On a free boundary problem modeling the growth of necrotic tumors in presence of inhibitors.

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Abstract

We study a model of 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 its interaction with the nutrients. We show the existence and uniqueness of the solution of the model under suitable conditions on the inhibitors interaction and the tumor growth .

Modeling.

The growth of a tumor is a complicated phenomenon. In this process many different biological aspects arise: the *necrosis* (death of cells caused by insufficient level of nutrients), *apoptosis* (natural cell death, it is intrinsic property of the cell), the *mitosis* (birth of cells by cells divisions), the diffusion of nutrients and inhibitors and *vascularization* (contribution of nutrients through vessels ducts). We study here a simple mathematical model for this process. Previous similar models were considered by Greenspan [1972], Byrne and Chaplain [1996], Friedman and Reitich [1998] and Cui and Friedman [1998].

The tumor comprised a central necrotic core, where the cells die caused by necrosis, when the concentration of nutrients $\widehat{\sigma}$ (oxygen, glucose, etc.) falls below a critical level σ_{nec}. Then there is an early disintegration of the cells into simpler chemical compounds. We assume the spherical symmetry on the tumor. The 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: one the outer boundary, denoted by $R(t)$ and delimiting the tumor, and a second, the inner free boundary, denoted by $\rho(t)$, separating the necrotic core of the remaining part.

By the principle of conservation of the mass, assuming the cell mass density constant, the tumor mass is proportional to the volume ($\frac{4}{3}\pi R(t)^3$). The balance between birth and death of cell is determinate by the concentration of nutrients. If we assume the presence of some inhibitors, and denote its concentration by $\widehat{\beta}$, the birth and death of cells clearly depend of $\widehat{\beta}$. Denoting by $\widehat{S}$ the above balance, after normalizing we obtain the law

$$\frac{d}{dt}(\frac{4}{3}\pi R(t)^3) = \int_{\{r<R(t)\}} \widehat{S}(\widehat{\sigma},\widehat{\beta})r^2 dr.$$

Depending of the kind of inhibitors, function $\widehat{S}$ admits different expressions. Greenspan [1972] study the problem in the presence of inhibitors and the possibility this affect mitosis, when the concentration of inhibitors 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 (1995), study the growth when the inhibitor affect the cell proliferation, and propose $\widehat{S}(\widehat{\sigma},\widehat{\beta}) = s(\widehat{\sigma}-\widetilde{\sigma})(1-\frac{\widehat{\beta}}{\widetilde{\beta}})$. In absence of inhibitors, or when inhibitor does not affect the mitosis, they take $\widehat{S}(\widehat{\sigma},\widehat{\beta}) = s\widehat{\sigma}(\widehat{\sigma}-\widetilde{\sigma})$. Friedman and Reitich [1998] and Cui and Friedman [1998] study the asymptotic behavior of the radius, $R(t)$, with the cell proliferation rate free of inhibitors action. 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 from ducts, named vasculature, occurs when the concentration is less than a certain level σ_B, and with a rate Γ_1. The nutrient consumption rate is $\lambda_1\widehat{\sigma}$. Both processes occur simultaneously in the exterior to the necrotic core. We suppose that the tumor is composed by an homogenous tissue, and that the diffusion coefficient is D_1. We also assume a constant diffusion coefficient for the inhibitor concentration $\widehat{\beta}$. The reaction between nutrients and inhibitors is modeled by some functions $\widehat{g}_i(\widehat{\sigma},\widehat{\beta})$. Adding initial and boundary conditions we obtain

$$\begin{cases} \dfrac{\partial\widehat{\sigma}}{\partial t} - \dfrac{D_1}{r^2}\dfrac{\partial}{\partial r}(r^2\dfrac{\partial}{\partial r}\widehat{\sigma}) - (\Gamma_1(\sigma_B-\widehat{\sigma}) - \lambda_1\widehat{\sigma})H(\widehat{\sigma}-\sigma_{nec}) - \widehat{g}_1(\widehat{\sigma},\widehat{\beta}) \ni 0, & 0<r<R(t), \\ \dfrac{\partial\widehat{\beta}}{\partial t} - \dfrac{D_2}{r^2}\dfrac{\partial}{\partial r}(r^2\dfrac{\partial}{\partial r}\widehat{\beta}) - \Gamma_2(\beta_B-\widehat{\beta})H(\widehat{\sigma}-\sigma_{nec}) - \widehat{g}_2(\widehat{\sigma},\widehat{\beta}) \ni 0, & 0<r<R(t), \\ R(t)^2\dfrac{dR(t)}{dt} = \displaystyle\int_0^{R(t)} \widehat{S}(\widehat{\sigma},\widehat{\beta})r^2dr, & t>0, \\ \dfrac{\partial\widehat{\sigma}}{\partial r}(0,t) = 0, \dfrac{\partial\widehat{\beta}}{\partial r}(0,t) = 0,\ \widehat{\sigma}(R(t),t) = \overline{\overline{\sigma}},\ \widehat{\beta}(R(t),t) = \overline{\overline{\beta}}, & t>0, \\ R(0) = R_0,\ \widehat{\sigma}(r,0) = \sigma_0(r),\ \widehat{\beta}(r,0) = \beta_0(r), & 0<r<R_0, \end{cases} \tag{1}$$

where $D_1, D_2, \Gamma_1, \Gamma_2, \sigma_B, \beta_B, \lambda_1, \sigma_{nec}, \overline{\overline{\sigma}}$ and $\overline{\overline{\beta}}$ are parameters of the problem.

After sending, in January of 1999, a short version of the result of this work to the organizers of this congress we learned, from A. Friedman, the apparition of the manuscript Cui and Friedman [1999], where the authors also extend the Byrne-Chaplain necrotic model by introducing some Heaviside function. The authors thank A. Friedman for several conversations hold on this subject and that, in fact, motivate this work.

Existence of solutions.

Theorem 1 *Assume $\widehat{g}_1, \widehat{g}_2$ and $\widehat{S}$ continuous functions, with a sublinear growth at the infinity. Let $R_0 > 0$ and σ_0, $\beta_0 \in L^2(0,R_0)$. Then (1) has, at least, a weak solution.*

Our proof starts by introducing an equivalent formulation but defined on a cylindrical global domain. We introduce the change of variables and unknowns by $x = \frac{r}{R(t)}$ and $u(t,\frac{r}{R(t)}) = \widehat{\sigma}(t,r) - \overline{\overline{\sigma}}$, $v(t,\frac{r}{R(t)}) = \widehat{\beta}(t,r) - \overline{\overline{\beta}}$. It is also useful to introduce the functions,

$$g_1(\sigma-\overline{\overline{\sigma}},\beta-\overline{\overline{\beta}})=-(\Gamma_1(\sigma_B-\widehat{\sigma})-\lambda_1\widehat{\sigma})H(\widehat{\sigma}-\sigma_{nec})-\widehat{g}_1(\widehat{\sigma},\widehat{\beta}) \tag{2}$$

$$g_2(\sigma-\overline{\overline{\sigma}},\beta-\overline{\overline{\beta}})=-\Gamma_2(\beta_B-\widehat{\beta})H(\widehat{\sigma}-\sigma_{nec})-\widehat{g}_2(\widehat{\sigma},\widehat{\beta}) \tag{3}$$

$$S(\widehat{\sigma}(t,r)-\overline{\overline{\sigma}},\widehat{\beta}(t,r)-\overline{\overline{\beta}}):=\widehat{S}(\widehat{\sigma},\widehat{\beta}). \tag{4}$$

Then problem (1) becomes

$$\begin{cases} \dfrac{\partial u}{\partial t}-\dfrac{1}{R(t)^2}\dfrac{D_1}{x^2}\dfrac{\partial}{\partial x}(x^2\dfrac{\partial}{\partial x}u)-u_x\dfrac{R'(t)}{R(t)}-g_1(u,v)\ni 0, & 0<x<1,\ t>0,\\ \dfrac{\partial v}{\partial t}-\dfrac{1}{R(t)^2}\dfrac{D_2}{x^2}\dfrac{\partial}{\partial x}(x^2\dfrac{\partial}{\partial x}v)-v_x\dfrac{R'(t)}{R(t)}-g_2(u,v)\ni 0, & 0\le x<1,\ t>0,\\ R(t)^{-1}\dfrac{dR(t)}{dt}=\displaystyle\int_0^1 S(u,v)x^2dx, & t>0,\\ \dfrac{\partial u}{\partial r}(0,t)=0,\ \dfrac{\partial v}{\partial r}(0,t)=0,\ u(1,t)=\ v(1,t)=0, & t>0,\\ R(0)=R_0,\ u(x,0)=u_0(x),\ v(x,0)=v_0(x), & t>0, 0<x<1. \end{cases} \tag{5}$$

For $c>0$ we introduce the Hilbert spaces $H(0,c)=\{(\varphi,\phi):(x\varphi,x\phi)\in L^2(0,c)^2\}$ and $V(0,c)=\{(\varphi,\phi)\in H,(x\frac{\partial}{\partial x}\varphi,x\frac{\partial}{\partial x}\phi)\in H(0,c),\varphi(c)=\phi(c)=0\}$. The scalar product in $V(0,c)$ is given by $<\varphi,\phi>_{V(0,c)}=\int_0^c x^2(\frac{\partial}{\partial x}\varphi)(\frac{\partial}{\partial x}\phi)dx$. For the sake of simplicity in the notation we use $H=H(0,1)$, $V(0,1)=V$.

Theorem 2 *Under the conditions of Theorem1 there exist, at least, a weak solution* $(R,u,v)\in H^1(0,T)\times[L^2(0,T:V)\cap C([0,T]:H)]^2$ *of problem* (5).

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

Proposition 1 *(Showalter[1996]) Let* $f\in L^2(0,T:V')$ *and* $u_0\in H$. *Let* $T>0$ *and let* $a(t,\varphi,\phi)$ *be a bilinear form such that* $a(t,.,.):V\times V:\longrightarrow R$ *is measurable,* $a(t,\varphi,\phi)\le M||\varphi||||\phi||$ *and* $a(t,\varphi,\varphi)\ge\alpha||\varphi||^2-c|\varphi|^2$, *where* $\alpha>0$ *and* $|.|$ *and* $||.||$ *are the norms in* H *and* V. *Then there exists* $u\in L^2(0,T:V)\cap C([0,T]:H)$, *such that* $\frac{\partial u}{\partial t}\in L^2(0,T:V')$ *and*

$$\begin{cases} <\frac{\partial u}{\partial t}(t),\phi>+a(t,u(t),\phi)=<f(t),\phi> \quad a.e\ t\in(0,T),\ \forall\phi\in V,\\ u(0)=u_0 \end{cases}$$

where H *and* V *are two Hilbert spaces,* $V\subset H$ *with continuous and dense embedding.*

Lemma 1 *(Simon [1987]) Let* B_0,B,B_1 *be three Banach spaces such that* $B_0\subset B\subset B_1$, *and the embedding* $B_0\subset B$ *is compact. Then the space* $W=\{v,v\in L^{p_0}(0,T;B_0),\ \frac{\partial v}{\partial t}\in L^{p_1}(0,T;B_1)\}$, *for some* $1<p_0,p_1<\infty$ *is compactly embedded in* $L^{p_0}(0,T,B)$.

PROOF OF THEOREM 2. We consider the operator $A(R(t)) : V \to V'$ defined by

$$A(R(t))(u,v) = \begin{pmatrix} -\frac{1}{R(t)^2}\frac{D_1}{x^2}\frac{\partial}{\partial x}(x^2\frac{\partial}{\partial x}u) - \frac{R'(t)}{R(t)}\frac{\partial}{\partial x}u & 0 \\ 0 & -\frac{1}{R(t)^2}\frac{D_1}{x^2}\frac{\partial}{\partial x}(x^2\frac{\partial}{\partial x}v) - \frac{R(t)'}{R(t)}\frac{\partial}{\partial x}v \end{pmatrix}$$

Without any difficulty we can see that A define a continuous bilinear form a which is coercive since

$$\begin{aligned} a(t,(u,v),(u,v)) &= \tfrac{D_1}{R(t)^2}\int_0^1 x^2(\tfrac{\partial}{\partial x}u)^2dx + \tfrac{D_2}{R(t)^2}\int_0^1 x^2(\tfrac{\partial}{\partial x}v)^2dx - \\ &\quad -\tfrac{R'(t)}{R(t)}\int_0^1 x^2(\tfrac{\partial}{\partial x}u)udx - \tfrac{R(t)'}{R(t)}\int_0^1 x^2(\tfrac{\partial}{\partial x}v)vdx \\ &\geq D\tfrac{1}{R(t)^2}(\int_0^1 x^2(\tfrac{\partial}{\partial x}u)^2dx + \int_0^1 x^2(\tfrac{\partial}{\partial x}v)^2dx) = \tfrac{D}{R(t)^2}||(u,v)||_V^2 \geq c||(u,v)||_V^2 \end{aligned}$$

where $D = \min\{D_1, D_2\}$. Let $G : V \to V'$ be defined by $G(u,v) = (g_1(u,v), g_2(u,v))$. Let $U_n = (u_n, v_n)$ and $R_{n-1}(t) = R(0)e^{\int_0^t\int_0^1 S(u_{n-1},v_{n-1})x^2dxds}$ be the solution of the problem:

$$\begin{cases} \frac{\partial U_n}{\partial t}(t) + A(R_{n-1}(t))U_n(t) = G(U_{n-1}) \quad in\ (0,1)\times(0,T) \\ U_n(0) = u_0. \end{cases} \tag{6}$$

By Proposition 1 there is a unique solution of (6). Moreover taking U_n as test function in (6) we obtain

$$\frac{d}{dt}\int_0^1 x^2\frac{1}{2}(U_n^2)dx + \frac{D}{R_{n-1}(t)^2}||U_n||_V^2 \leq ||G(U_{n-i})||_H||U_n||_H$$

and integrating in time

$$||U_n||^2_{L^2(0,T:V)} \leq \frac{R_{n-1}^2(T)}{D}(||G(U_{n-1})||_{L^2(0,T:H)}||U_n||_{L^2(0,T:H)} + \frac{1}{2}||U_0||_H^2).$$

Making a dilatation and replacing the domain $(0,1)$ by $(0,c)$, with $c \geq 1$, we get

$$||U_n||^2_{L^2(0,T:V(0,c))} \leq \frac{R_{n-1}^2(T)c}{D}(\frac{1}{c^3}||G(U_{n-1})||_{L^2(0,T:H(0,c))}||U_n||_{L^2(0,T:H(0,c))} + \frac{1}{2}||U_0||_H^2).$$

But $R_{n-1}^2(T) = R_0^2e^{\int_0^T\int_0^1 S(U_{n-1})x^2dxds}$ and since $\int_0^1 S(U_{n-1})x^2dx \leq s_0 + ||U_{n-1}||_H = s_0 + (\frac{1}{c})^3||U_{n-1}||_{H(0,c)}$, for some $s_0 > 0$ we get that $||U_n||^2_{L^2(0,T:V(0,c))}$ is majored by

$$\frac{R_0^2e^{s_0+\frac{1}{c^3}||U_{n-1}||_{H(0,c)}}}{D}(\frac{1}{c^2}||G(U_{n-1})||_{L^2(0,T:H(0,c))}||U_n||_{L^2(0,T:H(0,c))} + \frac{c}{2}||U_0||_H^2).$$

Using that $||G(U_{n-1})||_{L^2(0,T,H)} \leq G_0 + G_1||U_{n-1}||_{L^2(0,T,H)}$, for some positive G_0 and G_1, if we take $c = 2(G_0+G_1)\frac{R(0)^2e^{s+1}}{D} + 1$ and define $K = \{w \in L^2(0,T : V(0,c)) : ||w||_{L^2(0,T:V(0,c)} \leq c^{\frac{1}{2}}||U_0||\}$ then we have that $U_n \in K$. Moreover, since $\frac{\partial U_n}{\partial t}(t) = -A(R_{n-1}(t))U_n(t) + G(U_{n-1})$, then $\frac{\partial U_n}{\partial t}$ is bounded in $L^2(0,T : V'(0,c))$. Coming back to the original problem we can assume, again, $c = 1$. So, there exists a subsequence $U_n \in L^2(0,T : V)$ with $\frac{d}{dt}U_n \in L^2(0,T : V')$ such that $(U_n, \frac{d}{dt}U_n) \rightharpoonup (U, \frac{d}{dt}U)$ weakly

in $L^2(0,T:V)\times L^2(0,T:V')$. Using Lemma 1 we conclude that $U_n\to U$ strongly in $L^2(0,T:H)$. Moreover, the continuity of function S implies that $R_n\to R$ strongly in $H^1(0,T)$. Besides, it is easy to see that $G(U_{n-1})\rightharpoonup G(U)$ weakly in $L^2(0,T:H)$. Then taking limits as $n\to\infty$ in the weak formulation of the problem (6) we get

$$-\int_0^T <U,\frac{\partial\Phi}{\partial t}>_H dt+<U,\Phi>_H|_0^T+\int_0^T a(R(t),U,\Phi)dt=\int_0^T <G(U),\Phi>_H dt$$

for any $\Phi\in L^2(0,T:V)$. So (R,U) is a weak solution of the problem.

Uniqueness of solutions.

For $(\widehat{\sigma},\widehat{\beta})$ solutions of the problem (1) we define $\sigma=\widehat{\sigma}-\overline{\overline{\sigma}}$ and $\beta=\widehat{\beta}-\overline{\overline{\beta}}$. It is easy to see that (σ,β) verifies

$$\begin{cases}
\dfrac{\partial\sigma}{\partial t}-\dfrac{D_1}{r^2}\dfrac{\partial}{\partial r}(r^2\dfrac{\partial}{\partial r}\sigma)+g_1(\sigma,\beta)\ni 0, & 0<r<R(t),\ t>0,\\
\dfrac{\partial\beta}{\partial t}-\dfrac{D_2}{r^2}\dfrac{\partial}{\partial r}(r^2\dfrac{\partial}{\partial r}\beta)+g_2(\sigma,\beta)\ni 0, & 0\le r<R(t),\ t>0,\\
R(t)^2\dfrac{dR(t)}{dt}=\displaystyle\int_0^{R(t)} S(\sigma,\beta)dx, & t>0,\\
\dfrac{\partial}{\partial r}\sigma(0,t)=0,\ \dfrac{\partial\beta}{\partial r}(0,t)=0,\ \sigma(R(t),t)=0,\ \beta(R(t),t)=0, & t>0,\\
R(0)=R_0,\ \sigma(r,0)=\sigma_0(r),\ \beta(r,0)=\beta_0(r), & 0<r<R_0,
\end{cases}\tag{7}$$

where g_i were given by (2) and (3). We also define the real numbers $\sigma^*=\max\{0,\max\sigma_0(r)\}$, $\sigma_*=\min\{0,\min\sigma_0(r)\}$, $\beta^*=\max\{0,\max\beta_0(r)\}$ and $\beta_*=\min\{0,\min\beta_0(r)\}$. Now we replace the concrete g_i given in (2) and (3) by general functions g_i satisfying the following structural conditions

$$\begin{cases}
g_1(\sigma,\beta)\ge k_1((\beta-\beta^*)^+ +(\sigma-\sigma^*)^+), & \text{if } \sigma^*\le\sigma\\
g_2(\sigma,\beta)\ge k_2((\beta-\beta^*)^+ +(\sigma-\sigma^*)^+), & \text{if } \beta^*\le\beta\\
g_1(\sigma,\beta)\le k_3((\beta-\beta_*)^- +(\sigma-\sigma_*)^-), & \text{if } \sigma_*\ge\sigma\\
g_2(\sigma,\beta)\le k_4((\beta-\beta_*)^- +(\sigma-\sigma_*)^-), & \text{if } \beta_*\ge\beta
\end{cases}\tag{8}$$

where $(.)^+$ is the positive part and $(x)^-=(-x)^+$,

$$\begin{cases}
g_1(\sigma_1,\beta_1)-g_1(\sigma_2,\beta_2)\ge k_5((\sigma_1-\sigma_2-\sigma^{**})^+ +(\beta_1-\beta_2-\beta^{**})^+) & \text{if } \sigma_1\ge\sigma_2+\sigma^{**},\\
g_2(\sigma_1,\beta_1)-g_2(\sigma_2,\beta_2)\ge k_6((\sigma_1-\sigma_2-\sigma^{**})^+ +(\beta_1-\beta_2-\beta^{**})^+) & \text{if } \beta_1\ge\beta_2+\beta^{**},\\
g_1(\sigma_1,\beta_1)-g_1(\sigma_2,\beta_2)\le k_7((\sigma_1-\sigma_2-\sigma_{**})^- +(\beta_1-\beta_2-\beta_{**})^-) & \text{if } \sigma_1\le\sigma_2+\sigma_{**},\\
g_2(\sigma_1,\beta_1)-g_2(\sigma_2,\beta_2)\le k_8((\sigma_1-\sigma_2-\sigma_{**})^- +(\beta_1-\beta_2-\beta_{**})^-) & \text{f } \beta_1\le\beta_2+\beta_{**},
\end{cases}\tag{9}$$

$$S\in W^{1,\infty}(\mathbb{R}^2),\tag{10}$$

$$(g_1, g_2) \in (W^{1,\infty}(\mathbb{R}^2))^2, \tag{11}$$

$$\frac{\partial}{\partial v} g_1(u,v) \leq 0, \; \frac{\partial}{\partial u} g_2(u,v) \leq 0, \tag{12}$$

$$g_i(0,0) \leq 0 \text{ and } \frac{\partial}{\partial u} g_i(u,v) + \frac{\partial}{\partial v} g_i(u,v) \geq 0, \text{ for } i = 1,2. \tag{13}$$

Remark: When the functions (g_1, g_2) do not satisfy (13), it can be obtain taking $(\sigma, \beta) = e^{\omega t}(u,v)$.

The main result of this section is

Theorem 3 *Under conditions* $(8)-(13)$ *and starting from initial datum* $\sigma_0 \leq 0$, $\beta_0 \leq 0$,*there is, at most, one solution of* (6).

We shall need some previous results:

Lemma 2 *Any solution* (σ, β) *of problem* (7) *is bounded. Moreover,* $\sigma_* \leq \sigma \leq \sigma^*$ *and* $\beta_* \leq \beta \leq \beta^*$.

PROOF: Let H_ε be an approximation of the Heaviside function. Taking $H_\varepsilon(\sigma - \sigma^*)$ and $H_\varepsilon(\beta - \beta^*))$ as test functions and passing to the limit, we get that $\frac{d}{dt}\int_0^{R(t)} r^2(\sigma - \sigma^*)^+ dr \leq -\int_0^{R(t)} g_1(\sigma,\beta) H(\sigma - \sigma^*) r^2 dr$ and

$$\frac{d}{dt}\int_0^{R(t)} r^2(\beta - \beta^*)^+ dr \leq -\int_0^{R(t)} g_2(\sigma,\beta) H(\beta - \beta^*) r^2 dr.$$

By (8) we conclude that

$$\frac{d}{dt}\left(\int_0^{R(t)} r^2(\sigma - \sigma^*)^+ dr + \int_0^{R(t)} r^2(\beta - \beta^*)^+ dr\right) \leq$$
$$(k_1 - k_2)\left(\int_0^{R(t)} r^2(\sigma - \sigma^*)^+ dr + \int_0^{R(t)} r^2(\beta - \beta^*)^+ dr\right)$$

Then by Gronwall's Lemma.

$$\int_0^{R(t)} r^2(\sigma - \sigma^*)^+ dr + \int_0^{R(t)} r^2(\beta - \beta^*)^+ dr = 0$$

and so $\sigma \leq \sigma^*$ and $\beta \leq \beta^*$. Now we repeat the same operation but now with $H_\varepsilon(\sigma - \sigma_*) - 1$ and $H_\varepsilon(\beta - \beta_*) - 1$ as test functions. By (8) and using again Gronwall's Lemma we conclude that $\sigma_* \leq \sigma$ and $\beta_* \leq \beta$.∎

Like consequence of this lemma, is easy to proof that there exists a constant M, such that $R(t) \leq R(0)e^{Mt}$. We have proved that $(\sigma(r,t), \beta(r,t)) \in [\sigma_*, \sigma^*] \times [\beta_*, \beta^*]$, that is a compact set, like $\widehat{S}$ is a continuous function, it takes his maximum in this set, let M be this maximum. working with the change of variables of Theorem 1, we obtain, $R(t)^{-1}\frac{dR(t)}{dt} \leq \int_0^1 Mx^2 dx$, and then, $\frac{dR(t)}{dt} \leq MR(t)$, and by Gronwall's Lemma, it result $R(t) \leq R(0)e^{Mt}$.

Lemma 3 *There exist $k_9 \geq 0$, such that $r^2\frac{\partial}{\partial r}\sigma \leq k_9$ and $r^2\frac{\partial}{\partial r}\beta \leq k_9$.*

PROOF: In order to proof this lemma, we shall work with the extension of the solution, $(\widetilde{\sigma},\widetilde{\beta})$,is defined in $(0,T)\times(0,R(0)e^{MT}+1)$

$$(\widetilde{\sigma},\widetilde{\beta}) = \begin{cases} (\sigma,\beta), & \text{if } 0 \leq r \leq R(t) \\ (0,0), & \text{if } R(t) \leq r \leq R(0)e^{MT}+1, \end{cases} \tag{14}$$

then $(\widetilde{\sigma},\widetilde{\beta})$, is the solution of the next problem

$$\begin{cases} (\dfrac{\partial\widetilde{\sigma}}{\partial t} - \dfrac{D_1}{r^2}\dfrac{\partial}{\partial r}(r^2\dfrac{\partial}{\partial r}\widetilde{\sigma}) + g_1(\widetilde{\sigma},\widetilde{\beta}))H(R(t)-r) \ni 0, & 0 < r < R(0)e^{MT}+1,\ t>0, \\ (\dfrac{\partial\widetilde{\beta}}{\partial t} - \dfrac{D_2}{r^2}\dfrac{\partial}{\partial r}(r^2\dfrac{\partial}{\partial r}\widetilde{\beta}) + g_2(\widetilde{\sigma},\widetilde{\beta}))H(R(t)-r) \ni 0, & 0 \leq r < R(0)e^{MT}+1,\ t>0, \\ R(t)^2\dfrac{dR(t)}{dt} = \displaystyle\int_0^{R(t)} S(\widetilde{\sigma},\widetilde{\beta})dx, & t>0, \\ \dfrac{\partial}{\partial r}\widetilde{\sigma}(0,t)=0,\ \dfrac{\partial\widetilde{\beta}}{\partial r}(0,t)=0, & t>0, \\ \frac{\partial}{\partial r}\widetilde{\sigma}(R(0)e^{MT}+1,t)=0,\ \frac{\partial\widetilde{\beta}}{\partial r}(R(0)e^{MT}+1,t)=0, & \\ R(0)=R_0,\ \widetilde{\sigma}(r,0)=\widetilde{\sigma}_0(r),\ \widetilde{\beta}(r,0)=\widetilde{\beta}_0(r), & 0<r<R_0, \end{cases} \tag{15}$$

deriving respect to r the equation, we obtain the next equation.

$$\begin{cases} (\dfrac{\partial}{\partial t}(\dfrac{\partial\widetilde{\sigma}}{\partial r}) - \dfrac{\partial}{\partial r}(\dfrac{D_1}{r^2}\dfrac{\partial}{\partial r}(r^2\dfrac{\partial\widetilde{\sigma}}{\partial r})) + (\dfrac{\partial g_1}{\partial\widetilde{\sigma}})(\dfrac{\partial\widetilde{\sigma}}{\partial r}) + (\dfrac{\partial g_1}{\partial\widetilde{\beta}})(\dfrac{\partial\widetilde{\beta}}{\partial r}))H(R(t)-r)+ \\ +(\dfrac{\partial\widetilde{\sigma}}{\partial t} - \dfrac{D_1}{r^2}\dfrac{\partial}{\partial r}(r^2\dfrac{\partial}{\partial r}\widetilde{\sigma}) + g_1(\widetilde{\sigma},\widetilde{\beta}))\dfrac{\partial}{\partial r}(H(R(t)-r)) \ni 0,\ 0 \leq r < R(0)e^{MT}+1,\ t>0, \\ (\dfrac{\partial}{\partial t}(\dfrac{\partial\widetilde{\beta}}{\partial r}) - \dfrac{\partial}{\partial r}(\dfrac{D_1}{r^2}\dfrac{\partial}{\partial r}(r^2\dfrac{\partial\widetilde{\beta}}{\partial r})) + (\dfrac{\partial g_2}{\partial\widetilde{\sigma}})(\dfrac{\partial\widetilde{\sigma}}{\partial r}) + (\dfrac{\partial g_2}{\partial\widetilde{\beta}})(\dfrac{\partial\widetilde{\beta}}{\partial r}))H(R(t)-r)+ \\ +(\dfrac{\partial\widetilde{\beta}}{\partial t} - \dfrac{D_2}{r^2}\dfrac{\partial}{\partial r}(r^2\dfrac{\partial}{\partial r}\widetilde{\beta}) + g_2(\widetilde{\sigma},\widetilde{\beta}))\dfrac{\partial}{\partial r}(H(R(t)-r)) \ni 0,\ 0 \leq r < R(0)e^{MT}+1,\ t>0, \end{cases} \tag{16}$$

We start from initial datum $(\sigma_0(r),\beta_0(r))$ such that there exist k_9, satisfying $0 \leq r^2\frac{\partial}{\partial r}\sigma_0(r) \leq k_9$, and $0 \leq r^2\frac{\partial}{\partial r}\beta_0(r) \leq k_9$. We take $(H_\varepsilon(r^2\frac{\partial}{\partial r}\widetilde{\sigma}-k_9), H_\varepsilon(r^2\frac{\partial}{\partial r}\widetilde{\beta}-k_9))$ as test function in (17) and passing limit we get that:

$$\frac{d}{dt}\int_0^{R(t)} r^{-2}(r^2\frac{\partial}{\partial r}\widetilde{\sigma}-k_9)^+dr + \int_0^{R(t)}\frac{D_1}{r^2}(\frac{\partial}{\partial r}(r^2\frac{\partial\widetilde{\sigma}}{\partial r}))^2H'(r^2\frac{\partial}{\partial r}\widetilde{\sigma}-k_9)dr+$$

$$+\int_0^{R(t)}((\frac{\partial g_1}{\partial\widetilde{\sigma}})(\frac{\partial\widetilde{\sigma}}{\partial r})+(\frac{\partial g_1}{\partial\widetilde{\beta}})(\frac{\partial\widetilde{\beta}}{\partial r}))H(r^2\frac{\partial}{\partial r}\widetilde{\sigma}-k_9)dr - g_1(0,0)H(r^2\frac{\partial}{\partial r}\widetilde{\sigma}(R(t),t)-k_9) = 0$$

and

$$\frac{d}{dt}\int_0^{R(t)} r^{-2}(r^2\frac{\partial}{\partial r}\widetilde{\beta}-k_9)^+dr+\int_0^{R(t)}\frac{D_2}{r^2}(\frac{\partial}{\partial r}(r^2\frac{\partial\widetilde{\beta}}{\partial r}))^2H'(r^2\frac{\partial}{\partial r}\widetilde{\beta}-k_9)dr+$$

$$+\int_0^{R(t)}((\frac{\partial g_2}{\partial\widetilde{\beta}})(\frac{\partial\widetilde{\beta}}{\partial r})+(\frac{\partial g_2}{\partial\widetilde{\sigma}})(\frac{\partial\widetilde{\sigma}}{\partial r}))(H(r^2\frac{\partial}{\partial r}\widetilde{\beta}-k_9))dr-g_2(0,0)(H(r^2\frac{\partial}{\partial r}\widetilde{\beta}-k_9))=0$$

and by hypothesis (12) it result,

$$\frac{d}{dt}\int_0^{R(t)} r^{-2}(r^2\frac{\partial}{\partial r}\widetilde{\sigma}-k_9)^+dr\leq-\int_0^{R(t)}((\frac{\partial g_1}{\partial\widetilde{\sigma}})(\frac{\partial\widetilde{\sigma}}{\partial r})+(\frac{\partial g_1}{\partial\widetilde{\beta}})(\frac{\partial\widetilde{\beta}}{\partial r}))H(r^2\frac{\partial}{\partial r}\widetilde{\sigma}-k_9)dr\leq$$

$$\leq-\int_0^{R(t)} r^{-2}((\frac{\partial g_1}{\partial\widetilde{\sigma}})(r^2\frac{\partial\widetilde{\sigma}}{\partial r}-k_9)+(\frac{\partial g_1}{\partial\widetilde{\beta}})(r^2\frac{\partial\widetilde{\beta}}{\partial r}-k_9)+k_9(\frac{\partial g_1}{\partial\widetilde{\sigma}}+\frac{\partial g_1}{\partial\widetilde{\beta}}))H(r^2\frac{\partial}{\partial r}\widetilde{\sigma}-k_9)dr$$

and

$$\frac{d}{dt}\int_0^{R(t)} r^{-2}(r^2\frac{\partial}{\partial r}\widetilde{\beta}-k_9)^+dr\leq-\int_0^{R(t)}((\frac{\partial g_2}{\partial\widetilde{\sigma}})(\frac{\partial\widetilde{\sigma}}{\partial r})+(\frac{\partial g_2}{\partial\widetilde{\beta}})(\frac{\partial\widetilde{\beta}}{\partial r}))H(r^2\frac{\partial}{\partial r}\widetilde{\beta}-k_9)dr\leq$$

$$\leq-\int_0^{R(t)} r^{-2}((\frac{\partial g_2}{\partial\widetilde{\sigma}})(r^2\frac{\partial\widetilde{\sigma}}{\partial r}-k_9)+(\frac{\partial g_2}{\partial\widetilde{\beta}})(r^2\frac{\partial\widetilde{\beta}}{\partial r}-k_9)+k_9(\frac{\partial g_2}{\partial\widetilde{\sigma}}+\frac{\partial g_2}{\partial\widetilde{\beta}}))H(r^2\frac{\partial}{\partial r}\widetilde{\beta}-k_9)dr$$

and by (11), (12), (13) and adding two expressions it results:

$$\frac{d}{dt}(\int_0^{R(t)} r^{-2}(r^2\frac{\partial}{\partial r}\widetilde{\sigma}-k_9)^+dr+\int_0^{R(t)} r^{-2}(r^2\frac{\partial}{\partial r}\widetilde{\beta}-k_9)^+dr)\leq$$

$$k_{10}(\int_0^{R(t)} r^{-2}(r^2\frac{\partial}{\partial r}\widetilde{\sigma}-k_9)^+dr+\int_0^{R(t)} r^{-2}(r^2\frac{\partial}{\partial r}\widetilde{\beta}-k_9)^+dr)$$

and applying Gronwall 's Lemma, we obtain that $(r^2\frac{\partial}{\partial r}\widetilde{\sigma}-k_9)^+=(r^2\frac{\partial}{\partial r}\widetilde{\beta}-k_9)^+=0$.∎

Now, suppose that (σ_1,β_1,R_1) and (σ_2,β_2,R_2) are two different solutions. Let $R(t)=\min\{R_1(t),R_2(t)\}$. Define $\sigma=\sigma_1-\sigma_2$ and $\beta=\beta_1-\beta_2$. Then (σ,β) verifies that

$$\begin{cases}\frac{\partial\sigma}{\partial t}-\frac{D_1}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial}{\partial r}\sigma)+g_1(\sigma_1,\beta_1)-g_1(\sigma_2,\beta_2)\ni 0, & 0<r<R(t),\ t>0,\\ \frac{\partial\beta}{\partial t}-\frac{D_2}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial}{\partial r}\beta)+g_2(\sigma_1,\beta_1)-g_2(\sigma_2,\beta_2)\ni 0, & 0\leq r<R(t),\ t>0,\\ \frac{\partial\sigma}{\partial r}(0,t)=0,\ \sigma(R(t),t)=\sigma_1(R(t),t)-\sigma_2(R(t),t), & t>0,\\ \frac{\partial\beta}{\partial r}(0,t)=0,\ \beta(R(t),t)=\beta_1(R(t),t)-\beta_2(R(t),t), & t>0\\ \sigma(r,0)=0,\ \beta(r,0)=0, & 0<r<R_0.\end{cases}\tag{17}$$

Lemma 4 *$|\sigma|$ and $|\beta|$ take its maximum on the boundary $R(t)$.*

PROOF: Let $\sigma^{**} = max\{0, \sigma(R(t),t)\}$ and $\beta^{**} = max\{0, \beta(R(t),t)\}$. It is easy to see that $\sigma^{**} \in [0, 2\sigma^*]$ and $\beta^{**} \in [0, 2\beta^*]$. Taking $H_\varepsilon(\sigma - \sigma^{**})$ and $H\varepsilon(\beta - \beta^{**})$ as test function in (11) and passing limit we get that:

$$\frac{d}{dt}\int_0^{R(t)} r^2(\sigma-\sigma^{**})^+dr \leq -\int_0^{R(t)} (g_1(\sigma_1,\beta_1) - g_1(\sigma_2,\beta_2))H(\sigma-\sigma^{**}))r^2dr,$$

$$\frac{d}{dt}\int_0^{R(t)} r^2(\beta-\beta^{**})^+dr \leq -\int_0^{R(t)} (g_2(\sigma_1,\beta_1) - g_2(\sigma_2,\beta_2))H(\beta-\beta^{**})r^2dr.$$

Adding the two expressions and thanks to (9) we get that

$$\frac{d}{dt}(\int_0^{R(t)} r^2(\sigma-\sigma^{**})^+dr + \int_0^{R(t)} r^2(\beta-\beta^{**})^+dr) \leq$$

$$(k_5+k_6)(\int_0^{R(t)} r^2(\sigma-\sigma^{**})^+dr + \int_0^{R(t)} r^2(\beta-\beta^{**})^+dr).$$

Applying again Gronwall's Lemma we obtain that

$$\int_0^{R(t)} r^2(\sigma-\sigma^{**})^+dr + \int_0^{R(t)} r^2(\beta-\beta^{**})^+dr = 0.$$

So that σ and β take its maximum at the boundary. If we repeat the argument with test functions $H_\varepsilon(\sigma - \sigma_{**}) - 1$, and $H\varepsilon(\beta - \beta_{**}) - 1$ we get

$$\frac{d}{dt}\int_0^{R(t)} r^2(\sigma-\sigma_{**})^-dr \leq -\int_0^{R(t)} (g_1(\sigma_1,\beta_1) - g_1(\sigma_2,\beta_2))(H(\sigma-\sigma_{**})-1)r^2dr,$$
$$\frac{d}{dt}\int_0^{R(t)} r^2(\beta-\beta_{**})^-dr \leq -\int_0^{R(t)} (g_2(\sigma_1,\beta_1) - g_2(\sigma_2,\beta_2))(H(\beta-\beta_{**})-1)r^2dr.$$

Then, by (9), adding the two expressions it results that

$$\frac{d}{dt}(\int_0^{R(t)} r^2(\sigma-\sigma_{**})^-dr + \int_0^{R(t)} r^2(\beta-\beta_{**})^-dr) \leq$$
$$\leq (k_6+k_7)(\int_0^{R(t)} r^2(\sigma-\sigma_{**})^-dr + \int_0^{R(t)} r^2(\beta-\beta_{**})^-dr).$$

Finally, by Gronwall's Lemma, we obtain that (σ, β) take its minimum at the boundary, and so we conclude that $|\sigma|$ and $|\beta|$ take the maximum in $R(t)$.∎

End of the proof of Theorem 3. Let $\delta = \max\{|R_1(t) - R_2(t)|\}$. Using that

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

and since S is a Lipschitz function we obtain that $|\int_{R_1(t)}^{R_2(t)} S(\sigma_2,\beta_2)r^2dr| \leq M\ \delta$, where M is the $\max\{S(x,y), (x,y) \in [\sigma_*, \sigma^*] \times [\beta_*, \beta^*]\}$. Analogously,

$$\int_0^{R_1(t)} (S(\sigma_1,\beta_1) - S(\sigma_2,\beta_2)r^2)dr \leq C(||\sigma_1-\sigma_2||_{L^\infty} + ||\beta_1-\beta_2||_{L^\infty})$$

. By lemma 4, we know the maximum of $|\sigma|$ and $|\beta|$ is taken in $R(t)$,
Since like we start from negative initial datum, and applying lemma 3, we obtain

$$|\sigma(R(t),t)| \leq k_9 R_0^2 |R_1(t) - R_2(t)| \text{ and } |\beta(R(t),t)| \leq k_9 R_0^2 |R_1(t) - R_2(t)|.$$

Then $|R_1^2(t)R_1'(t) - R_2^2(t)R_2'(t)| \leq C_0\delta$ for some C_0 independent of δ. Integrating we get that $|R_1^3(t) - R_2^3(t)| \leq 3C_0\delta\ T$ and since $|R_1^3(t) - R_2^3(t)| \geq 3R_0^2|R_1(t) - R_2(t)|$ we conclude that, $\delta \leq k_0\delta\ T$. So, if $T < \frac{1}{k_0} = T_1$ necessarily $R_1(t) = R_2(t)$. Since σ and β take its maximum in $R(t) = R_1(t) = R_2(t)$ ~~and it is zero~~, we get that necessarily $\sigma = \beta = 0$. By repeating the process starting now from T_1 we get the uniqueness of solutions for any arbitrary $T > 0$.■

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