On the analysis and controllability of some systems modelling the growth of necrotic tumors

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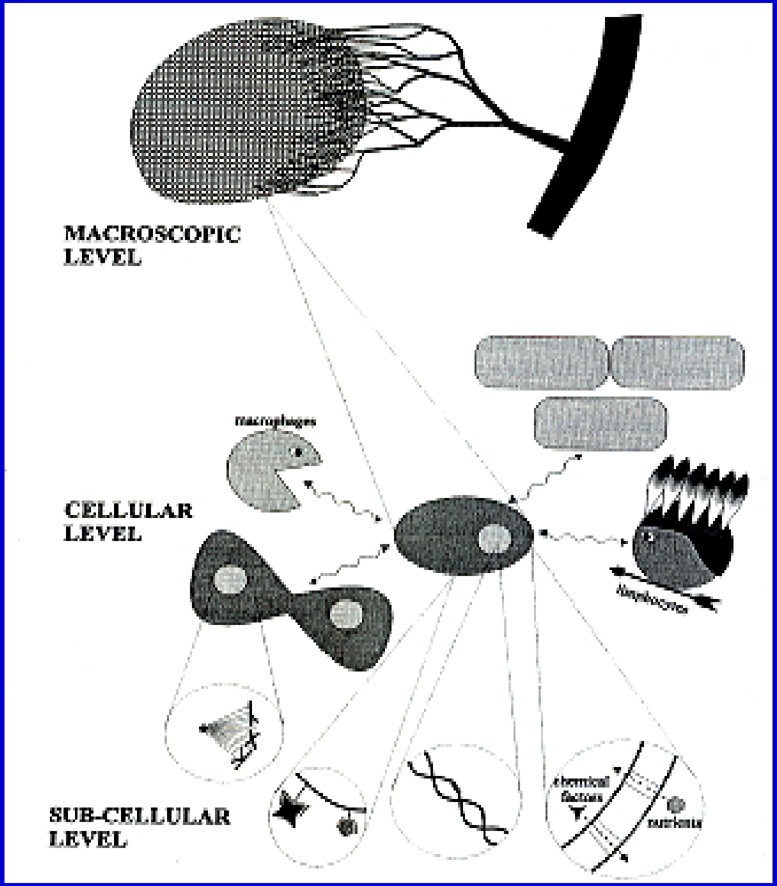
1. Introduction

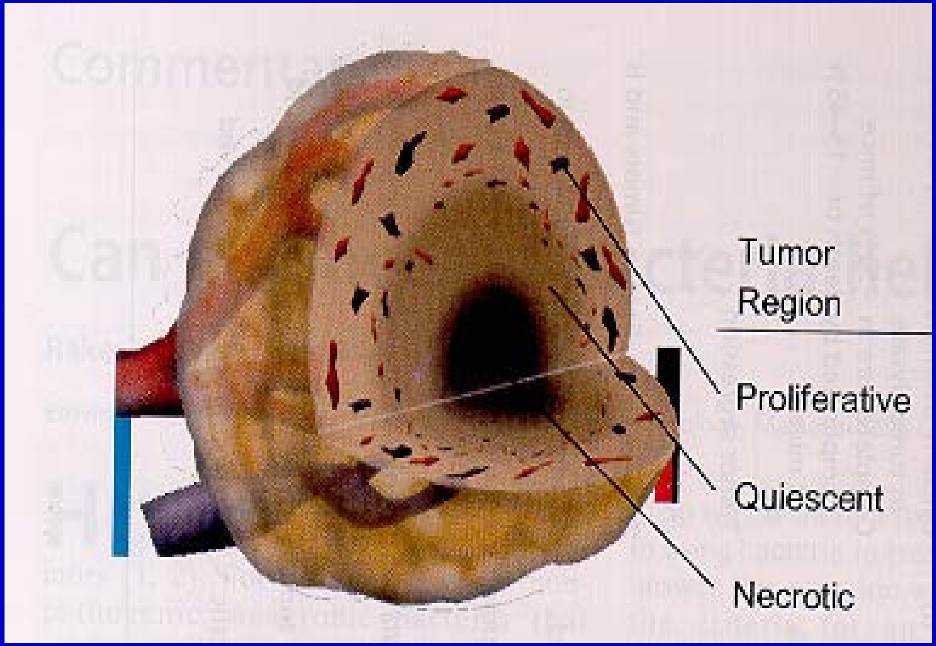
The development and growth of a tumor is a complicated phenomenon where many different aspects arise, from the subcellular scale to the body scale (metastasis).



This complexity causes different mathematical models to appear for each phase of the growth: "avascular phase", previous to vascularization (angiogenesis), "vascular phase".

Here we shall deal with a simple model of solid tumors

(H.P. Greenspan, 1972, H.M.Byrne and M.A.J.Chaplain (1995,...), A. Friedman *et al.* (F. Reitich, S. Cui,...) 1998,...



Joint works with J.I. Tello (Thesis UCM 2001, IMA Minnesota 2001, Nonlinear Analysis 2003, ...)

Personal motivation: 1998, ..., J.L. Lions (2000)

Madrid, January, 21, 2000, Jornada matemática,

Parlament of Spain,

¿ Es posible describir el mundo del inanimado y del ser vivo con los lenguajes matemático e informático?

Handbook of Numerical Analysis (Ph. Ciarlet, J.L. Lions), volume on “Virtual Human” (N. Ayache, ed.)

Survey (J.I.D.+J.I. Tello, to appear)

2. The model

Gene mutations can produce cell reproduction in uncontrolled way (malignant tumors).

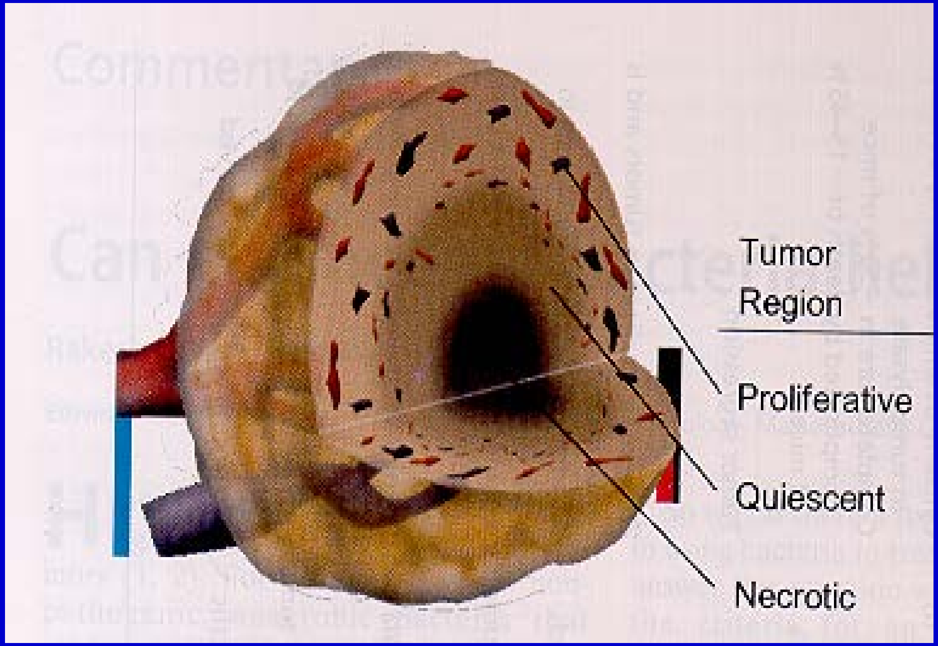
Gene mutations are transmitted producing a small spheroids of a few millimeters.

During this avascular phase, nutrients (glucose and oxygen) arrive to the cells through diffusion. As the spheroid grows, the level of nutrients in the interior of the tumor decreases due to consumption by the outer cells.

When the level of concentration of nutrients in the interior falls bellow a critical level, the cells can not live; this is the phenomenon (necrosis).

Then an inner region is formed in the center of the tumor by the dead cells.

We 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 between where the level of nutrients is enough for the cells to live, but not for proliferation.



As response to the low level of oxygen, the cells secrete some chemical substances, known as *Tumor Angiogenesis Factors* (TAFs). These substances are diffused through the surrounding tissue.

The process of formation of new vessels, known as *angiogenesis*, is one of the most decisive steps in the tumor's growth.

A rough classification in two classes of PDEs models: the *mixed models* (all the different population of cells are continuously present everywhere in the tumor, at all the times) and *segregated models* (less realistic but relevant for in vitro experiments: different populations of cells are separated by unknown interfaces or free boundaries.

Our analysis will be restricted to the second class of models (spherical tumors).

Several authors (Shimko and Glass (1976), Adam (1986), Britton and Chaplain (1993),...) studied the case in which cell proliferation is controlled by chemical substances Growth Inhibitor Factor (GIFs) (as chalones) secreted by the cells reduce the mitotic activity.

Two different kinds of inhibitors appear, depending on 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 (Attallah (1976)).

The outer boundary delimiting the tumor is denoted by R(t) and the concentration of nutrients by σ **and the inhibitors by** β

Mass conservation principle, assuming the cell mass density is constant, the tumor mass is proportional to its volume

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

$$\widehat{S}(\widehat{\sigma}, \widehat{\beta}) = sH(\widehat{\sigma} - \widetilde{\sigma})H(\widetilde{\beta} - \widehat{\beta})$$

Greenspan (presence of inhibitors, and the possibility that this affects mitosis,when the concentration of inhibitors is greater than a critical level)

$$\widehat{S}(\widehat{\sigma}, \widehat{\beta}) = s(\widehat{\sigma} - \widetilde{\sigma})(\widetilde{\beta} - \widehat{\beta})$$

Byrne and Chaplain (growth when the inhibitor affects the cell proliferation)

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

By using the maximal monotone graph of associate to the Heaviside function,

and taking into account a possible supply of inhibitors, localized on a small region, we arrive to

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

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

$$\hat{\sigma}(\tilde{x},t) = \bar{\bar{\sigma}}, \hat{\beta}(\tilde{x},t) = \bar{\bar{\beta}}, \quad |\tilde{x}| = R(t),$$

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

3. Existence of solutions

Structural assumptions

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

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

piecewise continuous functions (a finite number of discontinuous points) (multivalued upper semicontinuous: Vrabie (1987))

We introduce the change of variables and unknowns by

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

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

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

B= $\{x \in I\!R^3, |x| < 1\}$

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

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

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

The problem becomes

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

We introduce the Hilbert spaces

$$\mathbf{H}(B) := L^2(B)^2, \qquad \Lambda(\mathrm{B}) = \mathrm{H}^{0}_{J}(\mathrm{B})_{S},$$

Given $T > 0$, we introduce $\mathbf{U} = (u, v)$, $\mathbf{U}_0 = (u_0, v_0)$, $\mathbf{G} : I\!R^2 \longrightarrow 2^{I\!R^2} \times 2^{I\!R^2}$ and $\mathbf{F} : (0, T) \times B \longrightarrow I\!R^2$ 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 $(\mathbf{U}, R) \in L^2(0, T : \mathbf{V}) \times W^{1,\infty}(0, T : I\!R)$ is a weak solution of the problem (4.8) 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

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

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

$\forall\ \mathbf{\Phi} \in C^1([0, T] \times B)$, where

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

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

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

Theorem 4.1 *Assuming (4.1), (4.2), $R_0 > 0$ and $\sigma_0, \beta_0 \in L^2(0, R_0)$, problem (3.1)-(3.5) has at least a weak solution for any $T > 0$.*

We shall use an iterative method

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 $\mathbf{V} \times \mathbf{V}$,

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

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

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

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 $\mathbf{G}_1$, $\tilde{a}_{ij}$, are continuous functions from $L^2(0,T : \mathrm{H})$ with the usual topology to $L^2(0,T : \mathrm{H})$ with the weak topology. Notice that $\mathbf{G}_0$ and $\mathbf{G_1}$ are defined by

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

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

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

and

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

$\widehat{g}_i$ has a sublinear growth,

$$|\tilde{a}_{ij}| \leq C.$$

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

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

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

The operator $\mathbf{A}(R_n(t)) + \mathbf{G}_1(\mathbf{U}_{n-1})$ is defined, as usual, through the bilinear form

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

By (4.10) and definition of $\tilde{a}$, it results

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

and by Gronwall's lemma, it results

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

Since $\mathbf{U}_n$ is uniformly bounded in $\mathbf{H}$, by (4.2), we obtain

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

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

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

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

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

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

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

$$R_n \longrightarrow R \text{ in } C^0([0,T])$$

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

$$\int_0^T \frac{R_n'}{R_n}\int_B x\nabla\mathbf{U_n}\Phi dxdt = -\int_0^T \frac{R_n'}{R_n}\int_B \mathbf{U_n}\Phi dxdt - \int_0^T \frac{R_n'}{R_n}\int_B \mathbf{U_n}\nabla\Phi dxdt,$$

which converges to the limit integral.

4. Uniqueness of solutions

We need extra assumptions since 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 then it is possible to adapt the arguments of Díaz (1995) in order to construct more than one solution of the problem.

Two different cases: 3-dimensional case with forcing term and the symmetric case.

Consider the case of without necrotic core tumors and linear reaction terms,

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

$$\frac{\partial\widehat{\beta}}{\partial t} - d_2\Delta\widehat{\beta} - \widehat{r}_2(\beta_B - \widehat{\beta}) + \lambda_2\widehat{\beta} = f\chi_{\omega_0}, \qquad |x| < R(t),\ t \in (0,T).$$

We assume $d_1 = d_2 = d.$ **By normalizing the unknown densities**

$$\sigma := \widehat{\sigma} - \frac{\widehat{r}_1 \sigma_B (\widehat{r}_2 + \lambda_2) + \lambda \widehat{r}_2 \beta_B}{(\widehat{r}_1 + \lambda_1)(\widehat{r}_2 + \lambda_2)}, \qquad \beta := \widehat{\beta} - \frac{\widehat{r}_2 \beta_B}{\widehat{r}_2 + \lambda_2},$$

and denoting by

$$r_1 := \widehat{r}_1 + \lambda_1, \qquad r_2 := \widehat{r}_2 + \lambda_2, \qquad S(\sigma, \beta) := \frac{3}{4\pi} \widehat{S}(\widehat{\sigma}, \widehat{\beta}),$$

we get to

$$\begin{aligned}
&\frac{\partial \sigma}{\partial t} - d\Delta\sigma + r_1 \sigma + \lambda\beta = 0, \qquad |x| < R(t),\ t \in (0,T),\\
&\frac{\partial \beta}{\partial t} - d\Delta\beta + r_2 \beta = f\chi_{\omega_0}, \qquad |x| < R(t),\ t \in (0,T),\\
&R(t)^2 \frac{dR(t)}{dt} = \int_{|x|<R(t)} S(\sigma,\beta)\,dx, \qquad R(0) = R_0,\ t \in (0,T),\\
&\sigma(x,0) = \sigma_0(x), \qquad \beta(x,0) = \beta_0(x), \qquad |x| < R_0,\\
&\sigma(x,t) = \overline{\overline{\sigma}},\ \beta(x,t) = \overline{\overline{\beta}}, \qquad |x| = R(t),\ t \in (0,T),
\end{aligned}$$

We assume

$$\widehat{S} \in W^{1,\infty}(I\!R^2),$$

$$f\chi_{\tilde{\omega}_0^{\tilde{t}}} \in L^p((0,T)\times\Omega), \qquad p>4,$$

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

Corollary *Under the assumptions of Theorem 1, we have*

$$\int_0^T (\|\sigma\|^2_{W^{1,\infty}(R(t))} + \|\beta\|^2_{W^{1,\infty}(R(t))})dt \le k_0$$

for some $k_0 < \infty$.

Idea of the proof. **Let** $\tilde{t}(t) := \int_0^t R^{-2}(\rho)d\rho.$ **Then**

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

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

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

$$u(\tilde{x},\tilde{t}) = v(\tilde{x},\tilde{t}) = 0, \qquad \tilde{x}\in\partial B,\ \tilde{t}\in(0,\tilde{T}),$$

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

$\tilde{T} = \tilde{t}(T)$, $\tilde{\omega}_0^{\tilde{t}} = \{\tilde{x} \in B$ such that $R(t(\tilde{t}))\tilde{x} \in \omega_0\}$,

$$A(w) := -d\Delta w - R^2 \dot{R} \tilde{x} \cdot \nabla w.$$

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

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

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

(see e.g. Ladyzenkaya – Solonnikov – Uralceva [45], Theorem 9.1, Chap IV). Since $p > 4$, $W^{1,p}((0,T) \times B) \subset L^\infty([0, \tilde{T}] \times B)$, then

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

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

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

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

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

***Proof*. By contradiction, we assume that there exist two different solutions** (σ_1, β_1, R_1) and (σ_2, β_2, R_2). **Let**

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

Then

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

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

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

Then

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

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

***Proof*. Multiplying the equation by** $e^{r_1 t}$

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

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

$e^{r_1 t} z$ and $e^{r_2 t}\beta$ are bounded

$$z^{**} = max\{e^{r_1 t} z(x,t), t \in [0,T], x \in \partial B(R(t))\},$$

$$z_{**} = min\{e^{r_1 t} z(x,t), t \in [0,T], x \in \partial B(R(t))\},$$

$$\beta^{**} = max\{e^{r_2 t}\beta(x,t), t \in [0,T], x \in \partial B(R(t))\},$$

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

$z^{**} \geq 0$, $\beta^{**} \geq 0$, $z_{**} \leq 0$ and $\beta_{**} \leq 0$. Let T_k and T^k be defined

$$T_k(s) = \begin{cases} s, & \text{if } s > k, \\ k, & \text{if } s \leq k, \end{cases} \qquad T^k(s) = \begin{cases} k, & \text{if } s \geq k, \\ s, & \text{if } s < k. \end{cases}$$

Taking as test function $T_0(e^{r_1 t} z - z^{**})$

integrating by parts in B(R(t)) and after some manipulations

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

***End of the proof of the uniqueness Theorem*. Given** $t \in [0, T]$

We can assume, without lost of generality, that $R_1(t) \leq R_2(t)$

Using that

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

Since S is bounded,

$$|\int_{R_1(t)<|x|<R_2(t)} S(\sigma_2, \beta_2)dx| \leq N|R_1^3(t) - R_2^3(t)| \leq M|R_1(t) - R_2(t)|,$$

Since S is Lipschitz continuous, integrating in time,

$$\int_0^T \int_{B(R(t))} |S(\sigma_1,\beta_1) - S(\sigma_2,\beta_2)| dxdt \leq$$

$$\int_0^T \int_{B(R(t))} |S|_{W^{1,\infty}(\mathbb{R}^2)} (sup|\sigma| + sup|\beta|) dxdt \leq$$

$$\int_0^T \int_{B(R(t))} k_0 (\frac{1}{k_1} sup|z + k_2\beta| + sup|\beta|) dxdt \leq$$

$$\int_0^T \int_{B(R(t))} C(sup|z| + sup|\beta|) dxdt \leq$$

$$\int_0^T \int_{B(R(t))} C(sup|e^{-r_1 t} e^{r_1 t} z| + sup|e^{-r_2 t} e^{r_2 t} \beta|) dxdt \leq$$

$$\int_0^T \int_{B(R(t))} C(e^{|r_1|T} sup|e^{r_1 t} z| + e^{|r_2|T} sup|e^{r_2 t} \beta|) dxdt \leq$$

$$\int_0^T \int_{B(R(t))} k_3 (sup|e^{r_1 t} z| + sup|e^{r_2 t} \beta|) dxdt.$$

From the Lemma we know

$$\int_0^T \int_{B(R(t))} \sup|e^{r_1 t} z(x,t)| dxdt \leq e^{r_1 T} \frac{3\pi}{4} \int_0^T R^3(t) \sup_{|x|=R(t)} |z(x,t)| dt.$$

From the Corollary we deduce that $\int_0^T \|z\|^2_{W^{1,\infty}(B(R(t)))} dt \le K.$

Since

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

we deduce

$$e^{r_1 T}\frac{3\pi}{4}\int_0^T R^3(t) \sup_{|x|=R(t)} |z(x,t)| dt \le$$

$$k_4 \int_0^T \|\sigma_2\|_{W^{1,\infty}(B(R_2(t)))} + \|\beta_2\|_{W^{1,\infty}(B(R_2(t)))} |R_1(t) - R_2(t)| dt \le$$

$$k_4 \sup_{0<t<T} |R_1(t) - R_2(t)| T^{\frac{1}{2}} \int_0^T (\|\sigma_2\|^2_{W^{1,\infty}(B(R_2(t)))} + \|\sigma_2\|^2_{W^{1,\infty}(B(R_2(t)))}) dt \le$$

$$k \sup_{0<t<T} |R_1(t) - R_2(t)| T^{\frac{1}{2}}.$$

In the same way,

$$\int_0^T \int_{B(R(t))} k_3 sup|\beta| dx dt \le k \sup_{0<t<T} |R_1(t) - R_2(t)| T^{\frac{1}{2}}.$$

Then

$$\int_0^T |R_1^2(t)\dot{R}_1(t) - R_2^2(t)\dot{R}_2(t)| dt \le C_0 \sup_{0<t<T} |R_1(t) - R_2(t)| (T + T^{\frac{1}{2}}). \quad (5.25)$$

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

$$|R_1^3(t) - R_2^3(t)| \le 3C_0\delta(T + T^{\frac{1}{2}}),$$

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

***Remark*. A similar method applies to the case of radially necrotic tumors**

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

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

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

$$S(\sigma,\beta) \in W^{1,\infty}_{loc}(\mathbb{R}^2),$$

S is an increasing function in σ and decreasing in β

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

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

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

$$\sigma(R(t),t) = 0,\ \beta(R(t),t) = 0 \qquad 0<t<T.$$

5. Approximate controllability

We study the controllability of distribution of nutrients by the internal localized action of inhibitors.

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

$$\|\sigma(T) - \sigma^d\|_{L^p(B(R(T)))} \leq \epsilon,$$

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

We shall prove the result in several steps. For $n \in \mathbb{N}$, we start by assuming $R_n(t)$ prescribed and we look for a control f_n in ω_0 such that the solution of the the problem satisfies the required property. Then we obtain R_{n+1} and f_{n+1} from (σ_n, β_n) which allow to find $(\sigma_{n+1}, \beta_{n+1})$.

The proof of the theorem uses some methods introduced in the study of the approximate controllability J.L. Lions (1990),Fabre, Puel and Zuazua (1995) and Díaz and Ramos (1995)

Iterating the process we obtain a sequence and we show that there exists a subsequence such that converges to the searched control and the associate solution of problem.

Proposition *Let* $\omega_0 \subset B(R_0 exp\{-\|S\|_{L^\infty} T\}$, *and* $\sigma_0 = \beta_0 = \overline{\overline{\sigma}} = \overline{\overline{\beta}} = 0$. *Let* $R \in W^{1,\infty}(0,T)$ *a given function such that* $R(0) = R_0$, $|\dot{R}| \leq \|S\|_{L^\infty} R_0 \; exp \; \{|S|_{L^\infty} T\}$. *Then, given* $\widehat{\sigma}^d \in L^2_{loc}(I\!R^3)$, *there exists* $f \in L^p(\omega_0 \times (0,T))$, *with* $p > 4$, *such that, if* (σ, β) *is the solution of problem* *then*

$$\|\sigma(T) - \sigma^d\|_{L^p(B(R(T)))} \leq \epsilon,$$

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

Proof. Let $p' = \frac{p}{p-1}$, we consider the functional $J : L^{p'}(B(R(T))) \longrightarrow I\!R$ defined by

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

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

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

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

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

$$\varphi(x,t) = 0, \qquad \psi(x,t) = 0, \qquad |x| = R(t), \qquad t \in (0,T).$$

The existence and uniqueness of weak solutions of can be obtained as in previous sections.

Let us assume that J is convex, continuous and coercive. Then J takes a minimum φ_0 Moreover if (ξ,ζ) is the solution of the dual problem with initial datum $(\xi^0,0)$ then

$$\int_0^T \int_{\omega_0} |\psi|^{p'-2}\psi\zeta \, dx dt - \int_{B(R(T))} \sigma^d \xi^0 dx +$$

$$\epsilon \|\varphi^0\|^{1-p'}_{L^{p'}(B(R(T)))} \int_{B(R(T))} |\varphi^0|^{p'-2}\varphi^0 \xi^0 dx = 0.$$

Multiplying by (ξ,ζ) integrating by parts and applying Leibnitz theorem, we arrive to

$$-\int_0^T < \sigma, \frac{\partial \xi}{\partial t} > dt - d\int_0^T < \sigma, \Delta\xi > dt + \int_0^T \int_{B(R(t))} r_1 \sigma \xi dx dt +$$

$$\int_0^T \int_{B(R(t))} \lambda \beta \xi dx dt - \int_0^T < \beta, \frac{\partial \zeta}{\partial t} > dt - d\int_0^T < \beta, \Delta\zeta > dt +$$

$$\int_0^T \int_{B(R(t))} r_2 \beta \zeta dx dt - \int_0^T \int_{\omega_0} f \zeta dx dt + \int_{B(R(t))} \sigma \xi dx]_0^T + \int_{B(R(t))} \beta \zeta dx]_0^T = 0,$$

From the choice of (ξ, ζ) and since $\sigma(0,x) = \beta(0,x) = 0$ we obtain

$$-\int_0^T \int_{\omega_0} f \zeta dx dt + \int_{B(R(T))} \sigma(T) \xi^0 dx = 0.$$

Let us take $f := |\psi|^{p'-2}\psi.$ Substituting

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

for all $\xi^0 \in L^{p'}(B(R(T)))$. Taking $\xi^0 = (\sigma(T) - \sigma^d)^{\frac{1}{p'-1}} \in L^{p'}(B(R(T)))$

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

$$\epsilon \|\varphi^0\|_{L^{p'}(B(R(T)))}^{1-p'} \int_{B(R(T))} |\varphi^0|^{p'-2}\varphi^0 |\sigma(T) - \sigma^d|^{\frac{1}{p'-1}-1}(\sigma(T) - \sigma^d) dx.$$

By Hölder inequality,

$$\|\varphi^0\|_{L^{p'}(B(R(T)))}^{1-p'} \int_{B(R(T))} |\varphi^0|^{p'-2}\varphi^0 |\sigma(T)-\sigma^d|^{\frac{1}{p'-1}-1}(\sigma(T)-\sigma^d)dx \leq$$
$$\|\sigma(T)-\sigma^d\|_{L^p(B(R(T)))}^{p-1},$$

which leads to $\|\sigma(T)-\sigma^d\|_{L^p(B(R(T)))} \leq \epsilon$

So, it only remains to check the mentioned properties of J:
The convexity and continuity of J are easy

The harder part is to prove that J is coercive. It is a technical part which uses a unique continuation property (Chi-Cheung Poon 1996).

Proof of the Theorem. We consider the sequence $\{R_n(t)\}$

$$R_n^2(t)\dot{R}_n(t) = \int_{B(R_{n-1}(t))} S(\sigma_{n-1} + \sigma_{n-1}^s, \beta_{n-1} + \beta_{n-1}^s)dx, \quad R_n(0) = R_0,$$

$R_1(t) = R_0.$ S is bounded, $R_n \in W^{1,\infty}(0,T)$

R_{n_i} such that converges weakly to $R(t)$ in $W^{1,q}(0,T)$, for all q

By the Proposition , for each n there exists a minimum of the functional

$$J_n(\varphi_n^0) := \int_0^T \int_{\omega_0} |\psi_n|^{p'} dxdt + \epsilon \|\varphi_n^0\|_{L^{p'}(B(R_n(T)))} - \int_{B(R_n(T))} \sigma_n^d \varphi_0^n dx,$$

where $\sigma_n^d = \widehat{\sigma}^d \chi_{B(R_n(T))}$.

By similar arguments to the proof of the coercivednes of J it is show that the sequence $\|\varphi_n^0\|_{L^{p'}(B(R(T)))}$ is uniformly bounded and so $\|f_n\|_{L^p(0,T:L^p(\omega_0))} \leq C,$

Doing the change (4.3)-(4.5) and (5.6), applying Lemma 5.1, we obtain that (u_n, v_n, R_n) is uniformly bounded in $(W^{1,p}(B \times (0,\tilde{T}))^2, H^2(0,T))$ and there exists a subsequence (u_{ni}, v_{ni}, R_{ni}) such that converges strongly in $(C^\alpha((0,T] \times B)^2, C^1([0,T]))$ to (u, v, R) for $\alpha = \frac{1}{6}$, where (u_{ni}, v_{ni}) satisfies

$$\begin{cases} \dfrac{\partial u_{ni}}{\partial t} - \dfrac{d}{R_{ni}^2}\Delta u_{ni} - \dfrac{R'_{ni}}{R_{ni}}\tilde{x}\cdot\nabla u_{ni} + r_1 u_{ni} + \lambda v_{ni} = 0, & \text{in } B\times(0,T), \\ \dfrac{\partial v_{ni}}{\partial t} - \dfrac{d}{R_{ni}^2}\Delta v_{ni} - \dfrac{R'_{ni}}{R_{ni}}\tilde{x}\cdot\nabla v_{ni} + r_2 v_{ni} = f_n\chi_{\tilde{\omega}_0}, & \text{in } B\times(0,T), \\ u_{ni}(\tilde{x},t) = v_{ni}(\tilde{x},t) = 0, & \text{on } \partial B\times(0,T), \\ u_{ni}(\tilde{x},0) = u_{ni}^0(\tilde{x}),\ v_{ni}(\tilde{x},0) = v_{ni}^0(\tilde{x}), & \text{in } B, \end{cases}$$

and (u,v,R) is the solution of (5.7)-(5.11). In particular

$$\|u(T)-u_n(T)\|_{L^p(B)}^p \longrightarrow 0, \qquad \text{as } n_i \to +\infty.$$

Moreover

$$\|\sigma(T)-\sigma^d\|_{L^p(B(R(T)))} = \|\sigma(T)-\sigma_n(T)\|_{L^p(B(\min\{R(T),R_n(T)\}))} +$$

$$\|\sigma_n(T)-\sigma^d\|_{L^p(B(\min\{R(T),R_n(T)\}))} + \|\sigma-\sigma^d\|_{L^p(B_n^*(T))},$$

where

$$B_n^*(T) = \begin{cases} B(R(T))\cap B^c(B(R_n(T))), & \text{if } R(T) > R_n(T), \\ \emptyset, & \text{if } R(T) \le R_n(T). \end{cases}$$

Doing the change (5.6) and since

$$\|\sigma_n(T)-\sigma^d\|_{L^p(B(\min\{R(T),R_n(T)\}))} \le \epsilon,$$

we obtain

$$\|\sigma(T)-\sigma^d\|_{L^p(B(R(T)))} \leq \|u(T)-u_n(T)\|_{L^p(B)} + \|\sigma-\sigma^d\|_{L^p(B_n^*(T))} + \epsilon.$$

Since $\mu(B_n^*(T)) \longrightarrow 0$, by the Lebesgue dominated convergence theorem we obtain that

$$\lim_{n\to\infty} \|\sigma-\sigma^d\|_{L^p(B_n^*(T))} = 0.$$

Taking limits it results

$$\|\sigma(T)-\sigma^d\|_{L^p(B(R(T)))} \leq \epsilon,$$

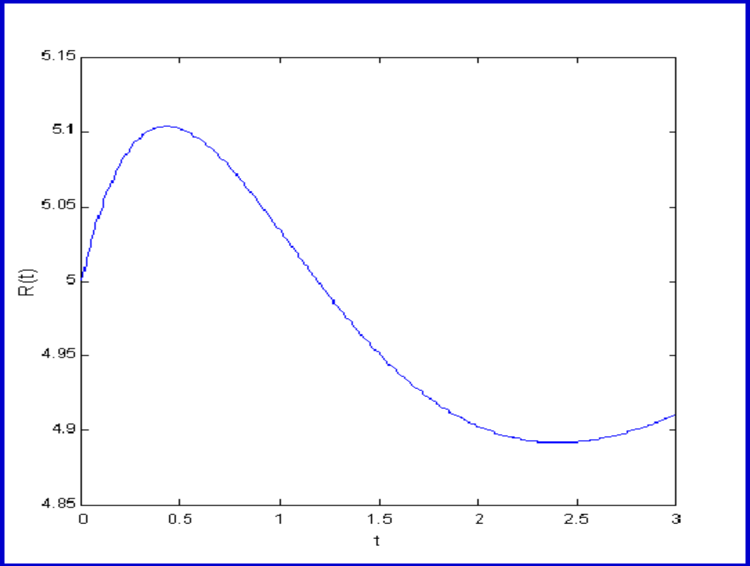
and the theorem is thereby proved in the case $p > 4$.

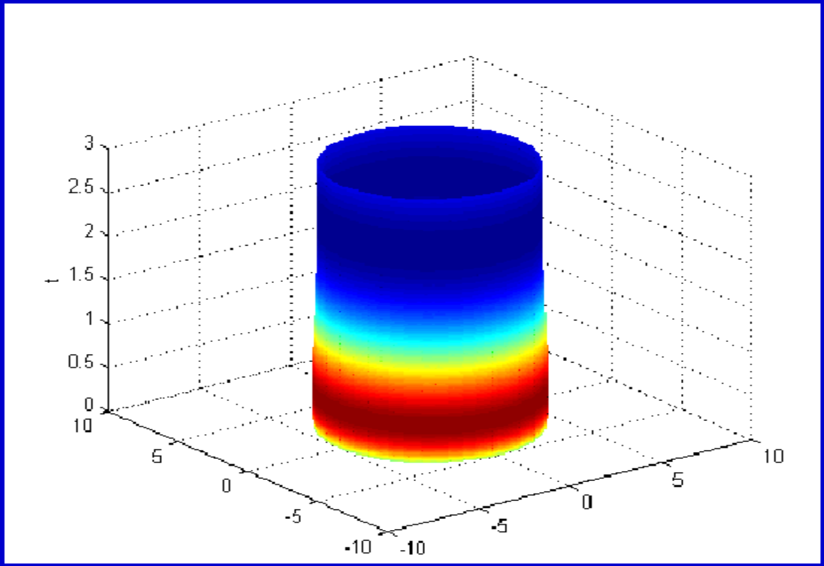
6. Some numerical experiences

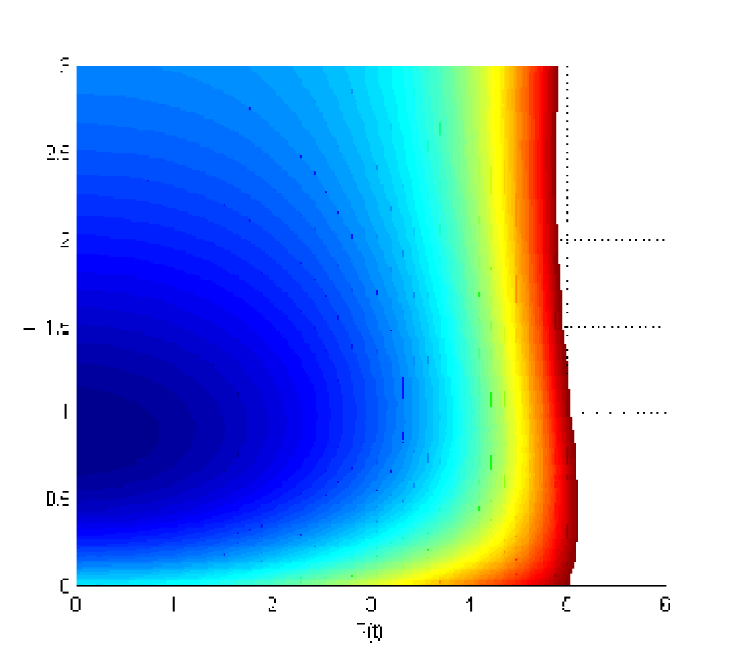
Time discretization scheme which leads implicitly with u and v and explicitlyfor the free boundary R. We assume radial symmetry, no forcing terms (i.e. f=0) and nonnecrotic core.

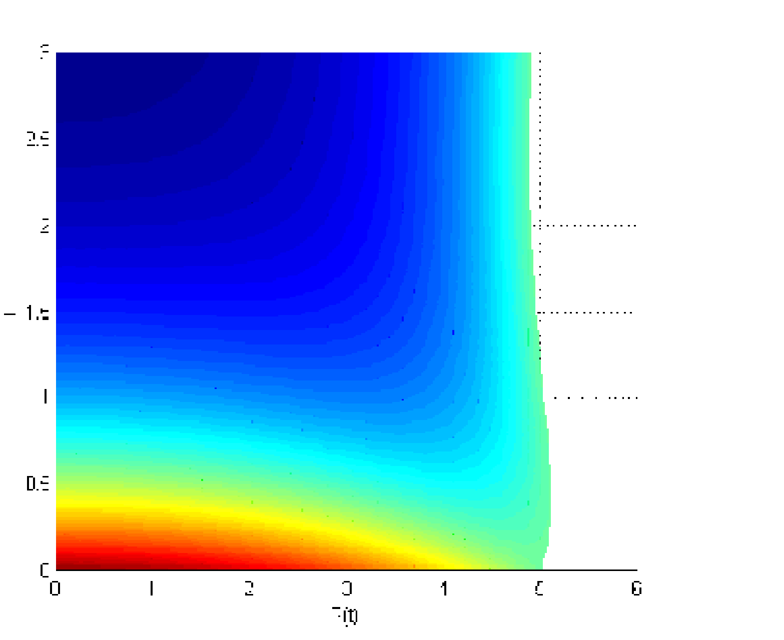
Numerical Experiments. We consider the special case of $S(\sigma, \beta) = \sigma - \widehat{\sigma}$, $T = 3$, $N = 501$, (i.e. $\Delta T = \frac{3}{500}$) and $s = 20$ (i.e. $h = \frac{1}{20}$) with the following choice of the parameters: $R_0 = 5$, $D_1 = D_2 = 1$, $\Gamma_1 = \Gamma_2 = \overline{\overline{\sigma}} = \overline{\overline{\beta}} = 1$.

$$\widehat{\sigma} = 0.75$$

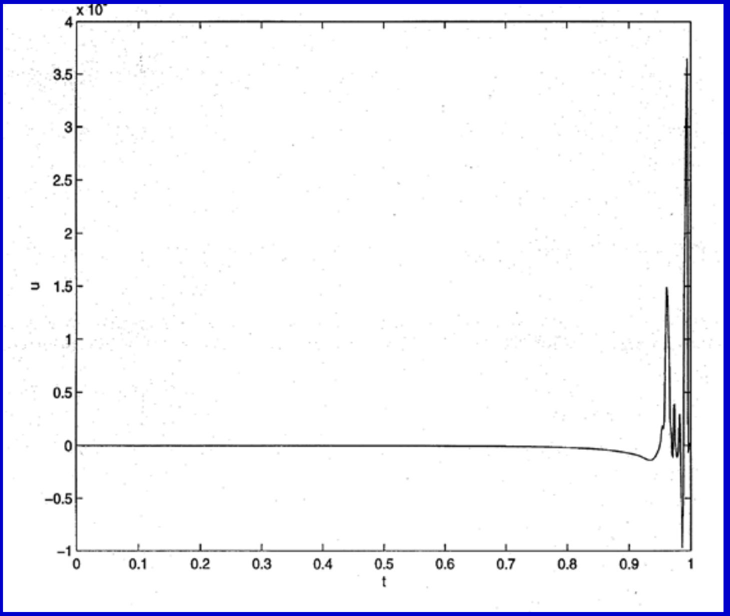

5.15
5.1
5.05
5
4.95
4.9
4.85
R(t)
0
0.5
1
1.5
2
2.5
3
t

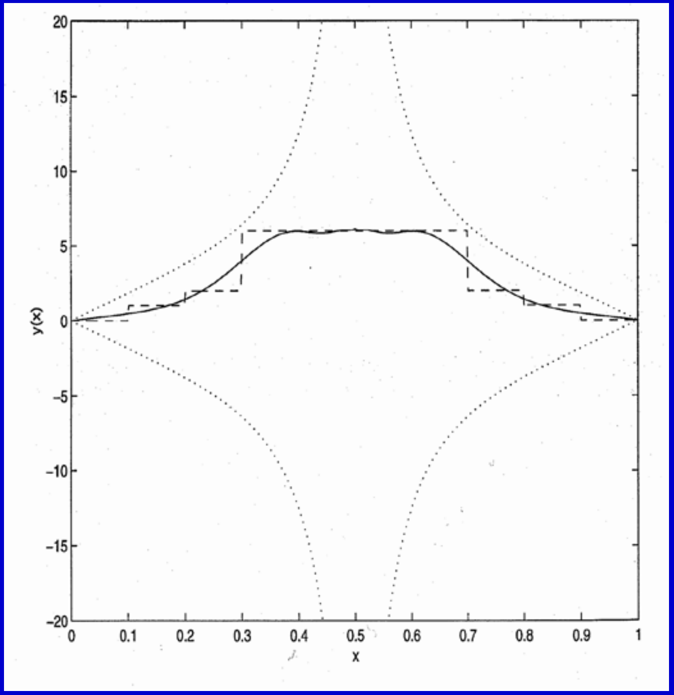

3
2.5
2
1.5
1
0.5
0
t
10
5
0
-5
-10
-10
-5
0
5
10

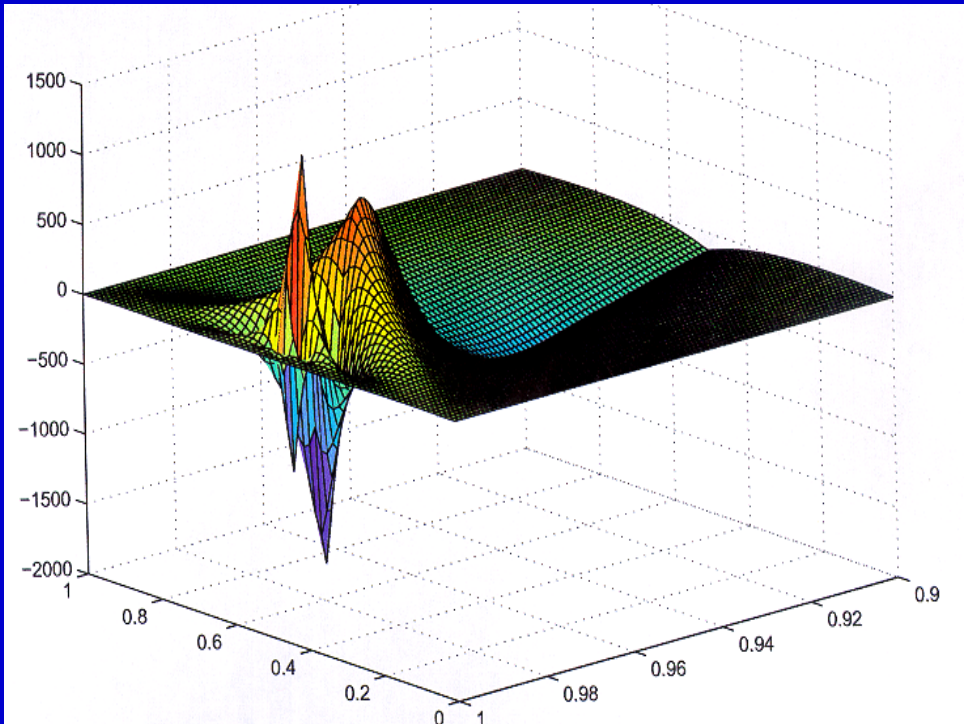




Control problem







Thanks for your attention