \end{cases} \tag{4.8}$$

We introduce the Hilbert spaces

$$\mathbf{H}(B) := L^2(B)^2, \qquad \mathbf{V}(B) = H_0^1(B)^2$$

and define inner products by

$$\langle \Phi,\Psi\rangle_{\mathbf{H}(B)} = \int_B \Phi\cdot\Psi^t\,\mathrm{d}x, \qquad \langle \Phi,\Psi\rangle_{\mathbf{V}(B)} = \sum_{i=1,2} d_i \int_B (\nabla\Phi_i)^t\cdot\nabla\Psi_i\,\mathrm{d}x$$

for all $\Phi=(\Phi_1,\Phi_2)$, $\Psi=(\Psi_1,\Psi_2)$.

For the sake of notational simplicity we use $\mathbf{H}=\mathbf{H}(B)$ and $\mathbf{V}=\mathbf{V}(B)$. Given $T>0$, we introduce $U=(u,v)$, $U_0=(u_0,v_0)$ and define $G:\mathbb{R}^2\to 2^{\mathbb{R}^2}\times 2^{\mathbb{R}^2}$ and $F:(0,T)\times B\to\mathbb{R}^2$ by

$$G(U) = \big(g_1(u,v), g_2(u,v)\big), \qquad F(t,x) = \big(0, f(t,x)\chi_{\tilde\omega_0^t}\big).$$

We have

$$\big|G(U)\big| = \big|g_1(u,v)\big| + \big|g_2(u,v)\big| \leqslant C_0 + C_1|U| = C_0 + C_1\big(|u|+|v|\big). \tag{4.9}$$

DEFINITION. $(U,R)\in L^2(0,T:\mathbf{V})\times W^{1,\infty}(0,T:\mathbb{R})$ is a weak solution of the problem (4.8) if there exists $g^*=(g_1^*,g_2^*)\in L^2(0,T:\mathbf{H})$ with $g^*(x,t)\in G(U(x,t))$ a.e. $(x,t)\in B\times(0,T)$ satisfying

$$\int_0^T -\langle U,\Phi_t\rangle_{\mathbf{H}}\,\mathrm{d}t + \int_0^T \tilde a(t,U,\Phi)\,\mathrm{d}t = \int_0^T \langle g^*,\Phi\rangle_{\mathbf{H}}\,\mathrm{d}t + \langle U_0,\Phi(0)\rangle_{\mathbf{H}} + \int_0^T \langle F(t),\Phi\rangle_{\mathbf{H}}\,\mathrm{d}t,$$

$\forall\Phi\in L^2(0,T:\mathbf{V})\cap H^1(0,T:\mathbf{H})$ with $\Phi(T)=0$, where

$$\tilde a(t,U,\Phi) := \frac{1}{R^2(t)}\langle U,\Phi\rangle_{\mathbf{V}} - \frac{R'(t)}{R(t)}\langle x\cdot\nabla U,\Phi\rangle_{\mathbf{H}} \tag{4.10}$$

and $R(t)$ is strictly positive and given by

$$R(t)^{-1}\frac{\mathrm{d}R(t)}{\mathrm{d}t} = \int_B S\big(U(x,t)\big)\,\mathrm{d}x \quad \text{for } t\in(0,T).$$

DEFINITION. (σ, β, R) is a weak solution of (3.1)–(3.5) if

$$\sigma(\tilde{x}, t) = u\left(\frac{\tilde{x}}{R(t)}, t\right) + \overline{\overline{\sigma}} \quad \text{and} \quad \beta(\tilde{x}, t) = v\left(\frac{\tilde{x}}{R(t)}, t\right) + \overline{\overline{\beta}},$$

for $t \in (0, T)$ and $\tilde{x} \in \mathbb{R}^3$, $|\tilde{x}| \leqslant R(t)$, where $(U = (u, v), R)$ is a weak solution of (4.8) for any $T > 0$.

REMARK 4.1. The definition of weak solution and the structural assumptions on G imply that $\partial U/\partial t \in L^2(0, T : \mathbf{V}(B)')$ and the equation holds in $D'(B \times (0, T))$.

THEOREM 4.1. *Assume* (4.1), (4.2), $R_0 > 0$ *and* $\sigma_0, \beta_0 \in L^2(0, R_0)$, *then problem* (3.1)–(3.5) *has at least a weak solution for each* $T > 0$.

PROOF. We shall use a Galerkin method to construct a weak solution. Let $R(t) \in W^{1,\infty}(0, T : \mathbb{R})$ such that $R'(t)/R(t) \geqslant -\lambda_0$ a.e. $t \in (0, T)$. For fixed $t \in (0, T)$, we consider the operator $\mathbf{A}(t) \equiv \mathbf{A}(R(t)) : \mathbf{V} \to \mathbf{V}'$ defined by

$$\mathbf{A}\big(R(t)\big)(U) = \begin{pmatrix} -\frac{d_1}{R(t)^2}\Delta u - \frac{R'(t)}{R(t)} x \cdot \nabla u & 0 \\ 0 & -\frac{d_2}{R(t)^2}\Delta v - \frac{R'(t)}{R(t)} x \cdot \nabla v \end{pmatrix}.$$

$\mathbf{A}(t)$ defines a continuous, bilinear form on $\mathbf{V} \times \mathbf{V}$,

$$\tilde{a}(t : \cdot, \cdot) : \mathbf{V} \times \mathbf{V} \to \mathbb{R}$$

for a.e. $t \in (0, T)$ (see (4.10)). Since $R'(t)/R(t) \geqslant -\lambda_0$, $\tilde{a}$ satisfies

$$\begin{aligned} \tilde{a}(t, U, U) &= \frac{1}{R^2(t)} \langle U, U \rangle_{\mathbf{V}} - \frac{R'(t)}{R(t)} \langle x \cdot \nabla U, U \rangle_{\mathbf{H}} \\ &= \frac{1}{R^2(t)} \langle U, U \rangle_{\mathbf{V}} + \frac{R'(t)}{2R(t)} \langle U, U \rangle_{\mathbf{H}} \\ &\geqslant \Big(\max_{0<t<T} \big\{ R(t) \big\} \Big)^{-2} \|U\|_{\mathbf{V}}^2 - \frac{\lambda_0}{2} \|U\|_{\mathbf{H}}^2. \end{aligned}$$ □

Now we establish some *a priori estimates* which will be used later. In fact, those estimates can be applied even for other existence methods, different from the Galerkin-type one, as, for instance, iterative methods, fixed point methods, etc. (see, for instance, SHOWALTER [1996]).

LEMMA 4.1.

$$\|U\|_{\mathbf{H}}^2 \leqslant C_0^2 \big(\exp\big\{ (\lambda_0 + 2C_1 + 1)T \big\} - 1 \big) + \|F\|_{L^2(0,T:\mathbf{H})}^2 + \|U_0\|_{\mathbf{H}}^2.$$

PROOF. Inserting U^t as test function into the weak formulation of (4.8), one obtains

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_B \frac{1}{2} U^2 \,\mathrm{d}x + \tilde{a}(t, U, U) + \int_B g^*(U) U^t \,\mathrm{d}x = \int_B F \cdot U^t \,\mathrm{d}x$$

for some $g^* \in L^2((0,T)\times B)^2$ and $g^*(x,t) \in G(U(x,t))$ for a.e. $(x,t) \in B \times (0,T)$. The definition of $\tilde{a}$ yields

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\|U\|^2_{\mathbf{H}} - \frac{\lambda_0}{2}\|U\|^2_{\mathbf{H}} \leqslant \big(\|g^*\|_{\mathbf{H}} + \|F\|_{\mathbf{H}}\big)\|U\|_{\mathbf{H}}. \tag{4.11}$$

Thus by Young's inequality and (4.9) imply

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\|U\|^2_{\mathbf{H}} - \left(\frac{\lambda_0}{2} + C_1 + \frac{1}{2}\right)\|U\|^2_{\mathbf{H}} \leqslant \frac{1}{2}\big(C_0^2 + \|F\|^2_{\mathbf{H}}\big).$$

Integrating with respect to time, we get

$$\frac{1}{2}\|U\|^2_{\mathbf{H}} - \frac{1}{2}\|U_0\|^2_{\mathbf{H}} - \left(\frac{\lambda_0}{2} + C_1 + \frac{1}{2}\right)\|U\|^2_{L^2(0,T:\mathbf{H})} \leqslant \frac{1}{2}\big(C_0^2 T + \|F\|^2_{L^2(0,T:\mathbf{H})}\big)$$

and by Gronwall's lemma,

$$\|U\|^2_{\mathbf{H}} \leqslant C_0^2\big(\exp\big\{(\lambda_0 + 2C_1 + 1)T\big\} - 1\big) + \|F\|^2_{L^2(0,T:\mathbf{H})} + \|U_0\|^2_{\mathbf{H}} \leqslant C. \tag{4.12}$$

□

REMARK 4.2. Since U is bounded in $\mathbf{H}$ (by (4.12)), R satisfies

$$R(t) = R_0 \exp\left\{\int_0^t\int_0^1 S(U)\,\mathrm{d}x\,\mathrm{d}t\right\} \leqslant R_0 \mathrm{e}^{K_1 t} \tag{4.13}$$

and

$$R(t) \geqslant R_0 \exp\{-\lambda_0 t\}, \tag{4.14}$$

consequently, $R \in W^{1,\infty}(0,T)$.

LEMMA 4.2. $\|U\|_{L^2(0,T:\mathbf{V})} \leqslant K(T,F,G,U_0)$.

PROOF. Selecting U as test function in (4.8), we have

$$\frac{D}{R_0^2\mathrm{e}^{2K_1T}}\|U\|^2_{L^2(0,T:\mathbf{V})} - \frac{\lambda_0}{2}\|U\|^2_{L^2(0,T:\mathbf{H})}$$
$$\leqslant C_1\|U\|^2_{L^2(0,T:\mathbf{H})} + \big(C_0 + \|F\|_{L^2(0,T:\mathbf{H})}\big)\|U\|_{L^2(0,T:\mathbf{H})}.$$

By (4.12), we get

$$\|U\|_{L^2(0,T:V)} \leqslant K(F,G,U_0,T). \tag{4.15}$$

□

REMARK 4.3. By Lemma 4.2 and Remark 4.2, we get that

$$u_t - \frac{d_1}{R^2}\Delta u \in L^2\big(0,T:L^2(B)\big), \qquad v_t - \frac{d_2}{R^2}\Delta v \in L^2\big(0,T:L^2(B)\big)$$

and obtain the extra regularity

$$U_t, \quad \Delta U \in \big[L^2\big(0,T:L^2(B)\big)\big]^2. \tag{4.16}$$

Now, as previously in the proof of Theorem 4.1, we consider the approximate problem

$$\begin{cases} \dfrac{\partial U^\varepsilon}{\partial t} + A\big(R^\varepsilon(t)\big)U^\varepsilon = G^\varepsilon\big(U^\varepsilon\big) + F(t) \quad \text{on } B\times(0,T), \\ U^\varepsilon(0,x) = U_0, \qquad U^\varepsilon = 0 \quad \text{on } \partial B, \\ \dfrac{1}{R^\varepsilon}\dfrac{\mathrm{d}R^\varepsilon}{\mathrm{d}t} = \displaystyle\int_B S(U^\varepsilon)\,\mathrm{d}x, \end{cases} \tag{4.17}$$

where $G^\varepsilon = (g_1^\varepsilon, g_2^\varepsilon)$ is a Lipschitz continuous function such that

$$G^\varepsilon \to G \quad \text{when } \varepsilon \to 0 \text{ a.e. in } \mathbb{R}^2.$$

G^ε is obtained replacing H by

$$H^\varepsilon(s) = \begin{cases} 0 & \text{if } s < 0, \\ \dfrac{s}{\varepsilon} & \text{if } 0 \leqslant s \leqslant \dfrac{1}{\varepsilon}, \\ 1 & \text{if } s > \dfrac{1}{\varepsilon}. \end{cases}$$

Now, we apply the Galerkin method to the approximated problem. Let λ_n and $\phi_n \in H_0^1(B)$ for $n \in \mathbb{N}$ be the eigenvalues and eigenfunctions associated to $-\Delta$ satisfying

$$-\Delta\phi_n = \lambda_n\phi_n.$$

We consider V_m the finite-dimensional vector space spanned by $\{\phi_1, \ldots, \phi_m\}$. We search for a solution $U_m^\varepsilon \in L^2(0, T : V_m)$ of the problem

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}U_m^\varepsilon + A\big(R_m^\varepsilon(t)\big)U_m^\varepsilon = G^\varepsilon\big(U_m^\varepsilon\big) + F_m(t), \\ U_m^\varepsilon(0) = U_{0,m}^\varepsilon, \\ R_m^\varepsilon(t)^{-1}\dfrac{\mathrm{d}R_m^\varepsilon(t)}{\mathrm{d}t} = \displaystyle\int_B S\big(U_m^\varepsilon(x,t)\big)\,\mathrm{d}x, \end{cases} \tag{4.18}$$

where the initial conditions $U_{0,m}^\varepsilon = P_m(U_0)$ (where P_m is the orthogonal projection from $L^2(B)$ onto V_m) and $F_m = P_m(F)$. Then

$$R_m^\varepsilon(t) = R_0 \exp\left\{\int_0^t\int_B S\big(U_m^\varepsilon(x,s)\big)\,\mathrm{d}x\,\mathrm{d}s\right\}.$$

PROPOSITION 4.1. (4.18) *has a unique solution* U_m^ε *for any* $T < \infty$.

PROOF. Problem (4.18) can be written as a suitable nonlinear ordinary differential system. Let $U_m^\varepsilon = (u_m^\varepsilon, v_m^\varepsilon)$ be defined by

$$u_m^\varepsilon(t) = \sum_{n=1,\ldots,m} a_n^{\varepsilon m}(t)\phi_n, \qquad v_m^\varepsilon(t) = \sum_{n=1,\ldots,m} b_n^{\varepsilon m}(t)\phi_n$$

and denote

$$a^{\varepsilon m} = \left(a_1^{\varepsilon m}, a_2^{\varepsilon m}, \dots, a_m^{\varepsilon m}\right), \quad b^{\varepsilon m} = \left(b_1^{\varepsilon m}, b_2^{\varepsilon m}, \dots, b_m^{\varepsilon m}\right),$$
$$\lambda_a = \left(\lambda_1 a_1^{\varepsilon m}, \dots, \lambda_m a_m^{\varepsilon m}\right) \quad \text{and} \quad \lambda_b = (\lambda_1 b_1^{\varepsilon m}, \dots, \lambda_m b_m^{\varepsilon m}).$$

Then $a^{\varepsilon m}$, $b^{\varepsilon m}$ and R_m^ε satisfy

$$\dot a^{\varepsilon m} + \frac{\lambda_a}{(R_m^\varepsilon)^2} + \phi_\varepsilon\left(a^{\varepsilon m}, b^{\varepsilon m}\right) L_1^m\left(a^{\varepsilon m}, b^{\varepsilon m}\right) = g_1^m\left(a^{\varepsilon m}, b^{\varepsilon m}\right),$$
$$\dot b^{\varepsilon m} + \frac{\lambda_b}{(R_m^\varepsilon)^2} + \phi_\varepsilon\left(a^{\varepsilon m}, b^{\varepsilon m}\right) L_2^m\left(a^{\varepsilon m}, b^{\varepsilon m}\right) = g_2^m\left(a^{\varepsilon m}, b^{\varepsilon m}\right) + F^m(t),$$
$$\frac{\dot R_m^\varepsilon}{R_m^\varepsilon} = \phi_\varepsilon\left(a^{\varepsilon m}, b^{\varepsilon m}\right),$$

where

$$\phi_\varepsilon\left(a^{\varepsilon m}, b^{\varepsilon m}\right) = \int_B S\left(U_m^\varepsilon\right) \mathrm{d}x,$$
$$L_1^m\left(a^{\varepsilon m}, b^{\varepsilon m}\right) = \int_B x \cdot \nabla u_m^\varepsilon \phi_n \,\mathrm{d}x \quad \text{for } n = 1, \dots, m,$$
$$L_2^m\left(a^{\varepsilon m}, b^{\varepsilon m}\right) = \int_B x \cdot \nabla v_m^\varepsilon \phi_n \,\mathrm{d}x \quad \text{for } n = 1, \dots, m,$$
$$g_1^m\left(a^{\varepsilon m}, b^{\varepsilon m}\right) = \int_B g_1^\varepsilon(u_m^\varepsilon, v_m^\varepsilon) \phi_n \,\mathrm{d}x \quad \text{for } n = 1, \dots, m,$$
$$g_2^m\left(a^{\varepsilon m}, b^{\varepsilon m}\right) = \int_B g_2^\varepsilon\left(u_m^\varepsilon, v_m^\varepsilon\right) \phi_n \,\mathrm{d}x \quad \text{for } n = 1, \dots, m.$$

Since G_ε is a Lipschitz function, we obtain that there exists a unique solution $a^{\varepsilon m}, b^{\varepsilon m}, R^{\varepsilon m}$ to the system for T small enough. Moreover, (4.12) and (4.14) hold, and we get the existence of a solution of (4.18) for any $T < \infty$. By (4.15) and (4.16), $\{(U_m^\varepsilon, \frac{\mathrm{d}}{\mathrm{d}t} U_m^\varepsilon)\}_{m=1,\infty}$ is uniformly bounded in $L^2(0, T : \mathbf{V}) \times L^2(0, T : \mathbf{V}')$. So, there exists a subsequence $U_{mi}^\varepsilon \in L^2(0, T : \mathbf{V})$ with $\frac{\mathrm{d}}{\mathrm{d}t} U_{mi}^\varepsilon \in L^2(0, T : \mathbf{V}')$ such that

$$\left(U_{mi}^\varepsilon, \frac{\mathrm{d}}{\mathrm{d}t} U_{mi}^\varepsilon\right) \rightharpoonup \left(U^\varepsilon, \frac{\mathrm{d}}{\mathrm{d}t} U^\varepsilon\right) \quad \text{weakly in } L^2(0, T : \mathbf{V}) \times L^2(0, T : \mathbf{V}'),$$

and $R_{mi}^\varepsilon \rightharpoonup R^\varepsilon$ weakly in $W^{1,p}(0, T)$ for $p < \infty$. Taking limits when $mi \to \infty$, we get the existence of a weak solution to (4.17) for any $T < \infty$.

To end the proof of Theorem 4.1, we take limits in the equation when $\varepsilon \to 0$. We employ (4.12) and (4.14) and the compact embedding $\mathbf{H}_0^1(B) \subset \mathbf{L}^s(B)$ (for $s < 6$) in order to obtain the existence of a subsequence $U^{\varepsilon i}$ such that

$$U^{\varepsilon i} \to U \quad \text{in } L^2\left(0, T : \left[L^s(B)\right]^2\right)$$

and in particular

$$U^{\varepsilon i} \to U \quad \text{in } L^2(0, T : \mathbf{H})$$

(see, e.g., SIMON [1987]). Since

$$H^{\varepsilon}\big(u^{\varepsilon}+\overline{\overline{\sigma}}\big) \rightharpoonup h \in H(u+c) \quad \text{weakly in } L^2\big(0,T:L^s(B)\big)$$

and

$$v^{\varepsilon} \to v \quad \text{in } L^2\big(0,T:L^s(B)\big)$$

(see Lemma 3.4.1 of VRABIE [1995]), we have

$$G^{\varepsilon i}\big(U^{\varepsilon i}\big) \rightharpoonup g^* \in G(U) \quad \text{weakly in } L^1(0,T:\mathbf{H}).$$

Since $|R'| \leqslant C$, there exists a subsequence $R_{\varepsilon ij}$ such that

$$R_{\varepsilon ij} \rightharpoonup R \quad \text{weakly in } W^{1,p}(0,T),\ \ p<\infty,$$

and we deduce that $R_{\varepsilon ij} \to R$ in $C^0([0,T])$. Finally, taking limits in the weak formulation of the problem (4.17), we get

$$\int_0^T \langle U_t,\Phi\rangle_{\mathbf{H}}\,\mathrm{d}t + \int_0^T \tilde{a}\big(R(t),U,\Phi\big)\,\mathrm{d}t + \int_0^T \langle g^*,\Phi\rangle_{\mathbf{H}}\,\mathrm{d}t = \int_0^T \langle F,\Phi\rangle_{\mathbf{H}}\,\mathrm{d}t$$

for all $\Phi \in L^2(0,T:V)$ and, moreover,

$$R(t)^{-1}\frac{\mathrm{d}R(t)}{\mathrm{d}t} = \int_B S\big(U(x,t)\big)\,\mathrm{d}x.$$

Notice that

$$\int_0^T \frac{R'_{\varepsilon ij}}{R_{\varepsilon ij}} \int_B x\cdot\nabla u_{\varepsilon ij}\psi\,\mathrm{d}x\,\mathrm{d}t = \int_0^T \frac{R'_{\varepsilon ij}}{R_{\varepsilon ij}} \int_B u_{\varepsilon ij}\psi - u_{\varepsilon ij}x\cdot\nabla\psi\,\mathrm{d}x\,\mathrm{d}t$$

and

$$\int_0^T \frac{R'_{\varepsilon ij}}{R_{\varepsilon ij}} \int_B x\cdot\nabla v_{\varepsilon ij}\psi\,\mathrm{d}x\,\mathrm{d}t = \int_0^T \frac{R'_{\varepsilon ij}}{R_{\varepsilon ij}} \int_B v_{\varepsilon ij}\psi - v_{\varepsilon ij}x\cdot\nabla\psi\,\mathrm{d}x\,\mathrm{d}t.$$

We conclude that (σ,β,R) defined by

$$\sigma(t,\tilde{x}) = u\left(t,\frac{\tilde{x}}{R(t)}\right)+\overline{\overline{\sigma}} \quad \text{and} \quad \beta(t,\tilde{x}) = v\left(t,\frac{\tilde{x}}{R(t)}\right)+\overline{\overline{\beta}}$$

is a weak solution to (3.1)–(3.5). The additional regularity

$$\sigma_t - d_1\Delta\sigma \quad \text{and} \quad \beta_t - d_2\Delta\beta \in L^2\left(\bigcup_{t\in[0,T]}\big(0,R(t)\big)\times\{t\}\right)$$

follows from the fact that

$$\frac{\partial U}{\partial t}(t) + \mathbf{A}\big(R(t)\big)U(t) \in L^2\big(0,T:L^2(B)^2\big). \qquad \square$$

5. Uniqueness of solutions

We begin by pointing out that if, for instance,

$$\sigma_n \geqslant \frac{r_1\sigma_B}{r_1+\lambda}, \quad r_1\sigma_B > 0, \ \hat{g}_1(\hat{\sigma}, \hat{\beta})$$

is a decreasing function of $\hat{\sigma}$ and independent of $\hat{\beta}$ and the initial datum $\sigma_0(\tilde{x})$ is such that $\sigma_0'(\rho_0) = \sigma_0''(\rho_0) = 0$, then it is possible to adapt the arguments of DÍAZ and TELLO [1999] in order to construct more than one solution of problem (3.1)–(3.5). This and the presence of non-Lipschitz terms at both equations clarify that any possible uniqueness result will require an significant set of additional conditions.

In this section we prove the uniqueness of solution for two different cases. CUI and FRIEDMAN [2000] prove uniqueness of radial symmetric solutions without forcing term (i.e., $f = 0$).

5.1. 3-dimensional case with forcing term

When a tumor does not have a necrotic core, Eqs. (3.1) and (3.2) simplify such that reaction terms become linear, i.e., the nutrients concentration $\hat{\sigma}$ and the inhibitors concentration $\hat{\beta}$ satisfy

$$\frac{\partial\hat{\sigma}}{\partial t} - d_1\Delta\hat{\sigma} - \hat{r}_1(\sigma_B - \hat{\sigma}) + \lambda_1\hat{\sigma} + \lambda\hat{\beta} = 0, \quad |x| < R(t),\ t \in (0,T),$$

$$\frac{\partial\hat{\beta}}{\partial t} - d_2\Delta\hat{\beta} - r_2(\beta_B - \hat{\beta}) = f\chi_{\omega_0}, \quad |x| < R(t),\ t \in (0,T).$$

For notational convenience we shall assume that the diffusion coefficients d_1 and d_2 are equal and constant $d_1 = d_2 = d$. Thus by normalizing the unknown densities

$$\sigma := \hat{\sigma} - \frac{\hat{r}_1\sigma_B + \lambda\beta_B}{(\hat{r}_1 + \lambda_1)}, \qquad \beta := \hat{\beta} - \beta_B,$$

and setting

$$r_1 := \hat{r}_1 + \lambda_1, \qquad S(\sigma,\beta) := \frac{3}{4\pi}\widehat{S}(\hat{\sigma},\hat{\beta}),$$

we arrive at the formulation

$$\frac{\partial\sigma}{\partial t} - d\Delta\sigma + r_1\sigma + \lambda\beta = 0, \quad |x| < R(t),\ t \in (0,T), \tag{5.1}$$

$$\frac{\partial\beta}{\partial t} - d\Delta\beta + r_2\beta = f\chi_{\omega_0}, \quad |x| < R(t),\ t \in (0,T), \tag{5.2}$$

$$R(t)^2\frac{\mathrm{d}R(t)}{\mathrm{d}t} = \int_{|x|<R(t)} S(\sigma,\beta)\,\mathrm{d}x, \quad R(0) = R_0,\ t \in (0,T), \tag{5.3}$$

$$\sigma(x,0) = \sigma_0(x), \qquad \beta(x,0) = \beta_0(x), \quad |x| < R_0, \tag{5.4}$$

$$\sigma(x,t) = \overline{\overline{\sigma}}, \qquad \beta(x,t) = \overline{\overline{\beta}}, \quad |x| = R(t),\ t \in (0,T), \tag{5.5}$$

where $R_0 > 0$, the normalized nutrient and inhibitor densities at the exterior of the tumor $\overline{\overline{\sigma}}$, $\overline{\overline{\beta}}$ and the initial densities (σ_0, β_0) are known. We introduce again the changes of unknown and variables (4.3)–(4.5) and set

$$\tilde{t}(t) := \int_0^t R^{-2}(\rho)\,\mathrm{d}\rho. \tag{5.6}$$

Note that since R is a continuous function and $1/R^2(t) > 0$, we obtain that $\tilde{t}(t) \in C^1([0, \widetilde{T}])$ and employing the implicit function theorem, one derives the existence of the inverse function $t(\tilde{t}) \in C^1([0, T])$. Then, problem (5.1)–(5.5) reduces to

$$\frac{\partial u}{\partial \tilde{t}} + A(u) + R^2 r_1 u = R^2\big(r_1\overline{\overline{\sigma}} + \lambda\big(v + \overline{\overline{\beta}}\big)\big), \quad \tilde{x} \in B,\ \tilde{t} \in (0, \widetilde{T}), \tag{5.7}$$

$$\frac{\partial v}{\partial \tilde{t}} + A(v) + R^2 r_2 v = R^2 f \chi_{\widetilde{\omega}_0^{\tilde{t}}} - R^2 r_2 \overline{\overline{\beta}}, \quad \tilde{x} \in B,\ \tilde{t} \in (0, \widetilde{T}), \tag{5.8}$$

$$R(\tilde{t})\frac{\mathrm{d}}{\mathrm{d}\tilde{t}}R(\tilde{t}) = \int_B S\big(u(\tilde{x}, \tilde{t}) + \overline{\overline{\sigma}}, v(\tilde{x}, \tilde{t}) + \overline{\overline{\beta}}\big)\,\mathrm{d}\tilde{x}, \quad R(0) = R_0, \tag{5.9}$$

$$u(\tilde{x}, \tilde{t}) = v(\tilde{x}, \tilde{t}) = 0, \quad \tilde{x} \in \partial B,\ \tilde{t} \in (0, \widetilde{T}), \tag{5.10}$$

$$u(\tilde{x}, 0) = u_0(\tilde{x}) = \sigma_0(\tilde{x} R_0), \qquad v(\tilde{x}, 0) = v_0(\tilde{x}) = \beta_0(\tilde{x} R_0), \tag{5.11}$$

where $\widetilde{T} = \tilde{t}(T)$, $\widetilde{\omega}_0^{\tilde{t}} = \{\tilde{x} \in B\colon\ R(t(\tilde{t}))\tilde{x} \in \omega_0\}$, for any $\tilde{t} \in [0, \widetilde{T}]$ and

$$A(w) := -d\Delta w - R\dot{R}\tilde{x} \cdot \nabla w.$$

We assume that

$$\widehat{S} \in W^{1,\infty}\big(\mathbb{R}^2\big), \tag{5.12}$$

$$f\chi_{\widetilde{\omega}_0^{\tilde{t}}} \in L^p\big((0, T) \times \Omega\big), \quad p > 4, \tag{5.13}$$

$$(\sigma_0, \beta_0) \in W^{2,\infty}\big(B(R_0)\big)^2. \tag{5.14}$$

LEMMA 5.1. *Assume* (5.12)–(5.14), *then the solution* (u, v, R) *to the problem* (5.7)–(5.11) *satisfies*

$$u \in L^q\big(0, \widetilde{T} : W^{2,q}(B)\big) \cap W^{1,q}\big(0, \widetilde{T} : L^q(B)\big)$$

for all $1 < q < \infty$ *and*

$$v \in L^p\big(0, \widetilde{T} : W^{2,p}(B)\big) \cap W^{1,p}\big(0, \widetilde{T} : L^p(B)\big).$$

PROOF. By Theorem 4.1, we know that

$$(u, v, R) \in \big[L^2\big(0, \widetilde{T} : H^1(B)\big)\big]^2 \times W^{1,\infty}(0, \widetilde{T}).$$

Since $v_0 \in H^2(B)$ and $f \in L^p((0, T) \times B)$, we get

$$v \in W^{1,p}\big((0, \widetilde{T}) \times B\big) \cap L^p\big(0, \widetilde{T} : W^{2,p}(B)\big)$$

(see, e.g., LADYZENSKAJA, SOLONNIKOV and URALSEVA [1991], Theorem 9.1, Chapter IV). Since $p > 4$, $W^{1,p}((0, T) \times B) \subset L^\infty([0, \widetilde{T}] \times B)$, hence

$$u \in W^{1,q}\big((0,T)\times B\big) \cap L^q\big(0,T : W^{2,q}(B)\big),$$

for $q \leqslant \infty$. Consequently, we get $R \in W^{2,p}(0,T)$. □

One obtains from the lemma, in view of $W_0^{1,p}(B \times [0,\widetilde{T}]) \subset L^\infty(B \times [0,\widetilde{T}])$ (for $p > 4$) the following corollary.

COROLLARY 5.1. $u, v \in L^\infty(B \times [0,\widetilde{T}])$.

Utilizing the continuous embedding

$$W^{1,q}\big((0,T)\times B\big) \cap L^q\big(0,T : W^{2,q}(B)\big) \subset L^2\big(0,T : W^{1,\infty}(B)\big),$$
$$W^{1,p}\big((0,\widetilde{T})\times B\big) \cap L^p\big(0,\widetilde{T} : W^{2,p}(B)\big) \subset L^2\big(0,T : W^{1,\infty}(B)\big),$$

and undoing the change of variables and unknown (4.3)–(4.5) and (5.17), we obtain

COROLLARY 5.2. *Under the assumptions of Theorem* 4.1*, we have*

$$\int_0^T \big(\|\sigma\|^2_{W^{1,\infty}(R(t))} + \|\beta\|^2_{W^{1,\infty}(R(t))}\big)\,\mathrm{d}t \leqslant k_0$$

for some $k_0 < \infty$.

The uniqueness of solutions is established in the next theorem.

THEOREM 5.1. *Let* $f \in L^p(\omega_0 \times (0,T))$ *with* $p > 4$, *and* $(\sigma_0 - \overline{\overline{\sigma}}, \beta_0 - \overline{\overline{\beta}}) \in W^{2,s}(B(R_0)) \cap H_0^1(B(R_0))$, *for* $s > 4$. *Then, there exists a unique solution to* (5.1)–(5.5).

PROOF. In arguing by contradiction, we assume that there exist two different solutions (σ_1, β_1, R_1) and (σ_2, β_2, R_2). Let

$$R(t) = \min\big\{R_1(t), R_2(t)\big\}, \qquad \sigma = \sigma_1 - \sigma_2, \qquad \beta = \beta_1 - \beta_2.$$

Then (σ, β, R) satisfies the problem,

$$\frac{\partial \sigma}{\partial t} - d\Delta\sigma + r_1\sigma + \lambda\beta = 0, \quad |x| < R(t),\ t \in (0,T), \tag{5.15}$$
$$\frac{\partial \beta}{\partial t} - d\Delta\beta + r_2\beta = 0, \quad |x| < R(t),\ t \in (0,T), \tag{5.16}$$
$$\sigma(x,0) = 0, \qquad \beta(x,0) = 0, \quad |x| < R_0, \tag{5.17}$$
$$\sigma(x,t) = \sigma_1(x,t) - \sigma_2(x,t), \quad |x| = R(t),\ t \in (0,T), \tag{5.18}$$
$$\beta(x,t) = \beta_1(x,t) - \beta_2(x,t), \quad |x| = R(t),\ t \in (0,T). \tag{5.19}$$

We introduce a new unknown defined by

$$z = k_1\sigma - k_2\beta,$$

with

$$k_1 = 1, \qquad k_2 = \frac{\lambda}{r_1 - r_2} \quad \text{if } r_1 \neq r_2,$$
$$k_1 = \frac{1}{2}, \qquad k_2 = \frac{\lambda}{r_1 - 2r_2} \quad \text{if } r_1 = r_2 \neq 0.$$

By construction of z, we have

$$\begin{cases} \dfrac{\partial z}{\partial t} - d\Delta z + r_1 z = 0, & |x| < R(t),\ t \in (0,T), \\ z(x,0) = 0, & |x| < R_0, \\ z = k_1\sigma - k_2\beta, & |x| = R(t),\ t \in (0,T). \end{cases} \tag{5.20}$$

We need the following preliminary result.

LEMMA 5.2. *Let z be the solution to the problem* (5.20) *and β the solution to* (5.16), (5.19)*, then $e^{r_1 t} z$ and $e^{r_2 t}\beta$ take their maximum and minimum on $|x| = R(t)$.*

PROOF. Multiplying Eq. (5.20) by $e^{r_1 t}$, we obtain that $e^{r_1 t} z$ satisfies

$$\begin{cases} \dfrac{\partial}{\partial t}\left(e^{r_1 t} z\right) - d\Delta\left(e^{r_1 t} z\right) = 0, & |x| < R(t),\ t \in (0,T), \\ z(x,0) = 0, & |x| < R_0, \\ e^{r_1 t} z = e^{r_1 t}(k_1\sigma - k_2\beta), & |x| = R(t),\ t \in (0,T). \end{cases} \tag{5.21}$$

In the same way, $e^{r_2 t}\beta$ satisfies

$$\begin{cases} \dfrac{\partial}{\partial t}\left(e^{r_2 t} \beta\right) - d\Delta\left(e^{r_2 t} \beta\right) = 0, & |x| < R(t),\ t \in (0,T), \\ \beta(x,0) = 0, & |x| < R_0, \\ e^{r_2 t} \beta = e^{r_2 t}(\beta_1 - \beta_2), & |x| = R(t),\ t \in (0,T). \end{cases} \tag{5.22}$$

Applying Corollary 5.1, we obtain that $e^{r_1 t} z$ and $e^{r_2 t}\beta$ are bounded. Let

$$z^{**} = \max\left\{e^{r_1 t} z(x,t), t \in [0,T], x \in \partial B\left(R(t)\right)\right\},$$
$$z_{**} = \min\left\{e^{r_1 t} z(x,t), t \in [0,T], x \in \partial B\left(R(t)\right)\right\},$$
$$\beta^{**} = \max\left\{e^{r_2 t} \beta(x,t), t \in [0,T], x \in \partial B\left(R(t)\right)\right\},$$
$$\beta_{**} = \min\left\{e^{r_2 t} \beta(x,t), t \in [0,T], x \in \partial B\left(R(t)\right)\right\}.$$

Notice that $z^{**} \geqslant 0$, $\beta^{**} \geqslant 0$, $z_{**} \leqslant 0$ and $\beta_{**} \leqslant 0$. Let T_k and T^k be defined by

$$T_k(s) = \begin{cases} s, & \text{if } s > k, \\ k, & \text{if } s \leqslant k, \end{cases} \quad \text{and} \quad T^k(s) = \begin{cases} k, & \text{if } s \geqslant k, \\ s, & \text{if } s < k. \end{cases}$$

Taking $T_0(e^{r_1 t} z - z^{**})$ as test function in (5.21) and integrating by parts over $B(R(t))$, we arrive after some manipulations at

$$\frac{d}{dt}\int_{B(R(t))} \left[T_0\left(e^{r_1 t} z - z^{**}\right)\right]^2 dx \leqslant 0.$$

We deduce that $\mathrm{e}^{r_1 t} z$ takes his maximum on $|x| = R(t)$. In the same way, taking $T^0(\mathrm{e}^{r_1 t} z - z_{**})$ as test function, we obtain

$$z_{**} \leqslant \mathrm{e}^{r_1 t} z \leqslant z^{**}. \tag{5.23}$$

The proof of

$$\beta_{**} \leqslant \mathrm{e}^{r_2 t} \beta \leqslant \beta^{**}, \tag{5.24}$$

is analogous. □

END OF THE PROOF OF THEOREM 5.1. Given $t \in [0, T]$, we can assume, without lost of generality, that $R_1(t) \leqslant R_2(t)$. Consider

$$R_1^2(t)\dot{R}_1(t) - R_2^2(t)\dot{R}_2(t) = \int_{B(R(t))} \big(S(\sigma_1, \beta_1) - S(\sigma_2, \beta_2)\big)\,\mathrm{d}x - \int_{R_1(t)<|x|<R_2(t)} S(\sigma_2, \beta_2)\,\mathrm{d}x.$$

Since S is bounded, then

$$\left| \int_{R_1(t)<|x|<R_2(t)} S(\sigma_2, \beta_2)\,\mathrm{d}x \right| \leqslant N\big|R_1^3(t) - R_2^3(t)\big| \leqslant M\big|R_1(t) - R_2(t)\big|,$$

where M depends only of $|S|_{L^\infty}$. Since S is Lipschitz continuous, integrating in time, it results

$$\begin{aligned}
&\int_0^T \int_{B(R(t))} \big|S(\sigma_1, \beta_1) - S(\sigma_2, \beta_2)\big|\,\mathrm{d}x\,\mathrm{d}t \\
&\quad\leqslant \int_0^T \int_{B(R(t))} |S|_{W^{1,\infty}(\mathbb{R}^2)} \big(\sup|\sigma| + \sup|\beta|\big)\,\mathrm{d}x\,\mathrm{d}t \\
&\quad\leqslant \int_0^T \int_{B(R(t))} k_0 \left(\frac{1}{k_1} \sup|z + k_2\beta| + \sup|\beta| \right)\mathrm{d}x\,\mathrm{d}t \\
&\quad\leqslant \int_0^T \int_{B(R(t))} C\big(\sup|z| + \sup|\beta|\big)\,\mathrm{d}x\,\mathrm{d}t \\
&\quad\leqslant \int_0^T \int_{B(R(t))} C\big(\sup\big|\mathrm{e}^{-r_1 t}\mathrm{e}^{r_1 t} z\big| + \sup\big|\mathrm{e}^{-r_2 t}\mathrm{e}^{r_2 t}\beta\big|\big)\,\mathrm{d}x\,\mathrm{d}t \\
&\quad\leqslant \int_0^T \int_{B(R(t))} C\big(\mathrm{e}^{|r_1|T} \sup\big|\mathrm{e}^{r_1 t} z\big| + \mathrm{e}^{|r_2|T} \sup\big|\mathrm{e}^{r_2 t}\beta\big|\big)\,\mathrm{d}x\,\mathrm{d}t \\
&\quad\leqslant \int_0^T \int_{B(R(t))} k_3\big(\sup\big|\mathrm{e}^{r_1 t} z\big| + \sup\big|\mathrm{e}^{r_2 t}\beta\big|\big)\,\mathrm{d}x\,\mathrm{d}t.
\end{aligned}$$

From Lemma 5.2, we know

$$\int_0^T \int_{B(R(t))} \sup\big|\mathrm{e}^{r_1 t} z(x,t)\big|\,\mathrm{d}x\,\mathrm{d}t \leqslant \mathrm{e}^{r_1 T} \frac{3\pi}{4} \int_0^T R^3(t) \sup_{|x|=R(t)} \big|z(x,t)\big|\,\mathrm{d}t.$$

By Corollary 5.2, we deduce that

$$\int_0^T \bigl(\|\sigma_2\|^2_{W^{1,\infty}(B(R(t)))} + \|\beta_2\|^2_{W^{1,\infty}(B(R(t)))}\bigr)\,\mathrm{d}t \leqslant K_0,$$

and consequently,

$$\int_0^T \|z\|^2_{W^{1,\infty}(B(R(t)))}\,\mathrm{d}t \leqslant K.$$

Since

$$\mathrm{e}^{r_1 t} z(x,t) = \mathrm{e}^{r_1 t}\bigl(k_1\bigl(\sigma_2(x,t) - \overline{\overline{\sigma}}\bigr) - k_2\bigl(\beta_2(x,t) - \overline{\overline{\beta}}\bigr)\bigr), \quad \text{on } |x| = R(t),$$

we deduce

$$\begin{aligned}
&\mathrm{e}^{r_1 T}\frac{3\pi}{4}\int_0^T R^3(t)\sup_{|x|=R(t)}\bigl|z(x,t)\bigr|\,\mathrm{d}t \\
&\quad\leqslant k_4\int_0^T \|\sigma_2\|_{W^{1,\infty}(B(R_2(t)))} + \|\beta_2\|_{W^{1,\infty}(B(R_2(t)))}\bigl|R_1(t) - R_2(t)\bigr|\,\mathrm{d}t \\
&\quad\leqslant k_4\sup_{0<t<T}\bigl|R_1(t) - R_2(t)\bigr|T^{1/2}\int_0^T \bigl(\|\sigma_2\|^2_{W^{1,\infty}(B(R_2(t)))} \\
&\qquad\qquad + \|\sigma_2\|^2_{W^{1,\infty}(B(R_2(t)))}\bigr)\,\mathrm{d}t \\
&\quad\leqslant k\sup_{0<t<T}\bigl|R_1(t) - R_2(t)\bigr|T^{1/2}.
\end{aligned}$$

In the same way,

$$\int_0^T\int_{B(R(t))} k_3 \sup|\beta|\,\mathrm{d}x\,\mathrm{d}t \leqslant k\sup_{0<t<T}\bigl|R_1(t) - R_2(t)\bigr|T^{1/2}.$$

Then

$$\int_0^T \bigl|R_1^2(t)\dot{R}_1(t) - R_2^2(t)\dot{R}_2(t)\bigr|\,\mathrm{d}t \leqslant C_0\sup_{0<t<T}\bigl|R_1(t) - R_2(t)\bigr|\bigl(T + T^{1/2}\bigr). \tag{5.25}$$

Let $\delta = \max_{t\in[0,T]}\{R_1(t) - R_2(t)\}$ then

$$\bigl|R_1^3(t) - R_2^3(t)\bigr| \leqslant 3C_0\delta\bigl(T + T^{1/2}\bigr),$$

since $|R_1^3(t) - R_2^3(t)| \geqslant 3R_0^2|R_1(t) - R_2(t)|$, it follows $\delta \leqslant k_0\delta(T + T^{1/2})$. Furthermore, if $T < T_1 = \min\{1/4k_0^2, 1\}$, necessarily $R_1(t) = R_2(t)$. Since $\mathrm{e}^{r_1 t}z$ and $\mathrm{e}^{r_2 t}\beta$ take their maximum and minimum on $R(t) = R_1(t) = R_2(t)$, and $R(t)$ is zero, $\beta = 0$ and $z = 0$, and we deduce $\sigma = 0$. Repeating the process, starting now from T_1, we conclude the uniqueness of solutions for any $T > 0$ provided $R(T) > 0$. □

REMARK 5.1. Other qualitative properties of the solutions of this type of models have been studied in the literature by different authors. In particular, we mention the study of the asymptotic behavior, when $t \to +\infty$ (see, e.g., BYRNE and CHAPLAIN [1996a], FRIEDMAN and REITICH [1999], CUI and FRIEDMAN [2000], CUI and FRIEDMAN

[2001]) and the continuous dependence and bifurcation phenomena with respect to parameters (see, e.g., BYRNE and CHAPLAIN [1995], FRIEDMAN and REITICH [2001], FRIEDMAN, HU and VELÁZQUEZ [2001], among others).

5.2. Uniqueness of solutions with radial symmetry

Let $(\hat{\sigma}, \hat{\beta})$ be a solution of problem (3.1)–(3.5) without forcing term (i.e., $f = 0$). We assume the solution is radially symmetric and define $\sigma = \hat{\sigma} - \overline{\overline{\sigma}}$, $\beta = \hat{\beta} - \overline{\overline{\beta}}$ and $r = |x|$. Then (σ, β) verifies

$$\begin{cases} \dfrac{\partial \sigma}{\partial t} - \dfrac{d_1}{r^2}\dfrac{\partial}{\partial r}\left(r^2 \dfrac{\partial}{\partial r}\sigma\right) \in g_1(\sigma, \beta), & 0 < r < R(t),\ 0 < t < T, \\ \dfrac{\partial \beta}{\partial t} - \dfrac{d_2}{r^2}\dfrac{\partial}{\partial r}\left(r^2 \dfrac{\partial}{\partial r}\beta\right) = g_2(\sigma, \beta), & 0 < r < R(t),\ 0 < t < T, \\ R(t)^2 \dfrac{\mathrm{d}R(t)}{\mathrm{d}t} = \displaystyle\int_0^{R(t)} S(\sigma, \beta) r^2 \,\mathrm{d}r, & 0 < t < T, \\ \dfrac{\partial \sigma}{\partial r}(0, t) = 0,\ \dfrac{\partial \beta}{\partial r}(0, t) = 0, & 0 < t < T, \\ \sigma\big(R(t), t\big) = 0,\ \beta\big(R(t), t\big) = 0, & 0 < t < T, \\ R(0) = R_0, & \\ \sigma(r, 0) = \sigma_0(r),\ \beta(r, 0) = \beta_0(r), & 0 < r < R_0, \end{cases} \tag{5.26}$$

where g_i are given by

$$g_1(\sigma, \beta) = -\big[(r_1 + \lambda)\big(\sigma + \overline{\overline{\sigma}}\big) - r_1 \sigma_B + \big(\beta + \overline{\overline{\beta}}\big)\big] H\big(\sigma + \overline{\overline{\sigma}} - \sigma_n\big), \tag{5.27}$$

$$g_2(\sigma, \beta) = -r_2\big(\beta + \overline{\overline{\beta}}\big). \tag{5.28}$$

We will assume in this subsection that

$$S \in W^{1,\infty}_{\mathrm{loc}}\big(\mathbb{R}^2\big), \tag{5.29}$$

$$S \text{ is an increasing function in } \sigma \text{ and decreasing in } \beta, \tag{5.30}$$

$$\sigma_n \geqslant \frac{r_1 \sigma_B - \overline{\overline{\beta}}}{r_1 + \lambda} \tag{5.31}$$

and the initial data $(\sigma_0 = \hat{\sigma} - \overline{\overline{\sigma}}, \beta_0 = \hat{\beta}_0 - \overline{\overline{\beta}})$ belong to $H^2(0, R_0)$ and satisfy

$$\frac{\partial \sigma_0}{\partial r}(0, t) = 0, \qquad \frac{\partial \beta}{\partial r}(0, t) = 0, \quad 0 < t < T, \tag{5.32}$$

$$\sigma\big(R(t), t\big) = 0, \qquad \beta\big(R(t), t\big) = 0, \quad 0 < t < T. \tag{5.33}$$

THEOREM 5.2. *There is, at most, one solution to* (5.26).

We will use some earlier results in the proof.

LEMMA 5.3. *Every solution* (σ,β) *of the problem* (5.26) *is bounded and satisfies* $\sigma_n \leqslant \sigma \leqslant \sigma_B$ *and* $-\overline{\overline{\beta}} \leqslant \beta \leqslant \max\{\beta_0\}$ *provided* $\sigma_n \leqslant \sigma_0 \leqslant \sigma_B$ *and* $-\overline{\overline{\beta}} \leqslant \beta_0$.

PROOF. By the "integrations by parts formula" (justifying the multiplication of the equation by $T_0(\sigma-\sigma_B)$ and posterior integrations in time and space, see ALT and LUCKHAUS [1983], Lemma 1.5), we have

$$\frac{1}{2}\int_0^{R(t)}\big[T_0(\sigma-\sigma_B)\big]^2 r^2\,\mathrm{d}r \leqslant \int_0^t\int_0^{R(s)} g_1(\sigma,\beta)T_0(\sigma-\sigma_B)r^2\,\mathrm{d}r\,\mathrm{d}s.$$

Since

$$\begin{aligned}
&-\big[(r_1+\lambda)\big(\sigma+\overline{\overline{\sigma}}\big)-r_1\sigma_B+\big(\beta+\overline{\overline{\beta}}\big)\big]H\big(\sigma+\overline{\overline{\sigma}}-\sigma_n\big)T_0(\sigma-\sigma_B)\\
&\quad=-(r_1+\lambda)T_0(\sigma-\sigma_B)^2-\big[(r_1+\lambda)\big(\sigma_B+\overline{\overline{\sigma}}\big)-r_1\sigma_B+\big(\beta-\overline{\overline{\beta}}\big)\big]T_0(\sigma-\sigma_B)\\
&\quad\leqslant-\big[\lambda\sigma_B+(r_1+\lambda)\overline{\overline{\sigma}}+\big(\beta+\overline{\overline{\beta}}\big)\big]T_0(\sigma-\sigma_B)\\
&\quad\leqslant T^0\big(\beta+\overline{\overline{\beta}}\big)T_0(\sigma-\sigma_B)\leqslant\frac{1}{2}\big(\big[T^0\big(\beta+\overline{\overline{\beta}}\big)\big]^2+\big[T_0(\sigma-\sigma_B)\big]^2\big),
\end{aligned}$$

we obtain

$$\int_0^{R(t)} T_0(\sigma-\sigma_B)^2 r^2\,\mathrm{d}r \leqslant \int_0^t\int_0^{R(s)}\big[T^0\big(\beta+\overline{\overline{\beta}}\big)^2+T_0(\sigma-\sigma_B)^2\big]r^2\,\mathrm{d}r\,\mathrm{d}s. \tag{5.34}$$

In the same way, we consider $T^0(\beta+\overline{\overline{\beta}})$, and since

$$r_2\big(\beta+\overline{\overline{\beta}}\big)H\big(\sigma+\overline{\overline{\sigma}}-\sigma_n\big)T^0\big(\beta+\overline{\overline{\beta}}\big)\leqslant r_2\big[T^0\big(\beta+\overline{\overline{\beta}}\big)\big]^2,$$

it follows that

$$\int_0^{R(t)}\big[T^0\big(\beta+\overline{\overline{\beta}}\big)\big]^2 r^2\,\mathrm{d}r \leqslant \int_0^t\int_0^{R(s)} r_2 T^0\big(\beta+\overline{\overline{\beta}}\big)r^2\,\mathrm{d}r\,\mathrm{d}s. \tag{5.35}$$

Adding (5.34) and (5.35), we obtain thanks to Gronwall's lemma

$$\sigma\leqslant\sigma_B\quad\text{and}\quad\beta\geqslant-\overline{\overline{\beta}}.$$

Notice that $\beta\geqslant-\overline{\overline{\beta}}$ implies $\hat{\beta}\geqslant 0$.

Let us consider $\varepsilon>0$ and take $T^0(\sigma-\sigma_n-\varepsilon)$ as test function in the weak formulation, then

$$\frac{1}{2}\int_0^{R(t)}\big[T^0(\sigma-\sigma_n-\varepsilon)\big]^2 r^2\,\mathrm{d}r\leqslant 0.$$

Now, taking limits as $\varepsilon\to 0$, one concludes

$$\frac{1}{2}\int_0^{R(t)}\big[T^0(\sigma-\sigma_n)\big]^2 r^2\,\mathrm{d}r\leqslant 0,$$

which proves $\sigma\geqslant\sigma_n$.

Knowing σ and R, β is well-defined as the unique solution of the equation

$$\frac{\partial\beta}{\partial t} - \frac{d_2}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial}{\partial r}\beta\right) = -r_2\bigl(\beta+\overline{\overline{\beta}}\bigr), \quad 0<r<R(t),\ 0<t<T,$$
$$\beta\bigl(R(t),t\bigr)=0, \qquad \frac{\partial\beta}{\partial r}=0 \quad \text{on } 0<t<T.$$

Since $\beta_0 \geqslant -\overline{\overline{\beta}}$, it follows that

$$\frac{\partial\beta}{\partial t} - \frac{d_2}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial}{\partial r}\beta\right) \leqslant 0,$$

and we obtain by maximum principle that $\beta \leqslant \max\{\beta_0\}$. □

COROLLARY 5.3. *There exists a positive constant M such that $R(t) \leqslant R_0 \mathrm{e}^{Mt}$ and $R'(t) \leqslant R_0 M \mathrm{e}^{MT}$.*

PROOF. The above result shows $(\sigma(r,t),\beta(r,t)) \in [\sigma_n,\sigma_B]\times[-\overline{\overline{\beta}},\max\{\beta_0\}]$. Since S is a continuous function, it attains its maximum (denoted by $3M$) on that set. Thus,

$$R^2(t)\frac{\mathrm{d}R(t)}{\mathrm{d}t} \leqslant \int_0^{R(t)} 3Mr^2\,\mathrm{d}r.$$

Integrating the above equation, we have $\mathrm{d}R(t)/\mathrm{d}t \leqslant MR(t)$. Finally, the conclusion follows by Gronwall's lemma. □

REMARK 5.2. As in the previous subsection the solution (σ,β) of (5.26) satisfies

$$\int_0^T \bigl(\|\sigma\|^2_{W^{1,\infty}(\varepsilon,R(t))} + \|\beta\|^2_{W^{1,\infty}(\varepsilon,R(t))}\bigr)\,\mathrm{d}t \leqslant C_1$$

for all $\varepsilon > 0$.

PROOF OF THEOREM 5.2. We argue by contradiction and assume that (σ_1,β_1,R_1) and (σ_2,β_2,R_2) are two solutions of the problem. Let $R(t) := \min\{R_1(t),\ R_2(t)\}$, $\sigma := \sigma_1-\sigma_2$ and $\beta := \beta_1-\beta_2$ be the solution to

$$\begin{cases} \dfrac{\partial\sigma}{\partial t} - \dfrac{d_1}{r^2}\dfrac{\partial}{\partial r}\left(r^2\dfrac{\partial}{\partial r}\sigma\right) = g_1(\sigma_1,\beta_1)-g_1(\sigma_2,\beta_2), & r<R(t),\ 0<t<T,\\ \dfrac{\partial\beta}{\partial t} - \dfrac{d_2}{r^2}\dfrac{\partial}{\partial r}\left(r^2\dfrac{\partial}{\partial r}\beta\right) = g_2(\sigma_1,\beta_1)-g_2(\sigma_2,\beta_2), & r<R(t),\ 0<t<T,\\ \dfrac{\partial\sigma}{\partial r}(0,t)=0,\ \dfrac{\partial\beta}{\partial r}(0,t)=0, & 0<t<T,\\ \sigma\bigl(R(t),t\bigr)=\sigma_1\bigl(R(t),t\bigr)-\sigma_2\bigl(R(t),t\bigr), & 0<t<T,\\ \beta\bigl(R(t),t\bigr)=\beta_1\bigl(R(t),t\bigr)-\beta_2\bigl(R(t),t\bigr), & 0<t<T,\\ \sigma(r,0)=0,\ \beta(r,0)=0, & 0<r<R_0. \end{cases} \tag{5.36}$$

Now, we state a technical lemma.

LEMMA 5.4. *$|\beta|$ takes the maximum on the boundary $R(t)$ and σ satisfies*

$$\int_0^{R(t)} \left[T_0(\sigma - \sigma^*)\right]^2 r^2 \,\mathrm{d}r \leqslant TC\Big[\max_{t\in[0,T]}\{\beta\}\Big]^2,$$

where

$$\sigma^* = \max_{t\in[0,T]}\big\{\sigma\big(R(t), t\big)\big\}.$$

PROOF. Let us consider $\beta_* = \min\{0, \beta(R(t), t)\}$ and

$$g_2(\beta_1) - g_2(\beta_2) = -r_2\big[\big(\beta_1 - \overline{\overline{\beta}}\big) - \big(\beta_2 - \overline{\overline{\beta}}\big)\big] = -r_2\beta,$$

then

$$\big(g_2(\beta_1) - g_2(\beta_2)\big)T^0(\beta - \beta_*) = -r_2\beta T^0(\beta - \beta_*) \leqslant 0.$$

Multiply the equation by $T^0(\beta - \beta_*)$, we get

$$\int_0^{R(t)} \left[T^0(\beta - \beta_*)\right]^2 r^2 \,\mathrm{d}r \leqslant 0$$

and obtain $\beta \geqslant \beta_*$. In the same way, we prove that β takes its maximum on $R(t)$.

Let us consider

$$\begin{aligned}
&g_1(\sigma_1, \beta_1) - g_1(\sigma_2, \beta_2)\\
&\quad = -\Big(\big[(r_1+\lambda)\big(\sigma_1 + \overline{\overline{\sigma}}\big) - r_1\sigma_B + \big(\beta_1 + \overline{\overline{\beta}}\big)\big]H\big(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n\big)\\
&\qquad - \big[(r_1+\lambda)\big(\sigma_2 + \overline{\overline{\sigma}}\big) - r_1\sigma_B + \big(\beta_2 + \overline{\overline{\beta}}\big)\big]H\big(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n\big)\Big)\\
&\quad = (r_1+\lambda)\big[\big(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n\big)H\big(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n\big) - \big(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n\big)H\big(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n\big)\big]\\
&\qquad + \big(-(r_1+\lambda)\sigma_n + r_1\sigma_B - \overline{\overline{\beta}}\big)\big(H\big(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n\big) - H\big(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n\big)\big)\\
&\qquad - \big[\beta_1 H\big(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n\big) - \beta_2 H\big(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n\big)\big].
\end{aligned}$$

Since $(\sigma + \overline{\overline{\sigma}} - \sigma_n)H(\sigma + \overline{\overline{\sigma}} - \sigma_n)$ is an increasing function of σ, we obtain that

$$\begin{aligned}
&-\big[\big(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n\big)H\big(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n\big) - \big(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n\big)H\big(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n\big)\big]\\
&\quad \times T_0(\sigma_1 - \sigma_2 - \sigma^*) \leqslant 0.
\end{aligned}$$

Since $-(r_1+\lambda)\sigma_n + r_1\sigma_B - \overline{\overline{\beta}} \leqslant 0$, it follows that

$$\begin{aligned}
&\big(-(r_1+\lambda)\sigma_n + r_1\sigma_B - \overline{\overline{\beta}}\big)\big(H\big(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n\big) - H\big(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n\big)\big)\\
&\quad \times T_0(\sigma_1 - \sigma_2 - \sigma^*) \leqslant 0.
\end{aligned}$$

Then

$$\begin{aligned}
&\big[g_1(\sigma_1, \beta_1) - g_1(\sigma_2, \beta_2)\big]T_0(\sigma_1 - \sigma_2 - \sigma^*)\\
&\quad \leqslant -\big[\beta_1 H\big(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n\big) - \beta_2 H\big(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n\big)\big]T_0(\sigma_1 - \sigma_2 - \sigma^*)\\
&\quad \leqslant -(\beta_1 - \beta_2)H\big(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n\big)T_0(\sigma_1 - \sigma_2 - \sigma^*)\\
&\quad \leqslant -T^0(\beta_1 - \beta_2)T_0(\sigma_1 - \sigma_2 - \sigma^*) \leqslant -\beta_* T_0(\sigma_1 - \sigma_2 - \sigma^*).
\end{aligned}$$

Multiplying the equation, as before, by $T_0(\sigma - \sigma^*)$, we get

$$\begin{aligned}
&\int_0^{R(t)} \big[T_0(\sigma - \sigma^*)\big]^2 r^2 \,\mathrm{d}r + \int_0^t \int_0^{R(s)} \left[\frac{\partial}{\partial r} T_0(\sigma - \sigma^*)\right]^2 r^2 \,\mathrm{d}r \,\mathrm{d}s \\
&\quad = \int_0^t \int_0^{R(s)} \big(g_1(\sigma_1, \beta_1) - g_1(\sigma_2, \beta_2)\big) T_0(\sigma - \sigma^*) r^2 \,\mathrm{d}r \,\mathrm{d}s \\
&\quad \leqslant - \int_0^t \int_0^{R(s)} \beta_* T_0(\sigma - \sigma^*) r^2 \,\mathrm{d}r \,\mathrm{d}s \\
&\quad \leqslant \frac{T\widetilde{C}}{\lambda} \beta_*^2 + \lambda \int_0^t \int_0^{R(s)} \big[T_0(\sigma_1 - \sigma_2 - \sigma^*)\big]^2 r^2 \,\mathrm{d}r \,\mathrm{d}s.
\end{aligned}$$

Now, we choose λ such that

$$\begin{aligned}
&\lambda \int_0^{R(s)} \big[T_0(\sigma_1 - \sigma_2 - \sigma^*)\big]^2 r^2 \,\mathrm{d}r \\
&\quad - \int_0^{R(s)} \left[\frac{\partial}{\partial r} T_0(\sigma - \sigma^*)\right]^2 r^2 \,\mathrm{d}r \leqslant 0 \quad \text{a.e. } t \in (0, T),
\end{aligned}$$

then,

$$\int_0^{R(t)} \big[T_0(\sigma - \sigma^*)\big]^2 r^2 \,\mathrm{d}r \leqslant T C \beta_*^2$$

holds, which ends the proof. □

END OF THE PROOF OF THEOREM 5.2. Let us define

$$\delta = \max_{t \in [0,T]} \big\{ \big| R_1(t) - R_2(t) \big| \big\} \geqslant 0,$$

and consider

$$\begin{aligned}
&R_1^2(t) R_1'(t) - R_2^2(t) R_2'(t) \\
&\quad = \int_0^{R(t)} \big(S(\sigma_1, \beta_1) - S(\sigma_2, \beta_2)\big) r^2 \,\mathrm{d}r \\
&\qquad + \int_{R(t)}^{R_1(t)} S(\sigma_1, \beta_1) r^2 \,\mathrm{d}r - \int_{R(t)}^{R_2(t)} S(\sigma_2, \beta_2) r^2 \,\mathrm{d}r.
\end{aligned} \tag{5.37}$$

By (5.29) and Lemma 5.3, we obtain

$$\left| \int_{R(t)}^{R_i(t)} S(\sigma_i, \beta_i) r^2 \,\mathrm{d}r \right| \leqslant M\delta \quad (\text{for } i = 1, 2), \tag{5.38}$$

where

$$M = \max\big\{ S(\sigma, \beta) \text{ for any } (\sigma, \beta) \in [\sigma_n, \sigma_B] \times \big[\overline{\overline{\beta}}, \max\{\beta_0\}\big]\big\}.$$

(5.29) and (5.30) imply

$$\int_0^{R(t)} \big(S(\sigma_1, \beta_1) - S(\sigma_2, \beta_2)\big) r^2 \,\mathrm{d}r \leqslant C \int_0^{R(t)} \big(T_0(\sigma) - T^0(\beta)\big) r^2 \,\mathrm{d}r.$$

Since $T_0(\sigma) \leqslant T_0(\sigma - \sigma^*) + \sigma^*$ and $-T^0(\beta) \leqslant -\beta_*$, we obtain

$$\begin{aligned}
&\int_0^{R(t)} \bigl(S(\sigma_1,\beta_1) - S(\sigma_2,\beta_2)\bigr) r^2\,\mathrm{d}r \\
&\quad \leqslant C \int_0^{R(t)} \bigl(T_0(\sigma - \sigma^*) + \sigma^* - \beta_*\bigr) r^2\,\mathrm{d}r \\
&\quad \leqslant C' \biggl(\biggl[\int_0^{R(t)} T_0(\sigma - \sigma^*)^2 r^2\,\mathrm{d}r \biggr]^{1/2} + \sigma^* - \beta_* \biggr).
\end{aligned}$$

By Lemma 5.4, it follows that

$$C' \biggl(\biggl[\int_0^{R(t)} T_0(\sigma - \sigma^*)^2 r^2\,\mathrm{d}r \biggr]^{1/2} + \sigma^* - \beta_* \biggr) \leqslant C''\bigl(\sigma^* - (T+1)\beta_*\bigr).$$

Since $\sigma_i(R_i(t),t) = 0$ (for $j = 1$ or 2), we obtain

$$\begin{aligned}
&\bigl|\sigma\bigl(R(t),t\bigr)\bigr| \leqslant \biggl(\sum_{i=1,2} \|\sigma_i\|_{W^{1,\infty}(R(t),R_i(t))} \biggr) \bigl|R_1(t) - R_2(t)\bigr|, \\
&\bigl|\beta\bigl(R(t),t\bigr)\bigr| \leqslant \biggl(\sum_{i=1,2} \|\beta_i\|_{W^{1,\infty}(R(t),R_i(t))} \biggr) \bigl|R_1(t) - R_2(t)\bigr|
\end{aligned}$$

and then

$$\int_0^{R(t)} \bigl(S(\sigma_1,\beta_1) - S(\sigma_2,\beta_2)\bigr) r^2\,\mathrm{d}r \leqslant C(T+2)\delta. \tag{5.39}$$

Integrating in time in (5.37), we get thanks to (5.38) and (5.39) that

$$R_1^3(t) - R_2^3(t) \leqslant TC(T+2)\delta + 2TM\delta. \tag{5.40}$$

On the other hand, one has

$$R_1^3(t) - R_2^3(t) = \bigl(R_1(t) - R_2(t)\bigr)\bigl(R_1^2 + R_1R_2 + R_1^3\bigr).$$

We can assume without lost of generality that $\delta = R_1(t_0) - R_2(t_0)$ (for some $t_0 \in [0,T]$), hence

$$R_1^3(t) - R_2^3(t) \geqslant 4R^2\delta.$$

Substituting this into (5.40) leads to $\delta \leqslant k_0\delta T$. Furthermore, taking $T_1 < 1/k_0$ necessitates $R_1(t) = R_2(t)$ for any $t \in [0,T_1]$. Since $|\beta|$ takes its maximum at $R(t) = R_1(t) = R_2(t)$ (and this maximum is 0), we get that $\beta = 0$. Substituting in (5.36) and taking σ as test function, we obtain

$$\int_0^{R(t)} \sigma^2 r^2\,\mathrm{d}r \leqslant \int_0^t \int_0^{R(s)} \bigl(g_1(\sigma_1,\beta_1) - g_1(\sigma_2,\beta_2)\bigr)\sigma r^2\,\mathrm{d}r\,\mathrm{d}s.$$

As in Lemma 5.4, since $(\sigma_i + \overline{\overline{\sigma}}_i - \sigma_n)H(\sigma_i + \overline{\overline{\sigma}} - \sigma_n)$ is a increasing function of σ, we obtain by (5.27) and Lemma 5.3 that $(g_1(\sigma_1,\beta_1) - g_1(\sigma_2,\beta_2))\sigma \leqslant 0$, which prove $\sigma = 0$.

Repeating the above process, starting now from T_1, we get the uniqueness of solutions for arbitrary $T > 0$, provided $R(T) > 0$. □

6. Approximate controllability

In this section we study the controllability of distribution of nutrients (in the usual weak sense of parabolic system) by the internal localized action of inhibitors. The main results of this section is the following theorem.

THEOREM 6.1. *Given* $T > 0$, $\omega_0 \subset B(R_0 \exp\{-\|S\|_{L^\infty} T\})$, $\varepsilon > 0$, *and* $\hat{\sigma}^d \in L^p_{\mathrm{loc}}(\mathbb{R}^3)$, *for some* $p > 1$, *there exists* $f \in L^p((0,T) \times \omega_0)$ *such that, if* (σ, β, R) *is the solution of the problem* (5.1)–(5.5), *then*

$$\left\|\sigma(T) - \sigma^d\right\|_{L^p(B(R(T)))} \leqslant \varepsilon, \tag{6.1}$$

where $\sigma^d := \hat{\sigma}^d \chi_{B(R(T))}$.

Due to some technical reasons, we shall prove the theorem firstly for $p > 4$. This assumption is a prerequisite in order to obtain the boundedness of the solution in the proof of Lemma 5.1 in view of the Sobolev compact embedding $W^{1,p}((0,T) \times B) \subset L^\infty((0,T) \times B)$. Finally, we prove the theorem for any $p > 1$ by Hölder inequality.

We shall establish the result in several steps. For $n \in \mathbb{N}$, we start by assuming $R_n(t)$ prescribed and look for a control f_n in ω_0 such that the solution (σ_n, β_n) of problem (5.1), (5.2), (5.4) and (5.5), satisfies (6.1). Then we obtain R_{n+1} and f_{n+1} from (σ_n, β_n) which allows us to find $(\sigma_{n+1}, \beta_{n+1})$. The proof of the theorem relies mostly on methods introduced in the study of approximate controllability (notion attributed to conclusions such as (6.1)) by different authors (see LIONS [1990], LIONS [1991], FABRE, PUEL and ZUAZUA [1995], GLOWINSKI and LIONS [1995] and DÍAZ and RAMOS [1995]). Iterating the process, we obtain a sequence $(R_n, f_n, \sigma_n, \beta_n)$ such as we shall show possesses a subsequence that converges to the searched control f and the associate solution of problem (5.1)–(5.5).

The next result shows the conclusion of Theorem 6.1 (the so-called approximate controllability in L^p) under some particular assumptions (mainly, $R(t)$ is a priori prescribed).

PROPOSITION 6.1. *Let* $\omega_0 \subset B(R_0 \exp\{-\|S\|_{L^\infty} T\})$ *and* $\sigma_0 = \beta_0 = \overline{\overline{\sigma}} = \overline{\overline{\beta}} = 0$. *Let* $R \in W^{1,\infty}(0,T)$ *a given function such that* $R(0) = R_0$, $|\dot{R}| \leqslant \|S\|_{L^\infty} R_0 \exp\{|S|_{L^\infty} T\}$. *Then, given* $\hat{\sigma}^d \in L^2_{\mathrm{loc}}(\mathbb{R}^3)$, *there exists* $f \in L^p(\omega_0 \times (0,T))$, *with* $p > 4$, *such that, if* (σ, β) *is the solution of problem* (5.1), (5.2), (5.4) *and* (5.5), *then*

$$\left\|\sigma(T) - \sigma^d\right\|_{L^p(B(R(T)))} \leqslant \varepsilon,$$

where $\sigma^d = \hat{\sigma}^d|_{B(R(T))}$.

PROOF. Let $p' = p/(p-1)$ and consider the functional $J : L^{p'}(B(R(T))) \to \mathbb{R}$ defined by

$$J(\varphi^0) = \frac{1}{p'} \int_0^T \int_{\omega_0} \left|\psi(x,t)\right|^{p'} \mathrm{d}x\, \mathrm{d}t + \varepsilon \left\|\varphi^0\right\|_{L^{p'}(B(R(T)))} - \int_{B(R(T))} \sigma^d \varphi^0 \, \mathrm{d}x,$$

where $\varphi_0 \in L^{p'}(B(R(T)))$, and (φ, ψ) is the solution to the adjoint problem

$$-\frac{\partial \varphi}{\partial t} - d\Delta\varphi + r_1\varphi = 0, \quad |x| < R(t),\ t \in (0,T), \tag{6.2}$$

$$-\frac{\partial \psi}{\partial t} - d\Delta\psi + r_2\psi + \lambda\varphi = 0, \quad |x| < R(t),\ t \in (0,T), \tag{6.3}$$

$$\varphi(x,T) = \varphi_0(x), \qquad \psi(x,T) = 0, \quad |x| < R(T), \tag{6.4}$$

$$\varphi(x,t) = 0, \qquad \psi(x,t) = 0, \quad |x| = R(t),\ t \in (0,T). \tag{6.5}$$

We point out that the existence of a weak solution (φ, ψ) of (6.2)–(6.5) can be obtained as in Section 5, by employing (4.3)–(4.5) and (5.6).

In order to prove the uniqueness of solutions by contradiction, we assume that there exist two solutions (φ_1, ψ_1), (φ_2, ψ_2). Then $\varphi := \varphi_1 - \varphi_2$ satisfies (6.2) and taking $|\varphi|^{p'-2}\varphi$ as test function and integrating by parts it follows that

$$-\frac{\mathrm{d}}{\mathrm{d}t}\int_{B(R(t))} |\varphi|^{p'}\,\mathrm{d}x \leqslant r_1 \int_{B(R(t))} |\varphi|^{p'}\,\mathrm{d}x.$$

We obtain $\varphi = \varphi_1 - \varphi_2 = 0$ by Gronwall's lemma. Having proved $\varphi \equiv 0$, in the same way, $\psi := \psi_1 - \psi_2$ satisfies (6.3) and taking $|\psi|^{p'-2}\psi$ as test function, we obtain $\psi \equiv 0$, which proves the uniqueness.

Let us assume that J is convex, continuous and coercive (in the sense that $\liminf J \to \infty$ as $\|\varphi^0\|_{L^{p'}(B(R_0))} \to \infty$), facts, which shall be proved at the end of the proposition. Then J takes a minimum φ_0 (see BREZIS [1983], Corollary III.20). Moreover, if (ξ, ζ) is the solution of the problem (6.2)–(6.5) with datum $(\xi^0, 0)$, we have

$$\begin{aligned}&\int_0^T \int_{\omega_0} |\psi|^{p'-2}\psi\zeta\,\mathrm{d}x\,\mathrm{d}t - \int_{B(R(T))} \sigma^d \xi^0\,\mathrm{d}x \\ &\quad + \varepsilon \|\varphi^0\|_{L^{p'}(B(R(T)))}^{1-p'} \int_{B(R(T))} \left|\varphi^0\right|^{p'-2}\varphi^0\xi^0\,\mathrm{d}x = 0.\end{aligned} \tag{6.6}$$

Multiplying (5.1), (5.2) by (ξ, ζ), integrating by parts and applying Leibnitz theorem, we arrive at

$$\begin{aligned}&-\int_0^T \left\langle \sigma, \frac{\partial \xi}{\partial t}\right\rangle \mathrm{d}t - d\int_0^T \langle \sigma, \Delta\xi\rangle\,\mathrm{d}t + \int_0^T \int_{B(R(t))} r_1\sigma\xi\,\mathrm{d}x\,\mathrm{d}t \\ &\quad + \int_0^T \int_{B(R(t))} \lambda\beta\xi\,\mathrm{d}x\,\mathrm{d}t - \int_0^T \left\langle \beta, \frac{\partial \zeta}{\partial t}\right\rangle \mathrm{d}t - d\int_0^T \langle \beta, \Delta\zeta\rangle\,\mathrm{d}t \\ &\quad + \int_0^T \int_{B(R(t))} r_2\beta\zeta\,\mathrm{d}x\,\mathrm{d}t - \int_0^T \int_{\omega_0} f\zeta\,\mathrm{d}x\,\mathrm{d}t + \int_{B(R(t))} \sigma\xi\,\mathrm{d}x\Big]_0^T \\ &\quad + \int_{B(R(t))} \beta\zeta\,\mathrm{d}x\Big]_0^T = 0,\end{aligned}$$

where $\langle\ ,\ \rangle$ is the duality product $W_0^{1,p'}(B(R(t))) \times W^{-1,p'}(B(R(t)))$. We obtain from the choice of (ξ, ζ) and $\sigma(0,x) = \beta(0,x) = 0$ that

$$-\int_0^T \int_{\omega_0} f\zeta\,\mathrm{d}x\,\mathrm{d}t + \int_{B(R(T))} \sigma(T)\xi^0\,\mathrm{d}x = 0. \tag{6.7}$$

Let us take

$$f := |\psi|^{p'-2}\psi.$$

Substituting this into (6.7) and using (6.6), one has

$$\int_{B(R(T))} \big(\sigma(T) - \sigma^d\big)\xi^0 \,\mathrm{d}x + \varepsilon \|\varphi^0\|^{1-p'}_{L^{p'}(B(R(T)))} \int_{B(R(T))} |\varphi^0|^{p'-2}\varphi^0\xi^0 \,\mathrm{d}x = 0,$$

for all $\xi^0 \in L^{p'}(B(R(T)))$. Taking

$$\xi^0 = \big(\sigma(T) - \sigma^d\big)^{\frac{1}{p'-1}} \in L^{p'}\big(B\big(R(T)\big)\big),$$

we obtain in view of $p = 1 + 1/(p' - 1)$ that

$$\begin{aligned} &\|\sigma(T) - \sigma^d\|^p_{L^p(B(R(T)))} \\ &\quad = \varepsilon\|\varphi^0\|^{1-p'}_{L^{p'}(B(R(T)))} \int_{B(R(T))} \big|\varphi^0\big|^{p'-2}\varphi^0 |\sigma(T) - \sigma^d|^{\frac{1}{p'-1}-1}\big(\sigma(T) - \sigma^d\big) \,\mathrm{d}x. \end{aligned}$$

By Hölder inequality, we have

$$\begin{aligned} &\|\varphi^0\|^{1-p'}_{L^{p'}(B(R(T)))} \int_{B(R(T))} \big|\varphi^0\big|^{p'-2}\varphi^0 |\sigma(T) - \sigma^d|^{\frac{1}{p'-1}-1}\big(\sigma(T) - \sigma^d\big) \,\mathrm{d}x \\ &\quad \leqslant \|\sigma(T) - \sigma^d\|^{p-1}_{L^p(B(R(T)))}, \end{aligned}$$

which leads to

$$\|\sigma(T) - \sigma^d\|_{L^p(B(R(T)))} \leqslant \varepsilon$$

and the conclusion holds.

So, it only remains to check the mentioned properties of J:

J is convex. We can write J as the sum of the functionals

$$\begin{aligned} &J_1\big(\varphi^0\big) := -\int_{B(R(T))} \sigma^d\varphi^0 \,\mathrm{d}x, \qquad J_2\big(\varphi^0\big) := \varepsilon\|\varphi^0\|_{L^{p'}(B(R(T)))}, \\ &J_3\big(\varphi^0\big) := \frac{1}{p'}\int_0^T \int_{B(R(t))} |\psi|^{p'} \,\mathrm{d}x \,\mathrm{d}t. \end{aligned}$$

First, we shall see that J_3 is convex. Let (φ_1, ψ_1) and (φ_2, ψ_2) be the solutions to (6.2)–(6.5) with datum $\varphi_1^0,\ \varphi_2^0 \in L^p(B(R(T)))$, respectively. Then, since the system is linear, we get, for $\alpha \in (0, 1)$,

$$J_3\big(\alpha\varphi_1^0 + (1-\alpha)\varphi_2^0\big) = \frac{1}{p'}\int_0^T \int_{B(R(t))} \big(\big|\alpha\psi_1 + (1-\alpha)\psi_2\big|^{p'}\big) \,\mathrm{d}x \,\mathrm{d}t$$

and then

$$\begin{aligned} &J_3\big(\alpha\varphi_1^0 + (1-\alpha)\varphi_2^0\big) - \alpha J_3\big(\varphi_1^0\big) - (1-\alpha)J_3\big(\varphi_2^0\big) \\ &\quad = \frac{1}{p'}\int_0^T \int_{B(R(t))} \big(\big|\alpha\psi_1 + (1-\alpha)\psi_2\big|^{p'} - \alpha|\psi_1|^{p'} - (1-\alpha)|\psi_2|^{p'}\big) \,\mathrm{d}x \,\mathrm{d}t. \end{aligned}$$

Since $p' > 1$, we obtain

$$\left|\alpha\psi_1 + (1-\alpha)\psi_2\right|^{p'} - \alpha|\psi_1|^{p'} - (1-\alpha)|\psi_2|^{p'} \leqslant 0,$$

and integrating, we have

$$\frac{1}{p'}\int_0^T \int_{B(R(t))} \left(\left|\alpha\psi_1 + (1-\alpha)\psi_2\right|^{p'} - \alpha|\psi_1|^{p'} - (1-\alpha)|\psi_2|^{p'}\right) \mathrm{d}x\,\mathrm{d}t \leqslant 0,$$

which proves the convexity of J_3. Finally, J_1 is linear and so convex and since $\|\cdot\|_{L^{p'}(B(R(T))}$ is convex, J_2 is also convex.

J is continuous. By construction, J_1 and J_2 are continuous. We are going to prove that J_3 is also continuous. Let $\varphi_n^0 \in L^{p'}(B(R(T)))$ such that $\varphi_n^0 \to \varphi^0$ and let (φ_n, ψ_n), (φ, ψ) be the solutions to (6.2)–(6.5) with datum φ_n^0 and φ^0. Subtracting both systems and taking

$$\left(p'|\varphi - \varphi_n|^{p'-2}(\varphi - \varphi_n),\, p'|\psi - \psi_n|^{p'-2}(\psi - \psi_n)\right)$$

as test function, using the integration by parts formula (see, e.g., ALT and LUCKHAUS [1983]) and Young's inequality, we arrive at

$$-\frac{\partial}{\partial t}\int_{B(R(t))}\left[|\varphi - \varphi_n|^{p'} + |\psi - \psi_n|^{p'}\right]\mathrm{d}x$$
$$+ \int_{B(R(t))}\left(r_1 p' - |\lambda|\right)|\varphi - \varphi_n|^{p'}\,\mathrm{d}x + \int_{B(R(t))}\left(r_2 p' - |\lambda|\right)|\psi - \psi_n|^{p'}\,\mathrm{d}x \leqslant 0.$$

Let X_n be defined by

$$X_n(t) = \|\varphi - \varphi_n\|_{L^{p'}(B(R(t)))}^{p'} + \|\psi - \psi_n\|_{L^{p'}(B(R(t)))}^{p'},$$

then,

$$-X_n'(t) \leqslant C X_n(t), \quad t \in (0, T), \qquad X_n(T) = \left\|\varphi_n^0 - \varphi^0\right\|_{L^{p'}(B(R(T))}^{p'}$$

are satisfied, where $C = \max\{-r_1 p' + |\lambda|, -r_2 p' + |\lambda|\}$. Thus, we obtain

$$0 \leqslant X_n(t) \leqslant \left|X_n(T)\right| \mathrm{e}^{-C(t-T)}.$$

Since

$$0 \leqslant \int_{\omega_0} |\psi - \psi_n|^{p'}\,\mathrm{d}x \leqslant X_n(t),$$

we conclude by integrating over $[0, T]$ and taking limits as $n \to \infty$ that

$$\int_0^T \int_{\omega_0} |\psi - \psi_n|^{p'}\,\mathrm{d}x\,\mathrm{d}t \leqslant \int_0^T X_n(t)\,\mathrm{d}t \to 0,$$

which proves the continuity of J_3.

J is coercive. Let $\varphi_n^0 \in L^{p'}(B(R(T)))$ such that $\|\varphi_n^0\|_{L^{p'}(B(R(T)))} \to \infty$, when $n \to \infty$. We claim

$$\liminf_{n\to\infty} \frac{J(\varphi_n^0)}{\|\varphi_n^0\|_{L^{p'}(B(R(T)))}} \geqslant \varepsilon.$$

Let

$$I := \liminf_{n\to\infty} \frac{J(\varphi_n^0)}{\|\varphi_n^0\|_{L^{p'}(B(R(T)))}} \geqslant -\|\sigma^d\|_{L^p(B(R(T)))}.$$

Then, there exists a minimizing subsequence (which we call again by φ_n^0) such that

$$\lim_{n\to\infty} \frac{J(\varphi_n^0)}{\|\varphi_n^0\|_{L^{p'}(B(R(T)))}} = I.$$

We define

$$\bar{\varphi}_n^0 := \frac{\varphi_n^0}{\|\varphi_n^0\|_{L^{p'}(B(R(T)))}},$$

and let $(\bar{\varphi}_n, \bar{\psi}_n)$ be the solution to (6.2)–(6.5) with data $(\bar{\varphi}_n^0, 0)$. Since the system is linear, we have

$$(\bar{\varphi}_n, \bar{\psi}_n) = \frac{1}{\|\varphi_n^0\|_{L^{p'}}}(\varphi_n, \psi_n).$$

Then

$$\frac{J(\varphi_n^0)}{\|\varphi_n^0\|_{L^{p'}(B(R(T)))}} = \|\varphi_n^0\|^{p'-1} \int_0^T \int_{\omega_0} |\bar{\psi}_n|^{p'} \,\mathrm{d}x\,\mathrm{d}t - \int_{B(R(T))} \sigma^d \bar{\varphi}_n^0 \,\mathrm{d}x + \varepsilon.$$

Now, it is clear that, if

$$\liminf_{n\to\infty} \int_0^T \int_{\omega_0} \bar{\psi}_n^{p'} \,\mathrm{d}x \geqslant \alpha_0, \tag{6.8}$$

for some positive α_0, then

$$\frac{J(\varphi_n^0)}{\|\varphi_n^0\|_{L^{p'}(B(R(T)))}} \geqslant \alpha_0 \|\varphi_n^0\|_{L^{p'}(B(R(T)))}^{p'-1} + \varepsilon - \|\sigma^d\|_{L^p(B(R(T)))} \to \infty$$

as $n \to \infty$, which proves the property. Let us assume that

$$\liminf \int_0^T \int_{\omega_0} |\bar{\psi}_n|^{p'} \,\mathrm{d}x = 0.$$

Then there exists a subsequence $\bar{\psi}_{n_i}$ such that

$$\int_0^T \int_{\omega_0} |\bar{\psi}_{n_i}|^{p'} \,\mathrm{d}x\,\mathrm{d}t \to 0,$$

therefore $\bar{\psi}_{n_i} \to 0$ in $L^{p'}(\omega_0 \times [0,T])$. Taking $(0,\zeta)$ as test function in (6.3), where $\zeta \in C_c^2((0,T)\times\omega_0)$, we obtain

$$\int_0^T \int_{\omega_0} \bar{\psi}_{n_i} \frac{\partial \zeta}{\partial t}\,\mathrm{d}x\,\mathrm{d}t - \int_0^T \int_{\omega_0} \bar{\psi}_{n_i} \Delta\zeta\,\mathrm{d}x\,\mathrm{d}t - r_2 \int_0^T \int_{\omega_0} \bar{\psi}_{n_i} \zeta\,\mathrm{d}x\,\mathrm{d}t + \lambda \int_0^T \int_{\omega_0} \bar{\varphi}_{n_i} \zeta\,\mathrm{d}x\,\mathrm{d}t = 0.$$

Taking limits, we conclude that

$$\int_0^T \int_{\omega_0} \bar{\varphi}_{n_i} \zeta\,\mathrm{d}x\,\mathrm{d}t \to 0, \tag{6.9}$$

where $\bar{\varphi}_{n_i}$ is the solution to

$$\begin{cases} -\dfrac{\partial \bar{\varphi}_{n_i}}{\partial t} - d\Delta\bar{\varphi}_{n_i} - r_1\bar{\varphi}_{n_i} = 0, & |x| < R(t),\ t \in (0,T), \\ \bar{\varphi}_{n_i}(t,x) = 0, & |x| = R(t),\ t \in (0,T), \\ \bar{\varphi}_{n_i}(T,x) = \bar{\varphi}^0, & |x| < R_0. \end{cases} \tag{6.10}$$

Repeating the change of (5.6) and introducing the unknown

$$\bar{u}_{n_i}(\tilde{x},\tilde{t}) := \bar{\varphi}_{n_i}\big(R\big(t(\tilde{t})\big)\tilde{x}, t(\tilde{t})\big),$$

we obtain

$$\begin{cases} -\dfrac{\partial \bar{u}_{n_i}}{\partial \tilde{t}} - d\Delta\bar{u}_{n_i} - R^2R'\tilde{x}\cdot\nabla\bar{u}_{n_i} + R^2 r_1\bar{u}_{n_i} = 0, & B\times(0,\widetilde{T}), \\ \bar{u}_{n_i}(\tilde{x},\tilde{t}) = 0, & \partial B\times(0,\widetilde{T}), \\ \bar{u}_{n_i}(\tilde{x},\widetilde{T}) = \bar{u}^0_{n_i}(\tilde{x}) = \bar{\varphi}^0_{n_i}(\tilde{x}R_0), & \tilde{x}\in B. \end{cases} \tag{6.11}$$

Since $\bar{u}^0_{n_i} \rightharpoonup \bar{u}_0$ belongs to $L^{p'}(B)$, it follows that $\bar{u}_{n_i} \rightharpoonup \bar{u}$ (the solution of (6.11) with $\bar{u}_0 = \bar{\varphi}^0$). By (6.9), $\bar{u}_{n_i} \to 0$ weakly in $L^{p'}(B(\widehat{\omega}_0))$, where $\widehat{\omega}_0$ is an open subset of B such that $\widehat{\omega}_0 \subset \widetilde{\omega}_0$. Consequently, $\bar{u} \equiv 0$ on $\widetilde{\omega}_0$ for all $0 \leqslant \tilde{t} \leqslant \widetilde{T}$. By the unique continuation of the solution to Eq. (6.11) (see FRIEDMAN [1964], CHI-CHEUNG POON [1996], Theorem 1.1′), we deduce that $\bar{u} = 0$ in $B\times(0,\widetilde{T})$, which implies $\bar{u}_0 \equiv 0$ and $\bar{\varphi}^0 \equiv 0$ by uniqueness of (6.11). Furthermore,

$$-\int_{B(R(T))} \sigma^d \bar{\varphi}^0\,\mathrm{d}x = 0$$

and $I = \varepsilon$, which proves the coerciveness of J. □

PROOF OF THEOREM 6.1. We consider the function $\theta : C^1([0,T]) \to H^2(0,T)$, $\theta(R^*) = R$, where R is defined by

$$R^2(t)\dot{R}(t) = \int_{B(R^*(t))} S\big(\sigma + \sigma^s, \beta + \beta^s\big)\,\mathrm{d}x, \qquad R^*(0) = R_0,$$

where (σ^s, β^s) is the solution to the problem (5.1), (5.2), (5.4) and (5.5), with $f \equiv 0$, and initial data $\sigma_{n-1}^s(x,0) = \sigma_0(x)$, $\beta^s(x,0) = \beta_0(x)$, and (σ, β) is the solution mentioned in Proposition 6.1. Since S is bounded, $R \in W^{1,\infty}(0,T)$. By Proposition 6.1, for each R^* there exists a minimum function φ_n^0 which minimize the functional

$$J(\varphi^0) := \frac{1}{p'} \int_0^T \int_{\omega_0} |\psi|^{p'} \,\mathrm{d}x\,\mathrm{d}t + \varepsilon \|\varphi^0\|_{L^{p'}(B(R^*(T)))} - \int_{B(R^*(T))} \sigma^d \varphi^0 \,\mathrm{d}x,$$

where $\sigma^d = \hat{\sigma}^d \chi_{B(R^*(T))}$. We are going to show that $\|\varphi^0\|_{L^{p'}(B(R^*(T)))}$ is uniformly bounded. To the contrary, we assume that there exists a sequence φ_n^0 such that $\|\varphi_n^0\|_{L^{p'}(B(R^*(T)))} \to \infty$ and get

$$\begin{aligned} \frac{J(\varphi_n^0)}{\|\varphi_n^0\|_{L^{p'}}} &= \frac{1}{p'} \|\varphi_n^0\|_{L^{p'}(B(R^*(T)))}^{p'-1} \int_0^T \int_{\omega_0} |\bar{\psi}_n|^{p'} \,\mathrm{d}x\,\mathrm{d}t \\ &\quad + \varepsilon - \int_{B(R^*(T))} \sigma_n^d \bar{\varphi}_n^0 \,\mathrm{d}x \leqslant 0 \end{aligned} \tag{6.12}$$

in view of $J_n(\varphi_n^0) \leqslant 0$. Since

$$\left| \int_{B(R^*(T))} \frac{\sigma_n^d \varphi_n^0}{\|\varphi_n^0\|_{L^{p'}(B(R^*(T)))}} \,\mathrm{d}x \right| \leqslant \|\sigma_n^d\|_{L^p(B(R^*(T)))} \leqslant \|\hat{\sigma}^d\|_{L^p(B(R_0 \exp\{MT\}))},$$

it follows, by (6.12) that

$$\int_0^T \int_{\omega_0} |\bar{\psi}_n|^{p'} \,\mathrm{d}x\,\mathrm{d}t \to 0 \quad \text{when } n \to \infty.$$

Using the same argument as in the proof of coerciveness of J, we obtain

$$\bar{\varphi}_n^0 \rightharpoonup 0 \quad \text{in } L^{p'}\big(B\big(R^*(T)\big)\big)$$

and

$$\liminf_{n\to\infty} \frac{J_n(\varphi_n^0)}{\|\varphi_n^0\|} \geqslant \varepsilon,$$

which contradicts (6.12). Consequently $\|\varphi_n^0\|_{L^{p'}(B(R^*(T)))}$ is uniformly bounded, hence $\|\varphi_n\|_{L^{p'}(B(R^*(T)))}$ is uniformly bounded. Furthermore, the set of controls is uniformly bounded. Performing the change of (4.3)–(4.5) and (5.6), applying Lemma 5.1, we obtain that θ is continuous and compact. Then, there exists a fixed point (σ, β, R) which satisfies (5.1)–(5.5) and condition (6.1). Thus the theorem is proved in the case $p > 4$.

In the case $p \leqslant 4$, we consider the control f for any $s > 4$, for instance $f \in L^5((0,T) \times \Omega)$, then

$$\begin{aligned} \|\sigma(T) - \sigma^d\|_{L^p(B(R(T)))} &\leqslant \left(\frac{3\pi}{4} \operatorname{meas}\{B(R(T))\}\right)^{\frac{5}{p(5-p)}} \|\sigma(T) - \sigma^d\|_{L^5(B(R(T)))} \\ &\leqslant \varepsilon \left(\frac{3\pi}{4} \exp\{T\|S\|_{L^\infty}\}\right)^{\frac{5}{p(5-p)}}, \end{aligned}$$

setting

$$\varepsilon = \varepsilon' \left(\frac{3\pi}{4} \exp\{T \|S\|_{L^\infty}\} \right)^{-\frac{p(5-p)}{5}},$$

we obtain the theorem. □

REMARK 6.1. Notice that the final observation is made regarding the density $\sigma(T,\cdot)$ and that once we have chosen the control to obtain (6.1). The free boundary, $R(t)$, and the inhibitor density $\beta(T,\cdot)$ are univocally determined.

REMARK 6.2. There exists a long literature on the application of Optimization and Control Theory to different mathematical tumor growth models. We refer the interested reader to the works by SWAM [1984], FISTER, LENHART and MCNALLY [1998], BELLOMO and PREZIOSI [2000] and the references therein.

7. Numerical analysis

In this section we establish a numerical solution to the problem (5.1)–(5.5) by employing a time discretization scheme which is implicit with respect to u and v and explicit for the free boundary R. We assume radial symmetry, no forcing terms (i.e., $f = 0$), and a nonnecrotic core. Let $x := r_1/R(t)$ and

$$u(x,t) = \sigma\big(xR(t),t\big) - \overline{\overline{\sigma}}, \qquad v(x,t) = \beta\big(xR(t),t\big) - \overline{\overline{\beta}}.$$

Then, problem (3.1)–(3.5) becomes

$$\begin{aligned}
&\frac{\partial u}{\partial t} = \frac{d_1}{x^2R^2}\frac{\partial}{\partial x}\left(x^2\frac{\partial}{\partial x}u\right) + x\frac{R'}{R}\frac{\partial u}{\partial x} - r_1u - \lambda v + r_1\overline{\overline{\sigma}} + \lambda\overline{\overline{\beta}}, \quad (0,1)\times(0,T),\\
&\frac{\partial v}{\partial t} = \frac{d_2}{x^2R^2}\frac{\partial}{\partial x}\left(x^2\frac{\partial v}{\partial x}\right) + x\frac{R'}{R}\frac{\partial}{\partial x}v - r_2v + r_2\overline{\overline{\beta}}, \quad (0,1)\times(0,T),\\
&R(t) = R_0\exp\left\{\int_0^t\int_0^1 x^2S(u,v)\,\mathrm{d}x\,\mathrm{d}t\right\}, \quad t>0,\\
&u_x(0,t) = v_x(0,t) = u(1,t) = v(1,t) = 0, \quad t>0,\\
&R(0) = R_0, \qquad u(x,0) = u_0(x), \qquad v(x,0) = v_0(x), \quad x\in(0,1).
\end{aligned}$$

7.1. *Time discretization*

Let $N \in \mathbb{N}$, $n = 1,\dots,N$ and $t_n = n(T/N)$. We introduce the approximations

$$\begin{aligned}
&u^n(x) \approx u(x,t_n), \qquad v^n(x) \approx v(x,t_n), \qquad R^n \approx R(t_n),\\
&\dot{R}^n \approx \frac{\mathrm{d}R(t)}{\mathrm{d}t} \quad \text{in } t = t_n,
\end{aligned}$$

defined by the following algorithm:

Step 0:

(0.1) $\big(R^0, u^0, v^0\big) = (R_0, u_0, v_0)$,

(0.2) $R^{1/2} = \dfrac{1}{2}\big(R_0 + R_0 e^{\Delta t \int_0^1 x^2 S(u^0, v^0)\,dx}\big)$,

(0.3) $\dot{R}^0 = R_0 \displaystyle\int_0^1 x^2 S(u^0, v^0)\,dx\, R_0 e^{\Delta t \int_0^1 x^2 S(u^0, v^0)\,dx}$.

Now, for $1 < n \leqslant N$, assuming $(R^{n-1}, u^{n-1}, v^{n-1})$ be given, we calculate (R^n, u^n, v^n) as follows:

Step n:

(n.1)

$$\begin{cases} \dfrac{v^n - v^{n-1}}{\Delta t} = \dfrac{d_2}{(R^{n-1})^2} x^{-2} \dfrac{\partial}{\partial x}\left(x^2 \dfrac{\partial}{\partial x} v^n\right) + x \dfrac{\dot{R}^{n-1}}{R^{n-1}} \dfrac{\partial}{\partial x} v^{n-1} \\ \qquad\qquad - r_2 v^n + r_2 \overline{\overline{\beta}}, \quad \text{in } 0 < x < 1, \\ \dfrac{\partial v^n}{\partial x}(0) = v^n(1) = 0, \end{cases}$$

(for $n = 1$, we use $R^{1/2}$).

(n.2)

$$\begin{cases} \dfrac{u^n - u^{n-1}}{\Delta t} = \dfrac{d_1}{(R^{n-1})^2} x^{-2} \dfrac{\partial}{\partial x}\left(x^2 \dfrac{\partial}{\partial x} u^n\right) + x \dfrac{\dot{R}^{n-1}}{R^{n-1}} \dfrac{\partial}{\partial x} u^{n-1} \\ \qquad\qquad - r_1 u^n - \lambda v^n + r_1 \overline{\overline{\sigma}} + \lambda \overline{\overline{\beta}}, \quad \text{in } 0 < x < 1, \\ \dfrac{\partial u^n}{\partial x}(0) = u^n(1) = 0. \end{cases}$$

(n.3) We compute R^n by integrating according the compound trapezium rule

$$\begin{aligned} R^n &= R_0 \exp\left\{\Delta t \sum_{j=0}^{n-1} \int_0^1 x^2 \frac{1}{2}\big(S\big(u^j, v^j\big) + S\big(u^{j+1}, v^{j+1}\big)\big)\,dx\right\} \\ &= R_0 \exp\left\{\Delta t \int_0^1 x^2 \left[\frac{1}{2}\big(S\big(u^0, v^0\big) + S\big(u^n, v^n\big)\big) + \sum_{j=1}^{n-1} S\big(u^j, v^j\big)\right] dx\right\}. \end{aligned}$$

(n.4)

$$\begin{aligned} \dot{R}^n = R_0 \int_0^1 x^2 S\big(u^n, v^n\big)\,dx \exp\Bigg\{\Delta t \sum_{j=0}^{n-1} \int_0^1 x^2 \frac{1}{2}\big(S\big(u^j, v^j\big)\,dx \\ + S\big(u^{j+1}, v^{j+1}\big)\,dx\big)\Bigg\} \end{aligned}$$

$$= R_0 \int_0^1 x^2 S\big(u^n, v^n\big)\,\mathrm{d}x \exp\left\{\Delta T \int_0^1 x^2 \left[\frac{1}{2}\big(S\big(u^0, v^0\big) + S\big(u^n, v^n\big)\big) + \sum_{j=1}^{n-1} S\big(u^j, v^j\big)\right]\mathrm{d}x\right\}.$$

7.2. Full discretization

We approximate $H^1(0,1)$ by space V_h defined by

$$V_h := \big\{\phi \in C^0\big([0,1]\big)\colon \phi|_{(x_{j-1},x_j)} \in P_1,\ \text{for } j = 1, s+1\big\},$$

where $x_j = j/(s+1)$ and P_1 is the space of those polynomials of degree 0 or 1. We approximate the above implicit–explicit scheme by the system

$$\frac{u_h^n - u_h^{n-1}}{\Delta T} = \frac{D_1}{(xR^{n-1})^2}\frac{\partial}{\partial x}\left(x^2 \frac{\partial}{\partial x}u_h^n\right) + x\frac{\dot R^{n-1}}{R^{n-1}}\frac{\partial}{\partial x}u_h^n - r_1 u_h^n - \lambda v_h^n + r_1\overline{\overline{\sigma}} + \lambda\overline{\overline{\beta}},$$
$$\text{in } 0 < x < 1,\ n = 1, \ldots, N,$$
$$\frac{v_h^n - v_h^{n-1}}{\Delta T} = \frac{D_2}{(xR^{n-1})^2}\frac{\partial}{\partial x}\left(x^2 \frac{\partial}{\partial x}v_h^n\right) + x\frac{\dot R^{n-1}}{R^{n-1}}\frac{\partial}{\partial x}v_h^n - r_2 v_h^n + r_2\overline{\overline{\beta}},$$
$$\text{in } 0 < x < 1,\ i = 1, \ldots, N,$$
$$u_h^n(1) = v_h^n(1) = 0, \qquad \frac{\partial u_h^n}{\partial x} = \frac{\partial v_h^n}{\partial x} = 0, \quad \text{on } x = 0,$$
$$R(0) = R_0, \qquad u_h^0(x) = u_{h,0}(x), \qquad v_h^0(x) = v_{h,0}(x),$$
$$R_h^n = R_0 \exp\left\{\Delta T \int_0^1 x^2 \left[\frac{1}{2}\big(S\big(u_h^0, v_h^0\big) + S\big(u_h^n, v_h^n\big)\big) + \sum_{j=1}^{n-1} S\big(u_h^j, v_h^j\big)\right]\mathrm{d}x\right\}.$$

7.3. Weak formulation of the discrete problem

Setting

$$b(\zeta, \varphi) = \int_0^1 x^2 \zeta\varphi\,\mathrm{d}x,$$

the weak formulation of the discrete problem is given by $(\forall\varphi \in V_h)$

$$(1 + \Delta T r_1) b\big(u_h^n, \varphi\big) + \frac{d_1 \Delta T}{(R^{n-1})^2} b\big(\big(u_h^i\big)_x, \varphi_x\big) - \frac{\Delta T \dot R^{n-1}}{R^{n-1}} b\big(x\big(u_h^n\big)_x, \varphi\big)$$
$$= b\big(u_h^{n-1} - v_h^n + \Gamma_1\overline{\overline{\sigma}} + \overline{\overline{\beta}}, \varphi\big) = b\big(u_n^{n-1} + \Delta T\big(-\lambda v_h^n + r_1\overline{\overline{\sigma}} + \lambda\overline{\overline{\beta}}\big), \varphi\big),$$
$$(1 + \Delta T r_2) b\big(v_h^n, \varphi\big) + \frac{d_1 \Delta T}{(R^{n-1})^2} b\big(\big(v_h^n\big)_x, \varphi_x\big) - \frac{\Delta T \dot R^{n-1}}{R^{n-1}} b\big(x\big(v_h^n\big)_x, \varphi\big)$$
$$= b\big(v_h^{n-1} + \Delta T r_2\overline{\overline{\beta}}, \varphi\big).$$

7.4. Numerical experiments

We consider the special case of $S(\sigma, \beta) = \sigma - \hat{\sigma}$, $T = 3$, $N = 501$, (i.e., $\Delta T = 3/500$) and $s = 20$ (i.e., $h = 1/20$) with the following choice of the parameters: $R_0 = 5$, $D_1 = D_2 = 1$, $\Gamma_1 = \Gamma_2 = \overline{\overline{\sigma}} = \overline{\overline{\beta}} = 1$. These values of the parameters have been taken merely with academical purpose. For other choices see, for instance, BYRNE and CHAPLAIN [1996a]. In Figs. 7.1, 7.5 and 7.9, we display the computed evolution of the radius of the tumor for experiments 1 ($\hat{\sigma} = 0.75$), 2 ($\hat{\sigma} = 1$) and 3 ($\hat{\sigma} = 1.5$). In Figs. 7.2, 7.6 and 7.10 we display visualized the computed evolution of the radius of the tumor in two

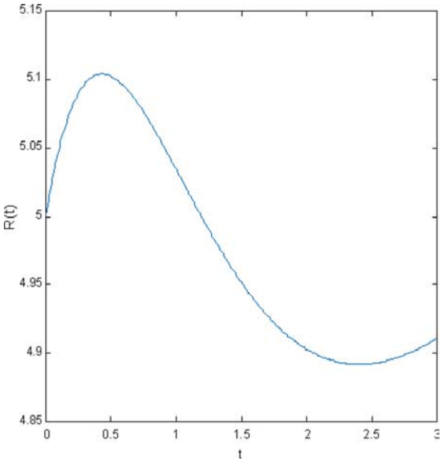

FIG. 7.1.

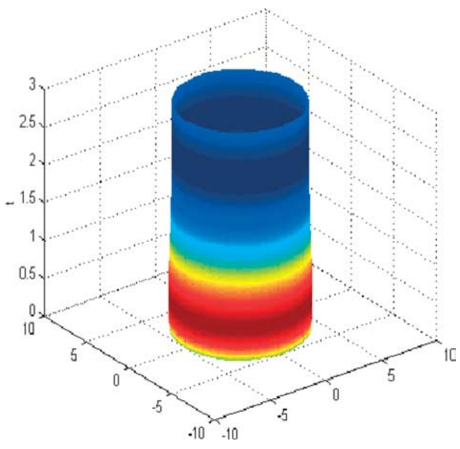

FIG. 7.2.

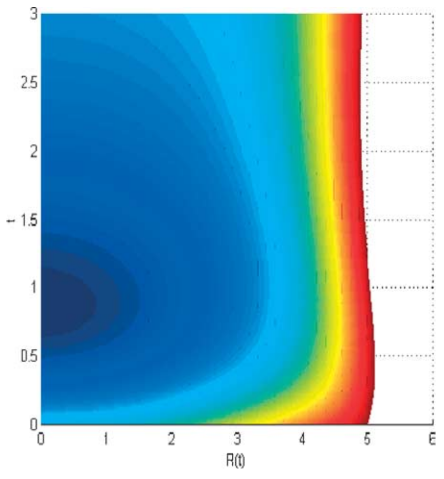

FIG. 7.3.

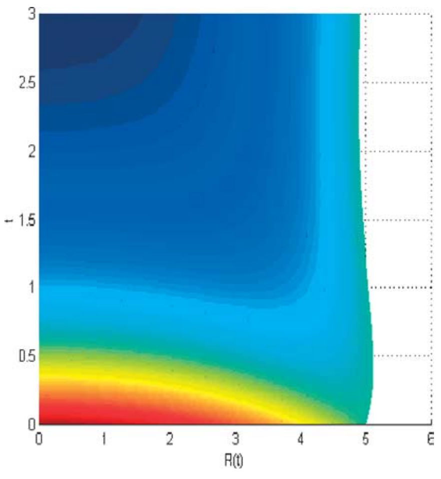

FIG. 7.4.

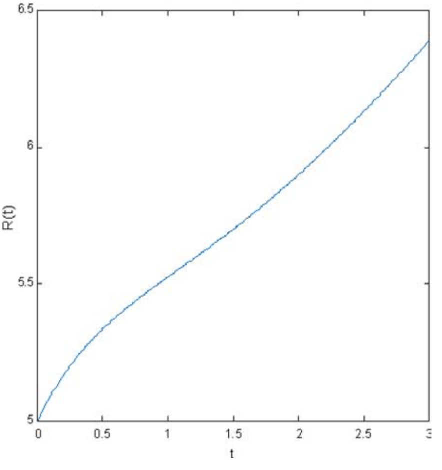

FIG. 7.5.

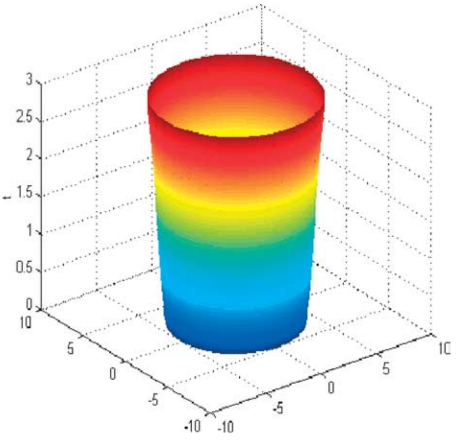

FIG. 7.6.

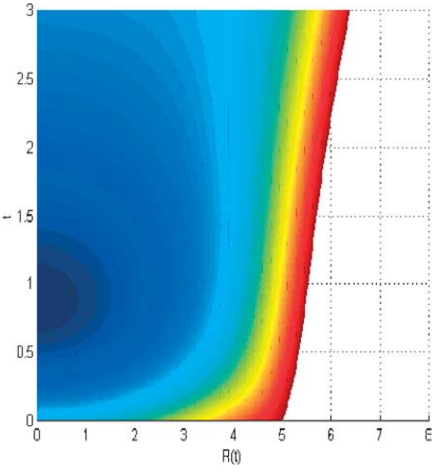

FIG. 7.7.

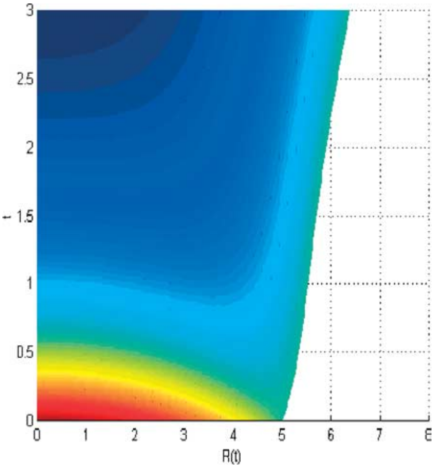

FIG. 7.8.

dimensions. Figs. 7.3, 7.7 and 7.11 show the computed evolution of the concentration of nutrients σ. Finally, in Figs. 7.4, 7.8 and 7.12 we exhibit the computed concentration of the inhibitors β. Numerical simulation of the model (when $S = \sigma - \tilde{\sigma}$) show us the importance of the parameter $\tilde{\sigma}$ in the behavior of the boundary. As it is expected, a smaller $\tilde{\sigma}$ produces a faster growth of the boundary. We can see in Figs. 7.1, 7.5 and 7.9 an initial concave growth of the radius that becomes convex after a time (which depends on $\tilde{\sigma}$). Among other different aspects it can be appreciated that the free boundary is not necessarily increasing in time (see Fig. 7.1).

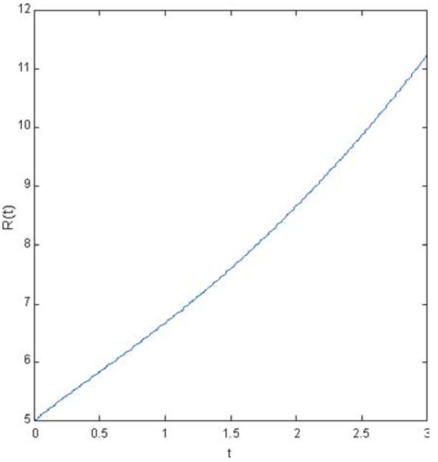

FIG. 7.9.

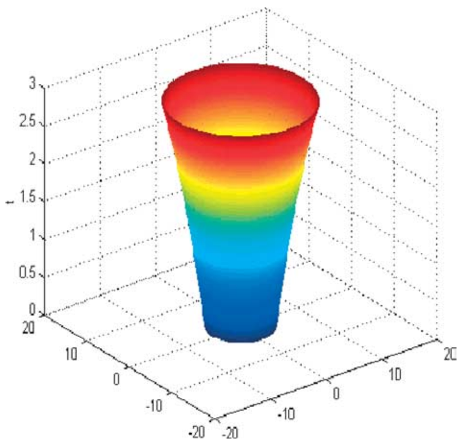

FIG. 7.10.

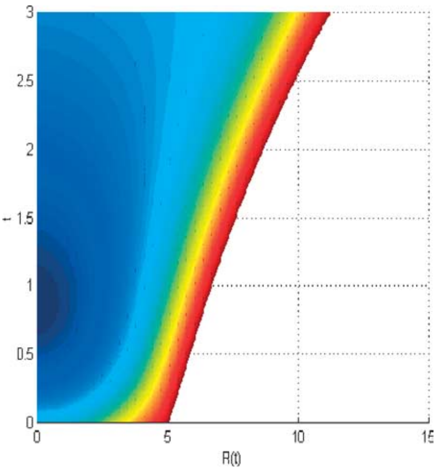

FIG. 7.11.

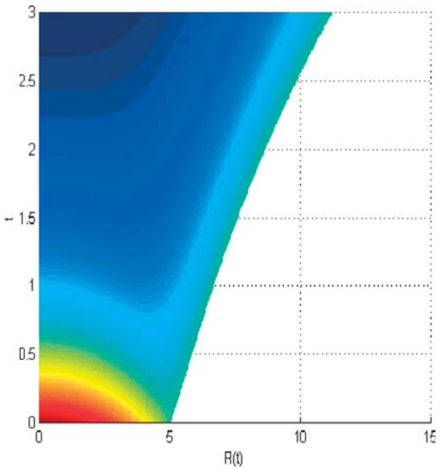

FIG. 7.12.

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References

ADAM, J.A. (1986). A simplified mathematical model of tumor growth. *Math. Biosci.* **81**, 229–244.

ADAM, J.A., BELLOMO, N. (1997). *A Survey of Models for Tumor–Immune System Dynamics* (Birkhäuser, Boston).

ALT, H.W., LUCKHAUS, S. (1983). Quasi-linear elliptic–parabolic differential equations. *Math. Z.* **183**, 311–341.

ANDERSON, A.R.A., CHAPLAIN, M.A.J. (1998). Continuous and discrete mathematical models of tumor-induced angiogenesis. *Bull. Math. Biology* **60**, 857–899.

ATTALLAH, A.M. (1976). Regulation of cell growth in vitro and in vivo: point/counterpoint. In: Houck, J.C. (ed.), *Chalones* (North-Holland, Amsterdam), pp. 141–172.

BAZALIY, B.V., FRIEDMAN, A. (2003). A free boundary problem for an elliptic–parabolic system: application to a model of tumor growth. *Comm. Partial Differential Equations* **28**, 517–560.

BELLOMO, N., PREZIOSI, L. (2000). Modelling and mathematical problems related to tumor evolution and its interaction with the immune system. *Math. Comput. Modelling* **32**, 413–452.

BERTUZZI, A., FASANO, A., GANDOLFI, A., MARANGI, D. (2002). Cell kinetics in tumour cords studied by a model with variable cell cycle length. *Math. Biosci.* **177–178**, 103–125.

BREZIS, H. (1983). *Analyse Fonctionnelle* (Masson, Paris).

BRITTON, N.F., CHAPLAIN, M.A.J. (1993). A qualitative analysis of some models of tissue growth. *Math. Biosci.* **113**, 77–89.

BYRNE, H.M. (1997a). The effect of time delays on the dynamics of avascular tumor growth. *Math. Biosci.* **144**, 83–117.

BYRNE, H.M. (1997b). The importance of intercellular adhesion in the development of carciomas. *IMA J. Math. Appl. Med. Biol.* **14**, 305–323.

BYRNE, H.M. (1999a). A comparison of the roles of localised and nonlocalised factors in solid tumour growth. *Math. Models Methods Appl. Sci.* **9**, 541–568.

BYRNE, H.M. (1999b). A weakly nonlinear analysis of a model of avascular solid tumour growth. *J. Math. Biol.* **39**, 59–89.

BYRNE, H.M., CHAPLAIN, M.A.J. (1995). Growth of nonnecrotic tumors in the presence and absence of inhibitors. *Math. Biosci.* **130**, 151–181.

BYRNE, H.M., CHAPLAIN, M.A.J. (1996a). Growth of necrotic tumors in the presence and absence of inhibitors. *Math. Biosci.* **135**, 187–216.

BYRNE, H.M., CHAPLAIN, M.A.J. (1996b). Modelling the role of cell–cell adhesion in the growth and development of carciomas. *Math. Comput. Modelling* **12**, 1–17.

BYRNE, H.M., MATTHEWS, P. (2002). Asymmetric growth of avascular solid tumors: exploiting symmetries, in press.

CHAPLAIN, M.A.J. (1996). Avascular growth, angiogenesis and vascular growth in solid tumours: the mathematical modelling of the stages of tumour development. *Math. Comput. Modelling* **23** (6), 47–87.

CHAPLAIN, M.A.J. (1999). Mathematical models for the growth, development and treatment of tumours. *Math. Models Methods Appl. Sci.* **9** (4), 171–206 (special issue).

CHAPLAIN, M.A.J., ANDERSON, A.R.A. (1997). Mathematical modelling, simulation and prediction of tumour-induced Angiogenesis. *Invas. Metast.* **16**, 222–234.

CHAPLAIN, M.A.J., PREZIOSI, P. (2002). Macroscopic modelling of the growth and development of tumour masses, in press.

CHI-CHEUNG POON (1996). Unique continuation for parabolic equations. *Comm. Partial Differential Equations* **21**, 521–539.

CUI, S., FRIEDMAN, A. (1999). Analysis of a mathematical of protocell. *Math. Anal. Appl.* **236**, 171–206.

CUI, S., FRIEDMAN, A. (2000). Analysis of a mathematical model of effect of inhibitors on the growth of tumors. *Math. Biosci.* **164**, 103–137.

CUI, S., FRIEDMAN, A. (2001). Analysis of a mathematical model of the growth of the necrotic tumors. *Math. Anal. Appl.* **255**, 636–677.

DE ANGELIS, E., PREZIOSI, L. (2000). Advection–diffusion models for solid tumor evolution in vivo and related free boundary problem. *Math. Models Methods Appl. Sci.* **10**, 379–407.

DÍAZ, J.I., RAMOS, A.M. (1995). Positive and negative approximate controllability results for semilinear parabolic equations. *Rev. Real Acad. Cienc. Exact., Fís. Natur. Madrid* **LXXXIX**, 11–30.

DÍAZ, J.I., TELLO, L. (1999). A nonlinear parabolic problem on a Riemannian manifold without boundary arising in Climatology. *Collect. Math.* **50**, 19–51.

DÍAZ, J.I., TELLO, J.I. (2003). On the mathematical controllability in a mathematical in a simple growth tumors model by the internal localized action of inhibitors. *Nonlinear Anal.: Real World Appl.* **4**, 109–125.

DÍAZ, J.I., TELLO, J.I. (2004). Mathematical analysis of a simple model for the growth of necrotic tumors in presence of inhibitors. Int. J. Pure Appl. Math., in press.

FABRE, C., PUEL, J.P., ZUAZUA, E. (1995). Approximate controllability of the semilinear heat equation. *Proc. Roy. Soc. Edinburgh Sect. A* **125**, 31–61.

FISTER, K.R., LENHART, S., MCNALLY, J.S. (1998). Optimizing chemotherapy in HIV model. *Electron. J. Differential Equations* **32**, 1–12.

FONTELOS, M.A., FRIEDMAN, A., HU, B. (2002). Mathematical analysis of a model for the initiation of angiogenesis. *SIAM J. Math. Anal.* **33** (6), 1330–1355.

FRIEDMAN, A. (1964). *Partial Differential Equations of Parabolic Type* (Prentice Hall, New York).

FRIEDMAN, A. (2002). A hierarchy of cancer models and their mathematical challenges. In: *Lecture at the Workshop on Mathematical Models in Cancer*, Vanderbilt University, May 3–5.

FRIEDMAN, A., HU, B., VELÁZQUEZ, J.J.L. (2001). A Stefan problem for a protocell model with symmetry-breaking bifurcations of analytic solutions. *Interfaces and Free Boundaries* **3**, 143–199.

FRIEDMAN, A., REITICH, F. (1999). Analysis of a mathematical model for the growth of tumors. *J. Math. Biol.* **38**, 262–284.

FRIEDMAN, A., REITICH, F. (2001). Symmetry-breaking bifurcation of analytic solutions to free boundary problems: An applications to a model of tumor growth. *Trans. Amer. Math. Soc.* **353**, 1587–1634.

FRIEDMAN, A., TELLO, J.I. (2002). Stability of solutions of chemotaxis equations in reinforced random walks. *Math. Anal. Appl.* **272**, 138–163.

GLOWINSKI, R., LIONS, J.L. (1995). Exact and approximate controllability for distributed parameter systems, Part II. *Acta Numer.*, 157–333.

GREENSPAN, H.P. (1972). Models for the growth of solid tumor by diffusion. *Stud. Appl. Math.* **52**, 317–340.

GREENSPAN, H.P. (1976). On the growth and stability of cell cultures and solid tumors. *J. Theoret. Biol.* **56**, 229–242.

HOLMES, M.J., SLEEMAN, B.D. (2000). A mathematical model of tumour angiogenesis incorporating cellular traction and viscoelastic effects. *J. Theoret. Biol.* **202**, 95–112.

LADYZENSKAJA, O.H., SOLONNIKOV, V.A., URALSEVA, N.N. (1991). *Linear and Quasi-linear Equations of Parabolic Type*, Transl. Math. Monogr. **23** (Amer. Math. Soc., Providence, RI).

LEVINE, H.A., SLEEMAN, B.P. (1997). A system of reaction diffusion equations arising in the theory of reinforced random walks. *SIAM J. Appl. Math.* **57**, 683–730.

LEVINE, H.A., PAMUK, S., SLEEMAN, B.P., NILSEN-HAMILTON, M. Mathematical modeling of capillary formation and development in tumor angiogenesis: Penetration into the stroma, in press.

LEVINE, H.A., SLEEMAN, B.P., NILSEN-HAMILTON, M. (2000). A mathematical modeling for the roles of pericytes and macrophages in the initiation of angiogenesis I. The role of protease inhibitors in preventing angiogenesis. *Math. Biosci.* **168**, 75–115.

LIONS, J.L. (1990). Remarques sur la contrôllabilité approchée. In: *Actas de Jornadas Hispano–Francesas sobre Control de Sistemas Distribuidos*, Universidad de Malaga, pp. 77–88.

LIONS, J.L. (1991). Exact Controllability for distributed systems: Some trends ans some problems. *Appl. Indust. Math.*, 59–84.

ORME, M.E., CHAPLAIN, M.A.J. (1995). Travelling waves arising in mathematical models of tumour angiogenesis and tumour invasion. *Forma* **10**, 147–170.

OTHMER, H.G., STEVENS, A. (1997). Aggregation, blowup, and collapse: The ABC's of taxis in reinforced random walks. *SIAM J. Appl. Math.* **57**, 1044–1081.

OWEN, M.R., SHERRATT, J.A. (1999). Mathematical modeling of macrophage dynamics in tumors. *Math. Models Methods Appl. Sci.* **9**, 513–539.

SIMON, J. (1987). Compact sets in the space $L^p((0,T),B)$. *Ann. Mat. Pura Appl.* **CXLVI**, 65–96.

SLEEMAN, B.D. (1996). Solid tumor growth: A case study in mathematical biology. In: Aston, Ph.J. (ed.), *Nonlinear Mathematics and its Applications* (Cambridge Univ. Press, Cambridge), pp. 237–254.

SHOWALTER, R.E. (1996). *Monotone Operator in Banach Space and Nonlinear Equations* (Amer. Math. Soc., Philadelphia).

SHYMKO, R.M., GLASS, L. (1976). Cellular and geometric control of tissue growth and mitotic instability. *J. Theoret. Biol.* **63**, 355–374.

SWAM, G. (1984). *Applications of Optimal Control Theory in Biomedicine* (Dekker, New York).

THOMPSON, K.E., BYRNE, H.M. (1999). Modelling the internalisation of labelled cells in tumour spheroids. *Bull. Math. Biol.* **61**, 601–623.

VALENCIANO, J., CHAPLAIN, M.A.J. (2003a). Computing highly accurate solutions of a tumour angiogenesis model. *Math. Models Methods Appl. Sci.* **13**, 747–766.

VALENCIANO, J., CHAPLAIN, M.A.J. (2003b). An explicit subparametric spectral element method of lines applied to a tumour angiogenesis system of partial differential equations. Math. Models Methods Appl. Sci., in press.

VRABIE, I.I. (1995). *Compactness Methods for Nonlinear Evolutions*, second ed. (Longman, Essex).

WARD, J.P., KING, J.R. (1998). Mathematical modelling of avascular tumor growth II: Modeling growth saturation. *IMA J. Math. Appl. Med. Biol.* **15**, 1–42.