On a simple model of tumor growth

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Abstract

We study a simple mathematical model for the growth of spherical 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 solutions under suitable conditions on the inhibitors interaction and the tumor growth.

Introduction.

We center our attention on a class of models proposed by Greenspan [10] and studied in Byrne and Chaplain [4], Friedman and Reitich [9], Cui and Friedman [5], [6], and Díaz and Tello [7]. We assume the density of living cells is proportional to the concentrations of the nutrients $\widehat{\sigma}(x,t)$, $x=(x_1,x_2,x_3)$. The tumor is represented by a ball of $I\!R^3$ of radius $R(t)$, which is unknown (reason why is usually denoted as 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 [10].

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 $\lambda\widehat{\sigma}$. Both processes, consumption and transference, occur simultaneously in the exterior of the necrotic core, where cells are inhibited by $\widehat{\beta}$. We assume that the host tissue is homogenous 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 $\widehat{\sigma}$) and some continuous functions $g_i(\widehat{\sigma},\widehat{\beta})$. Then $\widehat{\sigma}$ satisfies

$$\frac{\partial\widehat{\sigma}}{\partial t}-d_1\Delta\widehat{\sigma}\in r_1((\sigma_B-\widehat{\sigma})-\lambda_1\widehat{\sigma})H(\widehat{\sigma}-\sigma_n)+\widehat{g}_1(\widehat{\sigma},\widehat{\beta}). \tag{1}$$

We also assume a constant diffusion coefficient for the inhibitor concentration $\widehat{\beta}$, d_2. The model takes into account the permanent supply of inhibitors, $\tilde{f}$, localized on a small region ω_0 inside the tumor, which can be used when tumor is well localized, this term $\tilde{f}$ was introduced in Díaz and Tello [7]. Then $\widehat{\beta}$ satisfies

$$\frac{\partial \widehat{\beta}}{\partial t} - d_2 \Delta \widehat{\beta} \in r_2(\beta_B - \widehat{\beta}) H(\widehat{\sigma} - \sigma_n) + \widehat{g}_2(\widehat{\sigma}, \widehat{\beta}) + \tilde{f} \chi_{\omega_0}, \tag{2}$$

adding initial and boundary conditions we obtain

$$\widehat{\sigma}(\tilde{x}, t) = \overline{\overline{\sigma}}, \widehat{\beta}(\tilde{x}, t) = \overline{\overline{\beta}}, \quad |\tilde{x}| = R(t), \tag{3}$$

$$\widehat{\sigma}(\tilde{x}, 0) = \sigma_0(\tilde{x}), \ \widehat{\beta}(\tilde{x}, 0) = \beta_0(\tilde{x}), \quad |\tilde{x}| < R_0. \tag{4}$$

In this formulation, the presence of the maximal monotone graph H is the reason why the symbol $\in$ appears in equation (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 $\{r \in [0, R(t)) : \widehat{\sigma} \le \sigma_n\}$. 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 $\widehat{g}_1(\sigma_n, \widehat{\beta}) \in [0, r_1(\sigma_B - \sigma_n) - \lambda\sigma_n]$ for any $\widehat{\beta} \ge 0$, the above formulation leads to the associate double free boundary formulation in which $\widehat{\sigma}$ satisfies

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

The free boundary $R(t)$ is described by the ODE

$$\frac{d}{dt}\left(\frac{4}{3}\pi R^3(t)\right) = \int_{\{|\tilde{x}| < R(t)\}} \widehat{S}(\widehat{\sigma}(\tilde{x}, t), \widehat{\beta}(\tilde{x}, t)) d\tilde{x}, \quad R(0) = R_0. \tag{5}$$

We prove the solvability of the model equations: (1)-(5) and establish uniqueness of solutions under additional conditions. The existence result is present in Section 3 and proved by using a Galerkin approximation based on a weak formulation of the problem.

We have mentioned 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 $\widehat{\sigma}_d(\tilde{x})$.

The model.

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*). 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, $\widehat{\sigma}$, in the interior falls bellow a critical level, σ_n, 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.

In the study of the internal mechanisms of the tumor growth two unknown free boundaries appear: the outer boundary delimiting the tumor is denoted by $R(t)$ and the inner boundary by $\rho(t)$ (delimiting the necrotic core).

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 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

$$\frac{d}{dt}(\frac{4}{3}\pi R^3(t)) = \int_{\{|\tilde{x}|<R(t)\}} \widehat{S}(\widehat{\sigma}(\tilde{x},t),\widehat{\beta}(\tilde{x},t))d\tilde{x}. \tag{6}$$

Depending on the author, the function $\widehat{S}$ can be written in different ways. Greenspan [10] 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 $\widetilde{\beta}$. He proposed $\widehat{S}(\widehat{\sigma},\widehat{\beta}) = sH(\widehat{\sigma}-\widetilde{\sigma})H(\widetilde{\beta}-\widehat{\beta})$, where $H(\cdot)$ denotes the maximal monotone graph of $I\!R^2$ 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 [4] study the growth when the inhibitor affects the cell proliferation and propose $\widehat{S}(\widehat{\sigma}, \widehat{\beta}) = s(\widehat{\sigma} - \widetilde{\sigma})(\widetilde{\beta} - \widehat{\beta})$ (for a positive constant s). In the absence of inhibitors or in case that the inhibitor does not affect mitosis, they choose $\widehat{S}(\widehat{\sigma}, \widehat{\beta}) = s\widehat{\sigma}(\widehat{\sigma} - \widetilde{\sigma})$. Friedman and Reitich [9] and Cui and Friedman [5] study the asymptotic behavior of the radius, $R(t)$, with the cell proliferation rate free of the action of inhibitors. They assume that $\widehat{S} = s(\sigma - \widetilde{\sigma})$, where $s\sigma$ is the cell birth-rate and the death-rate is given by $s\widetilde{\sigma}$.

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 $\lambda\widehat{\sigma}$. Both processes, consumption and transference, occur simultaneously in the exterior of the necrotic core, where cells are inhibited by $\widehat{\beta}$. We assume that the host tissue is homogenous 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 $\widehat{\sigma}$) and some continuous functions $g_i(\widehat{\sigma}, \widehat{\beta})$. Then $\widehat{\sigma}$ satisfies

$$\begin{cases} \frac{\partial\widehat{\sigma}}{\partial t} \in d_1\Delta\widehat{\sigma} r_1((\sigma_B - \widehat{\sigma}) - \lambda_1\widehat{\sigma})H(\widehat{\sigma} - \sigma_n) + \widehat{g}_1(\widehat{\sigma}, \widehat{\beta}), & |\tilde{x}| < R(t), \\ \frac{\partial\widehat{\beta}}{\partial t} \in d_2\Delta\widehat{\beta} - r_2\widehat{\beta} + \widehat{g}_2(\widehat{\sigma}, \widehat{\beta}) + \tilde{f}\chi_{\omega_0}, & |\tilde{x}| < R(t), \\ R(t)^2\frac{dR(t)}{dt} = \int_{|\tilde{x}|<R(t)} \widehat{S}(\widehat{\sigma}, \widehat{\beta})d\tilde{x}, & 0 < t < T, \\ \widehat{\sigma}(\tilde{x}, t) = \overline{\overline{\sigma}}, \widehat{\beta}(\tilde{x}, t) = \overline{\overline{\beta}}, & |\tilde{x}| = R(t), \\ R(0) = R_0, \widehat{\sigma}(\tilde{x}, 0) = \sigma_0(\tilde{x}), \widehat{\beta}(\tilde{x}, 0) = \beta_0(\tilde{x}), & |\tilde{x}| < R_0. \end{cases} \tag{7}$$

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 (7) 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 (7) for which there are multiple solutions). The uniqueness of a weak solution to (7) is established here for radially symmetric solutions under some additional assumptions on $\widehat{S}$ when $f = 0$ and $\widehat{g}_1 = \widehat{g}_2 = 0$.

Existence of solutions

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

$$\widehat{g}_i \text{ are piecewise continuous, } |\widehat{g}_i(a,b)| \leq c_0 + c_1(|a| + |b|), \tag{8}$$

$$\widehat{S} \text{ is continuous and } -\lambda_0 \leq \widehat{S}(a,b) \leq c_0 + c_1(|a|^2 + |b|^2) \tag{9}$$

for some positives constants λ_0, c_0, c_1.

The above assumptions ((8) and (9)) 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

$$x = (x_1, x_2, x_3) = \frac{\tilde{x}}{R(t)}, \tag{10}$$

$$u(x,t) = \widehat{\sigma}(R(t)x, t) - \overline{\overline{\sigma}} \tag{11}$$

and

$$v(x,t) = \widehat{\beta}(R(t)x, t) - \overline{\overline{\beta}}. \tag{12}$$

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

$$\begin{cases} g_1(\widehat{\sigma} - \overline{\overline{\sigma}}, \widehat{\beta} - \overline{\overline{\beta}}) := r_1((\sigma_B - \widehat{\sigma}) - \lambda\widehat{\sigma} - \widehat{\beta})H(\widehat{\sigma} - \sigma_n) + \widehat{g}_1(\widehat{\sigma}, \widehat{\beta}), \\ g_2(\widehat{\sigma} - \overline{\overline{\sigma}}, \widehat{\beta} - \overline{\overline{\beta}}) := -r_2\widehat{\beta}H(\widehat{\sigma} - \sigma_n) + \widehat{g}_2(\widehat{\sigma}, \widehat{\beta}), \end{cases} \tag{13}$$

$$S(\widehat{\sigma} - \overline{\overline{\sigma}}, \widehat{\beta} - \overline{\overline{\beta}}) := \frac{4}{3\pi}\widehat{S}(\widehat{\sigma}, \widehat{\beta}) \tag{14}$$

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)-(5) becomes

$$\begin{cases} \frac{\partial u}{\partial t} - \frac{d_1}{R(t)^2}\Delta u - \frac{R'(t)}{R(t)}x \cdot \nabla u \in g_1(u,v) & x \in B,\ t > 0 \\ \frac{\partial v}{\partial t} - \frac{d_2}{R(t)^2}\Delta v - \frac{R'(t)}{R(t)}x \cdot \nabla v \in g_2(u,v) + f\chi_{\tilde{\omega}_0^t} & x \in B,\ t > 0 \\ R(t)^{-1}\frac{dR(t)}{dt} = \int_B S(u,v)dx & t > 0 \\ u(x,t) = v(x,t) = 0, & x \in \partial B\ t > 0 \\ R(0) = R_0,\ u(x,0) = u_0(x),\ v(x,0) = v_0(x) & x \in B. \end{cases} \tag{15}$$

We introduce the Hilbert spaces

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

and define inner products by

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

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 $G : I\!R^2 \longrightarrow 2^{I\!R^2} \times 2^{I\!R^2}$ and $F : (0,T) \times B \longrightarrow I\!R^2$ by

$$G(U) = (g_1(u,v), g_2(u,v)), \quad F(t,x) = (0, f(t,x)\chi_{\tilde{\omega}_0^t}).$$

We have:

$$|G(U)| = |g_1(u,v)| + |g_2(u,v)| \leq C_0 + C_1|U| = C_0 + C_1(|u| + |v|). \tag{16}$$

Definition $(U, R) \in L^2(0, T : \mathbf{V}) \times W^{1,\infty}(0, T : I\!R)$ is a weak solution of the problem (15) 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

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

$$< U_0, \Phi(0) >_{\mathbf{H}} + \int_0^T < F(t), \Phi >_{\mathbf{H}} dt$$

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

$$\tilde{a}(t, U, \Phi) := \frac{1}{R^2(t)} < U, \Phi >_{\mathbf{V}} - \frac{R'(t)}{R(t)} < x \cdot \nabla U, \Phi >_{\mathbf{H}} \tag{17}$$

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

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

Definition (σ, β, R) is a weak solution of (15) 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 $t \in (0, T)$ and $\tilde{x} \in I\!R^3, |\tilde{x}| \leq R(t)$, where $(U = (u, v), R)$ is a weak solution of (15) for any $T > 0$.

Remark 1 *The definition of weak solution and the structural assumptions on G imply that $\frac{\partial U}{\partial t} \in L^2(0, T : \mathbf{V}(B)')$ and the equation holds in $D'(B \times (0, T))$.*

Theorem 1 *Assume (8), (9), $R_0 > 0$ and σ_0, $\beta_0 \in L^2(0, R_0)$, then problem (1)-(5) has at least a weak solution for each $T > 0$.*

Proof. We shall use a Galerkin method to construct a weak solution. Let $R(t) \in W^{1,\infty}(0, T : I\!R)$ 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

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

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

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

for a.e. $t \in (0, T)$ (see (17)). Since $\frac{R'(t)}{R(t)} \geq -\lambda_0$, $\tilde{a}$ satisfies

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

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

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.

Lemma 1

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

Proof: Inserting U^t as test function into the weak formulation of (15), one obtains

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

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

$$\frac{1}{2}\frac{d}{dt}||U||^2_{\mathbf{H}} - \frac{\lambda_0}{2}||U||^2_{\mathbf{H}} \leq (||g^*||_{\mathbf{H}} + ||F||_{\mathbf{H}})||U||_{\mathbf{H}}. \tag{18}$$

Thus by Young's inequality and (16) imply

$$\frac{1}{2}\frac{d}{dt}||U||^2_{\mathbf{H}} - (\frac{\lambda_0}{2} + C_1 + \frac{1}{2})||U||^2_{\mathbf{H}} \leq \frac{1}{2}(C_0^2 + ||F||^2_{\mathbf{H}}).$$

Integrating with respect to time, we get

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

and by Gronwall's lemma

$$||U||^2_{\mathbf{H}} \leq C_0^2(exp\{(\lambda_0 + 2C_1 + 1)T\} - 1) + ||F||^2_{L^2(0,T:\mathbf{H})}) + ||U_0||^2_{\mathbf{H}} \leq C. \tag{19}$$

Remark 2 *Since U is bounded in* $\mathbf{H}$ *(by (19)), R satisfies*

$$R(t) = R_0 exp\{\int_0^t \int_0^1 S(U)dxdt\} \leq R_0 e^{K_1 t} \tag{20}$$

and

$$R(t) \geq R_0 exp\{-\lambda_0 t\} \tag{21}$$

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

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

Proof: Selecting U as test function in (19), we have

$$\frac{D}{R_0^2 e^{2K_1 T}} \|U\|^2_{L^2(0,T:\mathbf{V})} - \frac{\lambda_0}{2} \|U\|^2_{L^2(0,T:\mathbf{H})} \leq C_1 \|U\|^2_{L^2(0,T:\mathbf{H})} +$$

$$(C_0 + \|F\|_{L^2(0,T:\mathbf{H})}) \|U\|_{L^2(0,T:\mathbf{H})}.$$

By (19) we get

$$\|U\|_{L^2(0,T:V)} \leq K(F, G, U_0, T). \tag{22}$$

Remark 3 *By Lemma 2 and Remark 2 we get that*

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

and obtain the extra regularity

$$U_t, \ \Delta U \in [L^2(0,T:L^2(B))]^2 \tag{23}$$

Now, as previously in the proof of Theorem 2.1, we consider the approximate problem

$$\frac{\partial U^\epsilon}{\partial t} + A(R^\epsilon(t))U^\epsilon = G^\epsilon(U^\epsilon) + F(t) \text{ on } B \times (0,T)$$

$$U^\epsilon(0,x) = U_0, \quad U^\epsilon = 0 \text{ on } \partial B \tag{24}$$

$$\frac{1}{R^\epsilon}\frac{dR^\epsilon}{dt} = \int_B S(U^\epsilon)dx$$

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

$$G^\epsilon \longrightarrow G \text{ when } \epsilon \to 0 \text{ a.e. in } I\!R^2.$$

G^ϵ is obtained replacing H by

$$H^\epsilon(s) = \begin{cases} 0 & \text{if } s < 0 \\ \frac{s}{\epsilon} & \text{if } 0 \leq s \leq \frac{1}{\epsilon} \\ 1 & \text{if } s > \frac{1}{\epsilon}. \end{cases}$$

Now, we apply the Galerkin method to the approximated problem. Let λ_n and $\phi_n \in H_0^1(B)$ for $n \in I\!N$ 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 $\{\phi_1, \cdots \phi_m\}$. We search for a solution $U_m^\epsilon \in L^2(0, T : V_m)$ of the problem

$$\frac{d}{dt} U_m^\epsilon + A(R_m^\epsilon(t)) U_m^\epsilon = G^\epsilon(U_m^\epsilon) + F_m(t) \tag{25}$$

with

$$R_m^\epsilon(t)^{-1} \frac{dR_m^\epsilon(t)}{dt} = \int_B S(U_m^\epsilon(x,t)) dx.$$

Then

$$R_m^\epsilon(t) = R_0 exp\{\int_0^t \int_B S(U_m^\epsilon(x,s)) dx ds\}$$

and the initial conditions $U_m^\epsilon(0) = P_m(U_0)$ (where P_m is the orthogonal projection from $L^2(B)$ onto V_m) and $F_m = P_m(F)$.

Proposition 1 *(25) has a unique solution U_m^ϵ for arbitrary $T < \infty$ provided $R > 0$.*

Proof: Problem (25) can be written as a suitable nonlinear ordinary differential system. Let $U_m^\epsilon = (u_m^\epsilon, v_m^\epsilon)$ be defined by

$$u_m^\epsilon(t) = \sum_{n=1,\dots,m} a_n^{\epsilon m}(t)\phi_n, \quad v_m^\epsilon(t) = \sum_{n=1,\dots,m} b_n^{\epsilon m}(t)\phi_n$$

and denote

$$a^{\epsilon m} = (a_1^{\epsilon m}, a_2^{\epsilon m}, ..., a_m^{\epsilon m}), \quad b^{\epsilon m} = (b_1^{\epsilon m}, b_2^{\epsilon m}, ..., b_m^{\epsilon m}), \quad \lambda_a = (\lambda_1 a_1^{\epsilon m}, ..., \lambda_m a_m^{\epsilon m})$$

and $\lambda_b = (\lambda_1 b_1^{\epsilon m}, ..., \lambda_m b_m^{\epsilon m})$. Then $a^{\epsilon m}$, $b^{\epsilon m}$ and R_m^ϵ satisfy

$$\dot{a}^{\epsilon m} + \frac{\lambda_a}{(R_m^\epsilon)^2} + \phi_\epsilon(a^{\epsilon m}, b^{\epsilon m}) L_1^m(a^{\epsilon m}, b^{\epsilon m}) + g_1^m(a^{\epsilon m}, b^{\epsilon m}) = 0$$

$$\dot{b}^{\epsilon m} + \frac{\lambda_b}{(R_m^\epsilon)^2} + \phi_\epsilon(a^{\epsilon m}, b^{\epsilon m}) L_2^m(a^{\epsilon m}, b^{\epsilon m}) + g_2^m(a^{\epsilon m}, b^{\epsilon m}) = F^m(t),$$

$$\frac{\dot{R}_m^\epsilon}{R_m^\epsilon} = \phi_\epsilon(a^{\epsilon m}, b^{\epsilon m})$$

where

$$\phi_\epsilon(a^{\epsilon m}, b^{\epsilon m}) = \int_B S(U_m^\epsilon) dx$$

$$L_1^m(a^{\epsilon m}, b^{\epsilon m}) = \int_B x \cdot \nabla u_m^\epsilon \phi_n dx \text{ for } n = 1, ..., m$$

$$L_2^m(a^{\epsilon m}, b^{\epsilon m}) = \int_B x \cdot \nabla v_m^\epsilon \phi_n dx \text{ for } n = 1, ..., m$$

$$g_1^m(a^{\epsilon m}, b^{\epsilon m}) = \int_B g_1^\epsilon(u_m^\epsilon, v_m^\epsilon)\phi_n dx \text{ for } n = 1, ..., m$$

$$g_2^m(a^{\epsilon m}, b^{\epsilon m}) = \int_B g_2^\epsilon(u_m^\epsilon, v_m^\epsilon)\phi_n dx \text{ for } n = 1, ..., m.$$

Since G_ϵ is a Lipschitz function we obtain that there exists a unique solution $a^{\epsilon m}, b^{\epsilon m}, R^{\epsilon m}$ to the system for T small enough. Moreover, (19) and (21) hold, and we get the existence of a solution of (25) for any $T < \infty$.
By (23) and (22), $\{(U_m^\epsilon, \frac{d}{dt}U_m^\epsilon)\}_{m=1,\infty}$ is uniformly bounded in $L^2(0,T:\mathbf{V}) \times L^2(0,T:\mathbf{V}')$. So, there exists a subsequence $U_{mi}^\epsilon \in L^2(0,T:\mathbf{V})$ with $\frac{d}{dt}U_{mi}^\epsilon \in L^2(0,T:\mathbf{V}')$ such that

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

Taking limits when $mi \to \infty$ we get the existence of a weak solution to (24) for any $T < \infty$.

To end the proof of Theorem 2.1 we take limits in the equation when $\epsilon \to 0$. We employ (19) and (21) 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 $U^{\epsilon i}$ such that

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

and in particular

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

Since

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

and

$$v^\epsilon \longrightarrow v \text{ in } L^2(0,T:L^s(B))$$

(see Lemma 3.4.1 of Vrabie [16]) we have

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

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

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

By (18) we deduce that $R_{\epsilon ij} \longrightarrow R$ in $C^0([0,T])$. Finally, taking limits in the weak formulation of the problem (19) we get

$$\int_0^T < U_t, \Phi >_{\mathbf{H}} dt + \int_0^T \tilde{a}(R(t), U, \Phi) dt + \int_0^T < g^*, \Phi >_{\mathbf{H}} dt =$$
$$\int_0^T < F, \Phi >_{\mathbf{H}} dt$$

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

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

Notice that

$$\int_0^T \frac{R'_{\epsilon ij}}{R_{\epsilon ij}} \int_B x \cdot \nabla u_{\epsilon ij} \psi dx dt = \int_0^T \frac{R'_{\epsilon ij}}{R_{\epsilon ij}} \int_B u_{\epsilon ij}\psi - u_{\epsilon ij} x \cdot \nabla \psi dx dt$$

and

$$\int_0^T \frac{R'_{\epsilon ij}}{R_{\epsilon ij}} \int_B x \cdot \nabla v_{\epsilon ij} \psi dx dt = \int_0^T \frac{R'_{\epsilon ij}}{R_{\epsilon ij}} \int_B v_{\epsilon ij} \psi - v_{\epsilon ij} x \cdot \nabla \psi dx dt.$$

We conclude that (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 to (1)-(5). The additional regularity

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

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

Uniqueness of solutions with radial symmetry

We begin by pointing out that if, for instance, $\sigma_n \geq \frac{r_1 \sigma_B}{r_1 + \lambda}$, $r_1 \sigma_B > 0$, $\widehat{g}_1(\widehat{\sigma}, \widehat{\beta})$ is a decreasing function of $\widehat{\sigma}$ and independent of $\widehat{\beta}$ 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 L. Tello [8] in order to construct more than one solution of problem (1)-(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.

Let $(\widehat{\sigma}, \widehat{\beta})$ be a solution of problem (7). 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

$$\begin{cases} \frac{\partial \sigma}{\partial t} - \frac{d_1}{r^2} \frac{\partial}{\partial r}(r^2 \frac{\partial}{\partial r} \sigma) \in g_1(\sigma, \beta), & 0 < r < R(t) \; 0 < t < T, \\ \frac{\partial \beta}{\partial t} - \frac{d_2}{r^2} \frac{\partial}{\partial r}(r^2 \frac{\partial}{\partial r} \beta) \in g_2(\sigma, \beta), & 0 < r < R(t) \; 0 < t < T, \\ R(t)^2 \frac{dR(t)}{dt} = \int_0^{R(t)} S(\sigma, \beta) r^2 dr, & 0 < t < T, \\ \frac{\partial \sigma}{\partial r}(0, t) = 0, \; \frac{\partial \beta}{\partial r}(0, t) = 0, & 0 < t < T, \\ \sigma(R(t), t) = 0, \; \beta(R(t), t) = 0, & 0 < t < T, \\ R(0) = R_0, & \\ \sigma(r, 0) = \sigma_0(r), \beta(r, 0) = \beta_0(r), & 0 < r < R_0, \end{cases} \tag{26}$$

where g_i are given by

$$g_1(\sigma, \beta) = -[(r_1 + \lambda)(\sigma + \overline{\overline{\sigma}}) - r_1 \sigma_B + (\beta + \overline{\overline{\beta}})] H(\sigma + \overline{\overline{\sigma}} - \sigma_n) \tag{27}$$

$$g_2(\sigma, \beta) = -r_2(\beta + \overline{\overline{\beta}}). \tag{28}$$

We will assume in this section that

$$S(\sigma, \beta) \in W^{1,\infty}_{loc}(I\!R^2), \tag{29}$$

$$S \text{ is an increasing function in } \sigma \text{ and decreasing in } \beta \tag{30}$$

$$\sigma_n \geq \frac{r_1\sigma_B - \overline{\overline{\beta}}}{r_1+\lambda} \tag{31}$$

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

$$\frac{\partial \sigma_0}{\partial r}(0,t) = 0, \ \frac{\partial \beta}{\partial r}(0,t) = 0 \qquad 0 < t < T, \tag{32}$$

$$\sigma(R(t),t) = 0, \ \beta(R(t),t) = 0 \qquad 0 < t < T. \tag{33}$$

Theorem 2 *There is, at most, one solution to (26).*

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 *Every solution* (σ, β) *of the problem (26) 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

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

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

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

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

we obtain

$$\int_0^{R(t)} T_0(\sigma-\sigma_B)^2 r^2 dr \leq \int_0^t \int_0^{R(s)} [T^0(\beta + \overline{\overline{\beta}})^2 + T_0(\sigma - \sigma_B)^2] r^2 dr ds. \tag{34}$$

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

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

it follows that

$$\int_0^{R(t)} [T^0(\beta+\overline{\overline{\beta}})]^2 r^2 dr \leq \int_0^t \int_0^{R(s)} r_2 T^0(\beta+\overline{\overline{\beta}}) r^2 dr ds. \tag{35}$$

Adding (34) and (35), we obtain thanks to Gronwall′s Lemma

$$\sigma \leq \sigma_B \text{ and } \beta \geq -\overline{\overline{\beta}}.$$

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

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

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

Now take limits as $\epsilon \to 0$, one conclude

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

which proves $\sigma \geq \sigma_n$.

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

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

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

Since $\beta_0 \geq -\overline{\overline{\beta}}$ it follows 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 we get by maximum principle that $\beta \leq \max\{\beta_0\}$.

Corollary 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. 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,

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

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

Lemma 4 *The solution* (σ,β) *of (26) satisfies*

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

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 and so $(u,v) \in [L^2(0,T:H^1(B))]^2$. By (9) and

$$\tau(t) = \int_0^t R^{-2}(\rho)d\rho \tag{36}$$

we obtain $\tau(t) \in C^1$ and employing the implicit function theorem, one derives the existence of the inverse function $t(\tilde{t}) \in C^1([0,T])$, 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

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

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

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

and the proof ends.

Proof of Theorem 2. We argue by contradiction and assume that $(\sigma_1,\ \beta_1,\ R_1)$ 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

$$\begin{cases} \frac{\partial\sigma}{\partial t} - \frac{d_1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial}{\partial r}\sigma) = g_1(\sigma_1,\beta_1) - g_1(\sigma_2,\beta_2) & 0<r<R(t)\ 0<t<T, \\ \frac{\partial\beta}{\partial t} - \frac{d_2}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial}{\partial r}\beta) = g_2(\sigma_1,\beta_1) - g_2(\sigma_2,\beta_2) & 0<r<R(t)\ 0<t<T, \\ \frac{\partial\sigma}{\partial r}(0,t) = 0,\ \frac{\partial\beta}{\partial r}(0,t) = 0 & 0<t<T, \\ \sigma(R(t),t) = \sigma_1(R(t),t) - \sigma_2(R(t),t) & 0<t<T, \\ \beta(R(t),t) = \beta_1(R(t),t) - \beta_2(R(t),t) & 0<t<T, \\ \sigma(r,0) = 0,\ \beta(r,0) = 0 & 0<r<R_0. \end{cases} \tag{37}$$

Now, we state a technical lemma.

Lemma 5 *$|\beta|$ takes the maximum on the boundary $R(t)$ and σ satisfies*

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

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

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

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

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

and obtain $\beta \ge \beta_*$. 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 an increasing function of σ we obtain that

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

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

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

Then

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

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

$$-(\beta_1-\beta_2)H(\sigma_2+\overline{\overline{\sigma}}-\sigma_n)T_0(\sigma_1-\sigma_2-\sigma^*)\leq$$
$$-T^0(\beta_1-\beta_2)T_0(\sigma_1-\sigma_2-\sigma^*)\leq-\beta_* T_0(\sigma_1-\sigma_2-\sigma^*).$$

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

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

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

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

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

Now, 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

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

holds, which ends the proof.

End of the proof of Theorem 2. Let us define

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

and consider

$$R_1^2(t)R_1'(t)-R_2^2(t)R_2'(t)=\int_0^{R(t)}(S(\sigma_1,\beta_1)-S(\sigma_2,\beta_2))r^2dr+$$
$$\int_{R(t)}^{R_1(t)}S(\sigma_1,\beta_1)r^2dr-\int_{R(t)}^{R_2(t)}S(\sigma_2,\beta_2)r^2dr. \tag{38}$$

By (30) and Lemma 3, we obtain

$$|\int_{R(t)}^{R_i(t)}S(\sigma_i,\beta_i)r^2dr|\leq M\delta \text{ (for } i=1,2) \tag{39}$$

where

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

(29) and (30) imply

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

Since $T_0(\sigma) \le T_0(\sigma - \sigma^*) + \sigma^*$ and $-T^0(\beta) \le -\beta_*$ then

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

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

By Lemma 5 it follows that

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

Since $\sigma_i(R_i(t), t) = 0$ (for $j = 1$ or 2), σ and β satisfies

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

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

and then

$$\int_0^{R(t)} (S(\sigma_1, \beta_1) - S(\sigma_2, \beta_2))r^2 dr \le C(T+2)\delta. \tag{40}$$

Integrating in time in (38), we get thanks to (39) and (40) that

$$R_1^3(t) - R_2^3(t) \le TC(T+2)\delta + 2TM\delta. \tag{41}$$

On the other hand, one has

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

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

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

Substituting this into (41) leads to $\delta \le k_0 \delta T$. Furthermore, taking $T_1 < \frac{1}{k_0}$ 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 (37) and taking σ as test function we obtain

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

As in Lemma 5, 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 (30) that $(g_1(\sigma_1, 0) - g_1(\sigma_2, 0))\sigma \le 0$, which prove $\sigma = 0$.

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

Remark 4 *We can obtain uniqueness of solutions for more general reaction terms. When the functions g_i satisfies:*

$$\begin{cases} g_1(\sigma,\beta) \geq k_1((\beta-\beta^*)^+ + (\sigma-\sigma^*)^+), \\ \textit{if } \sigma^* \leq \sigma \\ g_2(\sigma,\beta) \geq k_2((\beta-\beta^*)^+ + (\sigma-\sigma^*)^+), \\ \textit{if } \beta^* \leq \beta \\ g_1(\sigma,\beta) \leq k_3((\beta-\beta_*)^- + (\sigma-\sigma_*)^-), \\ \textit{if } \sigma_* \geq \sigma \\ g_2(\sigma,\beta) \leq k_4((\beta-\beta_*)^- + (\sigma-\sigma_*)^-), \\ \textit{if } \beta_* \geq \beta. \end{cases}$$

$$(\frac{\partial}{\partial u} g_1(u,v))^- + (\frac{\partial}{\partial v} g_2(u,v))^- > k,$$

$$\frac{\partial}{\partial v} g_1(u,v) \leq 0,\ \frac{\partial}{\partial u} g_2(u,v) \leq 0$$

$$g_i(0,0) \leq 0,,\ \frac{\partial}{\partial u} g_i(u,v) + \frac{\partial}{\partial v} g_i(u,v) \geq 0,\ \textit{for } i=1,2,$$

$$(\sigma_0, \beta_0) \in W^{1,\infty},$$

$$\begin{cases} g_1(\sigma_1,\beta_1) - g_1(\sigma_2,\beta_2) \geq k_5((\sigma_1-\sigma_2-\sigma^{**})^+ + (\beta_1-\beta_2-\beta^{**})^+) \\ \textit{if } \sigma_1 \geq \sigma_2 + \sigma^{**}, \\ g_2(\sigma_1,\beta_1) - g_2(\sigma_2,\beta_2) \geq k_6((\sigma_1-\sigma_2-\sigma^{**})^+ + (\beta_1-\beta_2-\beta^{**})^+) \\ \textit{if } \beta_1 \geq \beta_2 + \beta^{**}, \\ g_1(\sigma_1,\beta_1) - g_1(\sigma_2,\beta_2) \leq k_7((\sigma_1-\sigma_2-\sigma_{**})^- + (\beta_1-\beta_2-\beta_{**})^-) \\ \textit{if } \sigma_1 \leq \sigma_2 + \sigma_{**}, \\ g_2(\sigma_1,\beta_1) - g_2(\sigma_2,\beta_2) \leq k_8((\sigma_1-\sigma_2-\sigma_{**})^- + (\beta_1-\beta_2-\beta_{**})^-) \\ \textit{if } \beta_1 \leq \beta_2 + \beta_{**}, \end{cases}$$

The above uniqueness result extends the uniqueness result by Cui and Friedman [5] for the non necrotic case (i.e. linear functions g_i).

Remark 5 *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 the solution is bounded and satisfies the original problem.*

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