On a mathematical model for the growth of necrotic tumors in presence of inhibitors

J.I. Díaz[1,2] and J.I. Tello[1]

Abstract

We study a mathematical model for the growth of tumors with two free boundaries: an inner boundary delaying the necrotic zone and the outer boundary delaying the tumor. We take into account the presence of inhibitors and establish the existence and uniqueness of the solution for the model under suitable conditions on the inhibitors interaction and the tumor growth.

1 Introduction

The growth of a tumor is a very complicated phenomenon where many different aspects arise from subcellular scale (gene mutation or secretion of substances) to the body scale (*metastasis*). In the behavior of the tumor cells there appears biological aspects such as *necrosis* (death of cells caused by insufficient level of nutrients), *apoptosis* (natural cell death, it is an intrinsic property of the cell), *mitosis* (birth of cells by cells divisions), diffusion of nutrients and inhibitors and *vascularization* (contribution of nutrients through vessels). We study a simple mathematical model for this process. Previous similar models were considered by Greenspan [10], Byrne and Chaplain [4], Friedman and Reitich [9] and Cui and Friedman [5] [6].The tumor comprised

[1]Departamento de Matemática Aplicada, Universidad Complutense de Madrid, 28040 Madrid.

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a central necrotic core, where the cells die as a result of necrosis, when the concentration of nutrients $\widehat{\sigma}$ (oxygen, glucose, etc.) falls below a critical level σ_n. Then there is an early disintegration of the cells into simpler chemical compounds (mainly water). These substances form a *necrotic* core in the center of the tumor. This necrotic core is covered by a layer, where apoptosis and mitosis occurs. In the study of the internal mechanisms of the tumor growth two unknown free boundaries appear: the outer boundary denoted by $R(t)$ (limiting the tumor) and the inner free boundary denoted by $\rho(t)$ (separating the necrotic core of the remaining part).

We consider the presence of *Growth Inhibitor Factors* (GIFs) as chalones in the same spirit than the pioneering papers by Greenspan [10], [11]. As in any tissue, the cell proliferation is controlled by chemical substances (GIFs) secreted by the cells, which reduce the mitotic activity. Two different kind of inhibitors appear, depending of the phase of the cell cycle stage at which inhibition has been shown. The inhibitor can act before DNA synthesis (as epidermal chalon in Melanoma or granulocyte chalon in Leukemia) or before mitosis (see Attallah [2]). The properties of these chemical inhibitors have been studied in several works (see e.g. Inversen [12], [13]).

The effectiveness of an anticancer drug delivered to the tumor can be compared with therapy designed to administer the drug by diffusion from neighboring tissue.

According to the mass conservation principle, assuming the cell mass density is constant and the tumor is radially symmetric, we obtain that the tumor mass is proportional to its volume $\frac{4}{3}\pi R^3(t)$. The balance between birth and death of the cells is determined by the concentration of nutrients and inhibitors (denoted by $\widehat{\beta}$). Let $\widehat{S}$ be the above balance, then

$$\frac{d}{dt}\left(\frac{4}{3}\pi R^3(t)\right) = \int_{\{|\tilde{x}|<R(t)\}} \widehat{S}(\widehat{\sigma}(\tilde{x},t), \widehat{\beta}(\tilde{x},t))\,d\tilde{x}. \tag{1.1}$$

Depending on the tumor and the GIF, the function $\widehat{S}$ admits different expressions. Greenspan [10] studied the problem in the presence of inhibitors which affects mitosis when its concentration is greater than a critical level $\widetilde{\beta}$. He proposed $\widehat{S}(\widehat{\sigma},\widehat{\beta}) = sH(\widehat{\sigma}-\widetilde{\sigma})H(\widetilde{\beta}-\widehat{\beta})$, where $H(\cdot)$ is the Heaviside function. Byrne and Chaplain [4] study the growth when the inhibitor affects the cell proliferation and proposed $\widehat{S}(\widehat{\sigma},\widehat{\beta}) = s(\widehat{\sigma}-\widetilde{\sigma})(\widetilde{\beta}-\widehat{\beta})$ outside of necrotic region. In absence of inhibitors or when the inhibitor does not affect the mitosis, they take $\widehat{S}(\widehat{\sigma},\widehat{\beta}) = s\widehat{\sigma}(\widehat{\sigma}-\widetilde{\sigma})$. Friedman and Reitich [9] and Cui and Friedman [5] study the asymptotic behavior of the tumor radius with $\widehat{S} = s(\widehat{\sigma}-\widetilde{\sigma})$, where $s\widehat{\sigma}$ is the cell birth-rate and the death-rate is given by $s\widetilde{\sigma}$. The transfer of nutrients to the tumor from ducts occurs when the concentration is less than a certain level σ_B and with a rate r_1 (we assume a similar structure on the inhibitor absorption, for some $r_2 \geq 0$). The nutrient consumption rate is $\lambda_1\widehat{\sigma}$. Both processes occur simultaneously in the exterior of the necrotic core. We assume that the tumor is situated in an homogenous tissue and that the diffusion coefficient of nutrients is d_1. We also assume constant diffusion coefficient for the inhibitor concentration $\widehat{\beta}$, d_2. The interaction between nutrients and inhibitors is modeled by some continuous functions $\widehat{g}_i(\widehat{\sigma},\widehat{\beta})$. We assume we can intervene in the production of inhibitors through external localized action $\tilde{f}$ in a small region ω_0 in the inner of the tumor. Adding initial and boundary conditions we obtain

$$\begin{cases} \frac{\partial\widehat{\sigma}}{\partial t} \in d_1\Delta\widehat{\sigma} r_1((\sigma_B-\widehat{\sigma})-\lambda_1\widehat{\sigma})H(\widehat{\sigma}-\sigma_n)+\widehat{g}_1(\widehat{\sigma},\widehat{\beta}), & |\tilde{x}|<R(t),\\ \frac{\partial\widehat{\beta}}{\partial t} \in d_2\Delta\widehat{\beta} - r_2\widehat{\beta}+\widehat{g}_2(\widehat{\sigma},\widehat{\beta})+\tilde{f}\chi_{\omega_0}, & |\tilde{x}|<R(t),\\ R(t)^2\frac{dR(t)}{dt} = \int_{|\tilde{x}|<R(t)} \widehat{S}(\widehat{\sigma},\widehat{\beta})d\tilde{x}, & 0<t<T,\\ \widehat{\sigma}(\tilde{x},t) = \overline{\overline{\sigma}},\ \widehat{\beta}(\tilde{x},t)=\overline{\overline{\beta}}, & |\tilde{x}|=R(t),\\ R(0)=R_0,\ \widehat{\sigma}(\tilde{x},0)=\sigma_0(\tilde{x}),\ \widehat{\beta}(\tilde{x},0)=\beta_0(\tilde{x}), & |\tilde{x}|<R_0. \end{cases} \tag{1.2}$$

In this formulation H is the maximal monotone graph of $I\!R^2$ associated to the Heaviside function, i.e. $H(r)=0$ if $r<0$, $H(r)=1$ if $r>0$ and $H(0)=[0,1]$. This is the reason for the symbol $\in$ instead of the equality (a precise notion of weak solution will be presented later). The reason to choose H in the frame work of possible multivalued maximal monotone graphs and not just the standard (singlevalued discontinous) Heaviside function comes from the correct mathematical treatment for the existence of solutions. Some counter examples for similar problems, when the standard Heaviside function is used, can be found already in the classical book K. Yosida [17] p.445. When the level of nutrients falls below the critical level σ_n, cells can not live; this is the phenomenon called *necrosis.* $\overline{\overline{\sigma}}$ and $\overline{\overline{\beta}}$ are the concentration of nutrients and inhibitors at the exterior of the tumor. The diffusion operator Δ is the Laplacian operator and χ_{ω_0} is 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). The main difference between

(1.2) and previous models is the presence of the external localized action of inhibitors $\tilde{f}$.

Notice that the above formulation has a global nature and that the inner free boundary $\rho(t)$ is defined implicitly as the boundary of the set $\{r \in [0, R(t)) : \widehat{\sigma} \leq \sigma_n\}$. So if for instance, the initial datum σ_0 satisfies that $\sigma_0(\tilde{x}) = \sigma_n$ on $[0, \rho_0]$ for some $\rho_0 > 0$ and $\widehat{g}_1(\sigma_n, \widehat{\beta}) \in [0, r_1(\sigma_B - \sigma_n) - \lambda_1 \sigma_n]$ for any $\widehat{\beta} \geq 0$ then the above formulation leads to the associate double free boundary formulation in which $\widehat{\sigma}$ satisfies

$$\begin{cases} \frac{\partial \widehat{\sigma}}{\partial t} - d_1 \Delta \widehat{\sigma} + \lambda_1 \widehat{\sigma} = r_1(\sigma_B - \widehat{\sigma}) + \widehat{g}_1(\widehat{\sigma}, \widehat{\beta}) & \rho(t) < |\tilde{x}| < R(t), \\ \widehat{\sigma}(\tilde{x}, t) = \sigma_n & |\tilde{x}| \leq \rho(t), \\ \widehat{\sigma}(\tilde{x}, t) = \overline{\overline{\sigma}} & |\tilde{x}| = R(t), \\ R(0) = R_0, \ \rho(0) = \rho_0, \ \widehat{\sigma}(\tilde{x}, 0) = \sigma_0(\tilde{x}) & \rho_0 < |\tilde{x}| < R_0. \end{cases}$$

The content of the rest of the paper is the following: after introducing the structural assumptions on $\widehat{g}_i$ and $\widehat{S}$, some functional spaces and a useful change of variables, the existence of solutions of the global formulation (1.2) is proved in Section 2 by means of an iterative method. Section 3 is devoted to the question of the uniqueness of solutions. Some additional assumptions on the data are required (we send the reader to Díaz and L. Tello [8] for a related model leading to special formulations of (1.2) for which there are multiple solutions). The uniqueness of a weak solution to (1.2) is established here for radially symmetric solutions under some additional assumptions on $\widehat{S}$ when $f = 0$ and $\widehat{g}_1 = \widehat{g}_2 = 0$. Finally, some numerical experiences are reported and discussed in an appendix.

We mention that the study of the approximate controllability problem is considered in Díaz and Tello [7], where f is understood as a local control and the goal is to made the final nutrient concentration $\widehat{\sigma}(\tilde{x}, T)$ as closed as desired (in a suitable sense) to a given profile $\widehat{\sigma}_d(\tilde{x})$.

2 Existence of solutions

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

$$|\widehat{g}_i(a, b)| \leq c_0 + c_1(|a| + |b|) \tag{2.1}$$

and

$$-\lambda_0 \le \widehat{S}(a,b) \le c_0 + c_1(|a|^2 + |b|^2) \tag{2.2}$$

for some positives constants λ_0, c_0 and c_1. We also assume that $\widehat{S}$ and $\widehat{g}_i$ are piecewise continuous functions. The above assumptions ((2.1) and (2.2)) are not biological restrictions and previous models (see [4], [5], [6], [9] and [10]) satisfy them provided σ and β are bounded. They are introduced in order to carry out the mathematical treatment and its great generality allows to handle all the special cases mentioned on the previous literature: 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 approches would be needed in order to prove that the models admits a solution (in some very delicated sense).

We introduce the variables

$$x = (x_1, x_2, x_3) = \frac{\tilde{x}}{R(t)}, \tag{2.3}$$

$$u(x,t) = \widehat{\sigma}(R(t)x, t) - \overline{\overline{\sigma}} \tag{2.4}$$

and

$$v(x,t) = \widehat{\beta}(R(t)x, t) - \overline{\overline{\beta}}. \tag{2.5}$$

The unit ball $\{x \in I\!R^3, |x| < 1\}$ is denoted by B and we define the (multivalued) functions from $I\!R^2$ into $2^{I\!R^2}$ by

$$\begin{cases} g_1(\widehat{\sigma} - \overline{\overline{\sigma}}, \widehat{\beta} - \overline{\overline{\beta}}) := r_1((\sigma_B - \widehat{\sigma}) - \lambda_1\widehat{\sigma} - \widehat{\beta})H(\widehat{\sigma} - \sigma_n) + \widehat{g}_1(\widehat{\sigma}, \widehat{\beta}), \\ g_2(\widehat{\sigma} - \overline{\overline{\sigma}}, \widehat{\beta} - \overline{\overline{\beta}}) := -r_2\widehat{\beta} + \widehat{g}_2(\widehat{\sigma}, \widehat{\beta}), \end{cases} \tag{2.6}$$

$$S(\widehat{\sigma} - \overline{\overline{\sigma}}, \widehat{\beta} - \overline{\overline{\beta}}) := \frac{4}{3\pi}\widehat{S}(\widehat{\sigma}, \widehat{\beta}) \tag{2.7}$$

and

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

Problem (1.2) becomes

$$\begin{cases} \frac{\partial u}{\partial t} - \frac{d_1}{R(t)^2}\Delta u - \frac{R'(t)}{R(t)} x \cdot \nabla u \in g_1(u,v), & x \in B \ t > 0, \\ \frac{\partial v}{\partial t} - \frac{d_2}{R(t)^2}\Delta v - \frac{R'(t)}{R(t)} x \cdot \nabla v \in g_2(u,v) + f\chi_{\tilde{\omega}_0^t}, & x \in B \ t > 0, \\ R(t)^{-1}\frac{dR(t)}{dt} = \int_B S(u,v)dx, & t > 0, \\ u(x,t) = \ v(x,t) = 0, & x \in \partial B \ t > 0, \\ R(0) = R_0, \ u(x,0) = u_0(x), \ v(x,0) = v_0(x), & x \in B. \end{cases} \tag{2.8}$$

We introduce the Hilbert spaces

$$\mathbf{H}(B) := L^2(B)^2,$$

$$\mathbf{V}(B) := \{\Phi = (\Phi_1, \Phi_2) \in H(B), \ \nabla\Phi \in (H(B))^3, \Phi_1 = \Phi_2 = 0 \text{ on } \partial B\},$$
$$\mathbf{V}(B) = H_0^1(B)^2,$$

with inner products given by

$$< \Phi, \Psi >_{\mathbf{H}(B)} = \int_B \Phi(x) \cdot \Psi(x) dx, \qquad \forall \Phi, \Psi \in \mathbf{H}(B),$$

and

$$< \Phi, \Psi >_{\mathbf{V}(B)} = \sum_{i=1,2} d_i \int_B \nabla\Phi_i \cdot \nabla\Psi_i dx, \qquad \forall \Phi, \Psi \in \mathbf{V}(B).$$

For the sake of simplicity in the notation we use $\mathbf{H} = \mathbf{H}(B)$ and $\mathbf{V} = \mathbf{V}(B)$. Given $T > 0$, we introduce $\mathbf{U} = (u, v)$, $\mathbf{U}_0 = (u_0, v_0)$, $\mathbf{G} : I\!R^2 \longrightarrow 2^{I\!R} \times 2^{I\!R}$ and $\mathbf{F} : (0,T) \times B \longrightarrow I\!R$ given by

$$\mathbf{G}(\mathbf{U}) = \mathbf{G}(u, v) = (g_1(u, v), g_2(u, v)),$$

$$\mathbf{F}(t, x) = (0, f(t, x)\chi_{\tilde{\omega}_0^t}).$$

Definition 2.1 $(\mathbf{U}, R) \in L^2(0, T : \mathbf{V}) \times W^{1,\infty}(0, T : I\!R)$ *is a weak solution of the problem (2.8) if there exists* $\mathbf{g}^* = (g_1^*, g_2^*) \in L^2(0, T : \mathbf{H})$ *with* $\mathbf{g}^*(x, t) \in \mathbf{G}(\mathbf{U}(x, t))$ *a.e.* $(x, t) \in B \times (0, T)$ *and*

$$-\int_0^T < \mathbf{U}, \frac{\partial\Phi}{\partial t} >_{\mathbf{H}} dt + \int_0^T \mathfrak{a}(R(t), \mathbf{U}, \Phi) dt = \int_0^T < \mathbf{g}^*, \Phi >_{\mathbf{H}} dt +$$

$$< \mathbf{U}_0(\cdot), \Phi(0,\cdot) >_{\mathbf{H}} + \int_0^T < \mathbf{F}(t), \Phi >_{\mathbf{H}} dt,$$

$\forall\ \Phi \in C^1([0,T] \times B)$ with $\Phi(T,\cdot) = 0$, where

$$\mathfrak{a}(R(t), \mathbf{U}, \Phi) := \frac{1}{R^2(t)} < \mathbf{U}, \Phi >_{\mathbf{V}} - \frac{R'(t)}{R(t)} < x \cdot \nabla \mathbf{U}, \Phi >_{\mathbf{H}} \tag{2.9}$$

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

$$R(t)^{-1} \frac{dR(t)}{dt} = \int_B S(\mathbf{U}(x,t))dx, \text{ for any } t > 0.$$

Definition 2.2 *(σ, β, R) is a weak solution of (1.2) if*

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

for $t > 0$ and $\tilde{x} \in I\!R^3, |\tilde{x}| \leq R(t)$, where $(\mathbf{U} = (u,v), R)$ is the weak solution of (2.8) for any $T > 0$.

Remark 2.1 *We point out that from the definition of weak solution and the structural assumptions on $\mathbf{G}$ we conclude that $\frac{\partial \mathbf{U}}{\partial t} \in L^2(0, T : \mathbf{V}(B)')$ and the equation holds in $D'(B \times (0,T))$.*

Theorem 2.1 *Assuming (2.1), (2.2), $R_0 > 0$ and $\sigma_0,\ \beta_0 \in L^2(0, R_0)$ then problem (1.2) has at least a weak solution for any $T > 0$.*

We shall use an iterative method for the construction of a weak solution of (2.8).

Proof. Let $R(t) \in W^{1,\infty}(0, T : I\!R)$ such that $\frac{R'(t)}{R(t)} \geq -\lambda_0$ 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

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

Without any difficulty we can see that $\mathbf{A}$ defines a continuous bilinear form on $\mathbf{V} \times \mathbf{V}$

$$\mathfrak{a}(t : \cdot, \cdot) : \mathbf{V} \times \mathbf{V} \longrightarrow I\!R,$$

for a.e. $t \in (0,T)$, by (2.9). Since $\frac{R'(t)}{R(t)} \geq -\lambda_0$, $\mathfrak{a}(t,\cdot,\cdot)$ satisfies

$$\mathfrak{a}(t,\mathbf{U},\mathbf{U}) = \frac{1}{R^2(t)} < \mathbf{U},\mathbf{U} >_{\mathbf{V}} - \frac{R'(t)}{R(t)} < x\cdot\nabla\mathbf{U},\mathbf{U} >_{\mathbf{H}} =$$

$$\frac{1}{R^2(t)} < \mathbf{U},\mathbf{U} >_{\mathbf{V}} + \frac{R'(t)}{2R(t)} < \mathbf{U},\mathbf{U} >_{\mathbf{H}} \geq (\max_{0<t<T}\{R(t)\})^{-2}\|\mathbf{U}\|^2_{\mathbf{V}} - \frac{\lambda_0}{2}\|\mathbf{U}\|_{\mathbf{H}}.$$

Now, we can write $\mathbf{G} : I\!R^2 \longrightarrow 2^{I\!R} \times 2^{I\!R}$ as

$$\mathbf{G}(\mathbf{U}) = \mathbf{G}_1(\mathbf{U})\mathbf{U} + \mathbf{G}_0(\mathbf{U}),$$

where $\mathbf{G}_1(\mathbf{U}) \in \mathcal{M}_{2\times 2}$, $\mathbf{G}_0(\mathbf{U}) \in 2^{I\!R} \times 2^{I\!R}$ and the coefficients of $\mathbf{G}_1$ ($\mathfrak{a}_{\mathfrak{ij}}$) are continuous functions from $L^2(0,T:\mathbf{V})$ with the usual topology to $L^2(0,T:\mathbf{V})$ with the weak topology. Notice that $\mathbf{G}_0$ and $\mathbf{G}_1$ are defined by

$$\mathbf{G}_0(\mathbf{U}) = (g_0^1(u,v), g_0^2(u,v)),$$

$$g_0^1(u,v) = (r_1\sigma_B - (r_1+\lambda)(\sigma_n - \overline{\overline{\sigma}}) - \overline{\overline{\beta}})H(u - \sigma_n + \overline{\overline{\sigma}}) - \widehat{g}_1(\overline{\overline{\sigma}},\overline{\overline{\beta}}),$$
$$g_0^2(u,v) = -r_2\overline{\overline{\beta}} - \widehat{g}_2(\overline{\overline{\sigma}},\overline{\overline{\beta}}),$$

and

$$\mathbf{G}_1(\mathbf{U}) = \begin{pmatrix} \mathfrak{a}_{11} & \mathfrak{a}_{12} \\ \mathfrak{a}_{21} & \mathfrak{a}_{22} \end{pmatrix},$$

where

$$\mathfrak{a}_{11} = (r_1+\lambda)H(u-\sigma_n+\overline{\overline{\sigma}}) - \frac{\widehat{g}_1(u+\overline{\overline{\sigma}}, v+\overline{\overline{\beta}}) - \widehat{g}_1(\overline{\overline{\sigma}},\overline{\overline{\beta}})}{|u|+|v|}\mathrm{sign}_0(u),$$

$$\mathfrak{a}_{12} = -H(u-\sigma_n+\overline{\overline{\sigma}}) - \frac{\widehat{g}_1(u+\overline{\overline{\sigma}}, v+\overline{\overline{\beta}}) - \widehat{g}_1(\overline{\overline{\sigma}},\overline{\overline{\beta}})}{|u|+|v|}\mathrm{sign}_0(v),$$

$$\mathfrak{a}_{21} = -\frac{\widehat{g}_2(u+\overline{\overline{\sigma}}, v+\overline{\overline{\beta}}) - \widehat{g}_2(\overline{\overline{\sigma}},\overline{\overline{\beta}})}{|u|+|v|}\mathrm{sign}_0(u),$$

$$\mathfrak{a}_{22} = -r_2 - \frac{\widehat{g}_2(u+\overline{\overline{\sigma}}, v+\overline{\overline{\beta}}) - \widehat{g}_1(\overline{\overline{\sigma}},\overline{\overline{\beta}})}{|u|+|v|}\mathrm{sign}_0(v)$$

with $\text{sign}_0(w) = -1$ if $w < 0$, 0 if $w = 0$ and 1 if $w > 0$. Furthermore, since $\widehat{g}_i$ has a sublinear growth, we obtain

$$|\mathfrak{a}_{ij}| \leq C. \tag{2.10}$$

We construct the sequence $(\mathbf{U}_n, R_n)$, where R_n is given by

$$R_n(t) = R_0 exp\{\int_0^t \int_B S(\mathbf{U}_{n-1}(x,s))dxds\}, \tag{2.11}$$

and $\mathbf{U}_n \in L^2(0,T : \mathbf{V})$ is the unique weak solution of

$$\begin{cases} \frac{\partial \mathbf{U}_n}{\partial t} + \mathbf{A}(R_{n-1}(t))\mathbf{U}_n + \mathbf{g}^*_{1,n-1}\mathbf{U}_n = \mathbf{g}^*_{0,n-1} + \mathbf{F}, \quad \text{in } (0,T), \\ \\ \mathbf{U}_n(\cdot, 0) = \mathbf{U}_0(\cdot) \end{cases} \tag{2.12}$$

where $\mathbf{g}^*_{0,n-1}(x,t) \in \mathbf{G}_0(\mathbf{U}_{n-1}(x,t))$ for a.e. $(x,t) \in B \times (0,T)$. $\mathbf{g}^*_{0,n-1} \in L^2((0,T) \times B)^2$ is a selection of $\mathbf{G}_0(\mathbf{h})$ (for instance, the element on minimal norm of the set $\mathbf{G}_0(\mathbf{U}_{n-1})$ and starting with $\mathbf{g}^*_{0,0} \in \mathbf{G}_0(\mathbf{U}_0)$). In the same way $\mathbf{g}^*_{1,n-1}$ belongs to $\mathbf{G}_1(\mathbf{U}_{n-1})$. Notice that, by (2.2), $R_n(t) \geq R_0 e^{-\lambda_0 T}$ $\forall\, t \in (0,T)$ and $R'_n(t) \geq -\lambda_0 R_0 e^{-\lambda_0 T}$ for all $n \in I\!N$. The operator $\mathbf{A}(R_n(t)) + \mathbf{G}_1(\mathbf{U}_{n-1})$ is defined, as usual, through the bilinear form

$$a_n(t, \mathbf{U}, \mathbf{W}) = \mathfrak{a}(R_{n-1}(t), \mathbf{U}, \mathbf{W}) + < \mathbf{G}_1(\mathbf{U}_{n-1})\mathbf{U}, \mathbf{W} >_{\mathbf{H}} .$$

By (2.10) and definition of $\mathfrak{a}$, it results

$$a_n(t, \mathbf{U}, \mathbf{U}) \geq C\|\mathbf{U}\|^2_{\mathbf{V}} - \lambda_1 \|U\|^2_{\mathbf{H}}$$

for $\lambda_1 = C(\mathbf{G}_1) + \lambda_0$, where $C(\mathbf{G}_1)$ depends of the constant C defined in (2.10). Since $\mathbf{F} + \mathbf{g}^*_{0,n-1} \in (L^2((0,T) \times B))^2$ there exists a unique weak solution of problem (2.12) (see, for instance, Showalter [14]). Now taking $\mathbf{U}_n$ as test function in the weak formulation of (2.12) we obtain

$$\frac{d}{dt}\int_B \frac{1}{2}\mathbf{U}^2_n dx + \mathfrak{a}(R_{n-1}(t), \mathbf{U}_n, \mathbf{U}_n) + \int_B \mathbf{g}^*_{1,n-1}\mathbf{U}_n \cdot \mathbf{U}_n dx =$$

$$\int_B (\mathbf{g}^*_{0,n-1} + \mathbf{F}) \cdot \mathbf{U}_n dx$$

for some $\mathbf{g}^*_{i,n-1} \in L^2((0,T)\times B)^2$ with $\mathbf{g}^*_{i,n-1}(x,t) \in \mathbf{G}_i(\mathbf{U}_{n-1}(x,t))$ for a.e. $(x,t) \in B \times (0,T)$ and $i = 0,1$. By definition of $\mathfrak{a}$ it results

$$\frac{1}{2}\frac{d}{dt}||\mathbf{U}_n||^2_{\mathbf{H}} - \lambda_1||\mathbf{U}_n||^2_{\mathbf{H}} \leq (||\mathbf{g}_{0,n-1} + \mathbf{F}||_{\mathbf{H}})||\mathbf{U}_n||_{\mathbf{H}}. \tag{2.13}$$

By Young inequality we obtain

$$\frac{1}{2}\frac{d}{dt}||\mathbf{U}_n||^2_{\mathbf{H}} - (\lambda_1 + \frac{1}{2})||\mathbf{U}_n||^2_{\mathbf{H}} \leq \frac{1}{2}||\mathbf{g}_{0,n-1} + \mathbf{F}||^2_{\mathbf{H}}.$$

Integrating in time, we obtain

$$\frac{1}{2}||\mathbf{U}_n||^2_{\mathbf{H}} - \frac{1}{2}||\mathbf{U}_0||^2_{\mathbf{H}} - (\lambda_1 + \frac{1}{2})||\mathbf{U}_n||^2_{L^2(0,T:\mathbf{H})} \leq \frac{1}{2}||\mathbf{g}_{0,n-1} + \mathbf{F}||^2_{L^2(0,T:\mathbf{H})},$$

applying Gronwall's lemma it results

$$||\mathbf{U}_n||^2_{\mathbf{H}} \leq T exp\{(\lambda_1 + \frac{1}{2})T\}||\mathbf{g}^*_{0,n-1} + \mathbf{F}\|^2_{L^2(0,T:\mathbf{H})} + ||\mathbf{U}_0||^2_{\mathbf{H}} \leq C. \tag{2.14}$$

Since $\mathbf{U}_n$ is uniformly bounded in $\mathbf{H}$ (by (2.2)) we obtain

$$R_n(t) = R_0 exp\{\int_0^t \int_0^1 S(\mathbf{U}_{n-1})dxdt\} \leq R_0 e^{K_1 t}. \tag{2.15}$$

Since $\mathbf{U}_{n-1} \in L^\infty(0,T:\mathbf{H})$ we get $R_n \in W^{1,\infty}(0,T)$. Taking $\mathbf{U}_n$ as test function in (2.12) it results

$$\frac{D}{R_0^2 e^{2K_1 T}}\|\mathbf{U}_n\|^2_{L^2(0,T:\mathbf{V})} - \lambda_1\|\mathbf{U}_n\|^2_{L^2(0,T:\mathbf{H})} \leq$$

$$\leq C(\mathbf{G}_0)\|\mathbf{U}_n\|_{L^2(0,T:\mathbf{H})} + \|\mathbf{F}\|_{L^2(0,T:\mathbf{H})}\|\mathbf{U}_n\|_{L^2(0,T:\mathbf{H})}.$$

By (2.14) we get

$$\|\mathbf{U}_n\|_{L^2(0,T:V)} \leq K(T, \mathbf{F}, \mathbf{G}_0, \mathbf{G}_1). \tag{2.16}$$

Since $A(R_{n-1}(t))\mathbf{U}_n \in L^2(0,T:\mathbf{V}')$, by (2.16) and (2.15) we obtain that $\frac{d}{dt}\mathbf{U}_n$ is uniformly bounded in $L^2(0,T:\mathbf{V}')$. So there exists a subsequence $\mathbf{U}_n \in L^2(0,T:\mathbf{V})$ with $\frac{d}{dt}\mathbf{U}_n \in L^2(0,T:\mathbf{V}')$ such that

$$(\mathbf{U}_n, \frac{d}{dt}\mathbf{U}_n) \rightharpoonup (\mathbf{U}, \frac{d}{dt}\mathbf{U}) \text{ weakly in } L^2(0,T:\mathbf{V}) \times L^2(0,T:\mathbf{V}').$$

Using the compact embedding (see e.g. Simon [15]) it results

$$\mathbf{U}_n \to \mathbf{U} \text{ strongly in } L^2(0,T:\mathbf{H}).$$

From continuity of S and $\mathbf{G}$ from the strong to the weak topology (see Lemma 3.4.1 of Vrabie [16]) we obtain

$$\mathbf{G}(\mathbf{U}_{n-1}) \rightharpoonup \mathbf{g}^* \text{ weakly in } L^2(0,T:\mathbf{H})$$

with $\mathbf{g}^* = \mathbf{G}_1(\mathbf{U})\mathbf{U} + \mathbf{g}_0^*$, $\mathbf{g}_0^*(x,t) \in \mathbf{G}_0(\mathbf{U}(x,t))$ for a.e. $(x,t) \in B \times (0,T)$ and

$$\mathbf{S}(\mathbf{U}_{n-1}) \rightharpoonup \mathbf{S}(\mathbf{U}) \text{ weakly in } L^2(0,T:\mathbf{H}).$$

Since $|R'| \leq C$ there exists a subsequence R_{ni} such that

$$R_{ni} \rightharpoonup R \text{ in } W^{1,p}(0,T),\ p < \infty.$$

By (2.11) we deduce that $R_n \longrightarrow R$ in $C^0([0,T])$. Finally, passing to the limit in the weak formulation of the problem (2.12) we get

$$-\int_0^T < \mathbf{U}, \frac{\partial \Phi}{\partial t} >_{\mathbf{H}} dt + \int_0^T \mathfrak{a}(R(t), \mathbf{U}, \Phi) dt + \int_0^T < \mathbf{g_1^*}\mathbf{U}, \Phi >_{\mathbf{H}} dt =$$

$$< \mathbf{U}_0, \Phi(0,\cdot) >_{\mathbf{H}} + \int_0^T < \mathbf{g}_0^*, \Phi >_{\mathbf{H}} dt + \int_0^T < \mathbf{F}, \Phi >_{\mathbf{H}} dt$$

for all $\Phi \in C^1([0,T] \times B)$ with $\Phi(T,\cdot) = 0$ and moreover

$$R(t)^{-1} \frac{dR(t)}{dt} = \int_B S(\mathbf{U}(x,t)) dx.$$

Note that

$$\int_0^T \frac{R_n'}{R_n} \int_B x \cdot \nabla \mathbf{U}_n \Phi dx dt = -\int_0^T \frac{R_n'}{R_n} \int_B \mathbf{U}_n \Phi dx dt - \int_0^T \frac{R_n'}{R_n} \int_B \mathbf{U}_n \cdot \nabla \Phi dx dt$$

which converges to the limit integral.

We conclude that $(\mathbf{U}, R)$ is a weak solution of the problem (2.8) and consequently (σ, β, R) defined by

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

is a weak solution of problem (1.2). The additional regularity

$$\widehat{\sigma}_t - d_1 \Delta \widehat{\sigma} \text{ and } \widehat{\beta}_t - d_2 \Delta \widehat{\beta} \in L^2(\cup_{t \in [0,T]} (0, R(t)) \times \{t\})$$

is consequence of the fact that $\frac{\partial \mathbf{U}}{\partial t}(t) + \mathbf{A}(R(t))\mathbf{U}(t) \in L^2(0,T:L^2(B)^2)$. □

3 Uniqueness of solutions with radial symmetry

In this section we shall prove the uniqueness of radially symmetric weak solutions.

We start by pointing out that if, for instance, $\sigma_n < \frac{r_1\sigma_B - \overline{\overline{\beta}}}{r_1+\lambda}$, $\widehat{g}_1(\widehat{\sigma},\widehat{\beta})$ is independent of $\widehat{\beta}$ and the initial datum $\sigma_0(\tilde{x})$ satisfies $\sigma_0'(\rho_0) = \sigma_0''(\rho_0) = 0$ then it is possible to adapt the arguments of Díaz and L. Tello [8] in order to construct more than one solution of problem (1.2). This and the presence of non-Lipschitz terms at both equations make clear that any possible uniqueness result will require an important set of additional conditions.

Uniqueness of solution for the non necrotic case (i.e. linear functions g_i) was proved in Cui and Friedman [5]. In this section we use a similar idea for the proof of the necrotic case.

Let $(\widehat{\sigma},\widehat{\beta})$ be a solution of problem (1.2). We assume the solution is radially symmetric and define $\sigma = \widehat{\sigma} - \overline{\overline{\sigma}}$, $\beta = \widehat{\beta} - \overline{\overline{\beta}}$ and $r = |x|$. Then (σ,β) verifies

$$\begin{cases} \frac{\partial\sigma}{\partial t} - \frac{d_1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial}{\partial r}\sigma) \in g_1(\sigma,\beta), & 0<r<R(t)\ 0<t<T, \\ \frac{\partial\beta}{\partial t} - \frac{d_2}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial}{\partial r}\beta) \in g_2(\sigma,\beta), & 0<r<R(t)\ 0<t<T, \\ R(t)^2\frac{dR(t)}{dt} = \int_0^{R(t)} S(\sigma,\beta)r^2dr, & 0<t<T, \\ \frac{\partial\sigma}{\partial r}(0,t)=0,\ \frac{\partial\beta}{\partial r}(0,t)=0, & 0<t<T, \\ \sigma(R(t),t)=0,\ \beta(R(t),t)=0, & 0<t<T, \\ R(0)=R_0, & \\ \sigma(r,0)=\sigma_0(r),\ \beta(r,0)=\beta_0(r), & 0<r<R_0, \end{cases} \tag{3.1}$$

where g_i are given by

$$g_1(\sigma,\beta) = -[(r_1+\lambda)(\sigma+\overline{\overline{\sigma}}) - r_1\sigma_B + (\beta+\overline{\overline{\beta}})]H(\sigma+\overline{\overline{\sigma}}-\sigma_n) \tag{3.2}$$

$$g_2(\sigma,\beta) = -r_2(\beta+\overline{\overline{\beta}}). \tag{3.3}$$

We will assume throw this section that

$$S(\sigma,\beta) \in W^{1,\infty}_{loc}(I\!R^2), \tag{3.4}$$

$$S \text{ is an increasing function in } \sigma \text{ and decreasing in } \beta \tag{3.5}$$

$$\sigma_n \geq \frac{r_1\sigma_B - \overline{\overline{\beta}}}{r_1+\lambda} \tag{3.6}$$

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

$$\frac{\partial \sigma_0}{\partial r}(0,t) = 0,\ \frac{\partial \beta}{\partial r}(0,t) = 0 \qquad 0 < t < T, \tag{3.7}$$

$$\sigma(R(t),t) = 0,\ \beta(R(t),t) = 0 \qquad 0 < t < T. \tag{3.8}$$

Theorem 3.1 *There is, at most, one solution to (3.1).*

Let us introduce the functions

$$T_0(s) = \begin{cases} s & \text{if } s \geq 0, \\ 0 & \text{otherwise} \end{cases} \qquad T^0(s) = \begin{cases} s & \text{if } s \leq 0, \\ 0 & \text{otherwise} \end{cases}$$

which we will use in the proof of the theorem.

Lemma 3.1 *Every solution (σ,β) of the problem (3.1) is bounded and satisfies $\sigma_n \leq \sigma \leq \sigma_B$ and $-\overline{\overline{\beta}} \leq \beta \leq \max\{\beta_0\}$ provided $\sigma_n \leq \sigma_0 \leq \sigma_B$ and $-\overline{\overline{\beta}} \leq \beta_0$.*

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 [1] Lemma 1.5) we have

$$\frac{1}{2}\int_0^{R(t)} [T_0(\sigma-\sigma_B)]^2 r^2 dr \leq \int_0^t \int_0^{R(s)} g_1(\sigma,\beta) T_0(\sigma-\sigma_B) r^2 dr ds.$$

Since

$$-[(r_1+\lambda)(\sigma+\overline{\overline{\sigma}})-r_1\sigma_B+(\beta+\overline{\overline{\beta}})]H(\sigma+\overline{\overline{\sigma}}-\sigma_n)T_0(\sigma-\sigma_B)=$$

$$-(r_1+\lambda)T_0(\sigma-\sigma_B)^2-[(r_1+\lambda)(\sigma_B+\overline{\overline{\sigma}})-r_1\sigma_B+(\beta-\overline{\overline{\beta}})]T_0(\sigma-\sigma_B)\le$$

$$-[(\lambda\sigma_B+(r_1+\lambda)\overline{\overline{\sigma}}+(\beta+\overline{\overline{\beta}})]T_0(\sigma-\sigma_B)\le$$

$$T^0(\beta+\overline{\overline{\beta}})T_0(\sigma-\sigma_B)\le\frac{1}{2}([T^0(\beta+\overline{\overline{\beta}})]^2+[T_0(\sigma-\sigma_B)]^2)$$

we obtain

$$\int_0^{R(t)}T_0(\sigma-\sigma_B)^2r^2dr\le\int_0^t\int_0^{R(s)}[T^0(\beta+\overline{\overline{\beta}})^2+T_0(\sigma-\sigma_B)^2]r^2drds. \tag{3.9}$$

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

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

it results

$$\int_0^{R(t)}[T^0(\beta+\overline{\overline{\beta}})]^2r^2dr\le\int_0^t\int_0^{R(s)}r_2T^0(\beta+\overline{\overline{\beta}})r^2drds. \tag{3.10}$$

Adding (3.9) and (3.10) and thanks to Gronwall′s Lemma we obtain

$$\sigma\le\sigma_B \text{ and } \beta\ge-\overline{\overline{\beta}}.$$

Notice that $\beta\ge-\overline{\overline{\beta}}$ implies $\widehat{\beta}\ge 0$.

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

$$\frac{1}{2}\int_0^{R(t)}[T^0(\sigma-\sigma_n-\epsilon)]^2r^2dr\le 0$$

and taking limits as $\epsilon\to 0$ it results

$$\frac{1}{2}\int_0^{R(t)}[T^0(\sigma-\sigma_n)]^2r^2dr\le 0,$$

which proves $\sigma \geq \sigma_n$.

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

$$\frac{\partial \beta}{\partial t} - \frac{d_2}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial}{\partial r}\beta) = -r_2(\beta + \overline{\overline{\beta}}), \qquad 0 < r < R(t), \quad 0 < t < T$$

$$\beta(R(t), t) = 0, \qquad \frac{\partial \beta}{\partial r} = 0 \ \text{ on } \ 0 < t < T.$$

Since $\beta_0 \geq -\overline{\overline{\beta}}$ it results that

$$\frac{\partial \beta}{\partial t} - \frac{d_2}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial}{\partial r}\beta) \leq 0$$

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

Corollary 3.1 *There exists a positive constant M such that $R(t) \leq R_0 e^{Mt}$ and $R'(t) \leq R_0 M e^{MT}$.*

Proof. By the above result $(\sigma(r,t), \beta(r,t)) \in [\sigma_n, \sigma_B] \times [-\overline{\overline{\beta}}, \max\{\beta_0\}]$. Since S is a continuous function it results that it attains its maximum (denoted by $3M$) on that set. Then, we obtain

$$R^2(t)\frac{dR(t)}{dt} \leq \int_0^{R(t)} 3Mr^2 dr.$$

Integrating the above equation it results $\frac{dR(t)}{dt} \leq MR(t)$. Finally, by Gronwall's Lemma we get the conclusion. □

Lemma 3.2 *The solution (σ, β) of (3.1) satisfies*

$$\int_0^T (\|\sigma\|^2_{W^{1,\infty}(\epsilon,R(t))} + \|\beta\|^2_{W^{1,\infty}(\epsilon,R(t))})dt \leq C_1$$

for all $\epsilon > 0$.

Proof. The pair $(u(x,t), v(x,t)) = (\sigma(R(t)|x|,t), \beta(R(t)|x|,t))$ is a solution to (2.8) and so $(u,v) \in [L^2(0,T : H^1(B))]^2$. By (2.3) and

$$\tau(t) = \int_0^t R^{-2}(\rho)d\rho \tag{3.11}$$

we obtain $\tau(t) \in C^1$. By the Implicit Function Theorem there exists the inverse function $t(\tau) \in C^1$ and we deduce that $(u,v) \in L^2(0,T : H^2(B))^2$ (see, e.g., Brezis [3]). From the symmetry of the solution it results that

$$\tilde{u}(|x|,t) := u(x,t) \quad \text{and} \quad \tilde{v}(|x|,t) := v(x,t)$$

belong to $L^2(0,T : H^2(\epsilon_0,1)) \subset L^2(0,T : W^{1,\infty}(\epsilon_0,1))$ for all $\epsilon_0 > 0$. Doing the change of variable $r = R(t)|x|$ we obtain

$$\int_0^T (\|\sigma\|^2_{W^{1,\infty}(\epsilon,R(t))} + \|\beta\|^2_{W^{1,\infty}(\epsilon,R(t))})dt =$$

$$\int_0^T R^2(t)(\|\tilde{u}\|^2_{W^{1,\infty}(\frac{\epsilon}{R(t)},1)} + \|\tilde{v}\|^2_{W^{1,\infty}(\frac{\epsilon}{R(t)},1)})dt \leq$$

$$\int_0^T R^2(t)(\|\tilde{u}\|^2_{W^{1,\infty}(\epsilon_0,1)} + \|\tilde{v}\|^2_{W^{1,\infty}(\epsilon_0,1)})dt \leq C_1$$

and the proof ends. □

Proof of Theorem 3.1. We argue by contradiction and assume (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

$$\begin{cases} \frac{\partial \sigma}{\partial t} - \frac{d_1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial}{\partial r}\sigma) = g_1(\sigma_1,\beta_1) - g_1(\sigma_2,\beta_2) & 0<r<R(t) \; 0<t<T, \\ \frac{\partial \beta}{\partial t} - \frac{d_2}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial}{\partial r}\beta) = g_2(\sigma_1,\beta_1) - g_2(\sigma_2,\beta_2) & 0<r<R(t) \; 0<t<T, \\ \frac{\partial \sigma}{\partial r}(0,t) = 0, \; \frac{\partial \beta}{\partial r}(0,t) = 0 & 0<t<T, \\ \sigma(R(t),t) = \sigma_1(R(t),t) - \sigma_2(R(t),t) & 0<t<T, \\ \beta(R(t),t) = \beta_1(R(t),t) - \beta_2(R(t),t) & 0<t<T, \\ \sigma(r,0) = 0, \; \beta(r,0) = 0 & 0<r<R_0. \end{cases} \tag{3.12}$$

Now we introduce a technical lemma.

Lemma 3.3 *$|\beta|$ takes the maximum on the boundary $R(t)$ and σ satisfies*

$$\int_0^{R(t)} [T_0(\sigma-\sigma^*)]^2 r^2 dr \leq TC[\max_{t\in[0,T]}\{\beta\}]^2$$

where

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

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

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

then

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

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

$$\int_0^{R(t)} [T^0(\beta - \beta_*)]^2 r^2 dr \leq 0$$

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

Let us consider

$$g_1(\sigma_1, \beta_1) - g_1(\sigma_2, \beta_2) = -([(r_1+\lambda)(\sigma_1+\overline{\overline{\sigma}}) - r_1\sigma_B + (\beta_1+\overline{\overline{\beta}})]H(\sigma_1+\overline{\overline{\sigma}}-\sigma_n) -$$

$$[(r_1 + \lambda)(\sigma_2 + \overline{\overline{\sigma}}) - r_1\sigma_B + (\beta_2 + \overline{\overline{\beta}})]H(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n)) =$$

$$-(r_1 + \lambda)[(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n)H(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n) - (\sigma_2 + \overline{\overline{\sigma}} - \sigma_n)H(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n)] +$$

$$(-(r_1 + \lambda)\sigma_n + r_1\sigma_B - \overline{\overline{\beta}})(H(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n) - H(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n)) -$$

$$[\beta_1 H(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n) - \beta_2 H(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n)].$$

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

$$-[(\sigma_1+\overline{\overline{\sigma}}-\sigma_n)H(\sigma_1+\overline{\overline{\sigma}}-\sigma_n)-(\sigma_2+\overline{\overline{\sigma}}-\sigma_n)H(\sigma_2+\overline{\overline{\sigma}}-\sigma_n)]T_0(\sigma_1-\sigma_2-\sigma^*) \leq 0.$$

Since $-(r_1 + \lambda)\sigma_n + r_1\sigma_B - \overline{\overline{\beta}} \leq 0$ it results

$$(-(r_1+\lambda)\sigma_n+r_1\sigma_B-\overline{\overline{\beta}})(H(\sigma_1+\overline{\overline{\sigma}}-\sigma_n)-H(\sigma_2+\overline{\overline{\sigma}}-\sigma_n))T_0(\sigma_1-\sigma_2-\sigma^*) \leq 0.$$

Then

$$[g_1(\sigma_1, \beta_1) - g_1(\sigma_2, \beta_2)]T_0(\sigma_1 - \sigma_2 - \sigma^*) \leq$$

$$-[\beta_1 H(\sigma_1 + \overline{\overline{\sigma}} - \sigma_n) - \beta_2 H(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n)]T_0(\sigma_1 - \sigma_2 - \sigma^*) \leq$$

$$-(\beta_1 - \beta_2)H(\sigma_2 + \overline{\overline{\sigma}} - \sigma_n)T_0(\sigma_1 - \sigma_2 - \sigma^*) \leq$$

$$-T^0(\beta_1 - \beta_2)T_0(\sigma_1 - \sigma_2 - \sigma^*) \leq -\beta_* T_0(\sigma_1 - \sigma_2 - \sigma^*).$$

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

$$\int_0^{R(t)}[T_0(\sigma-\sigma^*)]^2r^2dr+\int_0^t\int_0^{R(s)}[\frac{\partial}{\partial r}T_0(\sigma-\sigma^*)]^2r^2drds=$$

$$\int_0^t\int_0^{R(s)}(g_1(\sigma_1,\beta_1)-g_1(\sigma_2,\beta_2))T_0(\sigma-\sigma^*)r^2drds\leq$$

$$-\int_0^t\int_0^{R(s)}\beta_*T_0(\sigma-\sigma^*)r^2drds\leq$$

$$\frac{T\tilde{C}}{\lambda}\beta_*^2+\lambda\int_0^t\int_0^{R(s)}[T_0(\sigma_1-\sigma_2-\sigma^*)]^2r^2drds$$

and we choose λ such that

$$\lambda\int_0^{R(s)}[T_0(\sigma_1-\sigma_2-\sigma^*)]^2r^2dr-\int_0^{R(s)}[\frac{\partial}{\partial r}T_0(\sigma-\sigma^*)]^2r^2dr\leq 0 \text{ a.e. } t\in(0,T).$$

Then, it results

$$\int_0^{R(t)}[T_0(\sigma-\sigma^*)]^2r^2dr\leq TC\beta_*^2$$

which end the proof. □

End of the proof of Theorem 3.1. Let

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

We get that

$$R_1^2(t)R_1'(t)-R_2^2(t)R_2'(t)=\int_0^{R(t)}(S(\sigma_1,\beta_1)-S(\sigma_2,\beta_2))r^2dr+$$

$$\int_{R(t)}^{R_1(t)}S(\sigma_1,\beta_1)r^2dr-\int_{R(t)}^{R_2(t)}S(\sigma_2,\beta_2)r^2dr. \tag{3.13}$$

By (3.5) and Lemma 3.1 we obtain that

$$|\int_{R(t)}^{R_i(t)}S(\sigma_i,\beta_i)r^2dr|\leq M\delta \text{ (for } i=1,2) \tag{3.14}$$

where

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

By (3.4) and (3.5) we get

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

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

$$\int_0^{R(t)} (S(\sigma_1,\beta_1) - S(\sigma_2,\beta_2))r^2 dr \leq C \int_0^{R(t)} (T_0(\sigma-\sigma^*) + \sigma^* - \beta_*)r^2 dr \leq$$

$$C'([\int_0^{R(t)} T_0(\sigma-\sigma^*)^2 r^2 dr]^{\frac{1}{2}} + \sigma^* - \beta_*).$$

By Lemma 3.3 it results

$$C'([\int_0^{R(t)} T_0(\sigma-\sigma^*)^2 r^2 dr]^{\frac{1}{2}} + \sigma^* - \beta_*) \leq C''(\sigma^* - (T+1)\beta_*).$$

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

$$|\sigma(R(t),t)| \leq (\sum_{i=1,2} \|\sigma_i\|_{W^{1,\infty}(R(t),R_i(t))})|R_1(t) - R_2(t)|,$$

$$|\beta(R(t),t)| \leq (\sum_{i=1,2} \|\beta_i\|_{W^{1,\infty}(R(t),R_i(t))})|R_1(t) - R_2(t)|$$

and then

$$\int_0^{R(t)} (S(\sigma_1,\beta_1) - S(\sigma_2,\beta_2))r^2 dr \leq C(T+2)\delta. \tag{3.15}$$

Integrating in time in (3.13) and thanks to (3.14) and (3.15) we get

$$R_1^3(t) - R_2^3(t) \leq TC(T+2)\delta + 2TM\delta. \tag{3.16}$$

On the other hand, it results

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

Without lost of generality we can assume that $\delta = R_1(t_0) - R_2(t_0)$ (for some $t_0 \in [0,T]$) and then

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

Substituting in (3.16) we conclude that $\delta \leq k_0 \delta T$. Furthermore, taking $T_1 < \frac{1}{k_0}$, necessarily $R_1(t) = R_2(t)$ for any $t \in [0, T_1]$. Since $|\beta|$ take their maximum at $R(t) = R_1(t) = R_2(t)$ (and it is 0) we get that $\beta = 0$. Substituting in (3.12) and taking σ as test function we obtain

$$\int_0^{R(t)} \sigma^2 r^2 dr \leq \int_0^t \int_0^{R(s)} (g_1(\sigma_1, 0) - g_1(\sigma_2, 0))\sigma r^2 dr ds.$$

As in Lemma 3.3, since $(\sigma_i + \overline{\overline{\sigma_i}} - \sigma_n)H(\sigma_i + \overline{\overline{\sigma}} - \sigma_n)$ is a increasing function of σ and by (3.5) we obtain $(g_1(\sigma_1, 0) - g_1(\sigma_2, 0))\sigma \leq 0$ which prove $\sigma = 0$.

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

Remark 3.1 *The reaction between nutrients and inhibitors can be modeled by more complicated functions $\tilde{g}_i$. Truncating the functions in the right levels (σ_n, $\overline{\overline{\beta}}$, σ_B and $\max\{\beta\}$) and extending them with continuous and linear growth at infinity, will enable us to apply the existence and uniqueness results of previous sections. Then, by Lemma 3.1 the solution is bounded and satisfies the original problem.*

4 Conclusion

In this paper we have considered a model for the growth of tumors which generalizes previous models proposed by Byrne and Chaplain [4] and Greenspan [10]. The inclusion of the term that models the injection of inhibitors ($f\chi_{\omega_0}$) is the main contribution to the modelling.

The mathematical analysis demonstrates existence of solutions for the model (1.2) under assumptions (2.1) and (2.2). In Section 3 we prove uniqueness for the necrotic case for a range of parameters $\sigma_n \geq \frac{r_1\sigma_B - \overline{\overline{\beta}}}{r_1 + \lambda}$ (uniqueness for the non necrotic model was proved in [5]). Uniqueness is not expected when $\sigma_n \leq \frac{r_1\sigma_B - \overline{\overline{\beta}}}{r_1 + \lambda}$.

Despite the discontinuity introduced in the model by $H(\sigma - \sigma_n)$, it has been proved that in the boundary of the necrotic core σ is a continuous function in space and belongs to a functional space. As we expected, the level of nutrients does not fall below the critical level σ_n (provided initial data $\sigma_0 \geq \sigma_n$).

Numerical simulations 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 the pictures an concave growth of the radius at the beginning and after a time (which depends of $\tilde{\sigma}$) we observe as the radius has a convex growth.

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Appendix: Numerical simulation

In this appendix we consider a numerical solution to (1.2) by using a time discretization scheme which leads implicitly with u and v and explicitly for the free boundary R. We assume radial symmetry, no forcing terms (i.e. $f = 0$) and nonnecrotic core. Let $x := \frac{r}{R(t)}$ and

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

Then, problem (3.1) becomes

$$\frac{\partial u}{\partial t} = \frac{D_1}{x^2R^2}\frac{\partial}{\partial x}(x^2\frac{\partial}{\partial x}u) + x\frac{R'}{R}\frac{\partial u}{\partial x} - r_1 u - v - r_1\overline{\overline{\sigma}} - \overline{\overline{\beta}},\ (0,1)\times(0,T),$$

$$\frac{\partial v}{\partial t} = \frac{D_2}{x^2R^2}\frac{\partial}{\partial x}(x^2\frac{\partial v}{\partial x}) + x\frac{R'}{R}\frac{\partial}{\partial x}v + -r_2 v - r_2\overline{\overline{\beta}},\ (0,1)\times(0,T),$$

$$R(t) = R_0 exp\{\int_0^t\int_0^1 x^2 S(u,v)dxdt\}, \qquad t > 0,$$

$$u_x(0,t) = \ v_x(0,t) = \ u(1,t) = \ v(1,t) = 0, \quad t > 0,$$

$$R(0) = R_0,\ u(x,0) = u_0(x),\ v(x,0) = v_0(x),\ x \in (0,1).$$

Time discretization. Let $N \in I\!N$, $n = 1,..N$ and $t_n = n\frac{T}{N}$. We introduce the approximations

$$u^n(x) \approx u(x,t_n), \qquad v^n(x) \approx v(x,t_n), \qquad R^n \approx R(t_n),$$

$$\dot{R}^n \approx \frac{dR(t)}{dt} \ \text{ in } t = t_n,$$

defined by the following algorithm:

Step 0:

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

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

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

Now, for $1 < n \leq N$, 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

$$\begin{cases} \frac{v^n - v^{n-1}}{\Delta t} = \frac{D_2}{(R^{n-1})^2} x^{-2} \frac{\partial}{\partial x}(x^2 \frac{\partial}{\partial x} v^n) + x \frac{\dot{R}^{n-1}}{R^{n-1}} \frac{\partial}{\partial x} v^{n-1} - r_2 v^n - r_2 \overline{\overline{\beta}}, \\ \frac{\partial v^n}{\partial x}(0) = v^n(1) = 0, \end{cases}$$

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

n.2

$$\begin{cases} \frac{u^n - u^{n-1}}{\Delta t} = \frac{D_1}{(R^{n-1})^2} x^{-2} \frac{\partial}{\partial x}(x^2 \frac{\partial}{\partial x} u^n) + x \frac{\dot{R}^{n-1}}{R^{n-1}} \frac{\partial}{\partial x} u^{n-1} - \\ r_1 u^n - v^n - r_1 \overline{\overline{\sigma}} - \overline{\overline{\beta}}, \text{ in } 0 < x < 1, \\ \frac{\partial u^n}{\partial x}(0) = u^n(1) = 0. \end{cases}$$

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

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

$$= R_0 \exp\{\Delta t \int_0^1 x^2 [\frac{1}{2}(S(u^0, v^0) + S(u^n, v^n)) + \sum_{j=1}^{n-1} S(u^j, v^j)]dx\}.$$

n.4

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

$$S(u^{j+1}, v^{j+1})dx)\} = R_0 \int_0^1 x^2 S(u^n, v^n)dx \exp\{\Delta T \int_0^1 x^2 [\frac{1}{2}(S(u^0, v^0) +$$

$$S(u^n, v^n)) + \sum_{j=1}^{n-1} S(u^j, v^j)]dx\}.$$

Full discretization. We approximate $H^1(0,1)$ by

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

where $x_j = \frac{j}{s+1}$ and P_1 is the space of those polynomials of degree 0 or 1. We approximate the above implicit-explicit scheme by the system

$$\frac{u_h^n - u_h^{n-1}}{\Delta T} = \frac{D_1}{(xR^{n-1})^2}\frac{\partial}{\partial x}(x^2\frac{\partial}{\partial x}u_h^n) + x\frac{\dot{R}^{n-1}}{R^{n-1}}\frac{\partial}{\partial x}u_h^n - r_1 u_h^n - v_h^n + r_1\overline{\overline{\sigma}} + \overline{\overline{\beta}},$$

$$\text{in } 0 < x < 1,\ n = 1...N,$$

$$\frac{v_h^n - v_h^{n-1}}{\Delta T} = \frac{D_2}{(xR^{n-1})^2}\frac{\partial}{\partial x}(x^2\frac{\partial}{\partial x}v_h^n) + x\frac{\dot{R}^{n-1}}{R^{n-1}}\frac{\partial}{\partial x}v_h^n - r_2 v_h^n + r_2\overline{\overline{\beta}},$$

$$\text{in } 0 < x < 1,\ i = 1...N,$$

$$u_h^n(1) = v_h^n(1) = 0, \qquad \frac{\partial u_h^n}{\partial x} = \frac{\partial v_h^n}{\partial x} = 0, \qquad \text{on } x = 0,$$

$$R(0) = R_0,\ u_h^0(x) = u_{h,0}(x),\ v_h^0(x) = v_{h,0}(x),$$

$$R_h^n = R_0 \exp\{\Delta T \int_0^1 x^2[\frac{1}{2}(S(u_h^0, v_h^0) + S(u_h^n, v_h^n)) + \sum_{j=1}^{n-1} S(u_h^j, v_h^j)]dx\}.$$

Weak formulation of the discrete problem. Let us define

$$b(\zeta, \varphi) = \int_0^1 x^2\zeta\varphi dx.$$

Then, the weak formulation of the problem is given by

$$(1 + r_1)b(u_h^n, \varphi) + \frac{D_1\Delta T}{(R^{n-1})^2}b((u_h^i)_x, \varphi_x) - \frac{\dot{R}^{n-1}}{R^{n-1}}b(x(u_h^n)_x, \varphi) =$$

$$= b(u_h^n - v_h^n + r_1\overline{\overline{\sigma}} + \overline{\overline{\beta}}, \varphi),$$

$$(1 + r_2)b(v_h^n, \varphi) + \frac{D_1\Delta T}{(R^{n-1})^2}b((v_h^n)_x, \varphi_x) - \frac{\dot{R}^{n-1}}{R^{n-1}}b(x(v_h^n)_x, \varphi) = b(v_h^n + r_2\overline{\overline{\beta}}, \varphi),$$

$$\forall\varphi \in V_h.$$

Numerical Experiments. We consider the special case: $S(\sigma, \beta) = \sigma - \widehat{\sigma}$, $T = 3$, $N = 501$ (i.e. $\Delta T = \frac{3}{500}$) and $s = 20$ (i.e. $h = \frac{1}{20}$). The parameters are taken as $R_0 = 5$, $D_1 = D_2 = 1$, $r_1 = r_2 = \overline{\overline{\sigma}} = \overline{\overline{\beta}} = 1$.

We have visualized the computed evolution of the radius of the tumor for $\widehat{\sigma} = 0.75$ (figure 1), $\widehat{\sigma} = 1$ (figure 2) and $\widehat{\sigma} = 1.5$ (figure 3).