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A THERAPY INACTIVATING THE TUMOR ANGIOGENIC FACTORS

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Abstract. This paper is devoted to a nonlinear system of partial differential equations modeling the effect of an anti-angiogenic therapy based on an agent that binds to the tumor angiogenic factors. The main feature of the model under consideration is a nonlinear flux production of tumor angiogenic factors at the boundary of the tumor. It is proved the global existence for the nonlinear system and the effect in the large time behavior of the system for high doses of the therapeutic agent.

1. **Introduction.**

Angiogenesis is a physiological process that involves the formation of new blood vessels from a pre-existing vascular network. Angiogenesis plays an important role in the development of embryo, wound healing or tumor growth.

In the beginning, solid tumors are avascular, i.e. they do not have their own blood supply. As the tumor grows there is an increasing demand of nutrients. At some moment the flux of nutrients through the surface of the tumor is too small to provide nutrients to all the malignant cells and it begins a necrotic core formation at the center of the tumor. As a response to nutrient deprivation like oxygen or glucose, cancer cells secrete a chemical factor known as *Tumor Angiogenesis Factors* (TAFs). TAFs diffuse in the extracellular matrix until they arrive to the endothelial cells which form the linings of the blood vessels. Next, TAFs activate endothelial cells after binding to specific receptors. Activated endothelial cells release enzymes that degrade the basal membrane of the blood vessels to allow the migration of endothelial cells, via chemotaxis, towards the source of TAF. The endothelial cells then proliferate into the surrounding matrix, interact with the components of the matrix, in particular fibronectin and form solid sprouts connecting neighboring vessels. Once the new capillary network penetrates the tumor, more nutrients are supplied to the tumor which grows further. See for instance [16] for details.

Since angiogenesis plays an important role in the development of the tumor, then it is expected that targeting tumor angiogenesis as a therapeutic strategy could provide promising results.

In order to avoid or reduce angiogenesis, anti-angiogenic molecules have been created. Anti-angiogenic molecules either act directly on the TAF molecules inactivating them with the formation of a complex or indirectly by binding to the TAF receptors on endothelial cells.

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The aim of this paper is to propose a macroscopic model of tumor angiogenesis with a therapeutic agent that inhibits TAF and also to analyze theoretically the model. We will consider five variables; u (endothelial cells), v (TAF), z (therapeutic agent), c (complex) and w (nutrient). We assume that variables are in a bounded connected domain denoted by Ω whose boundary $\partial\Omega$ is regular and has two components: Γ_1, the boundary of the tumor and Γ_2, a virtual boundary between the tumor and the surrounding vessels. We assume that the tumor has reached a critical size between 1-2 mm (see [18]) that is a starting point of the tumor angiogenesis. Additionally, we assume that the vasculature is developing more rapidly than the evolution of the tumor. Therefore, we suppose that the boundary of the tumor is fixed. In the following we propose equations for each variable.

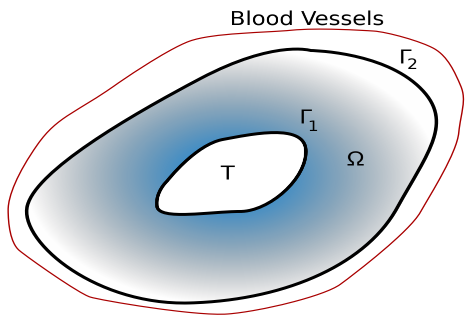

FIGURE 1. A particular example of domain Ω.

Endothelial cells

We assume that endothelial cells diffuse and move towards the gradient of TAF with a sensitivity $\alpha(v) \geq 0$. It is commonly assumed that α decreases with respect to v due the saturation of the receptors in the endothelial cells (see [15]). Additionally, we take the growth rate $\lambda\beta(v)u$ with $\lambda > 0$ and $\beta \geq 0$ an increasing function of v, that models the growth induced by v and $-\xi u^2$, the death of the endothelial cells:

$$u_t = \underbrace{D_u \Delta u}_{Diffusion} - \underbrace{\nabla \cdot (\alpha(v) u \nabla v)}_{Chemotaxis} + \underbrace{\lambda\beta(v)u - \xi u^2}_{Reaction} \quad in \;\; \Omega_T := \Omega \times (0, T).$$

At the boundary, we assume for the moment the following general boundary conditions:

$$D_u \frac{\partial u}{\partial n} - \alpha(v) u \frac{\partial v}{\partial n} = h_1(x, u, v) \quad on \;\; \Gamma_1 \times (0, T),$$

$$D_u \frac{\partial u}{\partial n} - \alpha(v) u \frac{\partial v}{\partial n} = h_2(x, u, v) \quad on \;\; \Gamma_2 \times (0, T),$$

where h_1 and h_2 are regular functions and n stands for the outward normal unitary vector.

TAF

The TAF diffuses and decays. Moreover, the association of TAF to the inhibitor z and the dissociation of the formed complex c enter the balance:

$$v_t = \underbrace{D_v \Delta v}_{Diffusion} \underbrace{-d_v v}_{Decay} + \underbrace{k_b c}_{Dissociation} \underbrace{-k_f v z}_{Association} \quad in \;\; \Omega_T.$$

We know that TAF is produced by hypoxic cells. Of course, hypoxic cells are usually far from the boundary but the oxygen level on the boundary as well as the shape of the boundary seem to be correlated indirectly with the TAF production. Let us note that, in view of the domain we have taken, we cannot track hypoxic cells. Therefore it could be reasonable to think that at the boundary the rate of production of TAF depends on the nutrients available at the boundary. In particular, low nutrients imply high rate of production and the other way round. Therefore, the amount of TAF that leaves the tumor on Γ_1 is $\gamma(w)$ where $\gamma \geq 0$ is a regular and decreasing function on w. On the other hand, at Γ_2 TAF leaves the domain by diffusion:

$$\frac{D_v \partial v}{\partial n} = \underbrace{\gamma(w)}_{TAF\,enter} \quad on \;\; \Gamma_1 \times (0,T),$$

$$\frac{D_v \partial v}{\partial n} = \underbrace{-\tau_2 v}_{TAF\,out} \quad on \;\; \Gamma_2 \times (0,T).$$

Therapeutic agent

The equation satisfied by the therapeutic agent it is similar to the equation for v. However, here we have an additional term $I_0(x,t)$ that it is the supply rate of therapeutic agent:

$$z_t = \underbrace{D_z \Delta z}_{Diffusion} \underbrace{-d_z z}_{Decay} + \underbrace{k_b c}_{Dissociation} \underbrace{-k_f v z}_{Association} + \underbrace{I_0}_{Input} \quad in \;\; \Omega_T.$$

At the boundary z leaves the domain. Therefore,

$$\frac{D_z \partial z}{\partial n} = \underbrace{-\theta_1 z}_{Anti-TAF\,out} \quad on \;\; \Gamma_1 \times (0,T),$$

$$\frac{D_z \partial z}{\partial n} = \underbrace{-\theta_2 z}_{Anti-TAF\,out} \quad on \;\; \Gamma_2 \times (0,T).$$

Complex

The complex that it formed when z binds to v satisfies

$$c_t = \underbrace{D_c \Delta c}_{Diffusion} \underbrace{-d_c c}_{Decay} \underbrace{-k_b c}_{Dissociation} + \underbrace{k_f v z}_{Association} \quad in \;\; \Omega_T,$$

$$\frac{D_c \partial c}{\partial n} = \underbrace{-\rho_1 c}_{Complex\,out} \quad on \;\; \Gamma_1 \times (0,T),$$

$$\frac{D_c \partial c}{\partial n} = \underbrace{-\rho_2 c}_{Complex\,out} \quad on \;\; \Gamma_2 \times (0,T).$$

Nutrients

Nutrients are provided by the blood supply. Let us note that tumor vessels are immature, as a consequence nutrient delivery is usually chaotic (see [17]). Therefore, it is possible to have a closed loop of endothelial cells without blood flow. Since we are not taking into account the blood flow we simplify the nutrients equation assuming that endothelial cells provide nutrients in the domain and those nutrients are consumed by the tumor at Γ_1. Therefore,

$$\begin{aligned} w_t &= \underbrace{D_w \Delta w}_{Diffusion} \underbrace{-d_w w}_{Decay} + \underbrace{\zeta u}_{Production} \quad in \ \ \Omega_T, \\ \frac{D_w \partial w}{\partial n} &= \underbrace{-\delta_1 w}_{Nutrients\, consumption} \quad on \ \ \Gamma_1 \times (0,T), \\ \frac{D_w \partial w}{\partial n} &= \underbrace{-\delta_2 w}_{Nutrients\, out} \quad on \ \ \Gamma_2 \times (0,T). \end{aligned}$$

Since consumption is much more effective than diffusion, then $\delta_1 >> \delta_2$. In particular, when $\delta_1 = +\infty$ we have the Dirichlet boundary $w = 0$ at Γ_1.

At this point, we come back to the boundary conditions for u. Let us observe that replacing the value of $\frac{\partial v}{\partial n}$ in the boundary conditions for u we get

$$\begin{aligned} D_u \frac{\partial u}{\partial n} &= h_1(x,u,v) + u\alpha(v)\gamma(w) = \overline{h}_1(x,u,v,w) \ \ on \ \ \Gamma_1 \times (0,T), \\ D_u \frac{\partial u}{\partial n} &= h_1(x,u,v) - \tau_2 u\alpha(v) = \overline{h}_2(x,u,v) \ \ on \ \ \Gamma_2 \times (0,T). \end{aligned}$$

It seems reasonable to assume that endothelial cells leave the domain at the boundary of the tumor. On the other hand, at Γ_2 we assume that endothelial cells enter the domain. Therefore, $\overline{h}_1(x,u,v,w) < 0$ and $\overline{h}_2(x,u,v) > 0$. The simplest functions that we can take are

$$h_1(x,u,v,w) = -\gamma_1 u\,,$$

$$h_2(x,u,v) = \gamma_2 u\,.$$

As in [4] we take a reference length $L = 0.2cm$ and $D_v \sim 10^{-6} cm^2 s^{-1}$ as a reference chemical diffusion coefficient. Since v and c are TAF and no active TAF we assume that $D_v = D_c$. Let u_0, v_0, w_0 reference values for endothelial cells, chemical molecules and nutrients. We introduce the non-dimensional variables

$$u^* = \frac{u}{u_0}\,, \ \ v^* = \frac{v}{v_0}\,, \ \ z^* = \frac{z}{v_0}\,, \ \ c^* = \frac{c}{v_0}\,, \ \ w^* = \frac{w}{w_0}\,, \ \ x^* = \frac{x}{L}\,, \ \ t^* = \frac{tD_v}{L^2}\,.$$

We define the following variables

$$\begin{gathered} D = \frac{D_u}{D_v}\,, \ \ \alpha^*(v^*) = \frac{v_0}{D_v}\alpha(v_0 v^*)\,, \ \ \lambda^* = \frac{\lambda L^2}{D_v}\,, \ \ \beta^*(v^*) = \beta(v_0 v^*)\,, \ \ \xi^* = \frac{\xi u_0 L^2}{D_v}\,, \\ \gamma_1^* = \frac{L\gamma_1}{D_u}\,, \ \ \gamma_2^* = \frac{L\gamma_2}{D_u}\,, \ \ d_v^* = \frac{d_v L^2}{D_v}\,, \ \ k_b^* = \frac{k_b L^2}{D_v}\,, \ \ k_f^* = \frac{k_f v_0 L^2}{D_v}\,, \\ \gamma^*(w^*) = \frac{L}{D_v v_0}\gamma(w_0 w^*)\,, \ \ \tau_2^* = \frac{L\tau_2}{D_v}\,, \ \ D_z^* = \frac{D_z}{D_v}\,, \ \ d_z^* = \frac{d_z L^2}{D_v}\,, \\ I_0^*(x^*,t^*) = \frac{L^2}{v_0 D_v} I_0\left(Lx^*, \frac{L^2}{D_v}t^*\right)\,, \ \ \theta_1^* = \frac{L\theta_1}{D_z}\,, \ \ \theta_2^* = \frac{L\theta_2}{D_z}\,, \ \ d_c^* = \frac{d_c L^2}{D_v}\,, \end{gathered}$$

$$\rho_1^* = \frac{L\rho_1}{D_c}\,, \quad \rho_2^* = \frac{L\rho_2}{D_c}\,, \quad D_w^* = \frac{D_w}{D_v}\,, \quad d_w^* = \frac{d_w L^2}{D_v}\,, \quad \zeta^* = \frac{\zeta u_0 L^2}{w_0 D_v}\,,$$

$$\delta_1^* = \frac{L\delta_1}{D_w}\,, \quad \delta_2^* = \frac{L\delta_2}{D_w}\,.$$

Dropping the asterisks we obtain the following non-dimensional system of partial differential equations

$$\begin{cases} u_t = D\Delta u - \nabla\cdot(\alpha(v)u\nabla v) + \lambda\beta(v)u - \xi u^2 & \text{in } \Omega_T\,, \\ v_t = \Delta v - d_v v - k_b c - k_f vz & \text{in } \Omega_T\,, \\ z_t = D_z\Delta z - d_z z + k_b c - k_f vz + I_0 & \text{in } \Omega_T\,, \\ c_t = \Delta c - d_c c - k_b c + k_f vz & \text{in } \Omega_T\,, \\ w_t = D_w\Delta w - d_w w + \zeta u & \text{in } \Omega_T\,, \\ B_1 u = B_3 z = B_4 c = B_5 w = (0,0) & \text{on } \partial\Omega_T\,, \\ B_2 v = (\gamma(w), 0) & \text{on } \partial\Omega_T\,, \\ (u,v,z,c,w)(x,0) = (u_0,v_0,z_0,c_0,w_0) & \text{in } \Omega\,, \end{cases} \tag{1}$$

where

$$B_1 u := \begin{cases} \dfrac{\partial u}{\partial n} + \gamma_1 u & \text{on } \Gamma_1, \\ \dfrac{\partial u}{\partial n} - \gamma_2 u & \text{on } \Gamma_2, \end{cases} \quad B_2 v := \begin{cases} \dfrac{\partial v}{\partial n} & \text{on } \Gamma_1, \\ \dfrac{\partial v}{\partial n} + \tau_2 v & \text{on } \Gamma_2, \end{cases}$$

$$B_3 z := \begin{cases} \dfrac{\partial z}{\partial n} + \theta_1 z & \text{on } \Gamma_1, \\ \dfrac{\partial z}{\partial n} + \theta_2 z & \text{on } \Gamma_2, \end{cases} \quad B_4 c := \begin{cases} \dfrac{\partial c}{\partial n} + \rho_1 c & \text{on } \Gamma_1, \\ \dfrac{\partial c}{\partial n} + \rho_2 c & \text{on } \Gamma_2, \end{cases}$$

$$B_5 w := \begin{cases} \dfrac{\partial w}{\partial n} + \delta_1 w & \text{on } \Gamma_1, \\ \dfrac{\partial w}{\partial n} + \delta_2 w & \text{on } \Gamma_2. \end{cases}$$

Here D is a small parameter. More precisely from [4] we have that $D \sim 10^{-3}$.

To our knowledge, one of the first papers related to discrete and continuous angiogenesis models was introduced in [3] (see also [5]). In the continuous framework TAF diffusivity is neglected. Moreover, the boundary conditions for the TAF at the blood vessel and tumor are of no-flux type. Such a condition was also assumed in [14]. More complex models of angiogenesis were introduced in [14]. For a simplification of the models considered in [14] it is proven in [11] the existence and uniqueness of a global-in-time solution and local stability of stationary solutions in 1-dimensional domains. In [16], it is criticized the no-flux boundary conditions.

A similar model to the one in the present paper, without a therapeutic agent, and a flux of TAF entering the domain depending only on the amount of TAF in the domain was studied in [10] as well as in [7].

The case with a therapy that block receptors in the membrane of the endothelial cells it is considered in [8].

The structure of the paper is as follows. In Section 2 we introduce some preliminaries that will be useful through the paper. Section 3 is devoted to the global in time existence for the problem. In the last Section we will show that high therapeutical doses induce a reduction in the amount of TAF.

2. **Preliminaries.** Let us first collect some results that will be used through the paper. Let $p \in (1,\infty)$, for $i=1,2,3,4,5$ A_i is defined in the following manner

$$A_1\xi := -D\Delta\xi + j_0\xi, \text{ for } \xi \in D_1(A_1) := \left\{\psi \in W^{2,p}(\Omega) : \ B_1(\psi)=0\right\},$$
$$A_2\xi := -\Delta\xi + d_v\xi, \text{ for } \xi \in D_2(A_2) := \left\{\psi \in W^{2,p}(\Omega) : \ B_2(\psi)=0\right\},$$
$$A_3\xi := -D_z\Delta\xi + d_z\xi, \text{ for } \xi \in D_3(A_3) := \left\{\psi \in W^{2,p}(\Omega) : \ B_3(\psi)=0\right\},$$
$$A_4\xi := -\Delta\xi + d_c\xi, \text{ for } \xi \in D_4(A_4) := \left\{\psi \in W^{2,p}(\Omega) : \ B_4(\psi)=0\right\},$$
$$A_5\xi := -D_w\Delta\xi + d_w\xi, \text{ for } \xi \in D_5(A_5) := \left\{\psi \in W^{2,p}(\Omega) : \ B_5(\psi)=0\right\}.$$

We denote by $\sigma(A_i,B_i)$ the spectrum of A_i with domains D_i, $i=1,2,3,4,5$. Let us observe that since $\tau_2,\theta_1,\theta_2,\delta_1,\delta_2>0$ then $Re\,\sigma(A_i,B_i)>0$ $i=2,3,4,5$. Moreover, we assume that $j_0>0$ sufficiently large to fulfill $Re\,\sigma(A_1,B_1)>0$. By the positivity of the spectrum, we have that the fractional powers of (A_i,B_i) $i=1,2,3,4,5$ are well-defined (see for instance [13, Ch. 1, Sec. 4]). Let

$$X^{\rho}_{i,p} := D_i(A_i^{\rho}) \text{ for } \rho\in(0,1) \ \ i=1,2,3,4,5.$$

then, by [13, Theorem 1.6.1], we have the following embeddings

$$\begin{array}{ll} X^{\rho}_{i,p} & \hookrightarrow W^{k,q}(\Omega) \text{ for } k-N/q<2\rho-N/p,\ q\geq p,\\ X^{\rho}_{i,p} & \hookrightarrow C^{\nu}(\overline{\Omega}) \text{ for } 0\leq\nu<2\rho-N/p. \end{array} \tag{2}$$

Moreover (A_i,B_i) $i=1,2,3,4,5$ are sectorial operators therefore

$$T_i(t) := e^{-t(A_i,B_i)} \ \ i=1,2,3,4,5$$

define analytic semigroups in $L^p(\Omega)$. Furthermore, by [13, Th. 1.3.4,Th. 1.4.3] T_i, $i=1,2,3,4,5$ satisfy the following:

1. For every $\delta\in(0,\min\{Re\,\sigma(A_0,B_i)\ i=1,2,3,4,5\})$, there exists $C>0$ such that
$$\|T_i(t)\|_{\mathcal{L}(L^p,L^p)} \leq Ce^{-\delta t} \ \ i=1,2,3,4,5.$$
2. Let $\rho\in(0,1)$ then there exists a constant C_ρ such that for every $u\in L^p(\Omega)$, $t>0$ and $\delta\in(0,\min\{Re\,\sigma(A_0,B_i)\ i=1,2,3,4,5\})$ we have
$$\|T_i(t)u\|_{X^{\rho}_{i,p}} \leq C_\rho t^{-\rho}e^{-\delta t}\|u\|_p \ \ i=1,2,3,4,5..$$
3. Let $p>N$. Combining (2) and an easy variant of [19, Lemma 1.3] then for all $u\in C_0^\infty(\overline{\Omega})$, $t>0$ we have
$$\|T_1(t)\nabla u\|_{C^0(\overline{\Omega})} \leq Ct^{-\gamma}e^{-\delta t}\|u\|_p,$$
for some constants $C>0$, $\gamma\in(0,1)$, $\delta>0$. In particular, the operator $T_1(t)\nabla$ admits an extension for all $u\in L^p(\Omega)$ where the above inequality holds.

In order to handle the nonlinear boundary condition in the v-equation, it will be useful to introduce the variations of constants formula for a parabolic problem with a non-homogeneous boundary condition. In particular, we consider

$$\left\{\begin{array}{ll} \psi_t + A_0\psi = f(t) & \text{in } \Omega\times(0,T),\\ B_2\psi = g(t) & \text{on } \partial\Omega\times(0,T),\\ \psi(x,0)=\psi_0(x), & \text{in } \Omega. \end{array}\right. \tag{3}$$

We define the space of functions

$$W^{s,p}_{B_2} := \left\{\begin{array}{ll} \{z\in W^{s,p}(\Omega) : B_2 z = 0\} & \text{if } 1+1/p<s\leq 2,\\ W^{s,p}(\Omega) & \text{if } -1+1/p<s<1+1/p,\\ (W^{-s,p'}(\Omega))' & \text{if } -2+1/p<s\leq -1+1/p. \end{array}\right.$$

It is known that (A_2, B_2) is in separated divergence form (see [1, pg. 21]), as a consequence, is normally elliptic. We denote by $A_{\alpha-1}$ the $W^{2\alpha-2,p}_{B_2}$-realization of (A_2, B_2) (see [1, pg. 39] for the precise definition). Since (A_2, B_2) is normally elliptic then $A_{\alpha-1}$ generates an analytic semigroup [1, Theorem 8.5]. Moreover, if

$$(f, g) \in C((0,T); W^{2\alpha-2,p}_{B_2}(\Omega) \times W^{2\alpha-1-1/p,p}_{B_2}(\partial\Omega))$$

for some $T > 0$ and $2\alpha \in (1/p, 1 + 1/p)$, then for any $t < T$ we rewrite (3) by the generalized variation of constants formula

$$\psi(t) = e^{-tA_{\alpha-1}}\psi_0 + \int_0^t e^{-(t-\tau)A_{\alpha-1}}(f(\tau) + A_{\alpha-1}(B_2)^c_\alpha g(\tau))d\tau,$$

where $(B_2)^c_\alpha$ is the continuous extension of $(B_2|_{Ker(A_0)})^{-1}$ to $W^{2\alpha-1-1/p,p}(\partial\Omega)$. Moreover,

$$A_{\alpha-1}(B_2)^c_\alpha \in \mathcal{L}(W^{2\alpha-1-1/p,p}(\partial\Omega), W^{2\alpha-2,p}_{B_2}).$$

Let $a \in L^\infty(\Omega)$, $b \in L^\infty(\Gamma_1)$ and $c \in L^\infty(\Gamma_2)$ the eigenvalue problem

$$\begin{cases} -\Delta\varphi + a(x)\varphi = \lambda\varphi & \text{in } \Omega, \\ \dfrac{\partial\varphi}{\partial n} = (-b(x)\varphi, -c(x)\varphi) & \text{on } \partial\Omega. \end{cases}$$

has a unique principal eigenvalue (i.e. an eigenvalue whose associated eigenfunction can be chosen positive in Ω) and it will be denoted by

$$\lambda_1(-\Delta + a; N + b; N + c).$$

Finally to conclude the section we remind an inequality that will be used in the last section, the Sobolev-Trace inequality, see for instance [12, Lemma 6].

Lemma 2.1. *(Sobolev-Trace inequality)*
For every $\epsilon > 0$, $\theta > 1$ there exists a constant $C = C(\Omega, \theta)$ such that

$$\int_{\partial\Omega} \varphi^2 \le \epsilon \int_\Omega |\nabla\varphi|^2 + C(\epsilon^{-\theta} + 1) \int_\Omega \varphi^2, \quad \forall \varphi \in W^{1,2}(\Omega).$$

3. **Global well posed-ness.** In what follows we introduce some additional notation. Through the rest of the paper $p > N$. For each $T > 0$ we define

$$\mathbf{X} := C^0(\overline{\Omega}) \times W^{1,p}(\Omega) \times (C^0(\overline{\Omega}))^3,$$

$$X_T := C([0,T]; C^0(\overline{\Omega})), \quad Y_T := C([0,T]; W^{1,p}(\Omega)),$$

$$\mathbf{X}_T := X_T \times Y_T \times (X_T)^3.$$

Theorem 3.1. *For each initial data $\mathbf{u_0} := (u_0, v_0, z_0, c_0, w_0) \in \mathbf{X}$ there exists $\tau(\|\mathbf{u_0}\|_{\mathbf{X}})$ such that the problem (1) has a unique local in time solution $\mathbf{u} \in \mathbf{X}_\tau$. Moreover, the solution depends continuously on the initial data, i.e. if $\mathbf{u}(\mathbf{u_0})$ and $(\overline{\mathbf{u}}_\mathbf{0})$ stand for the unique solution of (1) with initial data $\mathbf{u_0}$ and $\overline{\mathbf{u}}_\mathbf{0}$ respectively then $\mathbf{u}(\mathbf{u_0}) \to (\overline{\mathbf{u}}_\mathbf{0})$ in $\mathbf{X}_\tau$ when $\mathbf{u_0} \to \overline{\mathbf{u}}_\mathbf{0}$ in $\mathbf{X}$. Furthermore, the solution also depends continuously on I_0.*

Proof. The proof is based on the Banach fixed point Theorem. We pick $2\alpha \in (1, 1 + 1/p)$ and we denote by $\gamma_0 \in \mathcal{L}(C^0(\overline{\Omega}), C(\partial\Omega))$ the trace operator. We define the closed sets

$$B_X(R,T) := \{f \in X_T \,:\, \|f\|_{X_T} \le R\},$$
$$B_Y(R,T) := \{f \in Y_T \,:\, \|f\|_{Y_T} \le R\}$$

and $\mathbf{B}(R,T) := B_X(R,T) \times B_Y(R,T) \times (B_X(R,T))^3$. On $\mathbf{B}(R,T)$ we consider the operator

$$\mathbf{F}(u,v,z,c,w) := \begin{pmatrix} F_1(u,v,z,c,w) \\ F_2(u,v,z,c,w) \\ F_3(u,v,z,c,w) \\ F_4(u,v,z,c,w) \\ F_5(u,v,z,c,w) \end{pmatrix}$$

where

$$\begin{aligned}
&F_1(u,v,z,c,w) : \\
&\quad = T_1(t)u_0 + \int_0^t T_1(t-s)(-\nabla \cdot (\alpha(v)u\nabla v) + (\lambda\beta(v) + j_0)u - \xi u^2)ds\,, \\
&F_2(u,v,z,c,w) := T_2(t)v_0 + \int_0^t T_2(t-s)(k_b c - k_f vz + A_{\alpha-1}(B_2)^c_\alpha \gamma_0(\gamma(w)))ds\,, \\
&F_3(u,v,z,c,w) := T_3(t)z_0 + \int_0^t T_3(t-s)(k_b c - k_f vz + I_0)ds\,, \\
&F_4(u,v,z,c,w) := T_4(t)c_0 + \int_0^t T_4(t-s)(-k_b c + k_f vz)ds\,, \\
&F_5(u,v,z,c,w) := T_5(t)w_0 + \int_0^t T_5(t-s)\zeta u ds\,.
\end{aligned}$$

By the embedding

$$C(\partial\Omega) \hookrightarrow L^p(\partial\Omega) \hookrightarrow W^{2\alpha-1-1/p,p}(\partial\Omega),$$

we have that, in particular, $A_{\alpha-1}(B_2)^c_\alpha \gamma_0 \in \mathcal{L}(C^0(\overline{\Omega}), W^{2\alpha-2,p}_{B_2})$.

Step 1. There exist $R, t > 0$ such that $\mathbf{F}(\mathbf{B}(R,t)) \subset \mathbf{B}(R,t)$. For some constants $0 < \kappa < \rho < 1$ we have

$$\begin{aligned}
\|F_1\|_{C^0(\overline{\Omega})} &\le C\|\mathbf{u_0}\|_{\mathbf{X}_t} + \int_0^t \big(C(t-s)^{-\rho}\|\alpha(v)u\nabla v\|_p + \\
&\quad + C(t-s)^{-\kappa}e^{-\delta(t-s)}(\|\lambda(\beta(v)+j_0)u\|_p + \|u^2\|_p)\big)\, ds \\
&\le C\|\mathbf{u_0}\|_{\mathbf{X}_t} + C(\lambda\|\beta\|_\infty + j_0 + R(1+\|\alpha\|_\infty))R \max\left\{\frac{t^{1-\rho}}{1-\rho}, \frac{t^{1-\kappa}}{1-\kappa}\right\}.
\end{aligned}$$

By [9, Lemma 2.1], there exists $\eta \in (0,1)$ such that

$$\begin{aligned}
\|F_2\|_{1,p} &\le C\|v_0\|_{1,p} + \int_0^t C(t-s)^{-\eta}\Big(\|c - k_f vz\|_{W^{2\alpha-2,p}_{B_2}} + \\
&\quad + \|A_{\alpha-1}(B_2)^c_\alpha \gamma_0(\gamma(w))\|_{W^{2\alpha-2,p}_{B_2}}\Big)\, ds.
\end{aligned}$$

Since $A_{\alpha-1}(B_2)^c_\alpha \gamma_0 \in \mathcal{L}(C^0(\overline{\Omega}), W^{2\alpha-2,p}_{B_2})$ we have

$$\|F_2\|_{1,p} \le C\|\mathbf{u_0}\|_{\mathbf{X}_t} + C(\gamma(0) + R + R^2)\frac{t^{1-\eta}}{1-\eta}.$$

The rest of the terms can be estimated using just the maximum principle

$$\|F_3\|_{C^0(\overline{\Omega})} \le C\|\mathbf{u_0}\|_{\mathbf{X}_t} + (k_b R + k_f R^2 + \|I_0\|_{\mathbf{X}_t})t\,,$$

$$\|F_4\|_{C^0(\overline{\Omega})} \le C\|\mathbf{u_0}\|_{\mathbf{X}_t} + (k_b R + k_f R^2)t\,,$$

$$\|F_5\|_{C^0(\overline{\Omega})} \le C\|\mathbf{u_0}\|_{\mathbf{X}_t} + Rt\,.$$

We pick $R > C\|\mathbf{u_0}\|_{\mathbf{X}_t} + 1$. Previous estimates assert that there exists τ_0 such that for every $t \leq \tau_0$

$$\|\mathbf{F}(u, v, z, c, w)\|_{\mathbf{X}_t} \leq C\|\mathbf{u_0}\|_{\mathbf{X}_t} + 1\,.$$

Therefore, it follows that $\mathbf{F}(\mathbf{B}(R, t)) \subset \mathbf{B}(R, t)$.

Step 2. $\mathbf{F}$ is contractive in $\mathbf{B}(R, \tau)$ for some $\tau \leq \tau_0$. Let $t \leq \tau_0$ and

$$\mathbf{u} := (u, v, z, c, w) \in \mathbf{B}(R, t), \qquad \overline{\mathbf{u}} := (\overline{u}, \overline{v}, \overline{z}, \overline{c}, \overline{w}) \in \mathbf{B}(R, t).$$

We have

$$\begin{aligned}\|F_1(\mathbf{u}) - F_1(\overline{\mathbf{u}})\|_{C^0(\overline{\Omega})} \leq \int_0^t \Big(& \|T_1(t-s)\nabla \cdot (\alpha(v)u\nabla v - \alpha(\overline{v})\overline{u}\nabla\overline{v})\|_{C^0(\overline{\Omega})} + \\ & + \|T_1(t-s)((\lambda\beta(v) + j_0)u - (\lambda\beta(\overline{v}) + j_0)\overline{u})\|_{C^0(\overline{\Omega})} + \\ & + \|T_1(t-s)\xi(u^2 - \overline{u}^2)\|_{C^0(\overline{\Omega})}\Big) ds\,.\end{aligned}$$

We denote by $(b1)$, $(b2)$ and $(b3)$ the first, second and third term, respectively, in the right-hand side of the above inequality. In what follows, we estimate separately each term in the above inequality.

$$\begin{aligned}(b1) \leq & \int_0^t \|T_1(t-s)\nabla \cdot (\alpha(v)(u - \overline{u})\nabla v)\|_{C^0(\overline{\Omega})} + \\ & + \|T_1(t-s)\nabla \cdot (\alpha(v)\overline{u}\nabla(v - \overline{v}))\|_{C^0(\overline{\Omega})} + \\ & + \|T_1(t-s)\nabla \cdot (\alpha(v) - \alpha(\overline{v}))\overline{u}\nabla\overline{v})\|_{C^0(\overline{\Omega})} \\ \leq & \int_0^t C(t-s)^{-\rho} C(\|\alpha\|_\infty, R)(\|u - \overline{u}\|_{C^0(\overline{\Omega})} + \|v - \overline{v}\|_{W^{1,p}(\Omega)})\,,\end{aligned}$$

where $\rho \in (0, 1)$. Arguing in a similar way, we obtain

$$(b2) \leq \int_0^t C(t-s)^{-\kappa} C(j_0, \|\beta\|_\infty, R)(\|u - \overline{u}\|_{C^0(\overline{\Omega})} + \|v - \overline{v}\|_{1,p})\,,$$

$$(b3) \leq \int_0^t C(t-s)^{-\kappa} 2R\|u - \overline{u}\|_{C^0(\overline{\Omega})}\,,$$

for some $\kappa \in (0, 1)$. Therefore,

$$\|F_1(\mathbf{u}) - F_1(\overline{\mathbf{u}})\|_{C^0(\overline{\Omega})} \leq C(j_0, \|\alpha\|_\infty, \|\beta\|_\infty, R) \max\left\{\frac{t^{1-\rho}}{1-\rho}, \frac{t^{1-\kappa}}{1-\kappa}\right\} \|\mathbf{u} - \overline{\mathbf{u}}\|_{\mathbf{X}_t}\,.$$

For the second component of $\mathbf{F}$ we have

$$\begin{aligned}\|F_2(\mathbf{u}) - F_2(\overline{\mathbf{u}})\|_{1,p} \quad & \leq \int_0^t C(t-s)^{-\eta}(\|c - \overline{c}\|_{C^0(\overline{\Omega})} + \\ & \quad + R(\|v - \overline{v}\|_{1,p} + \|z - \overline{z}\|_{C^0(\overline{\Omega})}) + \|\gamma(w) - \gamma(\overline{w})\|_{C^0(\overline{\Omega})}) ds \\ & \leq C(C + R)\frac{t^{1-\eta}}{1-\eta}\|\mathbf{u} - \overline{\mathbf{u}}\|_{\mathbf{X}_t}.\end{aligned}$$

Finally,

$$\|F_3(\mathbf{u}) - F_3(\overline{\mathbf{u}})\|_{C^0(\overline{\Omega})} \leq C(C + R)t\|\mathbf{u} - \overline{\mathbf{u}}\|_{\mathbf{X}_t}\,.$$
$$\|F_4(\mathbf{u}) - F_4(\overline{\mathbf{u}})\|_{C^0(\overline{\Omega})} \leq C(C + R)t\|\mathbf{u} - \overline{\mathbf{u}}\|_{\mathbf{X}_t}\,.$$
$$\|F_5(\mathbf{u}) - F_5(\overline{\mathbf{u}})\|_{C^0(\overline{\Omega})} \leq Ct\|\mathbf{u} - \overline{\mathbf{u}}\|_{\mathbf{X}_t}\,.$$

Therefore, there exists $\tau \leq \tau_0$ such that $\mathbf{F}$ is contractive in $\mathbf{B}(R, \tau)$.

At the end we prove the continuity of the solutions respect to the initial data and the coefficient I_0. Let $R > C\max\{\|\mathbf{u_0}\|_{\mathbf{X_t}}, \|\overline{\mathbf{u}}_\mathbf{0}\|_{\mathbf{X_t}}\} + \mathbf{1}$. Then, there exists τ such that $\mathbf{F}$ is contractive; as a consequence, there exists $\kappa < 1$ such that

$$\begin{aligned}\|\mathbf{u}(\mathbf{u_0}) - \mathbf{u}(\overline{\mathbf{u}}_\mathbf{0})\|_{\mathbf{X}_\tau} &\leq \|T_1(t)(u_0 - \overline{u}_0)\|_{C^0(\overline{\Omega})} + \|T_2(t)(v_0 - \overline{v}_0)\|_{1,p} + \\ &\quad + \|T_3(t)(z_0 - \overline{z}_0)\|_{C^0(\overline{\Omega})} + \|T_4(t)(c_0 - \overline{c}_0)\|_{C^0(\overline{\Omega})} + \\ &\quad + \|T_5(t)(w_0 - \overline{w}_0)\|_{C^0(\overline{\Omega})} + \|\mathbf{F}(\mathbf{u}(\mathbf{u_0})) - \mathbf{F}(\mathbf{u}(\overline{\mathbf{u}}_\mathbf{0}))\|_{\mathbf{X}_\tau} \\ &\leq C\|\mathbf{u_0} - \overline{\mathbf{u}}_\mathbf{0}\|_{\mathbf{X}} + \kappa\|\mathbf{u}(\mathbf{u_0}) - \mathbf{u}(\overline{\mathbf{u}}_\mathbf{0})\|_{\mathbf{X}_\tau}\,.\end{aligned}$$

For the proof of the continuity on I_0 we just need to argue in the same way. □

Proposition 1. *Under conditions of Theorem 3.1, if the initial data of (1) are non-negative i.e.* $\mathbf{u}_0 \geq 0$ *for all* $x \in \Omega$ *and* $I_0(x,t) \geq 0$ *for all* $(x,t) \in \Omega \times (0,\tau)$*, then the solution* $\mathbf{u}$ *to (1) is also non-negative i.e.* $\mathbf{u} \geq 0$ *for all* $(x,t) \in \Omega \times (0,\tau)$.

Proof. The positivity of u follows from [1, Theorem 15.1] and the positivity of v, c, z, w it is a consequence a standard maximum principle for parabolic equations. □

Now we deal with the global existence result. By the continuation principle we just need to show that for every $t < T_{max}$

$$\|\mathbf{u}\|_{\mathbf{X}_t} \leq C(t).$$

Lemma 3.2. *For each* $t < T_{max}$ *we have that*

$$\|(c,v)\|_{X_t \times X_t} \leq C.$$

Proof. Let $s := c + v$ then s is a positive solution for the problem

$$\begin{cases} s_t = \Delta s - \min\{d_v, d_c\}s + \min\{(d_v - d_c)c, (d_c - d_v)v\} & \text{in } \Omega_t\,, \\ \dfrac{\partial s}{\partial n} = (\gamma(w) - \rho_1 c, -\min\{\rho_2, \tau_2\}s + \min\{(\rho_2 - \tau_2)v, (\tau_2 - \rho_2)c\}) & \text{on } \partial\Omega_t\,, \\ s(x,0) = c_0(x) + v_0(x) & \text{in } \Omega\,. \end{cases} \tag{4}$$

Since $\min\{(\rho_2 - \tau_2)v, (\tau_2 - \rho_2)c\} \leq 0$, $\min\{(d_v - d_c)c, (d_c - d_v)v\} \leq 0$ and γ is a decreasing function, then the unique positive solution θ of the linear problem

$$\begin{cases} \theta_t = \Delta\theta - \min\{d_v, d_c\}\theta & \text{in } \Omega_t\,, \\ \dfrac{\partial\theta}{\partial n} = (\gamma(0), -\min\{\rho_2, \tau_2\}\theta) & \text{on } \partial\Omega_t\,, \\ \theta(x,0) = c_0(x) + v_0(x) & \text{in } \Omega\,. \end{cases}$$

is a super solution of (4). Therefore, $0 < s(t) \leq \theta(t) \leq C$ and Lemma follows. □

Lemma 3.3. *Let* K *a positive constant. Assume that* $I_0(t) \leq K$ *for each* $t < T_{max}$ *then*

$$\|z\|_{X_t} \leq C.$$

Proof. By the previous Lemma, we know that $c \leq C$. We consider φ the unique solution to the linear parabolic problem

$$\begin{cases} \varphi_t = D_z\Delta\varphi - d_z\varphi + k_b C + K & \text{in } \Omega_t\,, \\ \frac{\partial\varphi}{\partial n} = (-\theta_1\varphi, -\theta_2\varphi) & \text{on } \partial\Omega_t\,, \\ \varphi(x,0) = z_0(x) & \text{in } \Omega\,. \end{cases}$$

By the comparison principle $0 < z(t) < \varphi(t) \leq C$. □

Lemma 3.4. *For each $t < T_{max}$ we have*

$$\|v\|_{Y_t} \le C$$

Proof. By the generalized variation of constants formula for v and applying the estimate provided in [6, Lemma 3.1] (that also holds in our case), we have that there exist constants $\delta > 0$, $\nu \in (0,1)$ such that

$$\|v(t)\|_{1,p} \le C\|v_0\|_{1,p} + C\int_0^t (t-s)^{-\nu} e^{-\delta(t-s)} h(s) ds$$

where

$$h(s) := \|c\|_{W^{2\alpha-2,p}_{B_2}} + \|vz\|_{W^{2\alpha-2,p}_{B_2}} + \|A_{\alpha-1}(B_2)^c_\alpha \gamma_0(\gamma(w))\|_{W^{2\alpha-2,p}_{B_2}}\,.$$

By the embedding

$$C^0(\overline{\Omega}) \hookrightarrow W^{2\alpha-2,p}_{B_2}$$

we obtain

$$\|v(t)\|_{1,p} \le C\|v_0\|_{1,p} + C\int_0^t (t-s)^{-\nu} e^{-\delta(t-s)} (\|c\|_{C^0(\overline{\Omega})} + \|vz\|_{C^0(\overline{\Omega})} + \|\gamma(w)\|_{C^0(\overline{\Omega})}) ds\,.$$

Therefore, by previous Lemmas and the monotonicity of γ we conclude the Lemma. □

Lemma 3.5. *For any $t < T_{max}$ we have that*

$$\|u\|_{X_t} \le C$$

Proof. We take the $C^0(\overline{\Omega})$-norm in the variations of constant formula of u to deduce that for some constants $0 < \kappa < \rho < 1$, we have

$$\begin{aligned} \|u\|_{C^0(\overline{\Omega})} \quad &\le C\|u_0\|_{C^0(\overline{\Omega})} + \int_0^t Ce^{-\delta(t-s)} \Big((t-s)^{-\rho}\|\alpha\|_\infty \|v\|_{1,p}\|u\|_{C^0(\overline{\Omega})} + \\ &+ (t-s)^{-\kappa}(\|\lambda\beta(v)u - \xi u^2\|_{C^0(\overline{\Omega})}\Big)\, ds\,. \end{aligned}$$

Since

$$\lambda\beta(v)u - \xi u^2 \le \lambda\|\beta\|_\infty u - \xi u^2 < C$$

then by the Gronwall Lemma we easily deduce the result. □

Lemma 3.6. *For any $t < T_{max}$ we have that*

$$\|w\|_{X_t} \le C$$

Proof. Let $C > 0$ the constant provided by the previous Lemma and φ the unique solution to the linear problem

$$\begin{cases} \varphi_t = D_w\Delta\varphi - d_w\varphi + \zeta C & \text{in } \Omega_t\,, \\ \dfrac{\partial\varphi}{\partial n} = (-\delta_1\varphi, -\delta_2\varphi) & \text{on } \partial\Omega_t\,, \\ \varphi(x,0) = w_0(x) & \text{in } \Omega\,. \end{cases}$$

Since φ is a positive supersolution to the w-equation then $0 < w(t) \le \varphi(t) \le C$. □

As a consequence of previous Lemmas and Theorem 3.1 we deduce global in time existence for problem (1).

Theorem 3.7. *Assume that the initial data $\mathbf{u}_0 \in \mathbf{X}$, $p > N$, with $\mathbf{u}_0 \ge 0$ in Ω and $I_0 \in C((0,\infty); C^0(\overline{\Omega}))$ with $I_0(x,t) \ge 0$ for $x \in \overline{\Omega}$, $t > 0$. Then, there exists a unique non-negative global in time solution to (1).*

4. **Large time behaviour of v when I_0 is large.** During this section we assume that I_0 is a constant sufficiently large.

Lemma 4.1. *There exist $\tau > 0$ and $\delta > 0$ such that for any $t > \tau$ the following inequality holds*

$$\|z(t)\|_{C^0(\overline{\Omega})} > \delta I_0.$$

Proof. By Lemma 3.2 we know that $v \leq C$ where C is a constant that does not depend on I_0. Therefore, the solution to the linear problem

$$\begin{cases} \varphi_t = D_z\Delta\varphi - d_z\varphi - k_f C\varphi + I_0 & \text{in } \Omega_t\,, \\ \dfrac{\partial\varphi}{\partial n} = (-\theta_1\varphi, -\theta_2\varphi) & \text{on } \partial\Omega_t\,, \\ \varphi(x,0) = z_0(x) & \text{in } \Omega\,, \end{cases}$$

is a subsolution to the z-equation. Thus, $0 < \varphi(t) \leq z(t)$. On the other hand, since $\lambda_1(-\Delta + 1; N + \theta_1; N + \theta_2) > 0$ then

$$\lim_{t\to+\infty} \|\varphi(t) - \varphi_e\|_{C^0(\overline{\Omega})} = 0 \tag{5}$$

where φ_e is the unique positive solution to

$$\begin{cases} D_z\Delta\varphi_e - d_z\varphi_e - k_f C\varphi_e + I_0 = 0 & \text{in } \Omega\,, \\ \dfrac{\partial\varphi_e}{\partial n} = (-\theta_1\varphi_e, -\theta_2\varphi_e) & \text{on } \partial\Omega\,, \end{cases}$$

Moreover, easily we can check that $\varphi_e = eI_0$, where e is the unique positive solution to

$$\begin{cases} D_z\Delta e - d_z e - k_f C e + 1 = 0 & \text{in } \Omega\,, \\ \dfrac{\partial e}{\partial n} = (-\theta_1 e, -\theta_2 e) & \text{on } \partial\Omega\,, \end{cases}$$

Additionally the strong maximum principle (see [2, Theorem 2.4]) entails that $\min_{x\in\overline{\Omega}} e = \kappa > 0$. Thus, $\varphi_e \geq kI_0$ and by (5) there exists $\tau > 0$ such that

$$\varphi(x,t) \geq (k/2)I_0, \text{ for every } x \in \overline{\Omega} \text{ and } t \geq \tau$$

Putting previous estimates together we infer

$$(k/2)I_0 < \varphi(x,t) < z(x,t) \text{ for every } x \in \overline{\Omega},\ t > \tau$$

and Lemma follows. ☐

Theorem 4.2. *There exist $C > 0$ and $\overline{\tau} > \tau$ such that*

$$\int_\Omega v(t)^2 \leq C I_0^{-1/3}$$

for each $t > \overline{\tau}$.

Proof. We multiply the v-equation by v and after integrating by parts to get

$$\begin{aligned} \frac{d}{2dt}\int_\Omega v^2 &= -\int_\Omega |\nabla v|^2 - \int_\Omega (d_v + k_f z)v^2 - k_b\int_\Omega cv + \int_{\Gamma_1}\gamma(w)v - \tau_2\int_{\Gamma_2} v^2 \\ &\leq -\int_\Omega |\nabla v|^2 - \int_\Omega (d_v + k_f z)v^2 + \frac{1}{4\epsilon}\int_{\Gamma_1} v^2 + \epsilon\gamma(0)^2|\Gamma_1|. \end{aligned}$$

We provide a bound for the boundary term using the Sobolev-Trace inequality

$$\frac{1}{4\epsilon}\int_{\Gamma_1} v^2 \leq \frac{\epsilon'}{4\epsilon}\int_\Omega |\nabla v|^2 + \frac{C((\epsilon')^{-2}+1)}{4\epsilon}\int_\Omega v^2\,.$$

Next, we pick $\epsilon' = 2\epsilon$ and ϵ such that $\frac{C((\epsilon')^{-2}+1)}{4\epsilon} \leq k_f \delta I_0$. In particular we can pick $\epsilon = CI_0^{-1/3}$ for some $C > 0$. Therefore,

$$\frac{d}{2dt}\int_\Omega v^2 \leq -\frac{1}{2}\int_\Omega |\nabla v|^2 - \frac{d_v}{2}\int_\Omega v^2 + (k_f\delta I_0 - k_f z)\int_\Omega v^2 + \epsilon\gamma(0)^2|\Gamma_1|.$$

By Lemma 4.1, $k_f\delta I_0 - k_f z < 0$ for each $t \geq \tau$. Thus, $y(t) = \int_\Omega v^2(t)$ satisfies for each $t \geq \tau$ the following differential inequality

$$y'(t) \leq -\frac{d_v}{2}y(t) + CI_0^{-1/3}\gamma(0)^2|\Gamma_1|\,, \quad y(\tau) = \int_\Omega v^2(\tau)\,.$$

Solving previous differential inequality, we have

$$y(t) \leq e^{-(d_v/2)t}y(\tau) + (2/d_v)CI_0^{-1/3}\gamma(0)^2|\Gamma_1|(1 - e^{(d_v/2)(\tau - t)})$$

and Theorem follows for t sufficiently large. □

REFERENCES

[1] H. Amann, *Nonhomogeneous linear and quasilinear elliptic and parabolic boundary value problems*, in “Function Spaces, Differential Operators and Nonlinear Analysis” (editors, H. J. Schmeisser and H. Triebel), Teubner, Stuttgart, Leipzig, (1993), 9–126.

[2] H. Amann and J. López-Gómez, *A priori bounds and multiple solutions for superlinear indefinite elliptic problems*, J. Differential Equations, **146** (1998), 336–374.

[3] A. R. A. Anderson and M. A. J. Chaplain, *Continuous and Discrete Mathematical Models of Tumor-induced Angiogenesis*, Bull. Math. Biol., **60** (1998), 857–899.

[4] M. A. J. Chaplain and A. M. Stuart, *A model mechanism for the chemotactic response of endothelial cells to tumour angiogenesis factor*, IMA J. Math. Appl. Med. Biol., **10** (1993), 149–168.

[5] M. A. J. Chaplain, *Avascular growth, angiogenesis and vascular growth in solid tumours: the mathematical modelling of the stages of tumor development*, Math. Comput. Modelling, **23** (1996), 47–87.

[6] T. Cieślak and C. Morales-Rodrigo, *Long-time behaviour of an angiogenesis model with flux at the tumor boundary*, Preprint, `arXiv:1202.4695`.

[7] M. Delgado, I. Gayte, C. Morales-Rodrigo and A. Suárez, *An angiogenesis model with nonlinear chemotactic response and flux at the tumor boundary*, Nonlinear Anal., **72** (2010), 330–347.

[8] M. Delgado, C. Morales-Rodrigo and A. Suárez, *Anti-angiogenic therapy based on the binding receptors*, Discrete Contin. Dyn. Syst. Ser A, **32** (2012), 3871–3894.

[9] M. Delgado, C. Morales-Rodrigo, A. Suárez and J. I. Tello, *On a parabolic-elliptic chemotactic model with coupled boundary conditions*, Nonlinear Analysis RWA, **11** (2010), 3884–3902.

[10] M. Delgado and A. Suárez, *Study of an elliptic system arising from angiogenesis with chemotaxis and flux at the boundary*, J. Differential Equations, **244** (2008), 3119–3150.

[11] M. A. Fontelos, A. Friedman and B. Hu, *Mathematical analysis of a model for the initiation of angiogenesis*, SIAM J. Math. Anal., **33** (2002), 1330–1350.

[12] J. García-Melián, J. D. Rossi and J. Sabina, *Existence and uniqueness of positive solutions to elliptic problems with sublinear mixed boundary conditions*, Comm. Comtemporary Math., **11** (2009), 585–613.

[13] D. Henry, “Geometric Theory of Semilinear Parabolic Equations,” Lecture Notes Math., 840, Springer 1981.

[14] H. A. Levine, B. D. Sleeman and M. Nilsen-Hamilton, *Mathematical modeling of the onset of capillary formation initiating angiogenesis*, J. Math. Biol., **42** (2001), 195–238.

[15] D. Manoussaki, *A mechanochemical model of angiogenesis and vasculogenesis*, ESAIM Math. Modelling Num. Anal., **37** (2003), 581–599.

[16] N. V. Mantzaris, S. Webb and H. G. Othmer, *Mathematical modeling of tumor induced angiogenesis*, J. Math. Biol., **49** (2004), 111–187.

[17] M. Owen, T. Alarcón, P. K. Maini and H. M. Byrne, *Angiogenesis and vascular remodelling in normal and cancerous tissues*, J. Math. Biol., **58** (2009), 689–721.

[18] R. M. Sutherland, *Cell and environment interactions in tumor microregions: The multicell spheroid model*, Science, **240** (1988), 177–184.

[19] M. Winkler, *Aggregation vs global diffusive behavior in the higher-dimensional Keller-Segel model*, J. Differential Equations, **248** (2010), 2889–2905.

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