ON A CHEMOTAXIS MODEL WITH COMPETITIVE TERMS ARISING IN ANGIOGENESIS

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Abstract. In this paper we study an anti-angiogenic therapy model that deactivates the tumor angiogenic factors. The model consists of four parabolic equations and considers the chemotaxis and a logistic law for the endothelial cells and several boundary conditions, some of them are non homogeneous. We study the parabolic problem, proving the existence of a unique global positive solution for positive initial conditions, and the stationary problem, justifying the existence of one real number, an eigenvalue of a certain problem, which determines if the semi-trivial solutions are stable or unstable and the existence of a coexistence state.

1. Introduction. This paper deals with the theoretical study of a system of PDEs which is related to an anti-angiogenic therapy model. It is well-known that tumor induced angiogenesis, a rather complex process where a tumor prompts the formation of a vascular network which starts in a close blood vessel and leads to vascular growth towards it to gain access to the necessary nutrients to continue growing. This process begins when the avascular tumor mass releases substances called tumor angiogenic factors (TAF) which diffuse through the surrounding tissue, and arrive to a blood vessel; the TAF weaken the wall of the vessel and provoke the uncontrolled growth of the endothelial cells (EC), which form the vessel, towards the tumor through the ECM (the extracellular matrix), forming an irregular vascular network which ends up arriving to it (cf. [17]).

In an anti-angiogenic process, there exists at least two possible action mechanisms. In [9] we proposed an antiangiogenic therapy model where a drug blocks the receptors of the TAF on the cellular membranes of the EC, leaving the TAF active but harmless in the ECM. In this paper we will introduce a new model where the drug deactivates the TAF directly.

Our process is modeled in the beginning by three equations, one for the EC density, another for the TAF concentration and the third one for the therapy. The first one is a parabolic equation for the EC 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

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decay term. We 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 models the introduction of the drug in the organism.

We assume a tumor, whose boundary is $\Gamma_1$, surrounded by blood vessels and we consider a “virtual” regular boundary, $\Gamma_2$, close to the vessels: our bounded regular domain, $\Omega \subset \mathbb{R}^N$ is limited by $\Gamma_1$ and $\Gamma_2$ (see Figure 1, where we have represented a particular situation).

![Figure 1. A particular example of domain $\Omega$.](image)

In this domain we consider the equations

$$
\begin{align*}
    u_t &= d_1 \Delta u - \nabla \cdot (\alpha(v, z)u \nabla v) + \lambda \beta(v, z)u - u^2 & \text{in } \Omega \times (0, T), \ T > 0 \\
    v_t &= d_2 \Delta v - v & \text{in } \Omega \times (0, T), \\
    z_t &= d_3 \Delta z - z + I_0 & \text{in } \Omega \times (0, T),
\end{align*}
$$

(1)

where $\Omega$ is a regular bounded domain, $u$ stands for the density of the EC, and $v$ and $z$ represent the concentration of the TAF and the drug, respectively. The positive constants $d_1, d_2$ and $d_3$ measure the diffusion of $u, v$ and $z$, respectively. The growth of the EC follows a logistic law, so $\lambda \beta$ represents the growth rate of $u$: $\lambda$ is a real parameter and $\beta$ is a function depending on $v$ and $z$. It is well-known, see for instance [5], that the proliferation of the EC initiates when TAF concentration reaches a threshold. For that, the authors have included the dependence on $v$ and $z$ in the function $\beta$, the function $\alpha$ represents for chemotactic sensitivity, which is signal-dependent and depends on $v$ and $z$, and $I_0$ stands the introduction of the therapy.

But, because of our antiangiogenic therapy, we must modify the model. In [9] the TAF is operative and the process depends on the free receptors; now, the drug binds the TAF and forms a complex that cannot attach to the receptors of the endothelial cells. Then, in the TAF, we can distinguish between the active TAF ($v_A$), promoter of the angiogenesis, and the harmless inactive TAF ($v_I$). For the same reasons of [9], we can conclude that the functions $\alpha$ and $\beta$ depend on the one variable which represents the activated TAF. The growth rate of the EC increase with the active TAF, so $\beta$ is an increasing function, the chemotactic sensitivity at least for large values of active TAF is decreasing because of the saturation of the receptors of the EC. Therefore the prototype functions of $\alpha$ and $\beta$ could be

$$
\alpha(s) = \frac{2 + s}{1 + s}, \quad \beta(s) = s.
$$
Thus, we will consider the equations

\[
\begin{align*}
\begin{cases}
  u_t &= d_1 \Delta u - \nabla \cdot (\alpha(v_A)u\nabla v_A) + \lambda \beta(v_A)u - u^2 & \text{in } \Omega \times (0, T), \ T > 0 \\
  (v_A)_t &= d_{2A} \Delta v_A - v_A - k_F v_A z + k_B v_I & \text{in } \Omega \times (0, T), \\
  (v_I)_t &= d_{2I} \Delta v_I - v_I + k_F v_A z - k_B v_I & \text{in } \Omega \times (0, T), \\
  z_t &= d_3 \Delta z - z + I_0 & \text{in } \Omega \times (0, T),
\end{cases}
\end{align*}
\]

(2)

where \(v_A\) and \(v_I\) stand for the concentration of the active TAF, inactive TAF, respectively. Here, \(d_{2A}\) and \(d_{2I}\) represent the diffusion of \(v_A\) and \(v_I\), respectively, \(k_F\) measures the efficacy of the drug in front of the TAF and \(k_B\) has in mind a partial recovery of the activity of the inactive TAF.

The function \(\gamma\) is supposed to be a decreasing function of \(u\) since the presence of blood vessels reduces the production of TAF by the tumor because the nutrients to the tumor are provided toward the vessels. In particular \(\gamma\) could be taken as

\[
\gamma(s) = \frac{1}{1 + s}.
\]

On the other hand, \(v_I\) is a harmless substance that penetrates in the domain through \(\Gamma_1\). Then, we arrive at the following boundary conditions

\[
B_1 u = B_3 z = (0, 0),
\]

(3)

being

\[
B_1 u := \begin{cases}
  \frac{\partial u}{\partial n} + \gamma_1 u & \text{on } \Gamma_1, \\
  \frac{\partial u}{\partial n} - \tau_1 u & \text{on } \Gamma_2,
\end{cases}
\]

\[
B_3 z := \begin{cases}
  \frac{\partial z}{\partial n} + \gamma_3 z & \text{on } \Gamma_1, \\
  \frac{\partial z}{\partial n} + \tau_3 z & \text{on } \Gamma_2,
\end{cases}
\]

(4)

for the variables \(v_A\) and \(v_I\) we will take

\[
\begin{cases}
  B_{2A} v_A = (\gamma(u), 0) & \text{on } \partial \Omega \times (0, T), \\
  B_{2I} v_I = (0, 0) & \text{on } \partial \Omega \times (0, T),
\end{cases}
\]

(5)

being

\[
B_{2A} v_A := \begin{cases}
  \frac{\partial v_A}{\partial n} + \gamma_2 v_A & \text{on } \Gamma_1, \\
  \frac{\partial v_A}{\partial n} + \tau_2 v_A & \text{on } \Gamma_2,
\end{cases}
\]

\[
B_{2I} v_I := \begin{cases}
  \frac{\partial v_I}{\partial n} + \delta_2 v_I & \text{on } \Gamma_1, \\
  \frac{\partial v_I}{\partial n} + \rho_2 v_I & \text{on } \Gamma_2,
\end{cases}
\]

for the same reasons as in the cited paper. Here \(\gamma_1, \gamma_2, \delta_2, \rho_2, \tau_2, \gamma_3, \tau_3 > 0\) and \(n\) denotes the outward unit normal vector.
Let us point out the main differences with our previous papers [6], [8] and [9]. The argument in the proof of Theorem 2.9 is new here. In addition, in order to study the steady-states we need to introduce the concept of eigenvalues for systems whereas in [8] and [9] it was enough to deal with scalar eigenvalue problems. Those eigenvalues are needed in order to determine the existence of the semi-trivial states. Furthermore, in the proof of Proposition 8 we apply the scaling, see [11], a method that was not used in our previous papers.

The results and the structure of this paper are the following: in Section 2, we study the parabolic problem (2), proving the existence of a unique global positive solution when the initial data are positive. Moreover, we prove that there exists a λ− ∈ R such that for λ < λ−, ∥u(t)∥C(Ω) goes to 0 when t → +∞, that is, the angiogenesis process stops when λ is negative and large, independently of the initial data of the problem.

We study the stationary problem in Section 3: we show the existence of semi-trivial solutions and their local stability and by the bifurcation method we prove the existence of a coexistence state when λ is sufficiently large.

Finally in Section 4, we interpret the results in the framework of the anti-angiogenic therapy.

2. The evolution problem. During this section we will deal with the evolution problem:

\[
\begin{cases}
    u_t - d_1 \Delta u = -\nabla \cdot (\alpha(v_A)u \nabla v_A) + \lambda \beta(v_A)u - u^2 & \text{in } \Omega \times (0, T), \\
    (v_A)_t - d_2 \Delta v_A = -v_A - k_F v_A z + k_B v_I & \text{in } \Omega \times (0, T), \\
    (v_I)_t - d_2 \Delta v_I = -v_I + k_F v_A z - k_B v_I & \text{in } \Omega \times (0, T), \\
    z_t - d_3 \Delta z = -z + I_0 & \text{in } \Omega \times (0, T), \\
    B_1 u = B_2 v_I = B_3 z = (0, 0) & \text{on } \partial \Omega \times (0, T), \\
    B_2 A v_A = (\gamma(u), 0) & \text{on } \partial \Omega \times (0, T), \\
    (u, v_A, v_I, z)(x, 0) = (u_0, v_{A0}, v_{I0}, z_0) & \text{in } \Omega.
\end{cases}
\]  

(6)

We assume the following hypotheses with respect to functions γ, β and α:

\[
(H) \begin{cases}
    \gamma \in C^1(\mathbb{R}), \gamma \text{ positive, decreasing and } \gamma(0) > 0, \\
    \alpha \in C^1(\mathbb{R}), \alpha \text{ positive and bounded,} \\
    \beta \in C^1(\mathbb{R}), \beta \text{ increasing, } \beta(0) = 0 \text{ and bounded.}
\end{cases}
\]

Let us first collect some results that we will need in order to prove that problem (6) possesses a unique global in time solution. Let p ∈ (1, ∞), for convenience we define the following operators and domains in \(L^p(\Omega)\)

\[
A_1 \varphi := -d_1 \Delta \varphi + j_0 \varphi, \text{ for } \varphi \in D(A_1) := \{ \varphi \in W^{2,p}(\Omega) ; B_1 \varphi = 0 \}, \\
A_2 \varphi := -d_2 A \Delta \varphi + \varphi, \text{ for } \varphi \in D(A_2) := \{ \varphi \in W^{2,p}(\Omega) ; B_2 A \varphi = 0 \}, \\
A_3 \varphi := -d_2 B_1 \Delta \varphi + \varphi, \text{ for } \varphi \in D(A_3) := \{ \varphi \in W^{2,p}(\Omega) ; B_2 \varphi = 0 \}, \\
A_4 \varphi := -d_3 \Delta \varphi + \varphi, \text{ for } \varphi \in D(A_4) := \{ \varphi \in W^{2,p}(\Omega); B_3 \varphi = 0 \}.
\]

We denote by σ(A_i) the spectrum of A_i with domains D(A_i). Since τ_2, δ_2, ρ_2, γ_3, τ_3 > 0, then Re σ(A_i) > 0 for i = 2, 3, 4. Moreover, we pick \(j_0 > 0\) sufficiently large to assure that Re σ(A_i) > 0. Therefore, the fractional powers of A_i for i = 1, 2, 3, 4 are well-defined (see for instance [12, Ch. 1, Sec. 4]). We also define the domains of the fractional powers

\[
X_{i,p}^\rho := D(A_i^\rho) \text{ for } \rho \in (0, 1), \quad i = 1, 2, 3, 4.
\]
By [12, Th. 1.6.1] we have the following embeddings
\[
X_{i,p}^\rho \hookrightarrow W^{k,q}(\Omega) \quad \text{for} \quad k - N/q < 2 - N/p, \: q \geq p, \\
X_{i,p}^\rho \hookrightarrow C^\nu(\Omega) \quad \text{for} \quad 0 \leq \nu < 2p - N/p. \tag{7}
\]
In addition, for \(i = 1, 2, 3, 4\) the operators \(A_i\) with their respective domains are sectorial operators, therefore
\[
T_i(t) := e^{-tA_i},
\]
define analytical semigroups in \(L^p(\Omega)\). Moreover, by [12, Th. 1.3.4, Th. 1.4.3] \(T_i, i = 1, 2, 3, 4\) satisfy the following:

1. Let \(\Sigma\) an spectral bound of the real part of the spectrum of \(A_i\) with their respective domain, then for every \(\delta \in (0, \Sigma)\) there exists \(C > 0\) such that
\[
\|T_i(t)\|_{\mathcal{L}(L^p, L^p)} \leq Ce^{-\delta t}.
\]
2. For any \(\rho \in (0, 1)\) and \(\delta\) as previously, there exists a constant \(C_\rho\) such that for any \(u \in L^p(\Omega), \: t > 0\) we have
\[
\|T_2(t)u\|_{X_{i,p}^\rho} \leq C_\rho t^{-\rho}e^{-\delta t}\|u\|_p.
\]
3. Let \(p > N\). Combining (7) and adapting the proof from [18], then for any \(u \in C_0^\infty(\Omega), \: t > 0\) we obtain
\[
\|T_1(t)\nabla u\|_{C^0(\Omega)} \leq Ct^{-\gamma}e^{-\delta t}\|u\|_p,
\]
for some constants \(C > 0, \: \gamma \in (0, 1)\) and \(\delta > 0\). In particular, the operator \(T_1(t)\nabla\) admits an extension for any \(u \in L^p(\Omega)\) such that the previous inequality holds.

Since we have a nonlinear boundary condition in the \(v_A\)-equation, it will be convenient to introduce the variations of the constants formula for a parabolic problem with a non-homogeneous boundary condition. To be more precise, we consider the problem
\[
\begin{cases}
\psi_t + A_2\psi = f(t) & \text{in } \Omega \times (0, T), \\
B_2A\psi = g(t) & \text{on } \partial\Omega \times (0, T), \\
\psi(x, 0) = \psi_0(x) & \text{in } \Omega.
\end{cases} \tag{8}
\]

It is known that \(A_2\) with the domain \(D(A_2)\) is in separated divergence form (see [3, pg. 21]), therefore, is normally elliptic. We denote by \(A_{\alpha-1}\) the \(W^{2a-2,p}_B\)-realization of \(A_2\) (see [3, pg. 39] for the precise definition) where
\[
W^{s,p}_{B_2} := \begin{cases}
\{ z \in W^{s,p}(\Omega); \: B_2Az = 0 \} & \text{if } 1 + 1/p < s \leq 2, \\
W^{s,p}(\Omega) & \text{if } -1 + 1/p < s < 1 + 1/p, \\
(W^{-s,p}(\Omega))' & \text{if } -2 + 1/p < s \leq -1 + 1/p.
\end{cases}
\]

Since \(A_2\) with the domain \(D(A_2)\) is normally elliptic, then \(A_{\alpha-1}\) generates an analytical semigroup [3, Th. 8.5]. Moreover, if
\[
(f, g) \in C((0, T); W^{2a-2,p}(\Omega) \times W^{2a-1-1/p,p}(\partial\Omega))
\]
for some \(T > 0\) and \(2a \in (1/p, 1 + 1/p)\), then for any \(t < T\) we rewrite (8) by the generalized variation of constants formula (see [3, (11.20)])
\[
\psi(t) = e^{-tA_{\alpha-1}}\psi_0 + \int_0^t e^{-(t-\tau)A_{\alpha-1}}(f(\tau) + A_{\alpha-1}(B_2c_\alpha g(\tau)))d\tau,
\]
where \((B_2c_\alpha)\) is the continuous extension of \((B_2|\text{Ker}(A_2))^{-1}\) to \(W^{2a-1-1/p}(\partial\Omega)\). In addition
\[
A_{\alpha-1}(B_2c_\alpha) \in \mathcal{L}(W^{2a-1-1/p}(\partial\Omega), W^{2a-2,p}_B).
\]
Let $p > N$. For each $T > 0$ we define
\[ X := C(\Omega) \times W^{1,p}(\Omega) \times (C(\Omega))^2, \]
\[ X_T := C([0, T]; C(\Omega)), \quad Y_T := C([0, T]; W^{1,p}(\Omega)), \]
\[ X_T := X_T \times Y_T \times (X_T)^2. \]

**Theorem 2.1.** Let $I_0 \in C((0, +\infty); C^0(\Omega))$ uniformly bounded. For each initial data $u_0 := (u_0, v_{A_0}, v_{I_0}, z_0) \in X$ there exists $\tau(\|u_0\|_X)$ such that the problem (6) possesses a unique local in time solution $u \in X_T$. Moreover, the solution depends continuously on the initial data, i.e. if $u(u_0)$ and $u(u_0)$ stand for the unique solution of (6) with initial data $u_0$ and $\bar{u}_0$ respectively then
\[ \|u(u_0) - u(\bar{u}_0)\|_X \leq C\|u_0 - \bar{u}_0\|_X \]
for some $C > 0$. Furthermore, the solution also depends continuously on $I_0$.

**Proof.** We will apply the Banach fixed point Theorem. We pick $2\alpha \in (1, 1 + 1/p)$ and we denote by
\[ \gamma_0 \in \mathcal{L}(C(\Omega), C(\partial\Omega)) \]
the trace operator. Additionally we define the closed sets
\[ B_X(R, T) := \{ g \in X_T : \|g\|_{X_T} \leq R \}, \quad B_Y(R, T) := \{ g \in Y_T : \|g\|_{Y_T} \leq R \} \]
and $B(R, T) := B_X(R, T) \times B_Y(R, T) \times (B_X(R, T))^2$. On $B(R, T)$ we consider the operator
\[ F(u, v_A, v_I, z) := \begin{pmatrix} F_1(u, v_A, v_I, z) \\ F_2(u, v_A, v_I, z) \\ F_3(u, v_A, v_I, z) \\ F_4(u, v_A, v_I, z) \end{pmatrix} \]
where
\[ F_1(u, v_A, v_I, z) := T_1(t)u_0 + \int_0^t T_1(t-s)(-\nabla \cdot (\alpha(v_A)u\nabla v_A) + (\lambda\beta(v_A) + j_0)u - u^2)ds, \]
\[ F_2(u, v_A, v_I, z) := T_2(t)v_{A_0} + \int_0^t T_2(t-s)(-k_Fv_A z + k_B v_I + A_{\alpha-1}(B_2)^{1/2} \gamma_0(\gamma(u)))ds, \]
\[ F_3(u, v_A, v_I, z) := T_3(t)v_{I_0} + \int_0^t T_3(t-s)(k_Fv_A z - k_B v_I)ds, \]
\[ F_4(u, v_A, v_I, z) := T_4(t)z_0 + \int_0^t T_4(t-s)(I_0)ds. \]

**Step 1.** There exist $R, t > 0$ such that $F(B(R, t)) \subset B(R, t)$. By the properties of the semigroup there exist constants $0 < \kappa < \rho < 1$ such that
\[ \|F_1\|_{C(\Omega)} \leq C\|u_0\|_X + \int_0^t (C(t-s)-\rho)\|\alpha(v_A)u\nabla v_A\|_p + \]
\[ + C(t-s)^{-\kappa} e^{-\delta(t-s)}(|\lambda\beta(v_A) + j_0|u_0 + \|u^2\|_p)ds \]
\[ \leq C\|u_0\|_X + C(\lambda\beta)^\infty + j_0 + R(1 + \|\alpha\infty)R \max \left\{ \frac{t^{1-\rho} - t^{1-\kappa}}{1 - \rho + 1 - \kappa} \right\}. \]

By [6, Lemma 3.1], there exists $\eta \in (0, 1)$ such that
\[ \|F_2\|_{1,p} \leq C\|v_{A_0}\|_{1,p} + \int_0^t C(t-s)^{-\eta}(|k_B v_I - k_Fv_A z|_{W^{2\alpha-2,p}} + \]
\[ + \|A_{\alpha-1}(B_2)^{1/2} \gamma_0(\gamma(u))\|_{W^{2\alpha-2,p}})ds. \]
In order to estimate the last term in the above inequality we just notice that by the embedding
\[ C(\partial \Omega) \hookrightarrow L^p(\partial \Omega) \hookrightarrow W^{2\alpha - 1 - 1/p, p}(\partial \Omega) \]
we have that
\[ A_{\alpha - 1}(B_2)(\alpha_0) \in L(C(\Omega), W^{2\alpha - 2, p}_2). \]
Therefore,
\[ \|F_2\|_{1,p} \leq C\|u_0\|X + C(\gamma(0) + R + R^2) \frac{t^{1-\eta}}{1-\eta}. \]
By the maximum principle we deduce that
\[ \|F_3\|_{C(\Omega)} \leq C\|u_0\|X + CR^2t, \]
\[ \|F_4\|_{C(\Omega)} \leq C\|u_0\|X + \|J_0\|_{C([0,t]: C(\Omega))}t. \]
We pick \( R > C\|u_0\|X + 1 \). Previous estimates assert that there exists \( \tau_0 \) such for every \( t \leq \tau_0 \)
\[ \|F(u,v_A,v_I,z)\|X \leq C\|u_0\|X + 1. \]
Therefore, it follows that \( F(B(R,t)) \subset B(R,t) \).

**Step 2.** \( F \) is contractive in \( B(R,\tau) \) for some \( \tau \leq \tau_0 \). Let \( t \leq \tau_0 \) and
\[ u := (u, v_A, v_I, z) \in B(R,t), \quad u := (\overline{u}, \overline{v}_A, \overline{v}_I, \overline{z}) \in B(R,t). \]
We know that
\[ \|F_1(u) - F_1(\overline{u})\|_{C(\Omega)} \leq \int_0^t \left( \|T_1(t - s)\nabla \cdot (\alpha(v_A)u\nabla v_A - \alpha(\overline{v}_A)u\nabla \overline{v}_A)\|_{C(\Omega)} + \right. \]
\[ + \|T_1(t - s)((\lambda\beta(v_A) + j_0)u - (\lambda\beta(\overline{v}_A) + j_0)\overline{v}_A)\|_{C(\Omega)} + \right. \]
\[ + \|T_1(t - s)(u^2 - \overline{v}_A^2)\|_{C(\Omega)} \right) ds. \]
The first, second and third term in the right-hand side of the above inequality are denoted by \( (a1) \), \( (a2) \) and \( (a3) \), respectively. Now, we will provide a suitable estimate for each term.

\[ (a1) \leq \int_0^t \left( \|T_1(t - s)\nabla \cdot (\alpha(v_A)(u - \overline{u})\nabla v_A)\|_{C(\Omega)} + \right. \]
\[ + \|T_1(t - s)\nabla \cdot (\alpha(v_A)\nabla(v_A - \overline{v}_A))\|_{C(\Omega)} + \right. \]
\[ + \|T_1(t - s)\nabla \cdot ((\alpha(v_A) - \alpha(\overline{v}_A))\nabla v_A)\|_{C(\Omega)} \right) ds \]
\[ \leq \int_0^t C(t - s)^{-\rho}C(\|\alpha\|_{\infty}, R)(\|u - \overline{u}\|_{C(\Omega)} + \|v_A - \overline{v}_A\|_{1,p})ds, \]
for some \( \rho \in (0,1) \). In the same fashion we obtain
\[ (a2) \leq \int_0^t C(t - s)^{-\kappa}C(j_0, \|\beta\|_{\infty}, R)(\|u - \overline{u}\|_{C(\Omega)} + \|v_A - \overline{v}_A\|_{1,p})ds, \]
\[ (a3) \leq \int_0^t C(t - s)^{-\frac{\kappa}{2}}2R\|u - \overline{u}\|_{C(\Omega)}ds, \]
where \( \kappa \in (0,1) \). Hence
\[ \|F_1(u) - F_1(\overline{u})\|_{C(\Omega)} \leq C(j_0, \|\alpha\|_{\infty}, \|\beta\|_{\infty}, R) \max \left\{ \frac{t^{1-\rho}}{1-\rho}, \frac{t^{1-\kappa}}{1-\kappa} \right\} \|u - \overline{u}\|_X. \]
Proof. In order to show that the first component of $F$, there exists $\eta \in (0, 1)$ such that

$$
\| F_2(u) - F_2(\overline{u}) \|_{1,p} \leq \int_0^t C(t-s)^{-\eta}(\| v_I - \overline{v}_I \|_{C(\overline{\Omega})} + R(\| v_A - \overline{v}_A \|_{1,p} + \| z - \overline{z} \|_{C(\overline{\Omega})}) + \| \gamma(u) - \gamma(\overline{u}) \|_{C(\overline{\Omega})}) ds
+ C(C + R) \frac{t^{1-\eta}}{1-\eta} \| u - \overline{u} \|_{X}.
$$

Finally the remaining components of $F$ are estimated as follows

$$
\| F_3(u) - F_3(\overline{u}) \|_{C(\overline{\Omega})} \leq C \max\{1, R\} \| u - \overline{u} \|_{X},
$$

$$
\| F_4(u) - F_4(\overline{u}) \|_{C(\overline{\Omega})} = 0.
$$

Therefore, there exists $\tau \in (0, \tau_0)$ such that $F$ is contractive in $B(R, \tau)$. At the end we prove the continuity of the solutions respect to the initial data and the coefficient $I_0$. Let $R > C \max\{\| u_0 - \overline{u}_0 \|\} + 1$. Then, there exists $\tau > 0$ such that $F$ is contractive; accordingly, there exists $\kappa < 1$ such that

$$
\| u(u_0) - u(\overline{u}_0) \|_{X} \leq \| T_1(t)(u_0 - \overline{u}_0) \|_{C(\overline{\Omega})} + \| T_2(t)(v_{A0} - \overline{v}_{A0}) \|_{C(\overline{\Omega})} + \| T_3(t)(v_{I0} - \overline{v}_{I0}) \|_{C(\overline{\Omega})} + \| T_4(t)(z_0 - \overline{z}_0) \|_{C(\overline{\Omega})} + \| F(u(u_0)) - F(u(\overline{u}_0)) \|_{X}
\leq C \| u_0 - \overline{u}_0 \|_{X} + \kappa \| u(u_0) - u(\overline{u}_0) \|_{X}.
$$

which proves that the solution depends continuously on the initial data. The proof of the continuity with respect to $I_0$ follows in a similar way.

**Proposition 1.** Under the conditions of Theorem 2.1, if the initial data of (6) are non-negative i.e. $u_0(x) \geq 0$ for any $x \in \Omega$ and $I_0(x, t) \geq 0$ for any $(x, t) \in \Omega \times (0, \tau)$, then the solution $u$ to (6) is also non-negative i.e. $u(x, t) \geq 0$ for any $(x, t) \in \Omega \times (0, \tau)$.

**Proof.** In order to show that the first component of $u$, i.e. $u$ is non-negative we apply [3, Theorem 15.1], and the positivity of the remaining components of $u$ follows from the standard maximum principle for parabolic equations.

During the rest of the section we assume that the initial data is non-negative. We will show that solutions provided by Theorem 2.1 can be prolonged till infinity i.e. $T_{\text{max}} = +\infty$ where $T_{\text{max}}$ denotes the maximal existence time. In particular we will prove that for every $t < T_{\text{max}}$

$$
\| u \|_{X} \leq C.
$$

For this purpose we will apply a bootstrap argument.

**Lemma 2.2.** For any $0 \leq t < T_{\text{max}}$ there exists a constant $C > 0$ such that

$$
\| v_A(t) \|_{1} + \| v_I(t) \|_{1} \leq C.
$$

**Proof.** Adding the $v_A$-equation to the $v_I$-equation and integrating in the spatial variables,

$$
\frac{d}{dt} \int_{\Omega} (v_A + v_I) = \int_{\Omega} d_{2A} \Delta v_A + \int_{\Gamma_1} d_{2I} \Delta v_I - \int_{\Omega} (v_A + v_I).
$$

Therefore,

$$
\frac{d}{dt} \int_{\Omega} (v_A + v_I) + \int_{\Omega} (v_A + v_I) = d_{2A} \int_{\Gamma_1} \gamma(u) - d_{2A} \gamma_2 \int_{\Gamma_1} v_A - d_{2I} \gamma_2 \int_{\Gamma_2} v_I - d_{2I} \rho_2 \int_{\Gamma_2} v_I.
$$
By Proposition 1 we know that $v_A, v_I, u \geq 0$ in $\Omega \times [0, T_{max})$, moreover $\gamma$ is a non-increasing function, as a consequence, we obtain
\[
\frac{d}{dt} \int_{\Omega} (v_A + v_I) + \int_{\Omega} (v_A + v_I) \leq d_{2A} \gamma(0) |\Gamma_1|,
\]
where $|\Gamma_1|$ stands for the $N$-1 dimensional Lebesgue measure of $\Gamma_1$. Hence, by the Gronwall Lemma
\[
\int_{\Omega} (v_A(t) + v_I(t)) \leq \max \left\{ \int_{\Omega} (v_A(0) + v_I(0)), d_{2A} \gamma(0) |\Gamma_1| \right\}
\]
for any $t < T_{max}$. Now, by Proposition 1, the claim follows.

Next, with the bound provided by Lemma 2.2 we can increase the regularity of $v_I$ using the regularization property of the parabolic equations. Let us observe that $z$ satisfies a linear equation, therefore the standard parabolic regularity asserts
\[
\|z(t)\|_{C(\pi)} \leq C
\]
for any $t < T_{max}$. As a consequence, if $\|v_A(t)\|_p \leq C$ then $\|v_A(t)z(t)\|_p \leq C$. Moreover, the previous estimate allows us to adapt the proof of [13, Lemma 4.1] to obtain the following result.

Lemma 2.3. Let $r \in [1, N]$ and $0 < \tau < \tau(\|u_0\|_{X})$ where $\tau(\|u_0\|_{X})$ is the local existence time provided by Theorem 2.1. If
\[
\|v_A(t)\|_r \leq C \quad \forall t \in (\tau, T_{max}),
\]
then
\[
\|v_I(t)\|_{1,q} \leq C \quad \forall t \in (\tau, T_{max})
\]
holds for all $q \in \left(1, \frac{rN}{r-1}\right)$.

Once we know the uniform in time boundedness of $v_I$ in $L^r(\Omega)$ for some $r > 1$, we can get the uniform in time boundedness of $v_A$ in $L^r(\Omega)$. During the proof of the following lemma we will need the Sobolev-Trace inequality that can be found in [10, Lemma 6].

Lemma 2.4. (Sobolev-Trace inequality) For every $\epsilon > 0$, $\theta > 1$ there exists a constant $C = C(\Omega, \theta)$ such that
\[
\int_{\Gamma_i} w^2 \leq \epsilon \int_{\Omega} |\nabla w|^2 + C(\epsilon^{-\theta} + 1) \int_{\Omega} w^2, \quad \forall w \in W^{1,2}(\Omega), \quad i = 1, 2.
\]

Lemma 2.5. Let $r \in (1, +\infty)$ and $\tau$ as Lemma 2.3. If
\[
\|v_I(t)\|_r \leq C \quad \forall t \in (\tau, T_{max})
\]
then
\[
\|v_A(t)\|_r \leq C \quad \forall t \in (\tau, T_{max}).
\]

Proof. On multiplying the $v_A$-equation by $v_A^{r-1}$ and integrating in the space variable we get
\[
\frac{1}{r} \frac{d}{dt} \int_{\Omega} v_A^r = -\frac{4d_{2A}(r-1)}{r^2} \int_{\Omega} |\nabla v_A^{r/2}|^2 + d_{2A} \int_{\Gamma_1} \gamma(u) v_A^r - d_{2A} \tau_2 \int_{\Gamma_2} v_A^r - \int_{\Omega} v_A^r - k_f \int_{\Omega} v_A z + k_b \int_{\Omega} v_I v_A^{r-1}.
\]
By the Sobolev-Trace inequality and the Hölder and Young inequalities we obtain
\[
\frac{1}{r} \frac{d}{dt} \int_\Omega v_A^r \leq -\frac{4d_2A(r-1)}{r^2} \int_\Omega |\nabla v_A^{r/2}|^2 + d_{2A} \gamma(0) \epsilon \left( \int_\Omega |\nabla v_A^{r/2}|^2 + \int_\Omega v_A^r \right) +
\]
\[
+C(\epsilon, r) - \int_\Omega v_A + k_\theta \left( \epsilon \int_\Omega v_A^{r/2} + C(\epsilon) \int_\Omega v_f^r \right),
\]
for any \( \epsilon > 0 \). Next, we pick \( \epsilon \) sufficiently small to get
\[
\frac{1}{r} \frac{d}{dt} \int_\Omega v_A^r \leq \frac{1}{2} \int_\Omega v_A^r + C(r),
\]
which concludes the proof.

Now, taking into account that \( \gamma \) is a non-increasing function, we can get a similar result to Lemma 2.3 for \( v_A \). For this purpose we should deal with the non-homogeneous boundary condition of \( v_A \).

**Lemma 2.6.** Let \( r \in (1, +\infty) \) and \( \tau \) as Lemma 2.3. If
\[
\|v_f(t)\|_r \leq C \quad \forall t \in (\tau, T_{\text{max}})
\]
then
\[
\|v_A(t)\|_{1,p} \leq C \quad \forall t \in (\tau, T_{\text{max}})
\]
holds for all \( p \in \left(1, \frac{N}{N-1}\right) \).

**Proof.** Let
\[
f(s) := -k_F v_A(s) z(s) + k_B v_f(s), \quad g(s) := \gamma_0(\gamma(u(s)))
\]
where \( \gamma_0 \) is the trace operator. For any \( \alpha, \beta \) such that \( 1 < \beta < 2\alpha < 1 + 1/r \) we take the \( W^{\beta,r} \) norm in a generalized variation of the constants formula for \( v_A \) to get, by [6, Lemma 3.1], that
\[
\|v_A(t)\|_{\beta,r} \leq \|v_A(0)\|_{\beta,r} + \int_0^t \|e^{-(t-s)\alpha A_0} v_A - e^{-s\alpha A_0} v_A + A_{\alpha-1}(B_2)_{\alpha} g(s)\|_{\beta,r} ds
\]
\[
\leq C \left( e^{-\delta t} \|v_A(0)\|_{W^{2\alpha-2,r}} + \int_0^t (t-s)^{-\theta} e^{-\delta(t-s)} \|f(s) + A_{\alpha-1}(B_2)_{\alpha}^c g(s)\|_{W^{2\alpha-2,r}} ds \right).
\]
Since
\[
A_{\alpha-1}(B_2)_{\alpha}^c \in \mathcal{L}(W^{2\alpha-1-1/r,\alpha}(\partial \Omega), W^{2\alpha-2,r}_B)
\]
and
\[
L'((\Omega) \hookrightarrow W^{2\alpha-2,r}_B, \quad L'((\partial \Omega) \hookrightarrow W^{2\alpha-1-1/r,\alpha}(\partial \Omega)
\]
we have
\[
\|v_A(t)\|_{\beta,r} \leq C \left( e^{-\delta t} \|v_A(0)\|_{\beta} + \int_0^t (t-s)^{-\theta} e^{-\delta(t-s)} \left( \|f(s)\|_{r} + \|g(s)\|_{L'((\partial \Omega))} \right) ds \right).
\]
Now, by the regularity of \( z \), the previous Lemma and taking into account that \( \gamma \) is non-increasing and the bounds provided by Theorem 2.1 and Lemmas 2.2, 2.3 and 2.5 we obtain
\[
\|f(s)\|_{r} \leq C, \quad \|g(s)\|_{L'((\partial \Omega))} \leq C \quad \forall s \in [0, t].
\]
Therefore, we obtain
\[
\|v_A(t)\|_{\beta,r} \leq C.
\]
In order to conclude we just need to observe that for any \( p \in \left(1, \frac{rN}{N-1}\right) \) we can find \( 1 < \beta < 2\alpha < 1 + 1/r \) such that
\[
W^{\beta,r}(\Omega) \hookrightarrow W^{1,p}(\Omega).
\]

At this point we just need to apply a bootstrap argument starting with Lemma 2.2 and combining Lemma 2.3, Lemma 2.5 and Lemma 2.6 together with the Sobolev embedding to get the desired bound for the components \( v_A \) and \( v_I \) of \( u \).

**Proposition 2.** Let \( p > N \), then there exists a constant \( C \) such that
\[
\|v_A(t)\|_{1,p} + \|v_I(t)\|_{C(\Omega)} \leq C \quad \forall t \in [0,T_{\text{max}}).
\]

**Remark 1.** Let us notice that the constant \( C \) that appears in the previous Proposition does not depend on the function \( \beta \).

Next we provide a uniform in time bound of \( u \) in \( L^p(\Omega) \). For the readers convenience we include the following estimate (see [9, Lemma 2.8]) that will be useful in the following proposition.

**Lemma 2.7.** Let \( s > N \), for every \( \delta > 0 \) there exist \( m > 1 \) and a constant \( C(\Omega) \) such that
\[
\int_\Omega |w \nabla v \cdot \nabla w| \leq C(\Omega) \|\nabla v\|_{s}(\delta\|w\|_{1,2}^2 + m\delta^{-m}\|w\|_2^2), \quad \forall w \in W^{1,2}(\Omega), \ v \in W^{1,s}(\Omega).
\]

**Proposition 3.** For any \( p > 1 \) we have that
\[
\|u(t)\|_{L^p(\Omega)} \leq C \quad \forall t \in [0,T_{\text{max}}).
\]

**Proof.** On multiplying the \( u \)-equation by \( u^{p-1} \) and integrating in the space variable we get
\[
\frac{1}{p} \frac{d}{dt} \int_\Omega u^p = -\frac{4(p-1)}{p^2} \int_\Omega |\nabla u^{p/2}|^2 - \int_{\Gamma_1} (\gamma_1 + \alpha(v)\gamma_2(u))u^p + \\
+ \int_{\Gamma_2} (\gamma_1 + \gamma_2 v_A \alpha(v_A))u^p + \frac{2(p-1)}{p} \int_\Omega \alpha(v_A)u^{p/2} \nabla v_A \cdot \nabla u^{p/2} + \\
+ \int_{\Omega} (\lambda \beta(v_A)u - u^2)u^{p-1}.
\]
Combining the previous proposition with Lemma 2.7 and the Sobolev-Trace inequality we infer
\[
\frac{1}{p} \frac{d}{dt} \int_\Omega u^p \leq C \int_\Omega u^p - \int_\Omega u^{p+1} \\
\leq (\epsilon' - 1) \int_\Omega u^{p+1} + C(\epsilon')
\]
for some \( C > 0 \) and any \( \epsilon' \in (0,1) \). Next, by the Hölder inequality we obtain
\[
\frac{1}{p} \frac{d}{dt} \int_\Omega u^p \leq -C_1 \left( \int_\Omega u^p \right)^{\frac{p+1}{p}} + C(\epsilon')
\]
for some \( C_1 > 0 \). The above differential inequality entails
\[
\int_\Omega u^p \leq \max \left\{ \int_{\Omega} u^p, \left( \frac{C(\epsilon')}{C_1} \right)^{\frac{p}{p+1}} \right\}
\]
\boxed{\quad \forall t \in [0,T_{\text{max}}).}
Proposition 4. We have that
\[ \|u(t)\|_{C(\overline{\Omega})} \leq C \quad \forall t \in [0, T_{max}). \]

Proof. By the variation of constants formula we have that
\[
    u(t) = T_1(t)u_0 + \int_0^t T_1(t-s)(-\nabla \cdot (\alpha(v_A)u\nabla v_A))ds + \\
    + \int_0^t T_1(t-s)((\lambda\beta(v_A) + j_0)u - u^2)ds \\
    := u_1(t) + u_2(t) + u_3(t)
\]

By the maximum principle \( u, u_1 \) and \( u_3 \) are nonnegative. Therefore,
\[
    \|u(t)\|_{C(\overline{\Omega})} = \max_{x \in \Omega} u(t) \leq \max_{x \in \Omega} u_1(t) + \max_{x \in \Omega} |u_2(t)| + \max_{x \in \Omega} u_3(t).
\]

Let us note that
\[
    (\lambda\beta(v_A) + j_0)u - u^2 \leq C,
\]
for some constant \( C > 0 \). Therefore, by the parabolic maximum principle we have that
\[
    \max_{x \in \Omega} u_1(t) \leq \max_{x \in \Omega} u_0
\]
and
\[
    u_3(t) \leq \int_0^t T_1(t-s)Cds
\]

As a consequence, for any \( p > N/2 \) there exists \( \rho \in (N/(2p), 1) \) and \( \delta > 0 \) such that
\[
    \max_{x \in \Omega} u_3(t) \leq \|C\|_p \int_0^t C(\rho)(t-s)^{-\rho}e^{-\delta(t-s)}ds,
\]
which implies the boundedness of \( u_3 \). Let \( p > N \), then for some \( \gamma \in (0, 1), \delta > 0 \) and \( C > 0 \) we have that
\[
    \max_{x \in \Omega} |u_2(t)| \leq C \int_0^t (t-s)^{-\gamma}e^{-\delta(t-s)}\|u\nabla v_A\|_{2p}ds \\
    \leq C \int_0^t (t-s)^{-\gamma}e^{-\delta(t-s)}\|u\|_{2p}\|\nabla v_A\|_{2p}ds.
\]

By the previous propositions we get the boundedness of \( |u_2| \). Collecting the boundedness of \( u_1, |u_2| \) and \( u_3 \) we get the desired result. \( \square \)

Remark 2. We would like to point out that if \( \lambda \leq 0 \) then
\[
    \lambda\beta(v_A)u - u^2 \leq 0.
\]

As a consequence, for any \( \lambda \leq 0 \) we have that
\[
    \|u(t)\|_{C(\overline{\Omega})} \leq C \quad \forall t \in [0, T_{max}),
\]
where \( C \) is a constant that does not depend on \( \lambda \leq 0 \).

Previous propositions entail the following:

Theorem 2.8. Let \( \mathbf{u}_0 \in X, \ p > N \) with \( \mathbf{u}_0 \geq 0 \) and \( I_0 \in C([0, +\infty); C(\overline{\Omega})) \) non-negative. Then, there exists a unique non-negative global in time solution
\[
    \mathbf{u} \in C([0, +\infty); C(\overline{\Omega})) \times C([0, +\infty); W^{1,p}(\Omega)) \times (C([0, +\infty); C(\overline{\Omega})))^2
\]
of (6).
Remark 3. We would like to point out that the above result is true even when $\beta$ does not satisfy (H) and it is not bounded. Observe that by Proposition 2, we have that $\|v_A(t)\|_{C(\overline{\Omega})} \leq C$ with $C$ not depending on $\beta$, see Remark 1.

The rest of the section is devoted to the proof of the following Theorem:

**Theorem 2.9.** There exists a $\lambda_0 < 0$ such that for any $\lambda < \lambda_0 < 0$ we have

$$\lim_{t \to +\infty} \|u(t)\|_{C(\overline{\Omega})} = 0.$$ 

Our first step in the proof is to show that $v_A$ is separated from zero when $t$ is sufficiently large.

**Lemma 2.10.** For any $\lambda < 0$ there exist $\tau > 0$ and $\delta > 0$ such that $v_A(x,t) \geq \delta \forall (x,t) \in \Omega \times [\tau, +\infty)$, where $\delta$ does not depend on $\lambda$.

**Proof.** We know that $v_A$ solves the equation

$$\begin{cases}
(v_A)_t = d_2A \Delta v_A - v_A - k_F v_A z + k_B v_I & \text{in } \Omega \times (0, +\infty), \\
B_2A v_A = (\gamma(u), 0) & \text{on } \partial \Omega \times (0, +\infty), \\
v_A(x,0) = v_{A0} & \text{in } \Omega.
\end{cases} \quad (12)$$

Let

$$C_1 := \sup_{(x,t) \in \Omega \times [0, +\infty)} z(x,t),$$

$$C_2 := \sup_{(x,t) \in \Omega \times [0, +\infty)} u(x,t).$$

We denote by $\varphi$ the solution to the linear equation

$$\begin{cases}
\varphi_t = \mathcal{L}\varphi & \text{in } \Omega \times (0, +\infty), \\
B_2A \varphi = (\gamma(C_2), 0) & \text{on } \partial \Omega \times (0, +\infty), \\
\varphi(x,0) = v_{A0} & \text{in } \Omega,
\end{cases} \quad (13)$$

where

$$\mathcal{L}\varphi := d_2A \Delta \varphi - \varphi - k_F C_1 \varphi.$$

Since $\gamma$ is a non-increasing function we have that $\varphi$ is a sub-solution to (12), therefore

$$\varphi(x,t) \leq v_A(x,t) \quad \forall (x,t) \in \Omega \times [0, +\infty). \quad (14)$$

On the other hand, it is clear that

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

where $\varphi^*$ is the unique positive solution of

$$\begin{cases}
\gamma \mathcal{L}\varphi^* = 0 & \text{in } \Omega, \\
B_2A \varphi^* = (\gamma(C_2), 0) & \text{on } \partial \Omega.
\end{cases}$$

Moreover, by the strong maximum principle [4] we have that there exists $\delta > 0$ such that $\varphi^*(x) > 2\delta$ for all $x \in \Omega$. Then, there exists $\tau > 0$ such that

$$\varphi(x,t) \geq \varphi^*(x) - \delta > \delta \quad \forall (x,t) \in \Omega \times [\tau, +\infty).$$

The above estimate together with (14) concludes the proof. \hfill \Box

**Lemma 2.11.** There exists $\lambda_0 < 0$ such that for any $\lambda \leq \lambda_0$

$$\|u(t)\|_2 \leq C e^{-\kappa t} \quad \forall t \geq \tau$$

and for some $\kappa > 0$. 

Proof. We multiply the $u$-equation by $u$ and we integrate in the spatial variable to get
\[ \frac{d}{dt} \int_{\Omega} u^2 = -d_1 \int_{\Omega} |\nabla u|^2 + \int_{\Omega} \alpha(v_A) u \nabla v_A \cdot \nabla u + \int_{\Omega} \lambda \beta(v_A) u^2 - \int u^3 - \int_{\Gamma_1} (\gamma_1 + \alpha(v_A) \gamma(u)) u^2 + \int_{\Gamma_2} (\tau_1 + \tau_2 v_A \alpha(v_A)) u^2. \]

Next we estimate the second term and last term in the right hand side with the Sobolev-Trace inequality and Lemma 2.7. Therefore for any $\epsilon > 0$, $\theta > 1$, $s > N$ and some $m > 1$ we have
\[ \frac{d}{dt} \int_{\Omega} u^2 \leq -d_1 \int_{\Omega} |\nabla u|^2 + \|\alpha\|_{\infty} C(\Omega) \|\nabla v_A\|_s \left( \epsilon \|u\|_{1,2} + m \epsilon^{-m} \|u\|_{2}^2 \right) + \int \lambda \beta(v_A) u^2 + \epsilon \int |\nabla u|^2 + C(\epsilon^{-\theta} + 1) \int u^2. \]

Since
\[ \sup_{t \geq \tau} \|v_A\|_{1,s} \leq C, \]
then we can pick $\epsilon > 0$ sufficiently small to arrive at
\[ \frac{d}{dt} \int_{\Omega} u^2 \leq -d_1 \int_{\Omega} |\nabla u|^2 + \int \lambda \beta(v_A) u^2. \]

At this point we apply Lemma 2.10 for any $t \geq \tau$ to get
\[ \frac{d}{dt} \int_{\Omega} u^2 \leq C \int_{\Omega} u^2 + \lambda \beta(\delta) \int u^2. \]

In order to conclude we pick $\lambda_0 < -C/\beta(\delta)$ and we integrate the above equation in the time variable between $\tau$ and $t > \tau$.

Proof of Theorem 2.9. Previous Lemma together with (11) provides that
\[ \lim_{t \to +\infty} \|u(t)\|_p = 0, \]
for any $p > 2$. Moreover, we can argue as in Lemma 3.7 of [8] to get
\[ \|u(t)\|_{X_{1,p}^\beta} \leq C, \quad \forall t \geq \tau, \]
where $2\beta \in (N/p, 1)$. We choose $k$, $m$ such that
\[ \frac{N}{p} < m < k < 2\beta. \]

By the embedding
\[ X_{1,p}^\beta \hookrightarrow W^{k,p}(\Omega) \]
and the Gagliardo-Nirenberg inequality
\[ \|u(t)\|_{m,p} \leq C \|u(t)\|_{k,p} \|u(t)\|_p \]
we infer that
\[ \lim_{t \to +\infty} \|u(t)\|_{m,p} = 0. \]

Since
\[ W^{m,p}(\Omega) \hookrightarrow C(\overline{\Omega}) \]
we deduce Theorem 2.9. \qed
3. The stationary problem. In this section we consider the stationary problem associated to (6), that is,

\[
\begin{aligned}
-d_1 \Delta u &= -\nabla \cdot (\alpha(v_A)u \nabla v_A) + \lambda \beta(v_A)u - u^2 \quad \text{in } \Omega, \\
-d_2 A \Delta v_A &= -v_A - k_F v_A z + k_B v_I \quad \text{in } \Omega, \\
-d_2 I \Delta v_I &= -v_I + k_F v_A z - k_B v_I \quad \text{in } \Omega, \\
-d_3 \Delta z &= -z + I_0 \quad \text{in } \Omega,
\end{aligned}
\]

(15)

where \( I_0 \in C^r(\Omega), \rho \in (0, 1) \) and it is a non-negative function.

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

\[
X_1 := \{ u \in C^{2,r}(\Omega) : B_1 u = (0, 0) \text{ on } \partial \Omega \},
\]

\[
X_2 := \{ v \in C^{2,r}(\Omega) : \partial I/\partial n + \tau_2 v = 0 \text{ on } \Gamma_2 \},
\]

\[
X_3 := \{ v \in C^{2,r}(\Omega) : B_2 v = (0, 0) \text{ on } \partial \Omega \}
\]

and finally

\[
X := X_1 \times X_2 \times X_3.
\]

3.1. A scalar eigenvalues problem. We need to introduce more notations. Given functions \( m, b \in C^0(\Omega), b > 0, a \in C^1(\Omega), a \geq a_0 > 0, c_i \in C(\Gamma_i), i = 1, 2, \) consider the eigenvalue problem

\[
\begin{aligned}
-\text{div}(a(x)\nabla \varphi) + m(x)\varphi &= \lambda b(x)\varphi \quad \text{in } \Omega, \\
B\varphi &= (0, 0) \quad \text{on } \partial \Omega,
\end{aligned}
\]

(16)

where \( B \) is given by

\[
B\varphi := \begin{cases}
\frac{\partial \varphi}{\partial n} + c_1(x)\varphi & \text{on } \Gamma_1, \\
\frac{\partial \varphi}{\partial n} + c_2(x)\varphi & \text{on } \Gamma_2.
\end{cases}
\]

(17)

In the following result we state the existence of principal eigenvalue of (16) and its main properties, see [16], i.e., eigenvalues which have an associated positive eigenfunction.

**Lemma 3.1.** There exists a unique principal eigenvalue of (16), we denote it by

\[
\lambda_1(a; m; b; c_1, c_2).
\]

Moreover, this eigenvalue is simple, and any positive eigenfunction, \( \phi \), verifies \( \phi \in W^{2,p}(\Omega) \) for any \( p > 1 \). In addition, \( \lambda_1(a; m; b; c_1, c_2) \) is continuous and increasing in \( a, m, c_1 \) and \( c_2 \). Furthermore,

1. If \( \lambda_1(a; m; 1; c_1, c_2) > 0 \), then \( \lambda_1(a; m; b; c_1, c_2) \) is decreasing in \( b \).
2. If \( \lambda_1(a; m; 1; c_1, c_2) < 0 \), then \( \lambda_1(a; m; b; c_1, c_2) \) is increasing in \( b \).
3. If \( \lambda_1(a; m; 1; c_1, c_2) = 0 \), then \( \lambda_1(a; m; b; c_1, c_2) = 0 \) for all \( b \).

**Proof.** The existence of principal eigenvalue and positive eigenfunction associated to it follow by Theorem 7.7 in [16]. The monotonicity properties with respect to \( a, m, c_1 \) and \( c_2 \) follow by Propositions 8.3 and 8.4 in [16]. The continuous dependence with respect to \( a \) and \( m \) is a consequence of Corollary 8.1 in [16] and with respect to \( c_1 \) and \( c_2 \) of Theorem 8.8 in [16].

On the other hand, observe that \( \lambda_1(a; m; b; c_1, c_2) \) is the unique real zero of the map

\[
\mu(\lambda) := \lambda_1(a; m - \lambda b; 1; c_1, c_2).
\]
Since $b > 0$, $\lambda \mapsto \mu(\lambda)$ is decreasing. In addition, $\mu(0) = \lambda_1(a; m; 1; c_1, c_2) > 0$ which implies that $\lambda_1(a; m; b; c_1, c_2) > 0$. Take $b_1 \leq b_2$ in $\Omega$, since the root of $\mu$ is positive we can consider $\lambda > 0$. Then

$$\lambda_1(a; m - \lambda b_2; 1; c_1, c_2) \leq \lambda_1(a; m - \lambda b_1; 1; c_1, c_2).$$

This concludes that $\lambda_1(a; m; b; c_1, c_2) \leq \lambda_1(a; m; b_1; c_1, c_2)$.

The cases $\lambda_1(a; m; 1; c_1, c_2) < 0$ and $\lambda_1(a; m; 1; c_1, c_2) = 0$ can be treated in a similar way. $\square$

The next result will be useful in what follows.

**Lemma 3.2.** Consider sequences $m_n, a_n, b_n \in C^0(\Omega), c_i^n \in C(\Gamma_i), i = 1, 2,$ with $b_n > 0$ and such that $m_n \to m, a_n \to a \geq a_0 > 0, b_n \to 0$ in $L^\infty(\Omega)$ and $c_i^n \to c_i$ in $C(\Gamma_i)$ as $n \to \infty$ for $i = 1, 2$. Then,

$$\lambda_1(a_n; m_n; b_n; c_1^n; c_2^n) \to \left\{ \begin{array}{ll}
+\infty & \text{if } \lambda_1(a; m; 1; c_1; c_2) > 0, \\
-\infty & \text{if } \lambda_1(a; m; 1; c_1; c_2) < 0.
\end{array} \right.$$

**Proof.** By Lemma 3.1 we have that $\mu_n := \lambda_1(a_n; m_n; 1; c_1^n; c_2^n) \to \lambda_1(a; m; 1; c_1; c_2)$. Assume that $\lambda_1(a; m; 1; c_1; c_2) > 0$, then for $n \geq n_0$ we get that $\mu_n > 0$.

On the other hand, denote $\lambda_n := \lambda_1(a_n; m_n; b_n; c_1^n; c_2^n)$ or equivalently,

$$0 = \lambda_1(a_n; m_n - \lambda_n b_n; 1; c_1^n; c_2^n),$$

that is, $\lambda_n$ are the zeros of the map $0 = \lambda_1(a_n; m_n - \lambda b_n; 1; c_1^n; c_2^n)$. Since $\mu_n > 0$ and $b_n > 0$, this implies the positivity of $\lambda_n$. Assume now that some subsequence of $\lambda_n$, denoted again $\lambda_n$, is bounded, hence as $b_n \to 0$

$$0 = \lambda_1(a_n; m_n - \lambda_n b_n; 1; c_1^n; c_2^n) \to \lambda_1(a; m; 1; c_1; c_2) > 0,$$

an absurdum. Since this argument can be repeated for any subsequence of $\lambda_n$, we conclude the result. The case $\lambda_1(a; m; 1; c_1; c_2) < 0$ can be studied in a similar way. $\square$

3.2. **A system eigenvalues problem.** On the other hand, we need to study the eigenvalue problem of a cooperative system. Denote

$$L := \text{diag}(-a_1\Delta, -a_2\Delta), \quad a_i > 0, \quad M = (m_{ij})_{1 \leq i, j \leq 2}, \quad m_{ij} \leq 0, i \neq j,$$

with $m_{ij} \in C^0(\Omega)$. The positivity of vectors is to be understood component-wise. Moreover, cooperative system means that $m_{ij} \leq 0, i \neq j$.

Consider the eigenvalue problem

$$\begin{cases}
LV + M(x)V = \lambda V & \text{in } \Omega, \\
BV = 0 & \text{on } \partial \Omega,
\end{cases}$$

(18)

where

$$V = (v_1, v_2)^T, \quad BV := (B_1 v_1; B_2 v_2)^T,$$

where $B_1$ and $B_2$ are boundary operators of the form (17).

Moreover, consider $H = (h_1, h_2)^T, F = (f_1, f_2)^T, G = (g_1, g_2)^T$ with $h_1, h_2 \in C^{\rho}(\Omega), f_1, g_1 \in C^{\gamma + \rho}(\Gamma_1)$ and $f_2, g_2 \in C^{\gamma + \rho}(\Gamma_2)$, and the linear problem

$$\begin{cases}
LV + M(x)V = H(x) & \text{in } \Omega, \\
BV = (F; G) & \text{on } \partial \Omega.
\end{cases}$$

(19)

In the next result, we collect some results from [2]:
Proposition 5. 1. There exists a principal eigenvalue of (18), denoted by $\sigma_1[\mathcal{L} + M; \mathcal{B}]$. Moreover, every other eigenvalue satisfies
\[ \text{Re}(\lambda) > \sigma_1[\mathcal{L} + M; \mathcal{B}]. \] (20)

2. $\sigma_1[\mathcal{L} + M; \mathcal{B}] > 0$ if and only if there exists a strict supersolution of (18), that is, there exists a positive function $V$ such that $\mathcal{L}V + M(x)V \geq 0$ in $\Omega$ and $BV \geq 0$ on $\partial\Omega$, and some inequality is strict.

3. If $\sigma_1[\mathcal{L} + M; \mathcal{B}] > 0$, there exists a unique positive solution of (19).

4. Let $V_1$ and $V_2$ the solutions to (19) with $(H, F, G) = (H_1, F_1, G_1)$ and $(H, F, G) = (H_2, F_2, G_2)$ respectively. If $(H_1, F_1, G_1) \leq (H_2, F_2, G_2)$ and $\sigma_1[\mathcal{L} + M; \mathcal{B}] > 0$ then $V_1 \leq V_2$.

Proof. The existence of the principal eigenvalue follows by Theorems 6 and 11 in [2]. Inequality (20) is deduced from Theorem 12 in [2]. Paragraph b) is a consequence of Theorem 13. Paragraph c) follows by Theorems 8 and 13 in [2]. For the last paragraph define $Z := V_1 - V_2$ and apply the paragraph c).

3.3. The semi-trivial solutions. When $I_0 \equiv 0$, since $\gamma_3, \tau_3 > 0$ then $z = 0$ and so, since $\delta_2, \rho_2 > 0$, and then system (15) is a system of two equations analyzed previously in [9].

Then, assume that $I_0 > 0$, then there exists a unique positive solution, $z$, of the fourth equation of (15). Observe that the unique semi-trivial solution is possible when $u \equiv 0$. In this case, $V_0 := (v_A^0, v_I^0)$ verifies
\[
\begin{cases}
\mathcal{L}V_0 + M_0(x)V_0 = 0 & \text{in } \Omega, \\
BV = (\gamma(0), 0; 0, 0) & \text{on } \partial\Omega.
\end{cases}
\] (21)

where
\[
\mathcal{L} = \text{diag}(-d_{2A}\Delta, -d_{2I}\Delta), \\
M_0(x) = \begin{pmatrix} 1 + k_Fz & -k_B \\ -k_Fz & 1 + k_B \end{pmatrix}, \\
\mathcal{B} := (B_{2A}; B_{2I}).
\]

In the following result we show that there exists a unique positive solution of (21).

Lemma 3.3. 1. It holds that
\[ \sigma_1[\mathcal{L} + M_0; \mathcal{B}] > 0. \] (22)

Hence, there exists a unique positive solution of (21), denoted by $V_0 := (v_A^0, v_I^0)$.

2. Assume that $(u, v_A, v_I)$ is a coexistence state of (15), then
\[ (v_A, v_I) \leq V_0 := (v_A^0, v_I^0). \] (23)

Proof. First we prove (22). Assume that $\sigma_1[\mathcal{L} + M_0; \mathcal{B}] \leq 0$ and denote by $(\varphi_1, \varphi_2)$ a positive eigenfunction associated to it. Then, $w = d_{2A}\varphi_1 + d_{2I}\varphi_2$ verifies
\[-\Delta w + \frac{1}{D} w \leq \sigma_1[\mathcal{L} + M_0; \mathcal{B}]w, \quad \text{in } \Omega, \quad \frac{\partial w}{\partial n} < 0 \quad \text{on } \Gamma_1, \quad \frac{\partial w}{\partial n} + \rho w \leq 0 \quad \text{on } \Gamma_2,
\]
where $D := \max\{d_{2A}, d_{2I}\}$, $\rho := \min\{\gamma_2, \rho_2\}$. Since $\lambda_1(1; \frac{\gamma_1}{D}; 1; 0; \rho) > 0$, the maximum principle implies that $w \leq 0$ in $\Omega$, an absurdum.

Since $\sigma_1[\mathcal{L} + M_0; \mathcal{B}] > 0$, by Proposition 5 it follows that (21) possesses a unique positive solution denoted $V_0 := (v_A^0, v_I^0)$. Moreover, thanks to that $\gamma(u) \leq \gamma(0)$, then by paragraph d) of Proposition 5 (23) is satisfied.
3.4. **Coexistence states.** Once resolved the fourth equation, we focus on the system of the first three equations.

In order to find positive solution of (15), we are going to apply the bifurcation method to the semi-trivial solution \( (u, v, v_I) = (0, V_0) \). 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 \(\lambda\), exactly,

\[
\lambda = \lambda_1(v_A^0),
\]

where \(\lambda_1(v_A^0)\) denotes the principal eigenvalue of the problem

\[
\begin{cases}
-d_1 \Delta \xi = -\nabla \cdot (\alpha(v_A^0)\xi \nabla v_A^0) + \lambda \beta(v_A^0)\xi & \text{in } \Omega, \\
B_1 \xi = (0, 0) & \text{on } \partial \Omega.
\end{cases}
\]

(24)

First, we show the main result on a priori bounds.

**Theorem 3.4.** Assume that \(\lambda \in \Lambda\), a compact of \(\mathbb{R}\). Then, there exists a constant \(C > 0\) such that

\[
\| (u, v_A, v_I) \|_X \leq C,
\]

for each solution \((u, v_A, v_I)\) of (15).

**Proof.** First, observe that

\[
-d_2 \Lambda A + (1 + k_F v) v = k_B v_I,
\]

and so by [1, Proposition 3.3], we get for \(s > 1\) that

\[
\| v_A \|_{1,s} \leq C \| \gamma(u) \|_{L^s(\partial \Omega)} + k_B \| v_I \|_s \leq C \| \gamma(0) \|_{L^s(\partial \Omega)} + \| v_I \|_s
\]

and hence using (23)

\[
\| v_A \|_{1,s} \leq C \quad \forall s > 1.
\]

(25)

Once the previous bound (25) is obtained, we can follow exactly the proof of [9, Lemma 3.4] and conclude

\[
\| u \|_p \leq C \quad \text{and} \quad \| u \|_{1,2} \leq C
\]

(26)

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

Consider now the \(u\)-equation,

\[
-d_1 \Delta u = -\alpha(v_A) \nabla u \cdot \nabla v - (\alpha(v_A) \nabla v_A) + \lambda \beta(v_A) u - u^2 := F.
\]

Taking into account that

\[
\nabla (\alpha(v_A) \nabla v_A) = \alpha'(v_A) |\nabla v_A|^2 + \alpha(v_A) \Delta v_A,
\]

and using (25), (26) and the expression for \(\Delta v_A\), we conclude that for any \(p > 1\) that

\[
\begin{cases}
\| u \alpha'(v_A) |\nabla v_A|^2 \|_{L^p(\Omega)}, \\
\| u \alpha(v_A) \Delta v_A \|_{L^p(\Omega)}, \\
\| \lambda \beta(v_A) u - u^2 \|_{L^p(\Omega)}.
\end{cases}
\]

(27)

On the other hand, by (25) and (26), we get

\[
\alpha(v_A) \nabla u \cdot \nabla v_A \in L^j(\Omega), \quad \text{for some } j < 2 \text{ and close to } 2.
\]

(28)

Hence, we deduce from (27) and (28) that \(F \in L^j(\Omega)\) and 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 that \(\| u \|_{C^1(\overline{\Omega})} \leq C\).

To prove the bounds for \((v_A, v_I)\) in \(C^1\), we can proceed as in Theorem 3.5 in [9]. This completes the proof. \(\square\)
In the following result, we show the non-existence of coexistence states for $\lambda$ small.

**Proposition 6.** There exists $\Lambda_0 \in \mathbb{R}$ such that if (15) possesses a coexistence state, then

$$\lambda \geq \Lambda_0.$$

**Proof.** Denote

$$\Upsilon(s) = \frac{1}{d_1} \int_0^s \alpha(t) dt.$$

Under the change of variable

$$u := e^{\Upsilon(v_A)} w,$$  \hspace{1cm} (29)

the first equation of (15) transforms into

$$\begin{cases}
-d_1 \text{div}(e^{\Upsilon(v_A)} \nabla w) = e^{\Upsilon(v_A)} w (\lambda \beta(v_A) - e^{\Upsilon(v_A)} w) & \text{in } \Omega, \\
\frac{\partial w}{\partial n} + c_1 w = 0 & \text{on } \Gamma_1, \\
\frac{\partial w}{\partial n} + c_2 w = 0 & \text{on } \Gamma_2,
\end{cases} \hspace{1cm} (30)$$

where

$$c_1 := \gamma_1 + \frac{\alpha(v_A)}{d_1} \gamma(e^{\Upsilon(v_A)} w), \quad c_2 := -\tau_1 - \frac{\tau_2}{d_1} v_A \alpha(v_A).$$

On the other hand, by (23), we obtain

$$0 < \beta(v_A)e^{\Upsilon(v_A)} \leq \beta(v_A^0)e^{\Upsilon(v_A^0)}, \quad v_A \alpha(v_A) \leq v_A^0 \alpha \| \alpha \|_{\infty}. \hspace{1cm} (31)$$

Hence, if $u$ is positive, then $w$ is positive and we can conclude from (30), Lemma 3.1 and (31) that

$$\lambda = \lambda_1(d_1 e^{\Upsilon(v_A)}; e^{2\Upsilon(v_A)} w; \beta(v_A)e^{\Upsilon(v_A)}; c_1; c_2) \geq \lambda_1(d_1; 0; \beta(v_A)e^{\Upsilon(v_A)}; \gamma_1; -\tau_1 - \frac{\tau_2}{d_1} v_A^0 \| \alpha \|_{\infty}).$$

Hence, if $\lambda_1(d_1; 0; 1; \gamma_1; -\tau_1 - \frac{\tau_2}{d_1} v_A^0 \| \alpha \|_{\infty}) > 0$, by Lemma 3.1 we have that

$$\lambda \geq \lambda_1(d_1; 0; \beta(v_A^0)e^{\Upsilon(v_A^0)}; \gamma_1; -\tau_1 - \frac{\tau_2}{d_1} v_A^0 \| \alpha \|_{\infty}) =: \Lambda_0;$$

if $\lambda_1(d_1; 0; 1; \gamma_1; -\tau_1 - \frac{\tau_2}{d_1} v_A^0 \| \alpha \|_{\infty}) = 0$, then

$$\lambda \geq \lambda_1(d_1; 0; \beta(v_A^0)e^{\Upsilon(v_A^0)}; \gamma_1; -\tau_1 - \frac{\tau_2}{d_1} v_A^0 \| \alpha \|_{\infty}) = 0 =: \Lambda_0.$$  

Finally, we consider the case $\lambda_1(d_1; 0; 1; \gamma_1; -\tau_1 - \frac{\tau_2}{d_1} v_A^0 \| \alpha \|_{\infty}) < 0$. Take $\lambda \leq 0$. Then, with a similar argument to the one used in the proof of Lemma 3.4 of [9], we can show that

$$\| u \|_{\infty} \leq C, \quad \text{with } C \text{ independent of } \lambda \leq 0. \hspace{1cm} (32)$$

Consider now the system

$$\begin{cases}
\mathcal{L} V + M_0(x) V = 0 & \text{in } \Omega, \\
B V = (\gamma(C), 0; 0, 0) & \text{on } \partial \Omega.
\end{cases} \hspace{1cm} (33)$$

Since $\gamma$ is decreasing, then $\gamma(u) \geq \gamma(C)$, and then by paragraph d) of Proposition 5 there exists a unique positive solution $V^* = (v^*_A, v^*_I)$ of (33) such that

$$V^* = (v^*_A, v^*_I) \leq (v_A, v_I). \hspace{1cm} (34)$$
From (34), we conclude that
\[ 0 < \beta(v^*_A) \leq \beta(v_A)e^{\tau(v_A)}, \]
and thus
\[ \lambda \geq \lambda_1(d_1; 0; \beta(v_A)e^{\tau(v_A)}; \gamma_1; -\tau_1 - \frac{d_1}{d_1}v^0_A\|\alpha\|_\infty) \]
\[ \geq \lambda_1(d_1; 0; \beta(v^*_A); \gamma_1; -\tau_1 - \frac{d_1}{d_1}v^0_A\|\alpha\|_\infty) := \Lambda_0. \]
This completes the proof. \( \square \)

Remark 4. Note that a similar change to (29), specifically,
\[ \xi := e^{\tau(v^*_A)}\zeta, \] transforms (24) into another eigenvalue problem, and so
\[ \lambda_1(v^0_A) = \lambda_1(d_1e^{\tau(v^*_A)}; 0; \beta(v^0_A)e^{\tau(v^0_A)}; c_1; c_2). \] (36)
where
\[ c_1 := \gamma_1 + \alpha(v^0_A)\frac{\gamma(0)}{d_1}, \quad c_2 := -\tau_1 - \frac{d_1}{d_1}v^0_A\alpha(v^0_A). \]

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

**Theorem 3.5.** Assume that
\[ \lambda > \lambda_1(v^0_A). \] (37)
Then, (15) possesses at least one positive solution.

**Proof.** We are going to apply the bifurcation method. We consider \( \lambda \) as bifurcation parameter. First, we apply the Crandall-Rabinowitz theorem, [7], in order to find the bifurcation point from the semi-trivial solution \((0, V_0)\). Consider the map
\[ \mathcal{F} : \mathbb{R} \times X_1 \times X_2 \times X_3 \mapsto C^\rho(\Omega) \times C^\rho(\Omega) \times C^\rho(\Omega) \times C^\rho(\Gamma_1) \]
defined by
\[ \mathcal{F}(\lambda, u, v_A, v_I) := \begin{pmatrix} -d_1\Delta u + \nabla \cdot (\alpha(u_A)u\nabla v_A) - \lambda\beta(u_A)u + u^2, \\ -d_2\Delta v_A + v_A + k_F v_A z - k_B v_I, \\ -d_2\Delta v_I + v_I - k_F v_A z + k_B v_I, \\ \frac{\partial v_A}{\partial n} - \gamma(u) \end{pmatrix}. \]
It is clear that \( \mathcal{F} \) is regular, that \( \mathcal{F}(\lambda, 0, 0) = 0 \) and
\[ D_{(u,V)}\mathcal{F}(\lambda_0, 0, v^0_A, v^0_I) \begin{pmatrix} \xi \\ \eta \\ \varphi \end{pmatrix} = \begin{pmatrix} -d_1\Delta \xi + \nabla \cdot (\alpha(v^0_A)\xi\nabla v^0_A) - \lambda\beta(v^0_A)\xi \\ -d_2\Delta \eta + (1 + k_F z)\eta - k_B \varphi \\ -d_2\Delta \varphi + (1 + k_B)\varphi - k_F z A \eta \\ \frac{\partial \eta}{\partial n} - \gamma'(0)\xi \end{pmatrix}. \]
Hence, for \( \lambda = \lambda_0 := \lambda_1(v^0_A) \), we get that
\[ \text{Ker}[D_{(u,V)}\mathcal{F}(\lambda_0, 0, v^0_A, v^0_I)] = \text{span}\{(\Phi_1, \Phi_2, \Phi_3)\} \]
where \( \Phi_1 \) is an eigenfunction of the eigenvalue problem (24) associated to \( \lambda_0 \) and
\[ L(\Phi_2, \Phi_3) + M_0(\Phi_2, \Phi_3) = (0, 0) \text{ in } \Omega, \quad (B_{2A}, B_{2I})(\Phi_2, \Phi_3) = (\gamma'(0)\Phi_1, 0) \text{ on } \partial\Omega. \]
Since \( \sigma_1[L + M_0, B] > 0 \) there exists a unique \((\Phi_2, \Phi_3)\) solution of the above equation. Hence, \( \text{dim}(\text{Ker}[D_{(u,V)}\mathcal{F}(\lambda_0, 0, v^0_A, v^0_I)]) = 1. \)
On the other hand, observe that

\[
D_{\lambda(u,V)}\mathcal{F}(\lambda_0, 0, V_0) \begin{pmatrix} \xi \\ \eta \\ \varphi \end{pmatrix} = \begin{pmatrix} -\beta(v^0_A)\xi \\ 0 \\ 0 \\ 0 \end{pmatrix}.
\]

We can show that \(D_{\lambda(u,V)}\mathcal{F}(\lambda_0, 0, V_0)(\Phi_1, \Phi_2, \Phi_3) \notin R(D_{(u,V)}\mathcal{F}(\lambda_0, 0, V_0))\). Indeed, suppose that there exists \((\xi, \eta, \varphi) \in X\) such that

\[
D_{(u,V)}\mathcal{F}(\lambda_0, 0, V_0)(\xi, \eta, \varphi)^T = (-\beta(v^0_0)\Phi_1, 0, 0, 0),
\]

and so

\[ -d_1\Delta\xi + \nabla \cdot (\alpha(v^0_A)\xi\nabla v^0_A) - \lambda_0\beta(v^0_A)\xi = -\beta(v^0_A)\Phi_1 \quad \text{in} \quad \Omega, \quad B_1\xi = (0, 0) \quad \text{on} \quad \partial\Omega. \]

Define \(\Phi^*_1\) as an adjoint positive eigenfunction of the eigenvalue problem (24) associated to \(\lambda_0\), then multiplying and integrating, we get that

\[ 0 = \int_{\Omega} \beta(v^0_A)\Phi_1\Phi^*_1, \]

an absurdum due to the positivity of \(\Phi_1\) and \(\Phi^*_1\). Similarly, it can be shown that \(R(D_{(u,V)}\mathcal{F}(\lambda_0, 0, V_0))\) has co-dimension 1.

Hence, from Theorem 1.7 in [7], the point \((\lambda, u, V) = (\lambda_0, 0, V_0)\) is a bifurcation point from the semi-trivial solution \((0, V_0)\).

Now, we apply the bifurcation method for elliptic systems. We summarize briefly its application. Denote by \(C^+\) the component (maximal continuum for the inclusion) of solutions of (15) emanating from the point \((\lambda, u, V) = (\lambda_0, 0, V_0)\) such that \(C^+ \subset \mathbb{R} \times \text{int}(P_X)\), where \(P_X\) is the positive cone of the space \(X\). This component has two possibilities:

i) \(C^+\) is unbounded in \(\mathbb{R} \times X\); or

ii) \(C^+\) is bounded in \(\mathbb{R} \times X\).

We are going to show that we can discard alternative ii). Assume that \(C^+\) is bounded in \(\mathbb{R} \times X\). Since \(C^+ \subset \mathbb{R} \times \text{int}(P_X)\) and it is maximal for the inclusion, there exists (see Theorem 4.1 of [14] and Theorem 7.2.2 in [15]) a sequence \((\lambda_n, u_n, V_n) \in C^+\) such that

\[ \lim_{n \to +\infty} (\lambda_n, u_n, V_n) = (\lambda^*, u^*, V^*) = (\lambda^*, u^*, v^*_A, v^*_I) \quad \text{in} \quad \mathbb{R} \times X \]

with \((\lambda^*, u^*, V^*) \in C^+ \cap (\mathbb{R} \times \partial(P_X))\). Thanks to the strong maximum principle either \(u^*_n = 0\), or \(v^*_A = 0\) or \(v^*_I = 0\). Due to the equation that \(v_A\) verifies, the corresponding boundary conditions, and \(\gamma(0) > 0\), it is not possible that \(v^*_A = 0\).

If \(v^*_I = 0\), then by the \(v_I\)-equation we deduce that \(v^*_A = 0\), again a contradiction. Finally, if \(u^*_n = 0\), then \(V^* = V_0\). Taking in this case

\[ U_n = \frac{u_n}{\|u_n\|_{\infty}}, \]

observe that \(U_n\) verifies

\[ -d_1\Delta U_n = -\nabla \cdot (\alpha(v^0_A)u_n\nabla v^0_A) + \lambda_0\beta(v^0_A)u_n = u_n\text{ in } \Omega, \quad B_1\|u_n\|_{\infty} = 0 \quad \text{on} \quad \partial\Omega, \]

where we have denoted \(V_n = ((v^0_A)_{n})\). By elliptic regularity and taking into account that \(\nabla v^0_A \rightarrow \nabla v^*_A = 0 = (v^0_I, v^*_I) \text{ in } X_2 \times X_3\), we conclude that \(U_n \rightarrow U^* \geq 0\) in \(C^1(\bar{\Omega})\) with \(U^* \neq 0\) because \(\|U_n\|_{\infty} = 1\) and \(U^*\) verifies

\[ -d_1\Delta U^* = -\nabla \cdot (\alpha(v^0_A)U^*\nabla v^0_A) + \lambda^*\beta(v^0_A)U^* \quad \text{in} \quad \Omega, \quad B_1U^* = 0 \quad \text{on} \quad \partial\Omega. \]
Hence, by the strong maximum principle it follows that $U^* > 0$ in $\Omega$. Then, $\lambda^*$ is an eigenvalue of (24) with a positive eigenfunction associated to it, that is $\lambda^* = \lambda_0$, again a contradiction because the point $(\lambda_0, 0, V_0)$ is the unique bifurcation point from $(0, V_0)$.

Then, alternative ii) is not possible and alternative i) holds. On the other hand, by Proposition 6, (15) does not possess positive solutions for $\lambda \leq \lambda_0$ and by Theorem 3.4, it follows that $C^+$ is bounded in $X$ uniformly on compact intervals of $\lambda$. Hence, we can conclude the existence of at least one coexistence state for $\lambda > \lambda_1(v^0_A)$.

This completes the proof. \hfill $\square$

Condition (37) is related to the local stability of $(0, V_0)$ with respect to the parabolic problem.

**Proposition 7.** If $\lambda < \lambda_1(v^0_A)$ (resp. $\lambda > \lambda_1(v^0_A)$), 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 $(\xi, \eta, \varphi) \in X \setminus \{(0, 0, 0)\}$

\[
\begin{cases}
-d_1 \Delta \xi + \nabla \cdot (\alpha(v^0_A)\xi \nabla v^0_A) - \lambda \beta(v^0_A)\xi = \sigma \xi & \text{in } \Omega, \\
\left(\begin{array}{cc}
-d_2 A \Delta & 0 \\
0 & -d_2 I \Delta
\end{array}\right) \left(\begin{array}{c}
\eta \\
\varphi
\end{array}\right) + M_0(x) \left(\begin{array}{c}
\eta \\
\varphi
\end{array}\right) = \sigma \left(\begin{array}{c}
\eta \\
\varphi
\end{array}\right) & \text{in } \Omega, \\
B_1 \xi = (0, 0) & \text{on } \partial \Omega, \\
B_2 A \eta = (\gamma'(0)\xi, 0) & \text{on } \partial \Omega, \\
B_2 \varphi = (0, 0) & \text{on } \partial \Omega.
\end{cases}
\]

Let $\lambda < \lambda_1(v^0_A)$. Assume that $\xi \equiv 0$, then $\text{Re}(\sigma) = \text{Re}(\sigma_j[\mathcal{L} + M_0, \mathcal{B}]) > \sigma_j[\mathcal{L} + M_0, \mathcal{B}] > 0$, where $\sigma$ is an eigenvalue of (38) and $\sigma_j[\mathcal{L} + M_0, \mathcal{B}]$ is some eigenvalue of (18) for $M = M_0$ and boundary conditions $\mathcal{B}V = 0$.

Suppose that $\xi \not\equiv 0$, denote by

$$\mathcal{A}\xi := -d_1 \Delta \xi + \nabla \cdot (\alpha(v^0_A)\xi \nabla v^0_A),$$

then

$$\text{Re} \left(\sigma\right) = \text{Re} \left(\lambda_j(\mathcal{A} - \lambda \beta(v^0_A), B_1)\right) \geq \lambda_1(\mathcal{A} - \lambda \beta(v^0_A), B_1) > 0$$

because $\lambda < \lambda_1(v^0_A)$.

Assume now that $\lambda > \lambda_1(v^0_A)$. Then,

$$\sigma_1 := \lambda_1(\mathcal{A} - \lambda \beta(v^0_A), B_1) < 0.$$

Denote by $\xi$ a positive eigenfunction associated to $\sigma_1$, that is

$$\mathcal{A}\xi - \lambda \beta(v^0_A)\xi = \sigma_1 \xi \quad \text{in } \Omega, \quad B_1 \xi = (0, 0) \quad \text{on } \partial \Omega.$$

Since $\sigma_1 < 0$, then by (22)

$$\sigma_1(\mathcal{L} + M_0 - \sigma_1 I: \mathcal{B}) > 0,$$

and so there exists $(\eta, \varphi)$ such that

$$\mathcal{L}(\eta, \varphi) + M_0(x)(\eta, \varphi) = \sigma_1(\eta, \varphi) \quad \text{in } \Omega, \quad \mathcal{B}(\eta, \varphi) = (\gamma'(0)\xi, 0, 0, 0) \quad \text{on } \partial \Omega.$$

Then, $\sigma_1 < 0$ is an eigenvalue of (38) with associated eigenfunction $(\xi, \eta, \varphi)$, so $(0, V_0)$ is unstable. \hfill $\square$
From the above results, it is evident that a study of the map $\lambda_1(v_A^0)$ is necessary. For that, we consider the specific case $I_0$ a positive constant.

In this case,

$$z := I_0e,$$

where $e$ is the unique positive solution of

$$-d_3\Delta e + e = 1 \quad \text{in } \Omega, \quad B_3e = (0, 0) \quad \text{on } \partial\Omega.$$

To study the map $I_0 \mapsto \lambda_1(v_A^0)$ we are going to use the expression (36). In fact, we will analyse the behaviour for $I_0 = 0$ and $I_0$ large.

Observe that for $I_0 = 0$, then $z \equiv 0$ and going back to (21) we obtain that $v_I^0 \equiv 0$. Then, in this case, $v_A^0$ is the unique positive solution of

$$-d_2A\Delta v_A^0 + v_A^0 = 0 \quad \text{in } \Omega, \quad B_2Av_A^0 = (\gamma(0), 0) \quad \text{on } \partial\Omega. \quad (40)$$

Now, we study the behaviour when $I_0 \to \infty$. For that, we first prove the following result:

**Proposition 8.** We have that

$$v_A^0 \to 0 \quad \text{in } L^\infty(\Omega) \text{ as } I_0 \to \infty. \quad (41)$$

**Proof.** First, we show that $v_A^0$ and $v_I^0$ are bounded. Indeed, denote by

$$v := d_2Av_A^0 + d_2Iv_I^0,$$

then

$$v \leq w_{max} \quad (42)$$

where $w_{max}$ stands for the unique positive solutions of

$$-\Delta w + \frac{1}{D}w = 0 \quad \text{in } \Omega, \quad \frac{\partial w}{\partial n} = \gamma(0)d_2A \quad \text{on } \Gamma_1, \quad \frac{\partial w}{\partial n} = 0 \quad \text{on } \Gamma_2,$$

with $D = \max\{d_2A, d_2I\}$.

Hence,

$$-d_2A\Delta v_A^0 + (1 + K_I I_0 e)v_A^0 = k_B v_I^0 \leq k_B w_{max} := f(x).$$

Now, we claim that the unique solution $v$ of the equation

$$\begin{equation}
\begin{cases}
-d_2A\Delta v + (1 + k_F I_0 e)v = f(x) & \text{in } \Omega, \\
\frac{\partial v}{\partial n} = \gamma(0) & \text{on } \Gamma_1, \\
\frac{\partial v}{\partial n} + \tau_2v = 0 & \text{on } \Gamma_2,
\end{cases}
\end{equation} \quad (43)$$

verifies

$$v(x) \leq CI_0^{-1/2} \quad \text{for } I_0 \text{ large.} \quad (44)$$

It is evident that (41) follows by (44) because $v_A^0 \leq v$. So, it suffices to show (44). For that, we use the blow-up argument as in [11]. Assume that (44) does not hold. Then there exist sequences $(I_0)_n \not\to \infty$, and $v_n \in C^{2,\alpha}(\Omega)$ solutions to (43) with $I_0 = (I_0)_n$ such that

$$(I_0)^{1/2}_n M_n \not\to \infty, \quad (45)$$
where $M_n$ stands for the maximum of $v_n$. Take a point $x_n \in \Omega$ where $v_n$ attains its maximum and assume with no loss of generality that $x_n \to x_0 \in \Omega$. We need to distinguish two cases: $x_0 \in \Omega$ or $x_0 \in \partial \Omega$.

**Case 1.** $x_0 \in \Omega$. Introduce the scaled functions
\[
    w_n(y) = \frac{v_n(x_n + (I_0)_n^{-1/2}y)}{M_n},
\]
which verify $w_n(0) = 1$, $0 \leq w_n \leq 1$ and
\[
    -d_{2A}\Delta w_n = -\frac{1 + k_F(I_0)_n c(x_n + (I_0)_n^{-1/2}y)}{(I_0)_n} w_n + \frac{f(x_n + (I_0)_n^{-1/2}y)}{M_n(I_0)_n}
\]
in $\Omega_n$, where $\Omega_n = (I_0)_n^{1/2}(-x_n + \Omega)$.

Given $R > 0$, there exists $n_0 \in \mathbb{N}$ such that $x_n + (I_0)_n^{-1/2}y \in \Omega$ for $n \geq n_0$ and for $y \in B(0, R)$. Hence, $w_n$ is bounded in $W^{2,p}(B(0, R))$ for all $p > 1$. Hence, we can infer that $w_n \to w$ in $C^1(\Omega)$ and
\[
    -d_{2A}\Delta w = -k_F c(x_0) w \quad \text{in } B(0, R)
\]
with $0 \leq w \leq 1$, $w(0) = 1$, which is impossible by the maximum principle.

**Case 2.** $x_0 \in \Gamma_1$. Under a new change of variable we can assume that a neighborhood of $x_0$ in $\Gamma_1$ is in the hyperplane $x^N = 0$ and that $\Omega$ is in $H := \{x \in \mathbb{R}^N : x^N > 0\}$. Then, given $R > 0$ for $n \geq n_0$, $w_n$ is defined in
\[
    H_{R,n} := B(0, R) \cap \left\{ y^N > \frac{x_n^N}{(I_0)_n^{1/2}} \right\}.
\]
Observe that since $x_n^N$ is bounded, we have $\frac{x_n^N}{(I_0)_n^{1/2}} \to 0$, thus, the set $H_{R,n}$ is approximating $B(0, R) \cap H$ as $n \to \infty$. In this case, $w_n$ verifies
\[
    \begin{cases}
    -d_{2A}\Delta w_n = -\frac{1 + k_F(I_0)_n c(x_n + (I_0)_n^{-1/2}y)}{(I_0)_n} w_n + \frac{f(x_n + (I_0)_n^{-1/2}y)}{M_n(I_0)_n} & \text{in } H \cap B_R, \\
    \frac{\partial w_n}{\partial n} = \frac{\gamma(0)}{M_n(I_0)_n^{1/2}} & \text{in } \partial H \cap B_R.
    \end{cases}
\]
Hence, we can pass to the limit and conclude the existence of a function $w \in C^2(\overline{H})$, where $w$ is a solution to
\[
    \begin{cases}
    -d_{2A}\Delta w = -k_F c(x_\infty) w & \text{in } H, \\
    \frac{\partial w}{\partial n} = 0 & \text{on } \partial H,
    \end{cases}
\]
with $0 \leq w \leq 1$, $w(0) = 1$. Applying the reflection principle we have that $w \in C^2(\overline{H})$, $w(0) = 1$ and $w$ solution to $-\Delta w = -k_F c(x_\infty) w$ in $\mathbb{R}^N$, a contradiction.

**Case 3.** Assume that $x_0 \in \Gamma_2$. In this case, we can proceed exactly as in Case 2, except that the boundary condition is
\[
    \frac{\partial w_n}{\partial n} = \frac{1}{M_n(I_0)_n^{1/2}} - \frac{w_n}{(I_0)_n^{1/2}}.
\]
In this case, also the limit is
\[
    \frac{\partial w}{\partial n} = 0.
\]
Proposition 9. Assume that $I_0 \geq 0$ is a non-negative constant and denote by

$$\lambda_1(I_0) := \lambda_1(v_A^0).$$

Then:

1. The map $I_0 \in [0, +\infty) \mapsto \lambda_1(I_0)$ is a regular map.
2. We have that $\lambda_1(0) = \lambda_1(v_A^0)$, where $v_A^0$ is the unique positive solution of (40).
3. Denote by $\lambda_\infty := \lambda_1(d_1; 0; 1; \frac{1}{d_1}a(0)\gamma(0); -\tau_1).$

We have that

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

Proof. Paragraph a) follows by the regularity of the eigenvalue. Using Proposition 8, $\beta(0) = 0$ and Lemma 3.2 we can conclude paragraph c).

4. Interpretation of the main results. In this section, we would like to give a biological interpretation to the main analytical results of the work. As we are interested in the process of angiogenesis and the therapy considered in the model, we study whether the variable $u$ goes to 0 or not as the time goes to infinity. In the first case, the EC disappears and we say that the therapy is successful. In the second one, the angiogenesis process occurs. To know if $u$ goes to zero, we analyse the stability of semi-trivial solution $(u, v) = (0, V_0)$. Recall that by Proposition 7, $(0, V_0)$ is stable (i.e. the therapy is successful) if $\lambda < \lambda_1(I_0)$ and $(0, V_0)$ is unstable (i.e. angiogenesis occurs) if $\lambda > \lambda_1(I_0)$. Hence, the stability of this solution depends on the relative position of $\lambda$ and $\lambda_1(I_0)$, which in turn depends on the sign of $\lambda_\infty$. We distinguish two cases:

1. Case 1: small growth rate of EC. Assume that $\lambda$ is small, that is $\lambda < \lambda_1(0)$. In this case, the angiogenesis does no occur and it is not necessary to introduce the medicine.

2. Case 2: large growth rate of EC. Assume that $\lambda$ is large, that is $\lambda > \lambda_1(0)$ and let us introduce medicine, that is $I_0 > 0$. Now, $(0, V_0)$ is stable if $\lambda < \lambda_1(I_0)$. We have studied this map in Proposition 9. We distinguish two cases:

   a) Assume that $\lambda_\infty > 0$. Then, $\lambda_1(I_0) \to \infty$ as $I_0 \to \infty$. Hence, in this case there exists a value of $I_1 > 0$ such that for $I_0 > I_1$ we have that $\lambda < \lambda_1(I_0)$.

   That means that introducing a sufficient quantity of medicine, $I_0 > I_1$, 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 be avoided even introducing a great quantity of medicine. Observe that the sign of $\lambda_\infty$ depends on the domain $\Omega$, and on the parameters $d_1, \gamma_1, a(0), \gamma(0)$ and $\tau_1$. For example, $\lambda_\infty < 0$ if $\tau_1$ is large, that is, if the number of EC which are introducing themselves themselves along $\Gamma_2$ is large, hence, even introducing a lot of medicine we can not eliminate the ECs.

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