Anti-angiogenic therapy based on the binding receptors

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Abstract

This paper deals with a nonlinear system of partial differential equations modeling the effect of an anti-angiogenic therapy based on an agent that binds specific receptors of the endothelial cells. We study the time-dependent problem as well as the stationary problem associated to it.

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1 Introduction

This paper deals with the theoretical study of a system of PDE which is related with a model of anti-angiogenic therapy. It is well-known that tumor induced angiogenesis is a complex process by which a tumor prompts the formation of a vascular network which starts of a near blood vessel and leads to vascular growth towards it to gain access to the necessary nutrients to continue growing. Also, the tumor cells acquire a means of transport to form a new colony in distant organs (metastases). This process begins when the avascular tumor mass releases substances called tumor angiogenic factors (TAF) which diffuse through the surrounding tissue, from which the extracellular matrix (ECM) is part, and arrive to a blood vessel; the TAF weaken the wall of the vessel and provoke the out of control growth of the endothelial cells (EC), which form the vessel, towards the tumor through the ECM, forming an irregular vascular network which ends up arriving to it (cf. [23]).

Among the continuum models, in a first step, the process is modeled by two equations, one for the EC density and another for the concentration of the TAF. The first one is a parabolic equation with a chemotaxis term, which takes into account the cellular movement towards the tumor, and a reaction term which models the growth of EC. The second one is a parabolic equation with a linear diffusion and a decay term. This basic model is sometimes completed with one equation for the ECM, a differential equation without diffusion and with a degradation term (see, for instance [24]); the statement of a variable for the ECM density allows to introduce in the EC equation the term of haptotaxis which takes into account the dragging of the EC on the ECM. Also, the time scale of the diffusion of the chemical substances (TAF) and the time scale of the cellular splitting underlying to the generation of the vascular network are different, and sometimes this is modeled by the statement of one elliptic (non parabolic) equation for the TAF.

Here, we are interested to model an anti-angiogenic therapy and we are going to complete the basic model with one equation for the therapy, which will be a parabolic equation with linear diffusion, a decay term and a term which model the introduction of the drug in the organism. We assume a tumor, whose boundary is Γ_1, surrounded by a vessel and we consider a "virtual" regular boundary, Γ_2, next to the vessel: our bounded regular domain, $\Omega \subset \mathbb{R}^N$ is limited by Γ_1 and Γ_2 (see Figure 1, where we have represented a particular situation).

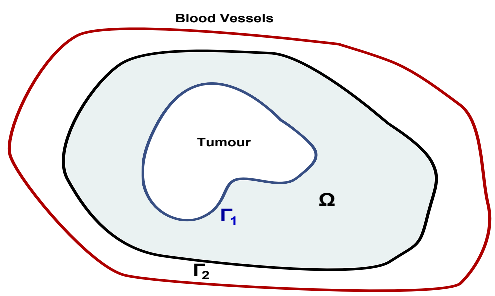

Figure 1: A particular example of domain Ω.

In this domain we consider the equations

$$\begin{cases} u_t = \Delta u - \nabla \cdot (\alpha(v,z)u\nabla v) + \lambda\beta(v,z)u - u^2 & \text{in } \Omega \times (0,T),\ T > 0 \\ v_t = \Delta v - v & \text{in } \Omega \times (0,T), \\ z_t = \Delta z - z + I_0 & \text{in } \Omega \times (0,T), \end{cases} \tag{1}$$

where u stands for the density of the EC, and v and z stand for the concentration of the TAF and the drug, respectively. The growth of the EC follows a logistic law and $\lambda\beta$ represents the rate growth; λ is a real parameter and β depends on v and z, because, for instance, it is known, [8], that there is no growing until the TAF exceed a threshold value. The function α represents for chemotactic sensitivity, which is signal-dependent and depends on v and z (see [19]). I_0 stands the introduction of the therapy and can be constant (constant introduction of medicine), periodic, etc.; in this paper I is a general function depending on x and t.

With respect to the domain, we consider the case

$$\partial\Omega = \Gamma_1 \cup \Gamma_2,$$

with $\Gamma_1 \cap \Gamma_2 = \emptyset$, being Γ_i closed and open in the relative topology of $\partial\Omega$. We assume Robin homogeneous boundary conditions on Γ_2 and also on Γ_1 for the first and third variables, but on Γ_2, the EC come in the domain and the TAF and the drug leave the domain toward the vessel and on Γ_1 the EC and the drug leave the domain penetrating in the tumor. For the second variable on Γ_1, it is known that the TAF is produced by hypoxic cells, that is, tumoral cells which have deprivation of oxygen. In order to avoid one equation for the oxygen, we include the relationship between the oxygen and the EC; in fact, the oxygen is transport by the red blood cells and these arrive at the tumor cells through the vascular network formed by the EC. So, a low EC level implies a low oxygen level and a high TAF level production, and the other way round. It is the reason because we consider a Neumann non-homogenous boundary condition where γ will be a positive and decreasing function. Then, we arrive to the following boundary conditions

$$\begin{cases} B_1 u = B_3 z = (0,0) & \text{on } \partial\Omega \times (0,T), \\ B_2 v = (\gamma(u), 0) & \text{on } \partial\Omega \times (0,T), \end{cases} \tag{2}$$

where we have denoted

$$B_1 u := \begin{cases} \dfrac{\partial u}{\partial n} + \gamma_1 u & \text{on } \Gamma_1, \\ \dfrac{\partial u}{\partial n} - \tau_1 u & \text{on } \Gamma_2, \end{cases} \quad B_2 v := \begin{cases} \dfrac{\partial v}{\partial n} & \text{on } \Gamma_1, \\ \dfrac{\partial v}{\partial n} + \tau_2 v & \text{on } \Gamma_2, \end{cases} \quad B_3 z := \begin{cases} \dfrac{\partial z}{\partial n} + \gamma_3 z & \text{on } \Gamma_1, \\ \dfrac{\partial z}{\partial n} + \tau_3 z & \text{on } \Gamma_2, \end{cases}$$

with $\gamma_1, \tau_1, \tau_2, \gamma_3, \tau_3 > 0$ and n denotes the outward unit normal vector.

We must consider closely the action mechanism of the angiogenic process. When the TAF arrive at the EC, the molecules must fit in some receptors existing in the cellular membrane through which can cross to the cytoplasm starting a chain of biochemical reactions whose result is the degradation of the basal lamina which cover the surface of the capillaries, the development of the foot-like structures on the normally smooth cell surface, the penetration of the basal lamina in the ECM and the proliferation of the EC towards the gradient of the TAF. So, a possible anti-angiogenic therapy consists in the introduction of a drug which blocks these receptors stopping the process; the TAF in the ECM is inactive and have not bad consequences. The introduction of this therapy gives rise to a complex situation in which there are free receptors, which can join to molecules of the TAF, occupied receptors by molecules of TAF and inactive receptors by the drug. The study of this system permits to conclude that the functions α and β depend on the one variable, s, which represents the free receptors, then

$$\alpha(v,z) = \alpha_R(s) \quad \text{and} \quad \beta(v,z) = \beta_R(s),$$

being α_R, β_R are regular functions in $[0,\infty)$. The TAF attract the EC, so the chemotactic sensitivity is positive and we will suppose α_R positive with $\alpha_R(0) > 0$. The rate growth of the EC will growth with a high level of free receptors, so we will asume that β_R is increasing and $\beta_R(0) = 0$. The dependence of s on v and z is also regular.

Various models of tumor induced angiogenesis, discrete as well as continuous, were introduced in [4]. In the continuous model it was supposed a non-diffusive equation and no-flux boundary condition for the TAF. Such a condition was also assumed in [20] where it is proposed an angiogenesis model that takes into account biochemical processes. Under the hypothesis that some of the biochemical processes are quasi-stationary it is proven in [16] existence and uniqueness of a global-in-time solution and local stability of stationary solutions in 1-Dimensional domains. The previous condition was discussed in [23].

A similar model to the one in the present paper, without an equation for the therapy, and a flux of TAF entering in the domain depending only of the amount of TAF in the domain was study in [12] for the linear case and [10] for the nonlinear case.

Let us mention [13] and [24] where it is proved the global existence and uniqueness of solution for a model of tumor invasion, another important process in the tumor development.

Finally, in [14, 15] different models of tumor in the breast are proposed and the effect of different therapies are studied by numerical experiments.

The structure of the paper is as follows. In Section 2, we study the evolution problem, proving the existence and the uniqueness of positive solution for the system. In Section 3 we study the stationary problem showing the existence of coexistence states for λ greater than a certain value. In Section 4, we apply our results in the particular case when I_0 is constant, with supplementary hypotheses on $\alpha_R,\ \beta_R$ and s.

2 The evolution problem

Let $\Omega \subset \mathbb{R}^N$ a bounded regular domain whose boundary $\partial\Omega := \Gamma_1 \cup \Gamma_2$ with Γ_1, Γ_2 open and closed sets in the relative topology of $\partial\Omega$. Let $\lambda \in \mathbb{R}$, $\gamma_1, \gamma_2, \tau_1, \tau_2, \tau_3, T$ positive constants and $I_0 \in C([0,T]; C^0(\overline{\Omega}))$. We consider the evolution problem

$$\begin{cases} u_t = \Delta u - \nabla \cdot (\alpha(v,z) u \nabla v) + \lambda \beta(v,z) u - u^2 & \text{in } \Omega \times (0,T), \\ v_t = \Delta v - v & \text{in } \Omega \times (0,T), \\ z_t = \Delta z - z + I_0 & \text{in } \Omega \times (0,T), \\ B_1 u = B_3 z = (0,0) & \text{on } \partial\Omega \times (0,T), \\ B_2 v = (\gamma(u), 0) & \text{on } \partial\Omega \times (0,T), \\ (u,v,z)(x,0) = (u^0, v^0, z^0) & \text{in } \Omega, \end{cases} \tag{3}$$

where B_i, $i = 1,2,3$ is defined above. During this work we assume the following hypotheses:

$$(H) \begin{cases} \gamma \in C^1(\mathbb{R}),\ \gamma \text{ decreasing and } \gamma(0) > 0, \\ \alpha(v,z) = \alpha_R(s),\ \beta(v,z) = \beta_R(s), \text{ where } s = s(v,z),\ s \in C^1(\mathbb{R}^2), \\ \alpha_R, \beta_R \in C^1([0,+\infty)),\ \alpha_R \text{ positive and } \alpha_R(0) > 0,\ \beta_R \text{ increasing and } \beta_R(0) = 0. \end{cases}$$

Remark 2.1. *If $p > N$ then by the embedding $W^{1,p}(\Omega) \hookrightarrow C^0(\overline{\Omega})$ and by (H), there exists $C > 0$ such that*

$$\|\alpha(v(t), z(t)) - \alpha(\overline{v}(t), \overline{z}(t))\|_{C^0(\overline{\Omega})} \le C \left(\|v(t) - \overline{v}(t)\|_{W^{1,p}(\Omega)} + \|z(t) - \overline{z}(t)\|_{C^0(\overline{\Omega})} \right),$$
$$\|\beta(v(t), z(t)) - \beta(\overline{v}(t), \overline{z}(t))\|_{C^0(\overline{\Omega})} \le C \left(\|v(t) - \overline{v}(t)\|_{W^{1,p}(\Omega)} + \|z(t) - \overline{z}(t)\|_{C^0(\overline{\Omega})} \right),$$

for all $t \in \mathbb{R}$, $v(t), \overline{v}(t) \in W^{1,p}(\Omega)$, $z(t), \overline{z}(t) \in C^0(\overline{\Omega})$.

Let $p \in (1, \infty)$, for $j > 0$ we define the operator

$$A(j)_0 w := -\Delta w + jw$$

with domains

$$D_i(A(j)_0) := \{w \in W^{2,p}(\Omega) :\ B_i(w) = 0\} \ \ i = 1,2,3.$$

We pick $j > 0$ sufficiently large such that $Re\,\sigma(A(j)_0, B_i) > 0$ $i = 1, 2, 3$ where $\sigma(A(j)_0, B_i)$ stand for the spectrum of $A(j)_0$ with domains D_i, $i = 1, 2, 3$. Observe that since $\tau_2, \tau_3, \gamma_3 > 0$ we can take $j = 1$ for $i = 2, 3$.

Let $\rho \in (0, 1)$. By the positivity of the spectrum we have that the fractional powers $(A(j)_0^\rho, B_i)$ $i = 1, 2, 3$ in the sense of [18, Ch. 1, Sec. 4] for $(A(j)_0, B_i)$ $i = 1, 2, 3$ are well-defined. Let

$$X^\rho_{i,p} := D_i(A(j)_0^\rho) \;\; i = 1, 2, 3$$

then by [18, Theorem 1.6.1] we have the following embedding properties

$$\begin{aligned} X^\rho_{i,p} &\hookrightarrow W^{k,q}(\Omega) \text{ for } k - N/q < 2\rho - N/p,\ q \geq p, \\ X^\rho_{i,p} &\hookrightarrow C^\nu(\overline{\Omega}) \text{ for } 0 \leq \nu < 2\rho - N/p. \end{aligned} \tag{4}$$

Since $(A(j)_0, B_i)$ $i = 1, 2, 3$ are sectorial operators then

$$T_1(t) := e^{-t(A(j)_0, B_1)} \quad T_i(t) := e^{-t(A(1)_0, B_i)} \;\; i = 2, 3$$

define analytical semigroups in $L^p(\Omega)$. Moreover having in mind [18, Th. 1.3.4,Th. 1.4.3] T_i $i = 1, 2, 3$ satisfy the following:

a) For every $\delta \in (0, \min\{Re\,\sigma(A(j)_0, B_i),\ i = 1, 2, 3\})$, there exists $C > 0$ such that

$$\|T_i(t)\|_{\mathcal{L}(L^p, L^p)} \leq Ce^{-\delta t} \;\; i = 1, 2, 3\,.$$

b) Let $\rho \in (0, 1)$ then there exists a constant C_ρ such that for every $u \in L^p(\Omega)$, $t > 0$ and $\delta \in (0, \min\{Re\,\sigma(A(j)_0, B_i),\ i = 1, 2, 3\})$ we have

$$\|T_i(t)u\|_{X^\rho_{i,p}} \leq C_\rho t^{-\rho} e^{-\delta t}\|u\|_p \;\; i = 1, 2, 3\,.$$

c) Let $p > N$. Combining (4) and an easy variant of [25, Lemma 1.3] then for all $u \in C_0^\infty(\overline{\Omega})$, $t > 0$ we have

$$\|T_1(t)\nabla u\|_{C^0(\overline{\Omega})} \leq Ct^{-\gamma}\|u\|_p,$$

for some constants $C > 0$, $\gamma \in (0, 1)$. In particular, the operator $T_1(t)\nabla$ admits an extension for all $u \in L^p(\Omega)$ where the above inequality holds.

Let

$$A(1)_0 = A_0.$$

It is known that (A_0, B_2) is a normally elliptic problem (see [3, p. 18]). Therefore we can construct an interpolation scales of spaces; let $E_0 = L^p$, $E_1 = W^{2,p}_{B_2}$ where

$$W^{s,\gamma}_{B_2} := \begin{cases} \{z \in W^{s,\gamma}(\Omega) \,:\, B_2 z = 0\} & \text{if } 1 + 1/\gamma < s \leq 2, \\ W^{s,\gamma}(\Omega) & \text{if } -1 + 1/\gamma < s < 1 + 1/\gamma, \\ (W^{-s,\gamma'}(\Omega))' & \text{if } -2 + 1/\gamma < s \leq -1 + 1/\gamma, \end{cases}$$

and E_1 is a completion of E_0 (see [3, p. 29]). Next we define

$$E_\theta := (E_0, E_1)_{\theta,p} = W^{2\theta,p}_{B_2} \quad \text{for } 2\theta \in (0, 2) \setminus \{1, 1 + 1/p\},$$

where $(\cdot,\cdot)_{\theta,p}$ denotes the real interpolation functor. Then, there exists a family of operators $A_\theta \in \mathcal{L}(E_{1+\theta}, E_\theta)$, with $-A_\theta$ the infinitesimal generator of an analytic semigroup on E_θ (see [3, p. 28-30]).

In our next result we show the existence and uniqueness of local in time weak solutions for the problem (3) and the continuity of the solutions respect to the initial data and the function I_0. Moreover, it is proven that, if the functions α, β and γ are regular, then the weak solution is classical.

Theorem 2.2. *Let $p > N$,*

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

and the initial data

$$\mathbf{u_0} := (u^0, v^0, z^0) \in \mathbf{X} := C^0(\overline{\Omega}) \times W^{1,p}(\Omega) \times C^0(\overline{\Omega}).$$

Then there exists $\tau(\|\mathbf{u_0}\|_{\mathbf{X}}) > \mathbf{0}$ such that the evolution problem (3) admits a unique solution

$$\mathbf{u} := (u, v, z) \in \mathbf{X}_\tau := X_\tau \times Y_\tau \times X_\tau.$$

Moreover, there exists $C > 0$ such that

$$\|\mathbf{u}(\mathbf{u_0}) - \mathbf{u}(\overline{\mathbf{u}}_\mathbf{0})\|_{\mathbf{X}_\tau} \le C\|\mathbf{u_0} - \overline{\mathbf{u}}_\mathbf{0}\|_{\mathbf{X}}$$

where $\mathbf{u}(\mathbf{u_0})$ and $\mathbf{u}(\overline{\mathbf{u}}_\mathbf{0})$ stand for the solutions to (3) with initial data $\mathbf{u_0}$ and $\overline{\mathbf{u}}_\mathbf{0}$, respectively. Furthermore, there exists $C > 0$ such that

$$\|\mathbf{u}(I_0) - \mathbf{u}(\overline{I}_0)\|_{\mathbf{X}_\tau} \le C\|I_0 - \overline{I}_0\|_{X_\tau}$$

where $\mathbf{u}(I_0)$ and $\mathbf{u}(\overline{I}_0)$ stand for the solutions to (3) with coefficients I_0 and $\overline{I}_0$, respectively.

Proof. In the proof we will use the Banach fixed point Theorem. Let $2\alpha \in (1, 1 + 1/p)$ and γ_0 the trace operator. We define the closed sets

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

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

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

where

$$\begin{aligned} F_1(u,v,z) &:= T_1(t)u^0 + \int_0^t T_1(t-s)(-\nabla\cdot(\alpha(v,z)u\nabla v) + (\lambda\beta(v,z) + j)u - u^2)ds\,, \\ F_2(u,v,z) &:= T_2(t)v^0 + \int_0^t T_2(t-s)(A_{\alpha-1}\mathcal{B}^c\gamma_0(\gamma(u)))ds\,, \\ F_3(u,v,z) &:= T_3(t)z^0 + \int_0^t T_3(t-s)I_0 ds\,. \end{aligned}$$

Here

$$\mathcal{B}^c := (B_2\rfloor_{KerA_0})^{-1}.$$

Let us point out that $A_{\alpha-1}\mathcal{B}^c \in \mathcal{L}(W^{2\alpha-1-1/p,p}(\partial\Omega), W^{2\alpha-2,p}_{B_2})$ and $\gamma_0 \in \mathcal{L}(C^0(\overline{\Omega}), C(\partial\Omega))$. Therefore by the embedding

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

$A_{\alpha-1}\mathcal{B}^c\gamma_0$ is well defined.

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

$$\begin{aligned}
\|F_1(u,v,z)\|_{C^0(\overline{\Omega})} &\le C\|u^0\|_{C^0(\overline{\Omega})} + \int_0^t \Big(\|T_1(t-s)(\nabla\cdot(\alpha(v,z)u\nabla v))\|_{C^0(\overline{\Omega})} + \\
&\quad + \|T_1(t-s)((\lambda\beta(v,z)+j)u)\|_{C^0(\overline{\Omega})} + \|T_1(t-s)u^2\|_{C^0(\overline{\Omega})}\Big)\, ds \\
&\le C\|\mathbf{u_0}\|_{\mathbf{X}_t} + \int_0^t \big(C(t-s)^{-\rho}\|\alpha(v,z)u\nabla v\|_p + \\
&\quad + C(t-s)^{-\kappa}e^{-\delta(t-s)}(\|\lambda(\beta(v,z)+j)u\|_p + \|u^2\|_p)\big)\, ds \\
&\le C\|\mathbf{u_0}\|_{\mathbf{X}_t} + C\|\alpha\|_\infty R^2\frac{t^{1-\rho}}{1-\rho} + C(\lambda\|\beta\|_\infty R + jR + R^2)\frac{t^{1-\kappa}}{1-\kappa}.
\end{aligned}$$

By [11, Lemma 2.1] there exists $\eta \in (0,1)$ such that

$$\|F_2(u,v,z)\|_{1,p} \le C\|v^0\|_{W^{1,p}(\Omega)} + \int_0^t C(t-s)^{-\eta}\|A_{\alpha-1}\mathcal{B}^c\gamma_0(\gamma(u))\|_{W^{2\alpha-2,p}_{B_2}} ds.$$

The last term in the right-hand side is estimated as follows

$$\begin{aligned}
\|A_{\alpha-1}\mathcal{B}^c\gamma_0(\gamma(u))\|_{W^{2\alpha-2,p}_{B_2}} &\le C\|\gamma_0(\gamma(u))\|_{W^{2\alpha-1-1/p,p}(\partial\Omega)} \\
&\le C\|\gamma_0(\gamma(u))\|_{C(\partial\Omega)} \\
&\le C\|\gamma(u)\|_{C^0(\overline{\Omega})}.
\end{aligned}$$

Thus, we get

$$\|F_2(u,v,z)\|_{1,p} \le C\|\mathbf{u_0}\|_{\mathbf{X}_t} + C\|\gamma\|_\infty\frac{t^{1-\eta}}{1-\eta}.$$

Finally for F_3 we can argue as for F_1 to obtain

$$\|F_3(u,v,z)\|_{C^0(\overline{\Omega})} \le C\|\mathbf{u_0}\|_{\mathbf{X}_t} + C\|I_0\|_{X_t}\frac{t^{1-\kappa}}{1-\kappa}$$

for some $\kappa \in (0,1)$. The previous estimates assert that there exists τ_0 such that for every $t \le \tau_0$

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

If we take $R > C\|\mathbf{u_0}\|_{\mathbf{X}_t} + 1$, it follows that 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 $\tau \le \tau_0$. Let $t \le \tau_0$ and $(u,v,z) \in \mathbf{B}(R,t)$, $(\overline{u},\overline{v},\overline{z}) \in \mathbf{B}(R,t)$. We have

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

We denote by $(a1)$, $(a2)$ and $(a3)$ the first, second and third term respectively in the right-hand side of the above inequality. In what follows we provide with a bound for each term in the above inequality.

$$\begin{aligned}(a1) \leq & \int_0^t \|T_1(t-s)\nabla\cdot(\alpha(v,z)(u-\overline{u})\nabla v)\|_{C^0(\overline{\Omega})} + \|T_1(t-s)\nabla\cdot(\alpha(v,z)\overline{u}\nabla(v-\overline{v}))\|_{C^0(\overline{\Omega})} + \\ & + \|T_1(t-s)\nabla\cdot(\alpha(v,z)-\alpha(\overline{v},\overline{z}))\overline{u}\nabla\overline{v})\|_{C^0(\overline{\Omega})} \\ \leq & \int_0^t C(t-s)^{-\rho} C(\|\alpha\|_\infty, R)(\|u-\overline{u}\|_{C^0(\overline{\Omega})} + \|v-\overline{v}\|_{W^{1,p}(\Omega)} + \|z-\overline{z}\|_{C^0(\overline{\Omega})})\,,\end{aligned}$$

where $\rho \in (0,1)$. In the same fashion for some $\kappa \in (0,1)$ we obtain

$$(a2) \leq \int_0^t C(t-s)^{-\kappa} C(j, \|\beta\|_\infty, R)(\|u-\overline{u}\|_{C^0(\overline{\Omega})} + \|v-\overline{v}\|_{1,p} + \|z-\overline{z}\|_{C^0(\overline{\Omega})})\,,$$

$$(a3) \leq \int_0^t C(t-s)^{-\kappa} 2R\|u-\overline{u}\|_{C^0(\overline{\Omega})}.$$

Putting the previous estimates together we get

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

Now, we deal with F_2:

$$\begin{aligned}\|F_2(u,v,z) - F_2(\overline{u},\overline{v},\overline{z})\|_{1,p} & \leq \int_0^t C(t-s)^{-\eta}\|\gamma(u)-\gamma(\overline{u})\|_{C^0(\overline{\Omega})} ds \\ & \leq C\frac{t^{1-\eta}}{1-\eta}\|u-\overline{u}\|_{X_t}.\end{aligned}$$

Finally,

$$\|F_3(u,v,z) - F_3(\overline{u},\overline{v},\overline{z})\|_{C^0(\overline{\Omega})} = 0\,.$$

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

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

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

The proof of the continuity on I_0 follows in the same fashion. ■

Proposition 2.3. *The local in time solution provided by the previous Theorem satisfies additionally*

$$(u,v,z) \in C^1((0,\tau); W^{1,p}(\Omega)) \times C^1((0,\tau); W^{1,p}(\Omega)) \times C^1((0,\tau); W^{2,p}(\Omega)).$$

Proof. Let us fix any $t \in (0, \tau)$ then by [18, Th. 3.5.2] for every $\rho \in (0, 1)$ we have that

$$\frac{du}{dt}(t) \in X^{\rho}_{1,p}\,, \quad \frac{dv}{dt}(t) \in X^{\rho}_{2,p}\,, \quad \frac{dz}{dt}(t) \in X^{\rho}_{3,p}.$$

In particular, by [11, Lemma 2.2] $X^{\rho}_{2,p} \hookrightarrow W^{1,p}(\Omega)$ for ρ sufficiently close to 1. Therefore, there exists $\rho < 1$ such that

$$\frac{du}{dt}(t) \in W^{1,p}(\Omega)\,, \quad \frac{dv}{dt}(t) \in W^{1,p}(\Omega)\,, \quad \frac{dz}{dt}(t) \in W^{1,p}(\Omega).$$

We observe that

$$\begin{cases} -\Delta v(t) + v(t) = -\frac{dv}{dt}(t) & \text{in } \Omega, \\ B_2(v(t)) = (\gamma(u(t)), 0) & \text{on } \partial\Omega. \end{cases}$$

Hence, the elliptic regularity [3, Th. 9.2] asserts $v(t) \in W^{1,p}(\Omega)$. In a similar way, we get $z(t) \in W^{2,p}(\Omega)$. Finally we rewrite the u-equation as follows

$$\begin{cases} -\Delta u(t) + ju(t) = h(t) & \text{in } \Omega, \\ B_1(u(t)) = (0, 0) & \text{on } \partial\Omega, \end{cases}$$

where

$$h(t) := -\nabla \cdot (\alpha(v(t), z(t))u(t)\nabla v(t)) + \lambda(\beta(v(t), z(t)) + j)u(t) - u(t)^2 - \frac{du}{dt}(t)\,.$$

Since $h(t) \in (W^{1,p}(\Omega))'$ then $u(t) \in W^{1,p}(\Omega)$. ∎

Remark 2.4. *Let $\nu \in (0, 1)$. If we additionally suppose that $\frac{\partial \alpha}{\partial v}$, γ' are Lipschitz and $I_0 \in C^1((0, T); C^{\nu}(\overline{\Omega}))$, then for every $t > 0$ the solution constructed in Theorem 2.2 is classical.*

Proposition 2.5. *Under conditions of Theorem 2.2, if $u^0(x), v^0(x), z^0(x) \geq 0$ for all $x \in \Omega$ and $I_0(x, t) \geq 0$ for all $(x, t) \in \Omega \times (0, \tau)$ then $u(x, t), v(x, t), z(x, t) \geq 0$ for all $(x, t) \in \Omega \times (0, \tau)$.*

Proof. Let $u_+ := \max\{u, 0\}$ and $u_- := \min\{u, 0\}$. We consider the problem

$$\begin{cases} u_t = \Delta u - \nabla \cdot (\alpha(v, z)u_+\nabla v) + \lambda\beta(v, z)u_+ - uu_+ & \text{in } \Omega \times (0, \tau), \\ v_t = \Delta v - v & \text{in } \Omega \times (0, \tau), \\ z_t = \Delta z - z + I_0 & \text{in } \Omega \times (0, \tau), \\ \dfrac{\partial u}{\partial n} = (-\gamma_1 u_+, \tau_1 u_+) & \text{on } \partial\Omega \times (0, \tau), \\ B_2 v = (\gamma(u), 0) & \text{on } \partial\Omega \times (0, \tau), \\ B_3 z = (0, 0) & \text{on } \partial\Omega \times (0, \tau), \\ (u, v, z)(x, 0) = (u^0, v^0, z^0) & \text{in } \Omega. \end{cases} \tag{5}$$

Since the positive part is a Lipschitz function then we can argue as in Theorem 2.2 to get a unique local solution solution to (5). Now, we take u_- as a test function in the u-equation and we integrate in the space variable to obtain

$$\frac{d}{dt}\int_{\Omega} (u_-)^2 = -\int_{\Omega} |\nabla u_-|^2\,.$$

Hence,

$$\int_\Omega u_-(t)^2 \leq \int_\Omega u_-(0)^2$$

for every $t \in (0,\tau)$. Thus, $u_-(t) \equiv 0$ in Ω for all $t \in (0,\tau)$. Since u is positive then we have $u = u_+$ and the unique solution to (5) is also the unique solution to (3). The positivity of v and z are consequence of a standard maximum principle for parabolic equations.

■

Remark 2.6. *Let us observe that we can argue as in Theorem 2.2 to get*

$$\|v\|_{1,p} \leq C\|v^0\|_{1,p} + C\gamma(0)\int_0^t e^{-\nu(t-s)}(t-s)^{-\eta} \leq C\|v_0\|_{1,p} + C\gamma(0)$$

for some $\nu > 0$, $p > 1$, $\eta \in (0,1)$ and for every $t < T_{max}$. Moreover,

$$\|z\|_{C(\overline{\Omega})} \leq C(\|z_0\|_{C(\overline{\Omega})} + \|I_0\|_{C(\overline{\Omega})}). \tag{6}$$

Let us denote T_{max} the maximal existence of time for the solutions constructed in Theorem 2.2. Taking into account that the equation for z is linear and (6), in order to show that $T_{\max} = +\infty$ we just need to find a function $w : (0,\infty) \to (0,\infty)$ such that for each $T > 0$,

$$\|(u(t), v(t))\|_{C^0(\overline{\Omega})\times W^{1,p}(\Omega)} \leq w(T), \quad 0 < t < \min\{T, T_{max}\}.$$

For this purpose we will use the following estimates. The first one is the Sobolev-Trace inequality, see for instance [17, Lemma 6].

Lemma 2.7. *(Sobolev-Trace inequality)*
For every $\epsilon > 0$, $\theta > 1$ there exists a constant $C = C(\Omega,\theta)$ such that

$$\int_{\Gamma_2} w^2 \leq \epsilon \int_\Omega |\nabla w|^2 + C(\epsilon^{-\theta} + 1)\int_\Omega w^2\,, \quad \forall w \in W^{1,2}(\Omega).$$

Lemma 2.8. *Let $s > N$, for every $\delta > 0$ there exist $m > 1$ and a constant $C(\Omega)$ such that*

$$\int_\Omega |w\nabla v \cdot \nabla w| \leq C(\Omega)\|\nabla v\|_s(\delta\|w\|_{1,2}^2 + m\delta^{-m}\|w\|_2^2)\,, \quad \forall w \in W^{1,2}(\Omega),\ v \in W^{1,s}(\Omega).$$

Proof. By the Hölder inequality

$$\int_\Omega |w\nabla v \cdot \nabla w| \leq \|\nabla v\|_s \|\nabla w\|_2 \|w\|_q,$$

such that $1/s + 1/q = 1/2$ and $q > 2$. Moreover, by the Gagliardo-Nirenberg interpolation inequality we get

$$\|w\|_q \leq C(\Omega)\|w\|_{1,2}^\theta \|w\|_2^{1-\theta} \quad \text{with } 2 < q < 2^* = 2N/(N-2),\ \theta \in (0,1).$$

Hence, using the above estimate we get

$$\int_\Omega |w\nabla v \cdot \nabla w| \leq C(\Omega)\|\nabla v\|_s \|w\|_{1,2}^{1+\theta}\|w\|_2^{1-\theta}.$$

Finally we deduce the result by the Young inequality with exponents r, r' and taking into account that $(1+\theta)r = (1-\theta)r' = 2$. ■

Now, we look for the bound of $u(t)$ in $C^0(\overline{\Omega})$. In a first step we provide a bound in $L^p(\Omega)$ for every $p \in [2, +\infty)$.

Proposition 2.9. *Let $t < T_{max}$ then we have that*

$$\|u(t)\|_p \leq C(t) \quad \forall p \in [2, \infty).$$

Proof. Let $w := u^{p/2}$. On multiplying the u-equation by u^{p-1} and integrating in the space variable we get

$$\begin{aligned}\frac{1}{p}\frac{d}{dt}\int_\Omega w^2 &= -\frac{4}{p^2}(p-1)\int_\Omega |\nabla w|^2 - \int_{\Gamma_1}(\gamma_1 + \alpha(v,z)\gamma(u))w^2 + \int_{\Gamma_2}(\tau_1 + \tau_2\alpha(v,z)v)w^2 + \\ &+\frac{2}{p}(p-1)\int_\Omega \alpha(v,z) w \nabla v \cdot \nabla w + \int_\Omega (\lambda\beta(v,z)u - u^2)u^{p-1}.\end{aligned}$$

Then,

$$\frac{1}{p}\frac{d}{dt}\int_\Omega w^2 \leq -\frac{4}{p^2}(p-1)\int_\Omega |\nabla w|^2 + C_1\int_{\Gamma_2} w^2 + C_2\int_\Omega |w\nabla v \cdot \nabla w| + \int_\Omega (\lambda\beta(v,z)u - u^2)u^{p-1},$$

where

$$C_1 := \tau_1 + \tau_2\|\alpha\|_\infty \|v\|_\infty\,, \quad C_2 := \frac{2(p-1)}{p}\|\alpha\|_\infty\,. \tag{7}$$

We apply Lemma 2.7 with $\theta = 2$ and Lemma 2.8 for some $s > N$ to obtain

$$\frac{1}{p}\frac{d}{dt}\int_\Omega w^2 \leq A(\delta,\epsilon)\int_\Omega |\nabla w|^2 + C(\delta,\epsilon)\int_\Omega w^2 + \int_\Omega (\lambda\beta(v,z)u - u^2)u^{p-1}\,,$$

where

$$A(\delta,\epsilon) := C_2 C(\Omega)\|\nabla v\|_s \delta + C_1\epsilon - \frac{4}{p^2}(p-1)\,,$$

$$C(\delta,\epsilon) := C_2 C(\Omega)\|\nabla v\|_s(\delta + m\delta^{-m}) + C_1 C(\epsilon^{-2} + 1)\,,$$

and the constants C and $C(\Omega)$ are given by Lemmas 2.7 and 2.8. We pick $\epsilon = \epsilon_0$, $\delta = \delta_0$ such that $A(\delta_0, \epsilon_0) < 0$. Thus,

$$\frac{1}{p}\frac{d}{dt}\int_\Omega w^2 \leq (C(\delta_0,\epsilon_0) + \lambda\|\beta\|_\infty)\int_\Omega w^2$$

and the result follows after integrating in the time variable. ∎

Finally for the bound in $C^0(\overline{\Omega})$ we have just to argue as in the bound for F_1 in Theorem 2.2.

Proposition 2.10. *Let $0 < \tau < t < T_{max}$ where τ is given in Theorem 2.2, then we have that*

$$\|u(t)\|_{C^0(\overline{\Omega})} \leq C(t)$$

Proof. For some constants $0 < \kappa < \rho < 1$ we have

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

By the Gronwall Lemma we easily deduce the result. ∎

Then, we can conclude:

Theorem 2.11. *Assume that the initial data* $(u^0, v^0, z^0) \in C^0(\overline{\Omega}) \times W^{1,p}(\Omega) \times C^0(\overline{\Omega})$, $p > N$, *with* $u^0(x), v^0(x), z^0(x) \geq 0$ *in* Ω *and* $I_0 \in C((0,\infty); C^0(\overline{\Omega}))$ *and* $I_0(x,t) \geq 0$ *for* $x \in \Omega$ *and* $t > 0$. *Then, there exists a unique non-negative global solution in time solution of (3).*

3 The stationary problem

In this section we consider the stationary problem associated to (3)

$$\begin{cases} -\Delta u = -\nabla \cdot (\alpha(v,z) u \nabla v) + \lambda \beta(v,z) u - u^2 & \text{in } \Omega, \\ -\Delta v = -v & \text{in } \Omega, \\ -\Delta z = -z + I_0 & \text{in } \Omega, \\ B_1 u = B_3 z = (0,0) & \text{on } \partial\Omega, \\ B_2 v = (\gamma(u), 0) & \text{on } \partial\Omega, \end{cases} \tag{8}$$

where $I_0 \in C^\rho(\overline{\Omega})$, $\rho \in (0,1)$ and non-negative function.

Along this section, we are going to use the following notation: for $\rho \in (0,1)$ we denote

$$X_1 := \{u \in C^{2,\rho}(\overline{\Omega}) : B_1 u = (0,0) \text{ on } \partial\Omega\},$$
$$X_2 := \{v \in C^{2,\rho}(\overline{\Omega}) : \partial v/\partial n + \tau_2 v = 0 \text{ on } \Gamma_2\},$$

and finally

$$X := X_1 \times X_2.$$

We need introduce more notations. Given functions $m, c, b \in C^0(\overline{\Omega})$, $b > 0$ and $a \in C^1(\overline{\Omega})$ we denote by

$$\mathcal{L}u := -\Delta u + c(x) \nabla a \cdot \nabla u$$

and consider the following eigenvalue problem

$$\begin{cases} \mathcal{L}\varphi + m(x)\varphi = \lambda b(x)\varphi & \text{in } \Omega, \\ B\varphi = (0,0) & \text{on } \partial\Omega, \end{cases} \tag{9}$$

being B an operator similar to B_1, B_2 or B_3, that is,

$$B\varphi := \begin{cases} \dfrac{\partial \varphi}{\partial n} + b_1 \varphi & \text{on } \Gamma_1, \\ \dfrac{\partial \varphi}{\partial n} + b_2 \varphi & \text{on } \Gamma_2, \end{cases}$$

with $b_1, b_2 \in \mathbb{R}$.

Since $b > 0$ in Ω, it is well-known (see for instance [6]) the existence of a principal eigenvalue of (9), denoted $\lambda_1(\mathcal{L} + m; b; B)$.

When no confusion arises, we delete the operator B in the notation of the principal eigenvalue.

On the other hand, if for $\lambda \in \mathbb{R}$ we denote by

$$\mu(\lambda) := \lambda_1(\mathcal{L} + m - \lambda b; 1)$$

then $\lambda_1(\mathcal{L}+m;b)$ is the principal eigenvalue of (9) if, and only if, $\lambda_1(\mathcal{L}+m;b)$ is a zero of $\mu(\lambda)$. Moreover, since $b>0$ the map $\mu(\lambda)$ is decreasing and so

$$\lambda_1(\mathcal{L}+m-\lambda b;1)>0 \text{ (resp. } <0) \Leftrightarrow \lambda<\lambda_1(\mathcal{L}+m;b) \text{ (resp. } \lambda>\lambda_1(\mathcal{L}+m;b)). \quad (10)$$

Finally, recall that $\lambda_1(\mathcal{L}+m;b;B)$ is continuous on b and m, see for instance [6]. Moreover, in Proposition 5.1 of [5] it is proved that $\lambda_1(\mathcal{L}+m;b;B)$ is also continuous with respect to the coefficient c when the boundary conditions are Dirichlet, see also [2]. In the following result, we show this continuity with the boundary conditions B.

Proposition 3.1. *The principal operator $\lambda_1(\mathcal{L}+m;b;B)$ is continuous with respect to the coefficient c in $L^\infty(\Omega)$.*

Proof. First, we make a change of variable which transforms (9) into another equivalent eigenvalue problem with Robin boundary condition and positive coefficients.

Since $\partial\Omega$ is regular, there exists $\psi\in C^2(\overline{\Omega})$ (see Proposition 3.4 in [22]) such that

$$\frac{\partial\psi}{\partial n}\geq\rho_0>0 \quad \text{on } \partial\Omega.$$

Under the change of variable

$$\varphi=e^{K\psi}w, \qquad K>0$$

problem (9) is transformed into

$$\begin{cases} -\Delta w+\vec{N}(x)\cdot\nabla w+M(x)w=\lambda b(x)w & \text{in } \Omega,\\ Bw=(0,0) & \text{on } \partial\Omega, \end{cases} \tag{11}$$

where

$$\begin{aligned} &\vec{N}(x):=-2K\nabla\psi+c(x)\nabla a,\\ &M(x):=-K^2|\nabla\psi|^2+Kc(x)\nabla a\cdot\nabla\psi-K\Delta\psi+m(x) \end{aligned}$$

and

$$Bw:=\begin{cases} \dfrac{\partial w}{\partial n}+R_1 w & \text{on } \Gamma_1,\\ \dfrac{\partial w}{\partial n}+R_2 w & \text{on } \Gamma_2, \end{cases}$$

being

$$R_i(x):=b_i+K\frac{\partial\psi}{\partial n}, \qquad i=1,2$$

and so, taking K large,

$$R_i>0 \quad \text{on } \partial\Omega \text{ for } i=1,2. \tag{12}$$

Fixed such K, we are going to prove the continuity of the principal eigenvalue of (11). Observe that when you move the coefficient c, you move M and $\vec{N}$. Since we know the continuity with respect to M, we fix our attention on the coefficient $\vec{N}$. On the other hand, it suffices to show the continuity of $\lambda_1(\mathcal{L}+M;1;B)$ because $\lambda_1(\mathcal{L}+M;b;B)$ is the zero of $\lambda_1(\mathcal{L}+M-\lambda b;1;B)$. Take $\vec{N}_i\in[C^0(\overline{\Omega})]^N$, $i=1,2$, such that

$$\|\vec{N}_1-\vec{N}_2\|_\infty\leq\varepsilon.$$

Denote by $\lambda_1(\vec{N}_i) := \lambda_1(\mathcal{L}_i + M; 1; B)$ with

$$\mathcal{L}_i w := -\Delta w + \vec{N}_i(x) \cdot \nabla w,$$

and w_i a positive eigenfunction associated to $\lambda_1(\vec{N}_i)$.
Step 1: Assume that $\lambda_1(\vec{N}_1) = 0$, and so

$$M_L := \inf_{x \in \overline{\Omega}} M(x) < 0.$$

Indeed, if $M \geq 0$, then positive constants are strict supersolutions of $(\mathcal{L}_1 + M, B_1)$ and so $\lambda_1(\vec{N}_1) > 0$.

Take $\rho \in (0, 1)$. Then,

$$\mathcal{L}_2 w_1^\rho + M(x) w_1^\rho = \rho(1-\rho) w_1^{\rho-2} |\nabla w_1|^2 + \rho w_1^{\rho-1} \nabla w_1 \cdot (\vec{N}_2 - \vec{N}_1) + M(x)(1-\rho) w_1^\rho \geq$$

$$\geq \rho(1-\rho) w_1^{\rho-2} |\nabla w_1|^2 - \rho w_1^{\rho-1} |\nabla w_1| |\vec{N}_2 - \vec{N}_1| + M(x)(1-\rho) w_1^\rho \geq$$

$$\geq \left[-\frac{\rho}{4(1-\rho)} \varepsilon^2 + M_L (1-\rho) \right] w_1^\rho.$$

Consider ρ such that

$$1 - \rho = \frac{\varepsilon}{2\sqrt{-M_L}}$$

we get that

$$\mathcal{L}_2 w_1^\rho + M(x) w_1^\rho \geq \varepsilon \left[-\sqrt{-M_L} + \frac{\varepsilon}{4} \right] w_1^\rho \quad \text{in } \Omega.$$

On the other hand,

$$\frac{\partial w_1^\rho}{\partial n} + R_i(x) w_1^\rho = (1-\rho) R_i(x) w_1^\rho > 0 \quad \text{on } \Gamma_i.$$

Hence, w_1^ρ is a supersolution of $(\mathcal{L}_2 + M - \varepsilon \left[-\sqrt{-M_L} + \frac{\varepsilon}{4} \right], B)$ and then

$$\lambda_1(\vec{N}_2) \geq \varepsilon \left[-\sqrt{-M_L} + \frac{\varepsilon}{4} \right],$$

that is

$$\varepsilon \left[\sqrt{-M_L} - \frac{\varepsilon}{4} \right] \geq \lambda_1(\vec{N}_1) - \lambda_1(\vec{N}_2). \tag{13}$$

Step 2: Assume now the general case that $\lambda_1(\vec{N}_1) \in \mathbb{R}$. Then, there exists a $K_1 \in \mathbb{R}$ such that

$$\lambda_1(\vec{N}_1; K_1) := \lambda_1(\mathcal{L}_1 + M + K_1; 1; B) = \lambda_1(\mathcal{L}_1 + M; 1; B) + K_1 = \lambda_1(\vec{N}_1) + K_1 = 0.$$

Then, applying the Step 1 and (13), we deduce that

$$\lambda_1(\vec{N}_1) - \lambda_1(\vec{N}_2) = \lambda_1(\vec{N}_1) + K_1 - (\lambda_1(\vec{N}_2) + K_1) = \lambda_1(\vec{N}_1; K_1) - \lambda_1(\vec{N}_2; K_1) \leq \varepsilon \left[\sqrt{-M_L} - \frac{\varepsilon}{4} \right].$$

Consider now $\lambda_1(\vec{N}_2) \in \mathbb{R}$. Then, there exists a $K_2 \in \mathbb{R}$ such that

$$\lambda_1(\vec{N}_2; K_2) = \lambda_1(\vec{N}_2) + K_2 = 0.$$

Then, applying again the Step 1 and interchanging the roles of $\vec{N}_1$ and $\vec{N}_2$, we deduce that

$$\lambda_1(\vec{N}_2)-\lambda_1(\vec{N}_1) = \lambda_1(\vec{N}_2)+K_2-(\lambda_1(\vec{N}_1)+K_2) = \lambda_1(\vec{N}_2;K_2)-\lambda_1(\vec{N}_1;K_2) \leq \varepsilon\left[\sqrt{-M_L}-\frac{\varepsilon}{4}\right].$$

Therefore,

$$|\lambda_1(\vec{N}_1)-\lambda_1(\vec{N}_2)| \leq \varepsilon\left[\sqrt{-M_L}-\frac{\varepsilon}{4}\right].$$

This concludes the result. ∎

The next result will be useful along the work.

Lemma 3.2. *Consider sequences $m_n, c_n, b_n \in C^0(\overline{\Omega})$, with $b_n > 0$ and such that $m_n \to m$, $c_n \to c$, $b_n \to 0$ as $n \to \infty$ in $L^\infty(\Omega)$. Denote by*

$$\mathcal{L}_n u := -\Delta u + c_n(x)\nabla a \cdot \nabla u, \qquad \mathcal{L}u := -\Delta u + c(x)\nabla a \cdot \nabla u.$$

Then,

$$\lambda_1(\mathcal{L}_n + m_n; b_n) \to \begin{cases} +\infty & \text{if } \lambda_1(\mathcal{L}+m;1) > 0, \\ -\infty & \text{if } \lambda_1(\mathcal{L}+m;1) < 0. \end{cases}$$

Proof. Denote by $\lambda_n := \lambda_1(\mathcal{L}_n + m_n; b_n)$ or equivalently $0 = \lambda_1(\mathcal{L}_n + m_n - \lambda_n b_n; 1)$. Assume that $\lambda_1(\mathcal{L}+m;1) > 0$, then by the continuity of the principal eigenvalue with respect to the coefficients we get that $\lambda_1(\mathcal{L}_n + m_n; 1) > 0$ for n large. Hence, since λ_n are the zeros of the maps $\lambda_1(\mathcal{L}_n + m_n - \lambda b_n; 1)$ we conclude that $\lambda_n > 0$ for n large. Assume that λ_n is bounded. Since

$$0 = \lambda_1(\mathcal{L}_n + m_n - \lambda_n b_n; 1)$$

then we conclude that $0 = \lambda_1(\mathcal{L}+m;1)$, an absurdum. ∎

Observe that since $\lambda_1(-\Delta+1;1;B_3) > 0$ and $I_0 \geq 0$ there exists a unique non-negative solution z_0 of

$$-\Delta z + z = I_0 \quad \text{in } \Omega, \qquad B_3 z = (0,0) \quad \text{on } \partial\Omega. \tag{14}$$

Then, to solve (8), we need to study the following system

$$\begin{cases} -\Delta u = -\nabla \cdot (\alpha(v,z_0)u\nabla v) + \lambda\beta(v,z_0)u - u^2 & \text{in } \Omega, \\ -\Delta v = -v & \text{in } \Omega, \\ B_1 u = (0,0), \quad B_2 v = (\gamma(u),0) & \text{on } \partial\Omega. \end{cases} \tag{15}$$

Observe now that (15) possesses the semi-trivial solution $(0,v_0)$ being v_0 the unique positive solution of

$$\begin{cases} -\Delta v + v = 0 & \text{in } \Omega, \\ B_2 v = (\gamma(0),0) & \text{on } \partial\Omega. \end{cases} \tag{16}$$

Observe that since $\lambda_1(-\Delta+1;1;B_2) > 0$ and $\gamma(0) > 0$, this positive solution exists.

In order to find positive solution of (15), we are going to use the bifurcation method from the semi-trivial solution $(0,v_0)$. In fact, we will show that a continuum of positive solutions emanates from the semi-trivial solution $(0,v_0)$ at a determined value of λ, exactly,

$$\lambda = \lambda_1(v_0, z_0),$$

where $\lambda_1(v_0, z_0)$ denotes the principal eigenvalue of the problem

$$\begin{cases} -\Delta\xi = -\nabla\cdot(\alpha(v_0,z_0)\nabla v_0\xi) + \lambda\beta(v_0,z_0)\xi & \text{in } \Omega, \\ B_1\xi = (0,0) & \text{on } \partial\Omega. \end{cases} \tag{17}$$

Observe that (17) is in the general setting of (9) with $b = \beta(v_0, z_0)$, $c = \alpha(v_0, z_0)$, $a = v_0$ and

$$m(x) := \alpha_v(v_0,z_0)|\nabla v_0|^2 + \alpha_z(v_0,z_0)\nabla v_0\cdot\nabla z_0 + \alpha(v_0,z_0)\Delta v_0.$$

We need some important previous results. In the first one we obtain a priori bounds of positive solution of (15). For that, we have divided the proof in different steps.

Lemma 3.3. *Let (u, v) be a solution of (15). Then,*

$$\begin{cases} \|v\|_\infty \le \|v_0\|_\infty, \\ \|v\|_{1,s} \le C\gamma(0), \\ \|v\|_{2,s} \le C\|\gamma(u)\|_{W^{1-1/s,s}(\Gamma_1)}, \end{cases} \tag{18}$$

for all $s \in (1,\infty)$, v_0 is the unique positive solution of (16) and C is a positive constant depending on Ω.

Proof. For the first inequality, observe that since $0 \le \gamma(u) \le \gamma(0)$ we have that

$$-\Delta v + v = 0 \quad \text{in } \Omega, \quad \frac{\partial v}{\partial n} \le \gamma(0) \quad \text{on } \Gamma_1, \quad \frac{\partial v}{\partial n} + \tau_2 v = 0 \quad \text{on } \Gamma_2,$$

and then

$$v \le v_0 \quad \text{in } \Omega.$$

The other inequalities are direct consequences of Proposition 3.3 in [1] and that $0 \le \gamma(u) \le \gamma(0)$. ■

In the second step, we show that u is bounded in $L^p(\Omega)$ for all $1 < p < \infty$.

Lemma 3.4. *Let (u, v) be a solution of (15). Then,*

$$\|u\|_p \le C \quad \textit{and} \quad \|u\|_{1,2} \le C \tag{19}$$

for all $p \in (1,\infty)$ and C is a positive constant depending on Ω.

Proof. Let us compute explicitly the constants appearing along the proof, because they will be used in the next results.

With a completely similar reasoning that Proposition 2.9, we get

$$0 \le -\frac{4}{p^2}(p-1)\int_\Omega |\nabla w|^2 + C_1\int_{\Gamma_2} w^2 + C_2\int_\Omega |w\nabla v\cdot\nabla w| + \int_\Omega (\lambda\beta(v,z_0)u - u^2)u^{p-1},$$

where $w = u^{p/2}$ and C_1 and C_2 are defined in (7). Then, by Lemmas 2.7 and 2.8 we get

$$\int_\Omega u^p + A\int_\Omega |\nabla u^{p/2}|^2 \le \int_\Omega [(\lambda\beta(v,z_0) + C_1C(\varepsilon^{-\theta}+1) + C_2C(\Omega)\|\nabla v\|_s(\delta + m\delta^{-m}) + 1)u^p - u^{p+1}], \tag{20}$$

where

$$A := \frac{4}{p^2}(p-1) - C_1\varepsilon - C_2 C(\Omega)\|\nabla v\|_s \delta. \tag{21}$$

Take ε and δ such that $A > 0$. Now, it is clear that for some constant $C > 0$

$$(\lambda\beta(v, z_0) + C_1 C(\varepsilon^{-\theta} + 1) + C_2 C(\Omega)\|\nabla v\|_s(\delta + m\delta^{-m}) + 1)u^p - u^{p+1} \leq C \quad \text{for all } u \geq 0,$$

and then u is bounded in $L^p(\Omega)$ for all $p \in (1, \infty)$. Also, using (20) with $p = 2$, we get that u is bounded in $H^1(\Omega)$. Finally, from (20) we deduce that $u^{p/2} \in H^1(\Omega)$. This completes the proof. ■

We are ready now to show the main result of a priori bound.

Theorem 3.5. *Assume that $\lambda \in \Lambda$, a compact of $\mathbb{R}$. Then, there exists a constant $C > 0$ such that*

$$\|(u, v)\|_X \leq C,$$

for all (u, v) solution of (15).

Proof. First, observe that since $u \in H^1(\Omega)$ and γ is a Lipschitz function, $\gamma(u) \in H^1(\Omega)$ and so $\gamma_0(\gamma(u)) \in H^{1/2}(\Gamma_1)$ and then by [1] we get that $v \in H^2(\Omega)$ and

$$\|v\|_{2,2} \leq C. \tag{22}$$

Now, we re-write the equation of u as

$$-\Delta u = -\alpha_v(v, z_0)u|\nabla v|^2 - \alpha_z(v, z_0)u\nabla v \cdot \nabla z_0 - \alpha(v, z_0)\nabla u \cdot \nabla v - \alpha(v, z_0)uv + \lambda\beta(v, z_0)u - u^2.$$

Observe that

$$\alpha_v(v, z_0) = \alpha_R'(s)\frac{\partial s}{\partial v}, \qquad \alpha_z(v, z_0) = \alpha_R'(s)\frac{\partial s}{\partial z},$$

and then taking into account that α_R is regular and β bounded, we get for any $p > 1$ that

$$\begin{cases} \alpha_v(v, z_0)u|\nabla v|^2 \in L^p(\Omega), \\ \alpha_z(v, z_0)u\nabla v \cdot \nabla z_0 \in L^p(\Omega), \\ \alpha(v, z_0)\nabla u \cdot \nabla v \in L^j(\Omega), \quad \text{for some } j < 2 \text{ and close to } 2, \\ -\alpha(v, z_0)uv + \lambda\beta(v, z_0)u - u^2 \in L^p(\Omega). \end{cases}$$

Hence, we can conclude that $u \in W^{2,j}(\Omega)$, and so picking j close to 2, $u \in W^{1,j^*}(\Omega)$ for $j^* > 2$. Repeating this argument several times, we can conclude the result. ■

The following result proves the non-existence of positive result for λ very negative.

Proposition 3.6. *There exists $\lambda_0 < 0$ such that if $\lambda \leq \lambda_0$,* (15) *does not possess positive solution.*

Proof. In the first part of the proof we use a Moser's argument to obtain a bound in $L^\infty(\Omega)$ for u independent of $\lambda \leq 0$. Indeed, denoting $w = u^{p/2}$, from (20), $\lambda \leq 0$ and Lemma 3.3 we get that

$$a\int_\Omega |\nabla w|^2 \leq b\int_\Omega w^2, \tag{23}$$

where

$$a := \frac{4}{p^2}(p-1) - C_1\varepsilon - \tilde{C}2\frac{p-1}{p}\delta,$$

$$b := C_1C(\varepsilon^{-\theta}+1) + \tilde{C}2\frac{p-1}{p}(\delta + m\delta^{-m}),$$

and

$$\tilde{C} := CC(\Omega)\gamma(0)\|\alpha\|_\infty.$$

where we have used (18). Taking

$$\delta = \frac{1}{p\tilde{C}} \quad \text{and} \quad \varepsilon = \frac{p-1}{p^2C_1},$$

we get

$$a = \frac{p-1}{p^2} > 0,$$

and so,

$$\int_\Omega |\nabla w|^2 \le \frac{b}{a}\int_\Omega w^2. \tag{24}$$

Now, we use $H^1(\Omega) \hookrightarrow L^r(\Omega)$, $r > 2$, and we get

$$\left(\int_\Omega w^r\right)^{1/r} \le C_3\left[\int_\Omega |\nabla w|^2 + \int_\Omega w^2\right]^{1/2}$$

and hence,

$$\left(\int_\Omega u^{p(r/2)}\right)^{2/(rp)} \le \left[C_3^2\left(\frac{b}{a}+1\right)\right]^{1/p}\left(\int_\Omega u^p\right)^{1/p}.$$

Denoting

$$R(p) := C_3^2\left(\frac{b}{a}+1\right).$$

we have that

$$R(p) = C_3^2\left(3 + C_1C\frac{p^2}{p-1} + C_1^{1+\theta}C\frac{p^{2+2\theta}}{(p-1)^{\theta+1}} + 2m\tilde{C}^{1+m}p^{1+m}\right).$$

Consider now $q = r/2 > 1$, we have that

$$\|u\|_{pq} \le (R(p))^{1/p}\|u\|_p. \tag{25}$$

Taking $p = 2q^n$, $n = 0, 1, 2...$ we get

$$\|u\|_{2q^{n+1}} \le (R(2))^{1/2}(R(2q))^{1/2q}(R(2q^2))^{1/2q^2}......(R(2q^n))^{1/2q^n}\|u\|_2. \tag{26}$$

It suffices to take $n \to \infty$ and take into account that

$$\lim_{n\to\infty}(R(2))^{1/2}(R(2q))^{1/2q}(R(2q^2))^{1/2q^2}......(R(2q^n))^{1/2q^n} \le C,$$

we conclude that

$$\|u\|_\infty \le C\|u\|_2.$$

Then, using (20),

$$\|u\|_\infty \leq C = C(\gamma(0), \Omega), \quad \text{independent of } \lambda \leq 0. \tag{27}$$

Consider now the v-equation. Then, since $\gamma(u) \geq \gamma(\|u\|_\infty) \geq \gamma(C)$, we have that

$$-\Delta v + v = 0 \quad \text{in } \Omega, \quad \frac{\partial v}{\partial n} \geq \gamma(C) \quad \text{on } \Gamma_1, \quad \frac{\partial v}{\partial n} + \tau_2 v = 0 \quad \text{on } \Gamma_2,$$

and then

$$v \geq v_* > 0,$$

being v_* the unique positive solution of the linear problem

$$-\Delta v + v = 0 \quad \text{in } \Omega, \quad \frac{\partial v}{\partial n} = \gamma(C) \quad \text{on } \Gamma_1, \quad \frac{\partial v}{\partial n} + \tau_2 v = 0 \quad \text{on } \Gamma_2.$$

Finally, observe that since $\lambda < 0$

$$\lambda\beta(v, z_0) + C_1 C(\varepsilon^{-\theta} + 1) + C_2 C(\Omega)\|\nabla v\|_s(\delta + m\delta^{-m}) + 1 \leq$$

$$\lambda\underline{\beta} + C_1 C(\varepsilon^{-\theta} + 1) + C_2 C(\Omega)\|\nabla v\|_s(\delta + m\delta^{-m}) + 1 \leq 0$$

for $\lambda \leq \lambda_0$ for some $\lambda_0 < 0$. Here, we have denoted $\underline{\beta} := \min_{v_* \leq v \leq v_0} \beta(v, z_0) > 0$. Now, it suffices to use (20). ∎

Now, we can prove the main theoretical result of this section:

Theorem 3.7. *Assume that*

$$\lambda > \lambda_1(v_0, z_0). \tag{28}$$

Then, (15) *possesses at least a positive solution.*

Proof. We are going to apply the bifurcation method. We consider λ as bifurcation parameter. First, we apply the Crandall-Rabinowitz theorem, [9], in order to find the bifurcation point from the semi-trivial solution $(0, v_0)$. Consider the map $\mathcal{F} : \mathbb{R} \times X_1 \times X_2 \mapsto C^\rho(\overline{\Omega}) \times C^\rho(\overline{\Omega}) \times C^\rho(\Gamma_1)$ defined by

$$\mathcal{F}(\lambda, u, v) := (-\Delta u + \nabla \cdot (\alpha(v, z_0)u\nabla v) - \lambda\beta(v, z_0)u + u^2, -\Delta v + v, \frac{\partial v}{\partial n} - \gamma(u)).$$

It is clear that $\mathcal{F}$ is regular, that $\mathcal{F}(\lambda, 0, v_0) = 0$ and

$$D_{(u,v)}\mathcal{F}(\lambda_1, u_1, v_1)\begin{pmatrix} \xi \\ \eta \end{pmatrix} = \begin{pmatrix} A_1(\xi, \eta) \\ -\Delta\eta + \eta \\ \dfrac{\partial \eta}{\partial n} - \gamma'(u_1)\xi \end{pmatrix},$$

where

$$\begin{aligned} A_1(\xi, \eta) := \quad & -\Delta\xi + \nabla \cdot ([\alpha(v_1, z_0)\xi + \alpha_v(v_1, z_0)\eta u_1]\nabla v_1 + \alpha(v_1, z_0)u_1\nabla\eta) \\ & -(\lambda_1\beta(v_1, z_0) - 2u_1)\xi - \lambda_1\beta_v(v_1, z_0)u_1\eta. \end{aligned}$$

Hence, for $\lambda = \lambda_0 := \lambda_1(v_0, z_0)$, see (17), and $(u_1, v_1) = (0, v_0)$ we get that

$$Ker[D_{(u,v)}\mathcal{F}(\lambda_0, 0, v_0)] = span\{(\Phi_1, \Phi_2)\}$$

where Φ_1 is an eigenfunction associated to λ_0 and

$$(-\Delta + 1)\Phi_2 = 0 \quad \text{in } \Omega, \quad B_2(\Phi_2) = (\gamma'(0)\Phi_1, 0) \quad \text{on } \partial\Omega.$$

Hence, $dim(Ker[D_{(u,v)}\mathcal{F}(\lambda_0, 0, v_0)]) = 1$.

On the other hand, observe that

$$D_{\lambda(u,v)}\mathcal{F}(\lambda_1, u_1, v_1)\begin{pmatrix} \xi \\ \eta \end{pmatrix} = \begin{pmatrix} -\beta(v_1, z_0)\xi - \beta_v(v_1, z_0)u_1\eta \\ 0 \\ 0 \end{pmatrix}.$$

We can show that $D_{\lambda(u,v)}\mathcal{F}(\lambda_0, 0, v_0)(\Phi_1, \Phi_2)^t \notin R(D_{(u,v)}\mathcal{F}(\lambda_0, 0, v_0))$. Indeed, suppose that there exists $(\xi, \eta) \in X$ such that $D_{(u,v)}\mathcal{F}(\lambda_0, 0, v_0)(\xi, \eta)^t = (-\beta(v_0, z_0)\Phi_1, 0, 0)$, and so

$$-\Delta\xi + \nabla\cdot(\alpha(v_0, z_0)\xi\nabla v_0) - \lambda_0\beta(v_0, z_0)\xi = -\beta(v_0, z_0)\Phi_1 \quad \text{in } \Omega, \quad B_1\xi = (0, 0) \quad \text{on } \partial\Omega.$$

Consider Φ_1^* the eigenfunction associated to the adjoint equation of Φ_1, that is

$$\begin{cases} -\Delta\Phi_1^* - \alpha(v_0, z_0)\nabla v_0\cdot\nabla\Phi_1^* = \lambda_0\beta(v_0, z_0)\Phi_1^* & \text{in } \Omega, \\ B_1^*\Phi_1^* = 0 & \text{on } \partial\Omega, \end{cases} \tag{29}$$

where

$$B_1^*\Phi_1^* := \begin{cases} \dfrac{\partial\Phi_1^*}{\partial n} + (\gamma_1 + \alpha(v_0, z_0)\gamma(0))\Phi_1^* & \text{on } \Gamma_1, \\ \dfrac{\partial\Phi_1^*}{\partial n} - (\tau_1 + \tau_2 v_0\alpha(v_0, z_0))\Phi_1^* & \text{on } \Gamma_2. \end{cases}$$

Then, multiplying the equation by Φ_1^*, we get

$$0 = \int_\Omega \beta(v_0, z_0)\Phi_1\Phi_1^*,$$

an absurdum. Again, it can be showed that $R(D_{(u,v)}\mathcal{F}(\lambda_0, 0, v_0))$ has co-dimension 1.

Hence, from [9], the point $(\lambda, u, v) = (\lambda_0, 0, v_0)$ is a bifurcation point from the semi-trivial solution $(0, v_0)$.

Now, we can apply Theorem 4.1 of [21] and conclude the existence of a continuum $\mathcal{C}^+ \subset \mathbb{R} \times X_1 \times X_2$ of positive solutions of (15) emanating from the point $(\lambda, u, v) = (\lambda_0, 0, v_0)$ such that:

i) $\mathcal{C}^+$ is unbounded in $\mathbb{R} \times X_1 \times X_2$; or

ii) there exists $\overline{\lambda} \in \mathbb{R}$ such that $(\overline{\lambda}, 0, 0) \in cl(\mathcal{C}^+)$.

Alternative ii) is not possible by the v-equation. Therefore, alternative i) holds. On the other hand, by Corollary 3.6, (15) does not possess positive solution for $\lambda \leq \lambda_0$ and by Theorem 3.5, it follows that $\mathcal{C}^+$ is bounded in X uniformly on compact subintervals of λ. Hence, we can conclude the existence of at least coexistence state for

$$\lambda > \lambda_1(v_0, z_0).$$

This completes the proof. ■

Condition (28) is related to the local stability of $(0, v_0)$ with respect to the parabolic problem.

Proposition 3.8. *Assume* $\lambda < \lambda_1(v_0, z_0)$ *(resp.* $\lambda > \lambda_1(v_0, z_0)$*). Then,* $(0, v_0)$ *is stable (resp. unstable).*

Proof. Observe that the stability of $(0, v_0)$ is given by the sign of the real parts of the eigenvalues for which the following problem admits a solution $(\xi, \eta) \in X \setminus \{(0,0)\}$

$$\begin{cases} -\Delta\xi + \nabla \cdot (\alpha(v_0, z_0)\xi\nabla v_0) - \lambda\beta(v_0, z_0)\xi = \sigma\xi & \text{in } \Omega, \\ -\Delta\eta + \eta = \sigma\eta & \text{in } \Omega, \\ B_1\xi = (0,0) & \text{on } \partial\Omega, \\ B_2\eta = (\gamma'(0)\xi, 0) & \text{on } \partial\Omega. \end{cases} \tag{30}$$

Assume that $\xi \equiv 0$, then $\sigma = \lambda_j(-\Delta + 1; 1; B_2) \geq \lambda_1(-\Delta + 1; 1; B_2) > 0$. Suppose that $\xi \not\equiv 0$, denote by

$$\mathcal{L}\xi := -\Delta\xi + \nabla \cdot (\alpha(v_0, z_0)\xi\nabla v_0),$$

then

$$\text{Re }\sigma = \text{Re }\lambda_j(\mathcal{L} - \lambda\beta(v_0, z_0); 1; B_1) \geq \lambda_1(\mathcal{L} - \lambda\beta(v_0, z_0); 1; B_1) > 0$$

because $\lambda < \lambda_1(v_0, z_0)$, where we have used (10).

Assume now that $\lambda > \lambda_1(v_0, z_0)$. Then,

$$\sigma_1 := \lambda_1(\mathcal{L} - \lambda\beta(v_0, z_0); 1; B_1) < 0.$$

Denote by ξ a positive eigenfunction associated to σ_1, that is

$$\mathcal{L}\xi - \lambda\beta(v_0, z_0)\xi = \sigma_1\xi \quad \text{in } \Omega, \qquad B_1\xi = (0,0) \quad \text{on } \partial\Omega.$$

Since $\sigma_1 < 0$, then

$$\lambda_1(-\Delta + 1 - \sigma_1; 1; B_2) > 0,$$

and so there exists η such that

$$-\Delta\eta + \eta = \sigma_1\eta \quad \text{in } \Omega, \quad B_2\eta = (\gamma'(0)\xi, 0) \quad \text{on } \partial\Omega.$$

Then, $\sigma_1 < 0$ is an eigenvalue of (30) with associated eigenfunction (ξ, η), so $(0, v_0)$ is unstable. ∎

4 Application and interpretation

In this section we consider the case $I_0 \geq 0$ is a positive constant. In this case, recall (14),

$$z_0 := I_0 e, \tag{31}$$

where e is the unique positive solution of

$$-\Delta e + e = 1 \quad \text{in } \Omega, \qquad B_3 e = (0,0) \quad \text{on } \partial\Omega.$$

We remind that the functions α and β depend on a variable s which represents the free receptors, so

$$s = s(v,z),\ \alpha(v,z) = \alpha_R(s(v,z)),\ \beta(v,z) = \beta_R(s(v,z)),$$

supposing α_R positive in $[0,+\infty)$ and β_R increasing with $\beta_R(0) = 0$, remember hypothesis ()

If we consider the behavior of the function $s = s(v,z)$, it is reasonable to think that when z is big (a lot of medicine), s tends to 0. Also, we will suppose that this rapprochement is regular and so, $s_v(v,z)$ and $s_z(v,z)$ tend also to 0 when z goes to $+\infty$. Finally, we will need the technical hypothesis that $zs_z(v,z)$ goes also to 0. These hypotheses move to α and β in the following way

$$\begin{cases} \alpha(v,z) \to \alpha_R(0), & \text{as } z \to \infty, \\ \alpha_v(v,z) \to 0, \\ s\alpha_z(v,z) \to 0, \\ \beta(v,z) \to \beta_R(0) = 0. \end{cases} \tag{32}$$

In the following result we study the principal eigenvalue $\lambda_1(v_0, z_0)$ in function of I_0, that is, the map

$$I_0 \in [0,\infty) \mapsto \lambda_1(v_0, z_0) = \lambda_1(v_0, I_0 e) := \lambda_1(I_0) \in \mathbb{R}.$$

Let us to introduce some notation before enunciating the result. Denote $\varphi_1(I_0)$ a principal eigenfunction associated to $\lambda_1(I_0)$, that is,

$$\begin{cases} -\Delta\varphi_1(I_0) = -\nabla\cdot(\alpha(v_0, I_0 e)\nabla v_0 \varphi_1(I_0)) + \lambda_1(I_0)\beta(v_0, I_0 e)\varphi_1(I_0) & \text{in } \Omega, \\ B_1\varphi_1(I_0) = (0,0) & \text{on } \partial\Omega. \end{cases} \tag{33}$$

We denote also $\varphi_1 := \varphi_1(0)$ a positive eigenfunction associated to $\lambda_1(0)$, that is

$$\begin{cases} -\Delta\varphi_1 + \nabla\cdot(\alpha(v_0,0)\nabla v_0\varphi_1) = \lambda_1(0)\beta(v_0,0)\varphi_1 & \text{in } \Omega, \\ B_1\varphi_1 = (0,0) & \text{on } \partial\Omega. \end{cases}$$

Moreover, φ_1^* stands for a positive eigenfunction associated to the adjoint problem, that is

$$\begin{cases} -\Delta\varphi_1^* - \alpha(v_0,0)\nabla v_0\cdot\nabla\varphi_1^* = \lambda_1(0)\beta(v_0,0)\varphi_1^* & \text{in } \Omega, \\ B_1^*\varphi_1^* = (0,0) & \text{on } \partial\Omega, \end{cases} \tag{34}$$

where

$$B_1^*\varphi_1^* := \begin{cases} \dfrac{\partial\varphi_1^*}{\partial n} + (\gamma_1 + \alpha(v_0,0)\gamma(0))\varphi_1^* & \text{on } \Gamma_1, \\ \dfrac{\partial\varphi_1^*}{\partial n} - (\tau_1 + \tau_2 v_0\alpha(v_0,0))\varphi_1^* & \text{on } \Gamma_2. \end{cases}$$

Finally, we denote by

$$\lambda_\infty := \lambda_1(\mathcal{L} + \alpha_R(0); 1; B_1).$$

where $\mathcal{L}\phi := -\Delta\phi + \alpha_R(0)\nabla v_0\cdot\nabla\phi$.

Proposition 4.1. *Then map $I_0 \mapsto \lambda_1(I_0)$ is derivable in $[0,\infty)$,*

$$\lambda_1'(0) = -\frac{\lambda_1(0)\displaystyle\int_\Omega \beta_z(v_0,0)e\varphi_1\varphi_1^* + \int_\Omega \alpha_z(v_0,0)e\varphi_1\nabla v_0\cdot\nabla\varphi_1^* + \int_{\partial\Omega}\alpha_z(v_0,0)e\varphi_1\varphi_1^*\frac{\partial v_0}{\partial n}}{\displaystyle\int_\Omega \beta(v_0,0)\varphi_1\varphi_1^*} \tag{35}$$

and

$$\lim_{I_0\to+\infty}\lambda_1(I_0) = \begin{cases} +\infty & \text{if } \lambda_\infty > 0, \\ -\infty & \text{if } \lambda_\infty < 0. \end{cases}$$

Proof. The regularity of the map $\lambda_1(I_0)$ follows by standard argument, see for instance [7]. Now, we can differentiate (33) with respect to I_0 at $I_0 = 0$ and obtain

$$\begin{cases} -\Delta\varphi_1' + \nabla\cdot(\alpha(v_0,0)\nabla v_0\varphi_1') - \lambda_1(0)\beta(v_0,0)\varphi_1' = & \\ -\nabla\cdot(\alpha_z(v_0,0)e\varphi_1\nabla v_0) + (\lambda_1'(0)\beta(v_0,0) + \lambda_1(0)\beta_z(v_0,0)e)\varphi_1 & \text{in } \Omega, \\ B_1\varphi_1' = (0,0) & \text{on } \partial\Omega. \end{cases}$$

Multiplying by φ_1^* and integrating we get (35).

To obtain the behaviour when $I_0 \to +\infty$, we re-write (33) as

$$-\Delta\varphi_1(I_0) + \alpha(v_0,I_0e)\nabla v_0\cdot\nabla\varphi_1(I_0) + M(I_0)\varphi_1(I_0) = \lambda_1(I_0)\beta(v_0,I_0e)\varphi_1(I_0)$$

where

$$M(I_0) := \alpha_v(v_0,I_0e)|\nabla v_0|^2 + I_0\alpha_z(v_0,I_0e)\nabla v_0\cdot\nabla e + \alpha(v_0,I_0e)v_0.$$

Taking into account the properties of the functions α and β in (32), we can show that as $I_0 \to \infty$

$$\begin{cases} \alpha(v_0,I_0e) \to \alpha_R(0) & \text{in } L^\infty(\Omega), \\ \alpha_v(v_0,I_0e) \to 0 & \text{in } L^\infty(\Omega), \\ I_0\alpha_z(v_0,I_0e) \to 0 & \text{in } L^\infty(\Omega), \\ \beta(v_0,I_0e) \to 0 & \text{in } L^\infty(\Omega), \end{cases}$$

and using Lemma 3.2 we conclude the result. ∎

Now, we would like to give a biological interpretation to the main results of the work. Basically, we compare the stability of the semi-trivial solution $(u,v) = (0,v_0)$ in the cases $I_0 = 0$ (absence of treatment) and $I_0 > 0$. We understand that if $(0,v_0)$ is stable, then the process of angiogenesis does not occur, that is, the EC disappear when time is large.

a) Case $I_0 = 0$: Observe that in absence of medicine, $I_0 = 0$, the semi-trivial solution $(0,v_0)$ is stable if $\lambda < \lambda_1(0) = \lambda_1(v_0,0)$ and unstable for $\lambda > \lambda_1(0)$. So, if the growth rate of the EC is less than $\lambda_1(0)$, then the angiogenesis does no occur and it is not necessary to introduce the medicine.

b) Case $I_0 > 0$: Assume that $\lambda > \lambda_1(0)$ and let us introduce medicine, that is $I_0 > 0$. Now, $(0,v_0)$ is stable if $\lambda < \lambda_1(I_0) = \lambda_1(v_0,z_0)$. We have studied this map in the last section. We distinguish two cases:

(a) Assume that $\lambda_\infty > 0$. Then, $\lambda_1(I_0) \to \infty$ as $I_0 \to \infty$. Hence, fix $\lambda > \lambda_1(v_0, 0)$, that is $(0, v_0)$ is not stable in absence de medicine. Then, in this case there exists a value of $I_0^1 > 0$ such that for $I_0 > I_0^1$ we have that

$$\lambda < \lambda_1(I_0).$$

That means that introducing a sufficient quantity of medicine, $I_0 > I_0^1$, we can avoid the angiogenesis.

(b) Assume that $\lambda_\infty < 0$. In this case, $\lambda_1(I_0) \to -\infty$ as $I_0 \to \infty$. So, we can not assure that the angiogenesis could avoid even introducing a great quantity of medicine. We try now to give an explication to this fact. Observe that the sign of λ_∞ depends on ∇v_0, $\alpha_R(0)$, the domain Ω and the boundary condition B_1. For example, $\lambda_\infty < 0$ if τ_1 is large, that is, if the number of EC which are introducing along Γ_2 is large, hence, even introducing a lot of medicine we can not eliminate the ECs. That is, the capacity of binding receptors is not sufficient to avoid angiogenesis, due to there are a lot of EC.

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