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Existence of solutions to a strongly coupled degenerated system arising in tumor modeling

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R.I. N^0 617 *Juin 2007*

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L. Hadjadj[*], K. Hamdache[†] and D. Hamroun[‡]

Abstract

In this work a mathematical modeling framework is presented to describe the growth of a vascular tumor.The resulting system of equations is reduced to a strongly 2×2 coupled parabolic system of degenerate type in a growing domain. For simplicity we suppose that there is internal conservation of mass and we present conditions on the boundary data which guarantee that the domain occupied by the tumor becomes constant. Then we prove existence of a global weak solution with finite entropy for the resulting system by using a time discrete scheme.

Key words: strongly degenerate parabolic system, global existence, time discretization, tumor modeling
Mathematics subject classification (MSC 2000): 35K 65, 49M 25, 00A 71

1 Introduction

This paper is concerned with the derivation and the discussion of global existence of solutions to the following system of PDE's which describes the growth of a vascular tumor in $(0,\infty)\times(0,l)$

$$\begin{cases} \alpha_t - \dfrac{1}{d}\Big(\left(2\lambda\alpha\left(1-\alpha\right) - \mu\theta\alpha\beta^2 + P_0\alpha\right)\alpha_x + \left(-2\mu\beta\alpha\left(1+\theta\alpha\right) + P_0\alpha\right)\beta_x\Big)_x = q_1 \\ \beta_t - \dfrac{1}{d}\Big(\left(-2\lambda\alpha\beta + \mu\theta\beta^2\left(1-\beta\right) + P_0\beta\right)\alpha_x + \left(2\mu\beta\left(1-\beta\right)\left(1+\theta\alpha\right) + P_0\beta\right)\beta_x\Big)_x = q_2. \end{cases} \tag{1}$$

$d, \lambda, \mu, \theta, P_0$ are positive constants and the source terms have the following model form

$$q_1 = q_1(\alpha,\beta) = k_1\alpha(1-\alpha-\beta) - k_2\alpha - k_3\alpha\left(\alpha+\beta\right) - k_4\alpha\beta$$

$$q_2 = q_2(\alpha,\beta) = k_5\beta + k_6\beta^2 - k_7\beta\left(1-\alpha\right) - k_8\alpha\beta$$

with $k_i \geq 0$, $i = 1,...,8$. We supplement the above system with the boundary conditions

$$\alpha(.,0) = \alpha^1 \ , \ \beta(.,0) = \beta^1 \text{ and } \alpha_x(.,l) = \beta_x(.,l) = 0 \tag{2}$$

and the initial data

$$\alpha(0,.) = \alpha_0 \ , \ \beta(0,.) = \beta_0. \tag{3}$$

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In (1)-(3) α and β are nonnegative functions which represent volume fractions of tumor cells and macrophages respectively, satisfying the constraint condition $\alpha + \beta \leq 1$.

We refer to the appendices, see section 6, for the derivation of the above system in a more general case. The theory of mixtures is used to develop a mathematical model that governs the interactions of macrophages, tumor cells and blood vessels within a vascular tumor, focusing on the ability of macrophages to both lyse tumor cells and stimulate angiogenesis. For more details and explanations, refer to [2], [3], [6] and [14] for example. In recent years a variety of macroscopic continuum models have been derived by using the theory of mixtures or multi-phase flows. The basic principle of the mixture theory is the principle of co-occupancy: "at each point of the space which is occupied by the mixture, there are at any time simultaneously particles belonging to each of the constituents". Therefore, within the context of an appropriate homogenization, each of the constituents can be viewed as a single continuum of its own right. The assumption of co-occupancy leads to the concept of volume fraction, then we write down conservation of mass and momentum equations which are very similar to the microscopic ones. Byrne and Preziosi in [7] used the mixture theory to develop a two-phase model of an avascular tumor, the feature of the model included the dependence of the cell proliferation rate on the cellular stress. The resulting model comprises two nonlinear parabolic equations and an integro-differential equation for the tumor boundary, the cellular diffusion being governed by drag and cell-cell interactions, see also [2], [14], [6], [3] and [18].

Throughout this paper we use the following notations: let l, T, τ and ε be positive real numbers, we will denote the interval $(0, l)$ by Ω and set $Q_T = (0, T) \times \Omega$ and $s^+ = \max(s, 0)$ the positive part of the real number s. We write $u_x := \partial_x u$, $u_t := \partial_t u$ for partial derivatives of a real-valued function $u = u(t, x)$. Moreover we will use the Sobolev space $H^1_D(\Omega) = \{u \in H^1(\Omega); u(0) = 0\}$ equipped with the norm of H^1, $(H^1)'$ the dual of H^1 and note down once for all, that the different constants (independent of τ and ε) will be denoted by the same letter C.

The problem (1)-(3) has to be solved in $(0, \infty) \times \Omega$. It is strongly coupled with full diffusion matrix:

$$A(\alpha, \beta) = \frac{1}{d} \begin{pmatrix} 2\lambda\alpha\,(1-\alpha) - \mu\theta\alpha\beta^2 + P_0\alpha & -2\mu\beta\alpha\,(1+\theta\alpha) + P_0\alpha \\ -2\lambda\alpha\beta + \mu\theta\beta^2\,(1-\beta) + P_0\beta & 2\mu\beta\,(1-\beta)\,(1+\theta\alpha) + P_0\beta \end{pmatrix}$$

which is generally not positive definite.

Nonlinear problems with full diffusion matrix are difficult to study. To our knowledge, the local or global existence theory of such strongly coupled degenerate parabolic systems is not established and the comparison principle no longer holds generally. In recent years cross-diffusion systems have drawn a great deal attention, but up to now only partial results are available in the literature concerning the well-posedness of such problems. For example, in [1], Amann considered a large class of strongly coupled parabolic systems and established local existence and uniqueness results. In [15], the global existence was established, as well as the existence of a global attractor, but in a case of triangular positive definite diffusion matrix. In [16], the well-posedness and the properties of steady states for a degenerate parabolic system with triangular positive (semi) definite matrix, modeling the chemotaxis movement of cells, were investigated. In [8], [9], [10], [12] and [13] the existence of global weak solution was shown for a nonlinear problem with full diffusion matrix. The proof was based on a symmetrization of the problem via an exponential transformation of variables, backward Euler approximation of the time derivative and an entropy functional. Here we use the same arguments but in our case, after the transformation of variables the resulting matrix B is not positive definite. To overcome this difficulty, we approximate B by positive definite matrices $\mathbf{D}^{\varepsilon}$ which tend to B as $\varepsilon \to 0$ if the condition $0 \le \alpha, \beta, \alpha+\beta \le 1$ is satisfied. This needs to prove that the set $\{(\alpha,\beta) \in L^{\infty}(\Omega) \times L^{\infty}(\Omega),\ 0 \le \alpha, \beta, \alpha+\beta \le 1\}$ is time invariant and this question cannot easily be solved. Comparatively, note that in [8], only the nonnegativity of solutions was required.

The remainder of this paper is organized as follows. In the next section we set the precise hypothesis, introduce the weak formulation of the problem and state our main existence result. In section 3, we define and solve an auxiliary elliptic problem which will be useful further. In section 4, we formulate a semi-discrete version in time of problem (6) using a backward Euler approximation. We obtain a recursive sequence of elliptic problems and prove uniform estimates with respect to the parameter τ of time discretization. In section 5, the limit $\tau \to 0$ is performed with help of Aubin compactness lemma and the Sobolev embedding $H^1(\Omega) \hookrightarrow L^{\infty}(\Omega)$ which is valid only in one space dimension. The first part of section 6 is devoted to the proof of a technical lemma and we develop in the second one following [2], [3], [6] and [14], a three-phase model describing vascular tumor growth using the theory of mixtures.

2 Assumptions and main result

The following assumptions will be used

(**A1**) we suppose that $\lambda = \mu = P_0$, $\theta = 0$ and set without loss of generality $\dfrac{2\lambda}{d} = 1$

(**A2**) $k_5 = 0$ and $k_7 \le k_6$

(**A3**) $\alpha_0, \beta_0 \in L^{\infty}(\Omega)$ such that $0 < \alpha_0, \beta_0, \alpha_0 + \beta_0 \le 1$

(**A4**) $\alpha^1, \beta^1 \in \mathbb{R}$ such that $0 < \alpha^1, \beta^1, \alpha^1 + \beta^1 \le 1$.

Under the above assumptions the problem (1)-(3) becomes strongly coupled with the full diffusion matrix

$$A(\alpha,\beta) = \begin{pmatrix} \alpha(\frac{3}{2} - \alpha) & \alpha(\frac{1}{2} - \beta) \\ \beta(\frac{1}{2} - \alpha) & \beta(\frac{3}{2} - \beta) \end{pmatrix}$$

The matrix A is not positive even if $0 \le \alpha, \beta, \alpha+\beta \le 1$. Therefore the problem (1)-(3) in general, has no classical solution. A weak solution is defined as follows

Definition 1 *Let* $(\mathbf{A1}) - (\mathbf{A4})$ *be satisfied. A couple of functions* (α, β) *is said to be a weak solution of problem (1)-(3) on* Q_T *if*

1. $\alpha, \beta \in L^{\infty}(Q_T)$ *with* $0 \le \alpha, \beta, \alpha+\beta \le 1$
2. $\alpha, \beta \in H^1(0,T;(H^1(\Omega))') \cap L^2(0,T;H^1(\Omega))$
3. $\alpha(0,x) = \alpha_0(x)$, $\beta(0,x) = \beta_0(x)$ *a.e. in* Ω
4. $\alpha(t,0) = \alpha^1, \beta(t,0) = \beta^1$ *a.e. in* $(0,T)$
5. α, β *satisfy the identities*

$$\int_0^T \langle \alpha_t, \varphi \rangle \, dt + \int_{Q_T} \Big(\alpha(\frac{3}{2} - \alpha)\alpha_x + \alpha(\frac{1}{2} - \beta)\beta_x \Big) \varphi_x dx dt = \int_{Q_T} q_1(\alpha,\beta) \varphi dx dt$$

$$\int_0^T \langle \beta_t, \psi\rangle \, dt + \int_{Q_T} \Big(\beta(\frac{1}{2} - \alpha)\alpha_x + \beta(\frac{3}{2} - \beta)\beta_x\Big)\psi_x dxdt = \int_{Q_T} q_2(\alpha,\beta)\psi dxdt$$

for every $\varphi, \psi \in L^2(0,T; H^1_D(\Omega))$ where $\langle , \rangle$ is the dual product between $(H^1(\Omega))'$ and $H^1(\Omega)$.

Our main result is the following

Theorem 1 *If assumptions* $(\mathbf{A1}) - (\mathbf{A4})$ *are satisfied, then for every fixed $T > 0$, there exists (at least) a weak solution (α,β) to the system (1)-(3). Moreover (α,β)satisfies*

$$\int_\Omega (G_1(\alpha(t,.)) + G_2(\beta(t,.)))\, dx + \frac{1}{4}\int_0^t \int_\Omega \left(|\alpha_x|^2 + |\beta_x|^2\right) dxds \leq \int_\Omega (G_1(\alpha_0) + G_2(\beta_0))\, dx + C$$

where $C > 0$ depends on T, α^1, β^1, $k_i, i = 1, ..., 8$ and

$$G_1(s) = s(\ln(s) - \ln(\alpha^1)) - s + \alpha^1,\ \ G_2(s) = s(\ln(s) - \ln(\beta^1)) - s + \beta^1. \tag{4}$$

Note that $G_1(s), G_2(s) \geq 0$ for all $s > 0$.

In order to derive uniform estimates in $L^2(0,T; H^1(\Omega))$ we observe that the system (1)-(3) possesses a functional whose derivative is uniformly bounded in time if $0 < \alpha, \beta, \alpha + \beta \leq 1$. Indeed we have

$$\frac{d}{dt}\int_\Omega (G_1(\alpha(t)) + G_2(\beta(t)))dx + \frac{1}{4}\int_\Omega (|\alpha_x|^2 + |\beta_x|^2)dx \leq \int_\Omega (G_1(\alpha_0) + G_2(\beta_0))dx + C. \tag{5}$$

To prove the last inequality we formally test the first equation of (1) with $\ln(\alpha) - \ln(\alpha^1)$, the second one with $\ln(\beta) - \ln(\beta^1)$ and integrate by parts (see section 3.4 for details).
The estimate (5) for $\alpha, \beta > 0$ suggests to use the change of unknown functions $u = \ln(\alpha)$ and $v = \ln(\beta)$. In the new state variables u and v the problem (1)-(3) transforms to

$$\begin{cases} (e^u)_t - \Big(e^{2u}(\frac{3}{2} - e^u)u_x + e^{u+v}(\frac{1}{2} - e^v)v_x\Big)_x = q_1(e^u, e^v) & \text{in } Q_T \\ (e^v)_t - \Big(e^{u+v}(\frac{1}{2} - e^u)u_x + e^{2v}(\frac{3}{2} - e^v)v_x\Big)_x = q_2(e^u, e^v) & \text{in } Q_T \\ u(t,0) = \ln(\alpha^1)\ ,\ v(t,0) = \ln(\beta^1)\ ,\ u_x(t,l) = v_x(t,l) = 0 & \text{in } [0,T] \\ u(0,x) = \ln(\alpha_0(x))\ ,\ v(0,x) = \ln(\beta_0(x)) & \text{in } \Omega \end{cases} \tag{6}$$

The new diffusion matrix is $B(u,v) = A(e^u, e^v)\ diag(e^u, e^v)$ and takes the form

$$B(u,v) = \begin{pmatrix} e^{2u}(\frac{3}{2} - e^u) & e^{u+v}(\frac{1}{2} - e^v) \\ e^{u+v}(\frac{1}{2} - e^u) & e^{2v}(\frac{3}{2} - e^v) \end{pmatrix}$$

Here again, the matrix $B(u,v)$ is not positive definite except if $e^u + e^v \leq 1$. The advantage of the above change of variables is twofold. First, the resulting diffusion matrix $B(u,v)$ is positive definite if $e^u + e^v \leq 1$ and $u, v \in L^\infty(Q_T)$. Second, the nonnegativity of solutions is obtained without using maximum principle because we have $\alpha = e^u$ and $\beta = e^v$.

3 Auxiliary elliptic problem

We shall use a time discretization scheme to study (6), then we need to solve the following auxiliary elliptic problem

$$\begin{cases} \dfrac{e^u - e^{\tilde{u}}}{\tau} - \Big(e^{2u}(\dfrac{3}{2} - e^u)u_x + e^{u+v}(\dfrac{1}{2} - e^v)v_x\Big)_x = q_1(e^u, e^v) & \text{in } \Omega \\ \dfrac{e^v - e^{\tilde{v}}}{\tau} - \Big(e^{u+v}(\dfrac{1}{2} - e^u)u_x + e^{2v}(\dfrac{3}{2} - e^v)v_x\Big)_x = q_2(e^u, e^v) & \text{in } \Omega \\ u(0) = \ln(\alpha^1)\ ,\ v(0) = \ln(\beta^1) \text{ and } u_x(l) = v_x(l) = 0 \end{cases} \tag{7}$$

where $0 < \tau < 1$ and $(\tilde{u}, \tilde{v}) \in (L^\infty(\Omega))^2$ are fixed. We shall make use of the following definition of weak solutions

Definition 2 *A pair (u, v) is called weak solution of (7) if $(u, v) \in \left(H^1(\Omega)\right)^2$, $u(0) = \ln(\alpha^1)$, $v(0) = \ln(\beta^1)$, $e^u + e^v \leq 1$ in Ω and if for every $\varphi, \psi \in H^1_D(\Omega)$ we have*

$$\begin{aligned} \int_\Omega \frac{e^u - e^{\tilde{u}}}{\tau} \varphi dx + \int_\Omega (e^{2u}(\frac{3}{2} - e^u)u_x + e^{u+v}(\frac{1}{2} - e^v)v_x)\varphi_x dx &= \int_\Omega q_1(e^u, e^v)\varphi dx \\ \int_\Omega \frac{e^v - e^{\tilde{v}}}{\tau} \psi dx + \int_\Omega (e^{u+v}(\frac{1}{2} - e^u)u_x + e^{2v}(\frac{3}{2} - e^v)v_x)\psi_x dx &= \int_\Omega q_2(e^u, e^v)\psi dx. \end{aligned}$$

3.1 Approximated problems

Let $\tau > 0$ and $(\tilde{u}, \tilde{v}) \in (L^\infty(\Omega))^2$ be fixed. In proving global existence for non elliptic system (7) we use the following approximated problem

$$\begin{cases} \dfrac{e^u - e^{\tilde{u}}}{\tau} - (\mathbf{D}^\varepsilon_{11}(u,v)u_x + \mathbf{D}^\varepsilon_{12}(u,v)v_x)_x = \bar{q}_1(u,v) & \text{in } \Omega \\ \dfrac{e^v - e^{\tilde{v}}}{\tau} - (\mathbf{D}^\varepsilon_{21}(u,v)u_x + \mathbf{D}^\varepsilon_{22}(u,v)v_x)_x = \bar{q}_2(u,v) & \text{in } \Omega \\ u(0) = \ln(\alpha^1)\ ,\ v(0) = \ln(\beta^1) \text{ and } u_x(l) = v_x(l) = 0 \end{cases} \tag{8}$$

where $\mathbf{D}^\varepsilon = D + \mathbb{D}^\varepsilon$, D and $\mathbb{D}^\varepsilon$ given by

$$D(r,s) = \begin{pmatrix} e^{2r}\Big(\dfrac{3}{2} - \min(e^r, 1-e^s) + f(r,s)\Big) & e^{r+s}(\dfrac{1}{2} - e^s) \\ e^{r+s}(\dfrac{1}{2} - e^r) & e^{2s}\Big(\dfrac{3}{2} - \min(e^s, 1-e^r) + g(r,s)\Big) \end{pmatrix}$$

and

$$\mathbb{D}^\varepsilon(r,s) = \begin{pmatrix} \varepsilon e^r + 5(e^r + e^s)g(r,s) & 0 \\ 0 & \varepsilon e^s + 5(e^r + e^s)f(r,s) \end{pmatrix}$$

with $f(r,s)=g(s,r)=e^s(e^r+e^s-1)^+$. It is clear that if $e^r+e^s\le 1$ we have almost everywhere $\lim\limits_{\varepsilon\to 0}\mathbf{D}^\varepsilon(r,s)=B(r,s)$. The functions $\bar q_1,\bar q_2$ are defined by

$$\bar q_1(r,s)=k_1e^r(1-e^r-e^s)^+-\min(e^r,1)\Big(k_2+k_3\min(e^r+e^s,1)+k_4\min(e^s,1)\Big)$$

$$\bar q_2(r,s)=\min(e^s,1)\Big(k_6\min(e^s,(1-e^r)^+)-k_7(1-e^r)^+-k_8\min(e^r,1)\Big).$$

We remark that $|\bar q_1(r,s)|,|\bar q_2(r,s)|\le C$ for all $(r,s)\in\mathbb{R}^2$.

3.2 Linear problems

Let $(\tilde u,\tilde v)$, $(\bar u,\bar v)\in(L^\infty(\Omega))^2$ be given. We consider the linear problem: find $(u,v)\in(H^1(\Omega))^2$ satisfying

$$\begin{cases} u(0)=\ln(\alpha^1), v(0)=\ln(\beta^1)\\ \displaystyle\int_\Omega \frac{e^{\bar u}-e^{\tilde u}}{\tau}\varphi dx+\int_\Omega\left(\mathbf{D}^\varepsilon_{11}(\bar u,\bar v)u_x+\mathbf{D}^\varepsilon_{12}(\bar u,\bar v)v_x\right)\varphi_x dx=\int_\Omega \bar q_1(\bar u,\bar v)\varphi dx\\ \displaystyle\int_\Omega \frac{e^{\bar v}-e^{\tilde v}}{\tau}\psi dx+\int_\Omega\left(\mathbf{D}^\varepsilon_{21}(\bar u,\bar v)u_x+\mathbf{D}^\varepsilon_{22}(\bar u,\bar v)v_x\right)\psi_x dx=\int_\Omega \bar q_2(\bar u,\bar v)\psi dx\end{cases}\tag{9}$$

for every $(\varphi,\psi)\in\left(H^1_D(\Omega)\right)^2$.

We have the following result

Lemma 1 *For $(\bar u,\bar v)$, $(\tilde u,\tilde v)$ fixed in $(L^\infty(\Omega))^2$, problem (9) has a unique solution $(u,v)\in(H^1(\Omega))^2$.*

Proof. To make Lax-Milgram lemma applicable, we set $\underline{u}=u-\ln(\alpha^1),\underline{v}=v-\ln(\beta^1)$. It is clear that $(\underline{u},\underline{v})$ satisfies

$$\begin{cases} \underline{u}(0)=0,\underline{v}(0)=0\\ \displaystyle\int_\Omega \frac{e^{\bar u}-e^{\tilde u}}{\tau}\varphi dx+\int_\Omega\left(\mathbf{D}^\varepsilon_{11}(\bar u,\bar v)\underline{u}_x+\mathbf{D}^\varepsilon_{12}(\bar u,\bar v)\underline{v}_x\right)\varphi_x dx=\int_\Omega \bar q_1(\bar u,\bar v)\varphi dx\\ \displaystyle\int_\Omega \frac{e^{\bar v}-e^{\tilde v}}{\tau}\psi dx+\int_\Omega\left(\mathbf{D}^\varepsilon_{21}(\bar u,\bar v)\underline{u}_x+\mathbf{D}^\varepsilon_{22}(\bar u,\bar v)\underline{v}_x\right)\psi_x dx=\int_\Omega \bar q_2(\bar u,\bar v)\psi dx\end{cases}\tag{10}$$

for every $(\varphi,\psi)\in\left(H^1_D(\Omega)\right)^2$. Then (9) is equivalent to (10).
Next, we define the bilinear form $a:(H^1_D(\Omega))^2\times(H^1_D(\Omega))^2\to\mathbb{R}$ by setting

$$\begin{aligned} a\left((\underline{u},\underline{v}),(\varphi,\psi)\right)= &\int_\Omega\left(\mathbf{D}^\varepsilon_{11}(\bar u,\bar v)\underline{u}_x+\mathbf{D}^\varepsilon_{12}(\bar u,\bar v)\underline{v}_x\right)\varphi_x dx\\ &+\int_\Omega\left(\mathbf{D}^\varepsilon_{21}(\bar u,\bar v)\underline{u}_x+\mathbf{D}^\varepsilon_{22}(\bar u,\bar v)\underline{v}_x\right)\psi_x dx\end{aligned}\tag{11}$$

and the linear functional $J:H^1_D(\Omega)\times H^1_D(\Omega)\to\mathbb{R}$

$$J(\varphi,\psi)=\int_\Omega\left(\frac{e^{\tilde u}-e^{\bar u}}{\tau}\varphi+\frac{e^{\tilde v}-e^{\bar v}}{\tau}\psi\right)dx+\int_\Omega(\bar q_1(\bar u,\bar v)\varphi+\bar q_2(\bar u,\bar v)\psi)dx.$$

The continuity of a and J follows from the boundedness of $\bar{u}, \bar{v}, e^{\bar{u}}$ and $e^{\bar{v}}$. For the coerciveness of a, it is sufficient to prove that $D(\bar{u},\bar{v})$ is positive definite. Let us compute $\xi^t D(\bar{u},\bar{v})\,\xi$ for $\xi=(\xi_1,\xi_2)\in\mathbb{R}^2$. We consider two cases

- In $\Omega_1=\{x\in\Omega;\ e^{\bar{u}}+e^{\bar{v}}\le 1\}$, we have

$$\xi^t D(\bar{u},\bar{v})\xi = e^{2\bar{u}}(\frac{3}{2}-e^{\bar{u}})\xi_1^2 + e^{2\bar{v}}(\frac{3}{2}-e^{\bar{v}})\xi_2^2 - e^{\bar{u}+\bar{v}}(e^{\bar{u}}+e^{\bar{v}}-1)\xi_1\xi_2. \tag{12}$$

We make use of the elementary inequality

$$1-a-b \le \sqrt{\frac{3}{2}-a}\sqrt{\frac{3}{2}-b} \quad \text{if} \quad 0\le a,b,\ a+b\le 1 \tag{13}$$

and Young inequality to get

$$-e^{\bar{u}+\bar{v}}(e^{\bar{u}}+e^{\bar{v}}-1)\xi_1\xi_2 \ge -\frac{1}{2}\Big(e^{2\bar{u}}(\frac{3}{2}-e^{\bar{u}})\xi_1^2 + e^{2\bar{v}}(\frac{3}{2}-e^{\bar{v}})\xi_2^2\Big)$$

which implies using (12)

$$\xi^t D(\bar{u},\bar{v})\xi \ge \frac{1}{2}\left(e^{2\bar{u}}(\frac{3}{2}-e^{\bar{u}})\xi_1^2 + e^{2\bar{v}}(\frac{3}{2}-e^{\bar{v}})\xi_2^2\right) \ge \frac{1}{4}\min(e^{-2\|\bar{u}\|_\infty}, e^{-2\|\bar{v}\|_\infty})\,\|\xi\|^2\,.$$

- Similarly, in $\Omega_2=\{x\in\Omega;\ e^{\bar{u}}+e^{\bar{v}}>1\}$, we have

$$\xi^t D(\bar{u},\bar{v})\xi = e^{2\bar{u}}(\frac{1}{2}+e^{\bar{v}}(e^{\bar{u}}+e^{\bar{v}}))\xi_1^2 + e^{2\bar{v}}(\frac{1}{2}+e^{\bar{u}}(e^{\bar{u}}+e^{\bar{v}}))\xi_2^2 - e^{\bar{u}+\bar{v}}(e^{\bar{u}}+e^{\bar{v}}-1)\xi_1\xi_2. \tag{14}$$

From the inequality

$$(1-e^{\bar{u}}-e^{\bar{v}})^2 \le (e^{\bar{u}}+e^{\bar{v}})^2 \le \frac{9}{4}(\frac{1}{2}+e^{\bar{v}}(e^{\bar{u}}+e^{\bar{v}}))(\frac{1}{2}+e^{\bar{u}}(e^{\bar{u}}+e^{\bar{v}})) \tag{15}$$

we deduce that

$$e^{\bar{u}}+e^{\bar{v}}-1 \le \frac{3}{2}\sqrt{\frac{1}{2}+e^{\bar{v}}(e^{\bar{u}}+e^{\bar{v}})}\sqrt{\frac{1}{2}+e^{\bar{u}}(e^{\bar{u}}+e^{\bar{v}})}$$

so thanks to Young inequality we find

$$-e^{\bar{u}+\bar{v}}(e^{\bar{u}}+e^{\bar{v}}-1)\xi_1\xi_2 \ge -\frac{3}{4}\Big(e^{2\bar{u}}(\frac{1}{2}+e^{\bar{v}}(e^{\bar{u}}+e^{\bar{v}}))\xi_1^2 + e^{2\bar{v}}(\frac{1}{2}+e^{\bar{u}}(e^{\bar{u}}+e^{\bar{v}}))\xi_2^2\Big).$$

From this inequality and (14), we infer that

$$\xi^t D(\bar{u},\bar{v})\xi \ge \frac{1}{8}\min(e^{-2\|\bar{u}\|_\infty}, e^{-2\|\bar{v}\|_\infty})\|\xi\|^2.$$

In summary, in both cases we have for all $(\xi_1,\xi_2)\in\mathbb{R}^2$

$$\xi^t D(\bar{u},\bar{v})\xi \ge C(\|\bar{u}\|_\infty, \|\bar{v}\|_\infty)\|\xi\|^2 \tag{16}$$

thus D is positive definite. Therefore, Lax-Milgram lemma implies the existence of a unique solution $(\underline{u},\underline{v})\in(H_D^1(\Omega))^2$ of problem (10) and $(u,v)=(\underline{u}+\ln(\alpha^1), \underline{v}+\ln(\beta^1))$ is the unique solution of (9). $\square$

3.3 The nonlinear problem

Theorem 2 *Let $(\tilde{u},\tilde{v}) \in (L^\infty(\Omega))^2$, for all $0<\tau<1$, there exists a unique weak solution $(u_\tau^\varepsilon, v_\tau^\varepsilon)$ of problem (8).*

Proof. Lemma 1 and the embedding $H^1(\Omega) \subset L^\infty(\Omega)$ in one dimension allow us to define the map $S : (L^\infty(\Omega))^2 \to (L^\infty(\Omega))^2$ by setting $S(\bar{u},\bar{v}) = (u,v)$ the solution of (9). The existence of a fixed point of S will be shown by using Leray-Schauder fixed point theorem.
First, we prove that S is continuous. Let $(\bar{u}_n,\bar{v}_n)$ be a sequence in $(L^\infty(\Omega))^2$ such that $(\bar{u}_n,\bar{v}_n) \to (\bar{u},\bar{v})$ strongly in $(L^\infty(\Omega))^2$ as $n\to\infty$ and let $S(\bar{u}_n,\bar{v}_n) = (u_n,v_n)$. We test the first equation of (9) with $u_n - \ln(\alpha^1) \in H_D^1(\Omega)$ and the second with $v_n - \ln(\beta^1) \in H_D^1(\Omega)$. Recalling estimate (16), we see that

$$\int_\Omega \frac{e^{\tilde{u}}-e^{\bar{u}_n}}{\tau}(u_n-\ln(\alpha^1))dx + \int_\Omega \frac{e^{\tilde{v}}-e^{\bar{v}_n}}{\tau}(v_n-\ln(\beta^1))dx + \int_\Omega \bar{q}_1(\bar{u}_n,\bar{v}_n)(u_n-\ln(\alpha^1))dx +$$
$$\int_\Omega \bar{q}_2(\bar{u}_n,\bar{v}_n)(v_n-\ln(\beta^1))dx \geq C(\|\bar{u}_n\|_\infty, \|\bar{v}_n\|_\infty)\Big(\|u_n-\ln(\alpha^1)\|_{H^1}^2 + \|v_n-\ln(\beta^1)\|_{H^1}^2\Big).$$

Taking into account the uniform boundedness of $\bar{q}_1, \bar{q}_2, e^{\tilde{u}}, e^{\tilde{v}}, e^{\overline{u}_n}$ and $e^{\overline{v}_n}$ and using Young and Poincaré inequalities, we get

$$\|u_n-\ln(\alpha^1)\|_{H^1}^2 + \|v_n-\ln(\beta^1)\|_{H^1}^2 \leq C_\tau \tag{17}$$

so u_n and v_n are bounded in $H^1(\Omega)$. Using the compactness of the embedding $H^1(\Omega) \hookrightarrow L^\infty(\Omega)$, we deduce that there exists a subsequence of (u_n,v_n), still denoted by (u_n,v_n) and a function (u,v) such that

$$u_n \longrightarrow u \ \ , \ v_n \longrightarrow v \text{ strongly in } L^\infty(\Omega)$$
$$u_n \rightharpoonup u \ , \ v_n \rightharpoonup v \text{ weakly in } H^1(\Omega).$$

The uniform boundedness of $(\overline{u}_n,\overline{v}_n)$ immediately gives the following weak convergences

$$e^{2\bar{u}_n}(\frac{3}{2}-e^{\bar{u}_n})u_{nx} \rightharpoonup e^{2\bar{u}}(\frac{3}{2}-e^{\bar{u}})u_x \ , \ e^{2\bar{v}_n}(\frac{3}{2}-e^{\bar{v}_n})v_{nx} \rightharpoonup e^{2\bar{v}}(\frac{3}{2}-e^{\bar{v}})v_x$$

$$e^{\bar{u}_n+\bar{v}_n}(\frac{1}{2}-e^{\bar{v}_n})v_{nx} \rightharpoonup e^{\bar{u}+\bar{v}}(\frac{1}{2}-e^{\bar{v}})v_x \ , \ e^{\bar{u}_n+\bar{v}_n}(\frac{1}{2}-e^{\bar{u}_n})u_{nx} \rightharpoonup e^{\bar{u}+\bar{v}}(\frac{1}{2}-e^{\bar{u}})u_x$$

in $L^2(\Omega)$. Hence there exists a subsequence of (u_n,v_n) which converges to $S(\bar{u},\bar{v})$. Moreover thanks to the uniqueness result for the system (9), we see that all the sequence (u_n,v_n) converges to $S(\bar{u},\bar{v})$. Therefore the proof of continuity of S is complete.
The compactness of S follows from the compactness of the embedding $H^1(\Omega)$ into $L^\infty(\Omega)$ and (17).
To complete the proof of theorem 2, let us prove that *the set*

$$\Lambda = \left\{(\bar{u},\bar{v}) \in (L^\infty(\Omega))^2 \ / \ (\bar{u},\bar{v}) = \delta S(\bar{u},\bar{v}), \ \delta\in[0,1]\right\}$$

is bounded. If $\delta = 0$ then $\Lambda = \{(0,0)\}$ and if $\delta \neq 0$ the equation $(\bar{u}, \bar{v}) = \delta S(\bar{u}, \bar{v})$ is equivalent to $(\bar{u}, \bar{v}) \in (H^1(\Omega))^2$ and

$$\begin{cases} \bar{u}(0) = \delta \ln(\alpha^1) \ , \ \bar{v} = \delta \ln(\beta) \\ \displaystyle\int_\Omega \frac{e^{\bar{u}} - e^{\tilde{u}}}{\tau} \varphi dx + \frac{1}{\delta} \int_\Omega (\mathbf{D}^\varepsilon_{11}(\bar{u}, \bar{v}) \bar{u}_x + \mathbf{D}^\varepsilon_{12}(\bar{u}, \bar{v}) \bar{v}_x) \varphi_x dx = \int_\Omega \bar{q}_1(\bar{u}, \bar{v}) \varphi dx \\ \displaystyle\int_\Omega \frac{e^{\bar{v}} - e^{\tilde{v}}}{\tau} \psi dx + \frac{1}{\delta} \int_\Omega (\mathbf{D}^\varepsilon_{21}(\bar{u}, \bar{v}) \bar{u}_x + \mathbf{D}^\varepsilon_{22}(\bar{u}, \bar{v}) \bar{v}_x) \psi_x dx = \int_\Omega \bar{q}_2(\bar{u}, \bar{v}) \psi dx \end{cases} \tag{18}$$

for any $(\varphi, \psi) \in \left(H^1_D(\Omega)\right)^2$. The remainder of the proof is a direct consequence of the following lemma which follows from some modifications of the proof of lemma 3.1 in [12]

Lemma 2 *Let* $(\mathbf{A1}) - (\mathbf{A4})$ *hold and let* $(\bar{u}, \bar{v}) \in \left(H^1(\Omega)\right)^2$ *be solution of (18). Then there exists a positive constant* $C(\tau, \varepsilon)$ *not depending on* δ *such that*

$$\varepsilon^2 \int_\Omega (|\bar{u}_x|^2 + |\bar{v}_x|^2) dx \leq C(\tau, \varepsilon).$$

Proof. Testing the first equation of (18) with $\varphi = \bar{u} - \delta \ln(\alpha^1) + 2\varepsilon(\left(\alpha^1\right)^{-\delta} - e^{-\bar{u}}) \in H^1_D(\Omega)$ and the second one with $\psi = \bar{v} - \delta \ln(\beta^1) + 2\varepsilon(\left(\beta^1\right)^{-\delta} - e^{-\bar{v}}) \in H^1_D(\Omega)$ leads to

$$\begin{aligned} &\int_\Omega \Big(\mathbf{D}^\varepsilon_{11}(\bar{u}, \bar{v}) \left(1 + 2\varepsilon e^{-\bar{u}}\right) |\bar{u}_x|^2 + \mathbf{D}^\varepsilon_{22}(\bar{u}, \bar{v}) \left(1 + 2\varepsilon e^{-\bar{v}}\right) |\bar{v}_x|^2 \Big) dx \\ &\qquad + \int_\Omega \Big(\mathbf{D}^\varepsilon_{12}(\bar{u}, \bar{v})(1 + 2\varepsilon e^{-\bar{u}}) + \mathbf{D}^\varepsilon_{21}(\bar{u}, \bar{v})(1 + 2\varepsilon e^{-\bar{v}}) \Big) \bar{u}_x \bar{v}_x dx \\ &= -\frac{\delta}{\tau} \int_\Omega \left((e^{\bar{u}} - e^{\tilde{u}})\varphi + (e^{\bar{v}} - e^{\tilde{v}})\psi \right) dx + \delta \int_\Omega \left(\bar{q}_1(\bar{u}, \bar{v}) \varphi + \bar{q}_2(\bar{u}, \bar{v}) \psi \right) dx. \end{aligned} \tag{19}$$

The first integral in the right hand side of (19) is estimated by using the convexity of e^s and the elementary inequality $e^s \geq 1 + s$ for all $s \in \mathbb{R}$. Indeed, we have

$$\begin{aligned} &\int_\Omega (e^{\bar{u}} - e^{\tilde{u}})(\bar{u} - \delta \ln(\alpha^1)) dx = \int_\Omega \left(e^{\bar{u}}(\bar{u} - \delta \ln(\alpha^1)) - e^{\bar{u}} + (\alpha^1)^\delta \right) dx \\ &- \int_\Omega \left(e^{\tilde{u}}(\tilde{u} - \delta \ln(\alpha^1)) - e^{\tilde{u}} + (\alpha^1)^\delta \right) dx + \int_\Omega \left((e^{\bar{u}} - e^{\tilde{u}}) - e^{\tilde{u}}(\bar{u} - \tilde{u}) \right) dx \\ &\geq \int_\Omega G_\delta(e^{\bar{u}}) dx - \int_\Omega G_\delta(e^{\tilde{u}}) dx \end{aligned} \tag{20}$$

where $G_\delta(s) = s(\ln(s) - \delta \ln(\alpha^1)) - s + (\alpha^1)^\delta \geq 0$ for all $s \in \mathbb{R}^\star_+$. Similarly

$$\begin{aligned} &\int_\Omega (e^{\bar{u}} - e^{\tilde{u}}) \left((\alpha^1)^{-\delta} - e^{-\bar{u}} \right) dx = \int_\Omega \left(e^{\bar{u} - \delta \ln(\alpha^1)} - \bar{u} + \delta \ln(\alpha^1) \right) dx \\ &- \int_\Omega \left(e^{\tilde{u} - \delta \ln(\alpha^1)} - \tilde{u} + \delta \ln(\alpha^1) \right) dx + \int_\Omega \left(e^{\tilde{u} - \bar{u}} - (\tilde{u} - \bar{u}) - 1 \right) dx \\ &\geq \int_\Omega G_{0\delta}(\bar{u}) dx - \int_\Omega G_{0\delta}(\tilde{u}) dx \end{aligned} \tag{21}$$

with $G_{0\delta}(s) = e^{s-\delta \ln(\alpha^1)} - s + \delta \ln(\alpha^1) \geq 0$ for all $s \in \mathbb{R}_+^\star$. Combining (20) and (21) finally give

$$\frac{\delta}{\tau}\int_\Omega \left(e^{\bar{u}} - e^{\tilde{u}}\right)\varphi dx \geq \frac{\delta}{\tau}\int_\Omega \left(G_\delta(e^{\bar{u}}) - G_\delta(e^{\tilde{u}})\right) dx + 2\varepsilon\frac{\delta}{\tau}\int_\Omega \left(G_{0\delta}(\bar{u}) - G_{0\delta}(\tilde{u})\right) dx \qquad (22)$$

and we obtain a similar estimate for $\dfrac{\delta}{\tau}\displaystyle\int_\Omega \left(e^{\bar{v}} - e^{\tilde{v}}\right)\psi dx$. Now we infer from the boundedness of $\bar{q}_1$ and $\bar{q}_2$ and Poincaré inequality that

$$\delta\int_\Omega \bar{q}_1\left(\bar{u},\bar{v}\right)(\bar{u} - \ln(\alpha^1))dx \leq C\int_\Omega |\bar{u} - \ln(\alpha^1)|dx \leq \frac{\varepsilon^2}{2}\int_\Omega |\bar{u}_x|^2\, dx + C(\varepsilon).$$

Moreover, since $|\bar{q}_1(r,s)| \leq Ce^r$, we get that $\delta\displaystyle\int_\Omega \bar{q}_1\left(\bar{u},\bar{v}\right)((\alpha^1)^{-\delta} - e^{-\bar{u}})dx$ is bounded. The same arguments permit to bound the terms $\delta\displaystyle\int_\Omega \bar{q}_2\left(\bar{u},\bar{v}\right)(\bar{v} - \ln(\beta^1))dx$ and $\delta\displaystyle\int_\Omega \bar{q}_2\left(\bar{u},\bar{v}\right)((\beta^1)^{-\delta} - e^{-\bar{v}})dx$. We end the proof of lemma 2 by estimating the left hand side of (19) using the following technical result which will be proved in the appendices (see section 6)

Lemma 3 *For all $(r,s),(\xi_1,\xi_2) \in \mathbb{R}^2$, we have*

$$\mathbf{D}^\varepsilon_{11}(r,s)\left(1 + 2\varepsilon e^{-r}\right){\xi_1}^2 + \mathbf{D}^\varepsilon_{22}(r,s)\left(1 + 2\varepsilon e^{-s}\right)\xi_2^2 +$$

$$\left(\mathbf{D}^\varepsilon_{12}(r,s)\left(1 + 2\varepsilon e^{-r}\right) + \mathbf{D}^\varepsilon_{21}(r,s)\left(1 + 2\varepsilon e^{-s}\right)\right)\xi_1\xi_2 \geq \varepsilon^2(\xi_1^2 + \xi_2^2). \qquad (23)$$

□

3.4 Uniform estimates with respect to ε

Let $(u^\varepsilon_\tau, v^\varepsilon_\tau)$ be the solution of (8) provided by theorem 2. We set $\tilde{\alpha} = e^{\tilde{u}}, \tilde{\beta} = e^{\tilde{v}}, \alpha^\varepsilon_\tau = e^{u^\varepsilon_\tau}, \beta^\varepsilon_\tau = e^{v^\varepsilon_\tau}$. We have

$$\begin{cases} \dfrac{\alpha^\varepsilon_\tau - \tilde{\alpha}}{\tau} - (\mathbf{C}^\varepsilon_{11}(\alpha^\varepsilon_\tau,\beta^\varepsilon_\tau)\alpha^\varepsilon_{\tau x} + \mathbf{C}^\varepsilon_{12}(\alpha^\varepsilon_\tau,\beta^\varepsilon_\tau)\beta^\varepsilon_{\tau x})_x = \bar{q}_1(\ln(\alpha^\varepsilon_\tau),\ln(\beta^\varepsilon_\tau)) \quad \text{in } \Omega \\ \dfrac{\beta^\varepsilon_\tau - \tilde{\beta}}{\tau} - (\mathbf{C}^\varepsilon_{21}(\alpha^\varepsilon_\tau,\beta^\varepsilon_\tau)\alpha^\varepsilon_{\tau x} + \mathbf{C}^\varepsilon_{22}(\alpha^\varepsilon_\tau,\beta^\varepsilon_\tau)\beta^\varepsilon_{\tau x})_x = \bar{q}_2(\ln(\alpha^\varepsilon_\tau),\ln(\beta^\varepsilon_\tau)) \quad \text{in } \Omega \\ \alpha^\varepsilon_\tau(0) = \alpha^1 \ ,\ \beta^\varepsilon_\tau(0) = \beta^1 \text{ and } \alpha^\varepsilon_{\tau x}(l) = \beta^\varepsilon_{\tau x}(l) = 0 \end{cases} \qquad (24)$$

in the weak sense, where the matrix $\mathbf{C}^\varepsilon(r,s)$ is given by

$$\mathbf{C}^\varepsilon(r,s) = \begin{pmatrix} r\Big(\dfrac{3}{2} - \min(r, 1-s)\Big) + h^\varepsilon(r,s) & r(\dfrac{1}{2} - s) \\ s(\dfrac{1}{2} - r) & s\Big(\dfrac{3}{2} - \min(s, 1-r)\Big) + h^\varepsilon(r,s) \end{pmatrix}$$

with $h^\varepsilon(r,s) = (r+s-1)^+(rs+5(r+s))+\varepsilon$. Clearly if $r+s \leq 1$ then $\lim_{\varepsilon\to 0}\mathbf{C}^\varepsilon(r,s) = A(r,s)$ a.e. We begin with the following L^∞ bounds

Lemma 4 *Let $0 < \tau < 1$, $(\tilde{\alpha},\tilde{\beta}) \in (L^\infty(\Omega))^2$ be such that $0 < \tilde{\alpha},\tilde{\beta},\tilde{\alpha}+\tilde{\beta} \leq 1$ in Ω. Let $(\alpha^\varepsilon_\tau,\beta^\varepsilon_\tau)$ be a solution of (24), we have*

$$0 < \alpha^\varepsilon_\tau,\ \beta^\varepsilon_\tau,\quad \alpha^\varepsilon_\tau + \beta^\varepsilon_\tau \leq 1.$$

Proof. Adding the equations of (24) and testing with $\varphi = (\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon - 1)^+ \in H_D^1(\Omega)$, we obtain

$$\begin{aligned}\int_\Omega \frac{\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon - (\tilde\alpha + \tilde\beta)}{\tau}\varphi dx \quad &+ \int_\Omega \left(\alpha_\tau^\varepsilon(\frac{1}{2} + \beta_\tau^\varepsilon + \beta_\tau^\varepsilon(\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon - 1)) + \beta_\tau^\varepsilon(\frac{1}{2} - \alpha_\tau^\varepsilon)\right)\alpha_{\tau x}^\varepsilon \varphi_x dx \\ &+ \int_\Omega \left(\beta_\tau^\varepsilon(\frac{1}{2} + \alpha_\tau^\varepsilon + \alpha_\tau^\varepsilon(\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon - 1)) + \alpha_\tau^\varepsilon(\frac{1}{2} - \beta_\tau^\varepsilon)\right)\beta_{\tau x}^\varepsilon \varphi_x dx \\ &+ \int_\Omega (5(\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon - 1)(\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon) + \varepsilon)(\alpha_{\tau x} + \beta_{\tau x})\varphi_x dx \le 0\end{aligned} \tag{25}$$

by using assumption (**A2**). This means that

$$\int_\Omega \frac{\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon - (\tilde\alpha + \tilde\beta)}{\tau}\varphi dx \le + \int_\Omega \left[\frac{1}{2}(\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon) + ((\alpha_\tau^\varepsilon\beta_\tau^\varepsilon + 5(\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon))(\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon - 1) + \varepsilon)\right] |\varphi_x|^2 dx$$

and lead to $\displaystyle\int_\Omega \frac{\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon - (\tilde\alpha + \tilde\beta)}{\tau}\varphi dx \le 0$. Let $\Phi(s) = \displaystyle\int_0^s (t-1)^+ dt$. From the convexity of Φ, we infer that $\displaystyle\int_\Omega \Phi(\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon)dx = \int_\Omega (\Phi(\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon) - \Phi(\tilde\alpha + \tilde\beta))dx \le 0$. In other words $\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon \le 1$. □

Therefore $(\alpha_\tau^\varepsilon, \beta_\tau^\varepsilon)$ also solves the problem

$$\begin{cases} \dfrac{\alpha_\tau^\varepsilon - \tilde\alpha}{\tau} - \left((\alpha_\tau^\varepsilon(\frac{3}{2} - \alpha_\tau^\varepsilon) + \varepsilon)\alpha_{\tau x}^\varepsilon + \alpha_\tau^\varepsilon(\frac{1}{2} - \beta_\tau^\varepsilon)\beta_{\tau x}^\varepsilon\right)_x = q_1(\alpha_\tau^\varepsilon, \beta_\tau^\varepsilon) \quad \text{in } \Omega \\ \dfrac{\beta_\tau^\varepsilon - \tilde\beta}{\tau} - \left(\beta_\tau^\varepsilon(\frac{1}{2} - \alpha_\tau^\varepsilon)\alpha_{\tau x}^\varepsilon + (\beta_\tau^\varepsilon(\frac{3}{2} - \beta_\tau^\varepsilon) + \varepsilon)\beta_{\tau x}^\varepsilon\right)_x = q_2(\alpha_\tau^\varepsilon, \beta_\tau^\varepsilon) \quad \text{in } \Omega \\ \alpha_\tau^\varepsilon(0) = \alpha^1 \ , \ \beta_\tau^\varepsilon(0) = \beta^1 \text{ and } \alpha_{\tau x}^\varepsilon(l) = \beta_{\tau x}^\varepsilon(l) = 0. \end{cases} \tag{26}$$

The following inequality is the key estimate of this paper

Lemma 5 *Let $0 < \tau < 1, (\tilde\alpha, \tilde\beta) \in (L^\infty(\Omega))^2$ be such that $0 < \tilde\alpha, \tilde\beta, \tilde\alpha + \tilde\beta \le 1$ in Ω. Then there exists a positive constant C independent of τ and ε such that the solution $(\alpha_\tau^\varepsilon, \beta_\tau^\varepsilon)$ of (26) provided by theorem 2 satisfies the entropy inequality*

$$\int_\Omega (G_1(\alpha_\tau^\varepsilon) + G_2(\beta_\tau^\varepsilon))dx + \frac{\tau}{4}\int_\Omega (|\alpha_{\tau x}^\varepsilon|^2 + |\beta_{\tau x}^\varepsilon|^2)dx \le \int_\Omega (G_1(\tilde\alpha) + G_2(\tilde\beta))dx + C\tau \tag{27}$$

where G_1 and G_2 are defined by (4).

Proof. Testing the first equation of (26) with $\varphi_\tau^\varepsilon = \ln(\alpha_\tau^\varepsilon) - \ln(\alpha^1) \in H_D^1(\Omega)$ and the second one with $\psi_\tau^\varepsilon = \ln(\beta_\tau^\varepsilon) - \ln(\beta^1) \in H_D^1(\Omega)$ leads to the equality

$$\begin{aligned} &\int_\Omega \left(\frac{\alpha_\tau^\varepsilon - \tilde\alpha}{\tau}\varphi_\tau^\varepsilon + \frac{\beta_\tau^\varepsilon - \tilde\beta}{\tau}\psi_\tau^\varepsilon + (1 - \alpha_\tau^\varepsilon - \beta_\tau^\varepsilon)\,\alpha_{\tau x}^\varepsilon\beta_{\tau x}^\varepsilon\right)dx + \varepsilon\int_\Omega \left(\frac{|\alpha_{\tau x}^\varepsilon|^2}{\alpha_\tau^\varepsilon} + \frac{|\beta_{\tau x}^\varepsilon|^2}{\beta_\tau^\varepsilon}\right)dx \\ &+ \int_\Omega \left((\frac{3}{2} - \alpha_\tau^\varepsilon)\,|\alpha_{\tau x}^\varepsilon|^2 + (\frac{3}{2} - \beta_\tau^\varepsilon)\,|\beta_{\tau x}^\varepsilon|^2\right)dx = \int_\Omega \left(q_1(\alpha_\tau^\varepsilon, \beta_\tau^\varepsilon)\,\varphi_\tau^\varepsilon + q_2(\alpha_\tau^\varepsilon, \beta_\tau^\varepsilon)\,\psi_\tau^\varepsilon\right)dx. \end{aligned} \tag{28}$$

Then using (13) and Young inequality, we get

$$-\int_\Omega (\alpha_\tau^\varepsilon + \beta_\tau^\varepsilon - 1)\,\alpha_{\tau x}^\varepsilon\beta_{\tau x}^\varepsilon dx \ge -\frac{1}{2}\int_\Omega \left((\frac{3}{2} - \alpha_\tau^\varepsilon)\,|\alpha_{\tau x}^\varepsilon|^2 + (\frac{3}{2} - \beta_\tau^\varepsilon)\,|\beta_{\tau x}^\varepsilon|^2\right)dx \tag{29}$$

so inserting (29) into (28) and using the fact that $\dfrac{3}{2}-\alpha_\tau^\varepsilon,\ \dfrac{3}{2}-\beta_\tau^\varepsilon \geq \dfrac{1}{2}$, we see that

$$\int_\Omega \Big(\frac{\alpha_\tau^\varepsilon-\tilde{\alpha}}{\tau}\varphi_\tau^\varepsilon+\frac{\beta_\tau^\varepsilon-\tilde{\beta}}{\tau}\psi_\tau^\varepsilon\Big)dx+\frac{1}{4}\int_\Omega\Big(|\alpha_{\tau x}^\varepsilon|^2+|\beta_{\tau x}^\varepsilon|^2\Big)\,dx \geq \\ \int_\Omega \Big(q_1\left(\alpha_\tau^\varepsilon,\beta_\tau^\varepsilon\right)\varphi_\tau^\varepsilon+q_2\left(\alpha_\tau^\varepsilon,\beta_\tau^\varepsilon\right)\psi_\tau^\varepsilon\Big)dx. \tag{30}$$

The right hand side of (30) can be estimated by using the boundedness of $q_1\left(\alpha_\tau^\varepsilon,\beta_\tau^\varepsilon\right)$ and $q_2\left(\alpha_\tau^\varepsilon,\beta_\tau^\varepsilon\right)$, and the fact that the function $s\ln(s)$ is bounded in $[0,1]$. Thus

$$\int_\Omega \Big(q_1\left(\alpha_\tau^\varepsilon,\beta_\tau^\varepsilon\right)\varphi_\tau^\varepsilon+q_2\left(\alpha_\tau^\varepsilon,\beta_\tau^\varepsilon\right)\psi_\tau^\varepsilon\Big)dx \leq C. \tag{31}$$

Thanks to the convexity of the functions G_1 and G_2, the first term on left hand side of (30) can be estimated as follows

$$\int_\Omega \Big(\frac{\alpha_\tau^\varepsilon-\tilde{\alpha}}{\tau}\varphi_\tau^\varepsilon+\frac{\beta_\tau^\varepsilon-\tilde{\beta}}{\tau}\psi_\tau^\varepsilon\Big)dx \geq \frac{1}{\tau}\int_\Omega\left(G_1\left(\alpha_\tau^\varepsilon\right)+G_2\left(\beta_\tau^\varepsilon\right)\right)dx-\frac{1}{\tau}\int_\Omega (G_1(\tilde{\alpha})+G_2(\tilde{\beta}))dx \tag{32}$$

and lemma 5 follows at once from (30), (31) and (32). $\square$

Hence the limit $\varepsilon \to 0$ can be performed to obtain thanks to the uniform bounds (27), a weak solution of the following problem

$$\begin{cases} \dfrac{\alpha_\tau-\tilde{\alpha}}{\tau}-\Big(\alpha_\tau(\dfrac{3}{2}-\alpha_\tau)\alpha_{\tau x}+\alpha_\tau(\dfrac{1}{2}-\beta_\tau)\beta_{\tau x}\Big)_x=q_1(\alpha_\tau,\beta_\tau) & \text{in } \Omega \\ \dfrac{\beta_\tau-\tilde{\beta}}{\tau}-\Big(\beta_\tau(\dfrac{1}{2}-\alpha_\tau)\alpha_{\tau x}+\beta_\tau(\dfrac{3}{2}-\beta_\tau)\beta_{\tau x}\Big)_x=q_2(\alpha_\tau,\beta_\tau) & \text{in } \Omega \\ \alpha_\tau(0)=\alpha^1\ ,\ \beta_\tau(0)=\beta^1 \text{ and } \alpha_{\tau x}(l)=\beta_{\tau x}(l)=0. \end{cases} \tag{33}$$

4 Uniform estimates with respect to τ

In order to pass to the limit as $\tau \to 0$, we are going to derive some uniform estimates with respect to the parameter τ for the solution to the semi-discrete scheme (which will be described below).

In the following let $T>0$ be fixed (but arbitrary). We discretize the time by backward Euler approximation of time derivative $\alpha_t \simeq \dfrac{1}{\tau}(\alpha(t_k)-\alpha(t_{k-1}))$ and $\beta_t \simeq \dfrac{1}{\tau}(\beta(t_k)-\beta(t_{k-1}))$. We divide the time interval $I=(0,T)$ into N subintervals $I_k=(t_{k-1},t_k]$ of the same length $\tau=\dfrac{T}{N}$. Then we define recursively (α_k,β_k), $k=1,...,N$ as solution of (33) corresponding to the data $(\tilde{\alpha},\tilde{\beta})=(\alpha_{k-1},\beta_{k-1})$ i.e.

$$\begin{cases} \dfrac{\alpha_k-\alpha_{k-1}}{\tau}-\Big(\alpha_k(\dfrac{3}{2}-\alpha_k)\alpha_{kx}+\alpha_k(\dfrac{1}{2}-\beta_k)\beta_{kx}\Big)_x=q_1(\alpha_k,\beta_k) & \text{in } \Omega \\ \dfrac{\beta_k-\beta_{k-1}}{\tau}-\Big(\beta_k(\dfrac{1}{2}-\alpha_k)\alpha_{\tau x}+\beta_k(\dfrac{3}{2}-\beta_k)\beta_{kx}\Big)_x=q_2(\alpha_k,\beta_k) & \text{in } \Omega \\ \alpha_k(0)=\alpha^1\ ,\ \beta_k(0)=\beta^1 \text{ and } \alpha_{kx}(l)=\beta_{kx}(l)=0 \end{cases} \tag{34}$$

(α_0,β_0) being the initial condition of problem (1)-(3). Let $\alpha^{(\tau)}$, $\bar{\alpha}^{(\tau)}\ \in L^\infty\left(Q_T\right)$ be the piecewise constant in time interpolation on $(0,T)$ of α_1, α_2,..., α_N and α_0, α_1,..., α_{N-1} respectively i.e.

$$\alpha^{(\tau)}(t,x) = \alpha_k(x),\ \bar{\alpha}^{(\tau)}(t,x) = \alpha_{k-1}(x) \text{ on } (t_{k-1},t_k]\times\Omega,\ k=1,...,N.$$

We define similarly $\beta^{(\tau)}$, $\bar{\beta}^{(\tau)}$ then the functions $\tilde{\alpha}^{(\tau)}, \tilde{\beta}^{(\tau)}$ by setting

$$\begin{cases} \tilde{\alpha}^{(\tau)}(t,x) = \dfrac{t-k\tau}{\tau}\left(\alpha^{(\tau)}(t,x) - \bar{\alpha}^{(\tau)}(t,x)\right) + \alpha^{(\tau)}(t,x) \\ \tilde{\beta}^{(\tau)}(t,x) = \dfrac{t-k\tau}{\tau}\left(\beta^{(\tau)}(t,x) - \bar{\beta}^{(\tau)}(t,x)\right) + \beta^{(\tau)}(t,x) \end{cases}$$

on $(t_{k-1},t_k]\times\Omega$, $k=1,...,N$. Therefore we can rewrite (34) as

$$\begin{cases} \tilde{\alpha}_t^{(\tau)} - \left(\alpha^{(\tau)}(\frac{3}{2}-\alpha^{(\tau)})\alpha_x^{(\tau)} + \alpha^{(\tau)}(\frac{1}{2}-\beta^{(\tau)})\beta_x^{(\tau)}\right)_x = q_1(\alpha^{(\tau)},\beta^{(\tau)}) \quad \text{in } \Omega \\ \tilde{\beta}_t^{(\tau)} - \left(\beta^{(\tau)}(\frac{1}{2}-\alpha^{(\tau)})\alpha_x^{(\tau)} + \beta^{(\tau)}(\frac{3}{2}-\beta^{(\tau)})\beta_x^{(\tau)}\right)_x = q_2(\alpha^{(\tau)},\beta^{(\tau)}) \quad \text{in } \Omega \\ \alpha^{(\tau)}(0) = \alpha^1\ ,\ \beta^{(\tau)}(0) = \beta^1 \text{ and } \alpha_x^{(\tau)}(l) = \beta_x^{(\tau)}(l) = 0. \end{cases} \tag{35}$$

Now we set

$$\eta_k = \int_\Omega \left(G_1(\alpha_k) + G_2(\beta_k)\right)dx, \quad k=0,...,N$$

and

$$\eta^{(\tau)}(t) = \eta_k \text{ for all } t\in(t_{k-1},t_k],\ k=1,...,N.$$

Hereafter, we give some uniform bounds in order to prepare the passing to the limit as $\tau\to 0$ in the problem (35)

Lemma 6 *We have $0\le \alpha^{(\tau)},\ \ \beta^{(\tau)},\ \ \alpha^{(\tau)}+\beta^{(\tau)}\le 1$ a.e. in Q_T. Moreover there exists a positive constant C independent of τ such that*

$$\|\eta^{(\tau)}\|_{L^\infty(0,T)}, \|\alpha^{(\tau)}\|_{L^2(0,T;H^1(\Omega))},\ \|\beta^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} \le C. \tag{36}$$

Proof. The first part is an immediate consequence of lemma 4. For the second one, lemma 5 leads to

$$\eta_k - \eta_{k-1}\ \le -\frac{1}{4}\int_\Omega \tau(|\alpha_{kx}|^2+|\beta_{kx}|^2)dx\ + C\tau \text{ for } k=1,...,N.$$

Summing these inequalities from $k=1$ to $k=m$, for $1\le m\le N$, we get

$$\eta_m - \eta_0\ \le -\frac{1}{4}\sum_{k=1}^m\int_\Omega \tau(|\alpha_{kx}|^2+|\beta_{kx}|^2)dx + Cm\tau$$

then

$$\max_{1\le m\le N}\eta_m + \frac{1}{4}\sum_{k=1}^N\int_\Omega \tau(|\alpha_{kx}|^2+|\beta_{kx}|^2)dx \le \eta_0\ + CT$$

which can be written as

$$\|\eta^{(\tau)}\|_{L^\infty(0,T)} + \frac{1}{4}\int_\Omega\sum_{k=1}^N\int_{t_{k-1}}^{t_k}(|\alpha_{kx}|^2+|\beta_{kx}|^2)dtdx \le \eta_0 + CT.$$

This means that

$$\|\eta^{(\tau)}\|_{L^\infty(0,T)} + \frac{1}{4}\int_{Q_T}(|\alpha_x^{(\tau)}|^2 + |\beta_x^{(\tau)}|^2)dtdx \leq \eta_0 \ + CT. \quad \square$$

As a final preparation we state the following result

Lemma 7 *There exists a positive constant C independent of τ such that*

$$\|\tilde{\alpha}^{(\tau)}\|_{H^1\left(0,T;(H^1(\Omega))'\right)}, \quad \|\tilde{\alpha}^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} \leq C \tag{37}$$

$$\|\tilde{\beta}^{(\tau)}\|_{H^1\left(0,T;(H^1(\Omega))'\right)}, \quad \|\tilde{\beta}^{(\tau)}\|_{L^2(0,T;H^1(\Omega))} \leq C \tag{38}$$

$$\|\tilde{\alpha}^{(\tau)} - \alpha^{(\tau)}\|_{L^2\left(0,T;(H^1(\Omega))'\right)}, \quad \|\tilde{\beta}^{(\tau)} - \beta^{(\tau)}\|_{L^2\left(0,T;(H^1(\Omega))'\right)} \leq C\tau. \tag{39}$$

Proof. We use (36) and the boundedness of $\alpha^{(\tau)}$ and $\beta^{(\tau)}$ to deduce that $\|\tilde{\alpha}_t^{(\tau)}\|_{L^2\left(0,T;(H^1(\Omega))'\right)}$ and thus $\|\tilde{\alpha}^{(\tau)}\|_{H^1\left(0,T;(H^1(\Omega))'\right)}$ are uniformly bounded.
Since $\tilde{\alpha}_x^{(\tau)} = (\frac{t}{\tau} - k + 1)\alpha_x^{(\tau)} + (k - \frac{t}{\tau})\bar{\alpha}_x^{(\tau)}$ on $(t_{k-1}, t_k] \times \Omega$ and $(k - \frac{t}{\tau}) \in [0,1]$, $k = 1, ..., N$ then thanks to lemma 6, we deduce that $\|\tilde{\alpha}^{(\tau)}\|_{L^2(0,T;H^1(\Omega))}$ is uniformly bounded. Now for (39), we have $\|\tilde{\alpha}^{(\tau)} - \alpha^{(\tau)}\|_{(H^1(\Omega))'} = |t - k\tau|\|\tilde{\alpha}_t^{(\tau)}\|_{(H^1(\Omega))'}$ which leads to the result by using (37). (38) and the second part of (39) are obtained similarly. $\square$

5 Passing to the limit as $\tau \to 0$: End of proof of theorem 1

Using (37) and (38) we deduce the existence of two functions α, β belonging to $L^2(0,T;H^1(\Omega)) \cap H^1(0,T;\left(H^1(\Omega)\right)')$ such that, as $\tau \to 0$, at least for some subsequences

$$\tilde{\alpha}^{(\tau)} \rightharpoonup \alpha \text{ and } \tilde{\beta}^{(\tau)} \rightharpoonup \beta \text{ weakly in } L^2\left(0,T;H^1(\Omega)\right) \cap H^1(0,T;\left(H^1(\Omega)\right)'). \tag{40}$$

Then Aubin compactness lemma and the compactness of the embedding of $H^1(\Omega)$ into L^∞ lead to the strong convergences

$$\tilde{\alpha}^{(\tau)} \longrightarrow \alpha \ \text{ and } \tilde{\beta}^{(\tau)} \longrightarrow \beta \text{ strongly in } L^2\left(0,T;L^\infty(\Omega)\right). \tag{41}$$

Moreover by lemma 6, we infer the existence of functions α', β' in $L^2\left(0,T;H^1(\Omega)\right)$ such that, as $\tau \to 0$, at least for some subsequences

$$\alpha^{(\tau)} \rightharpoonup \alpha' \ \text{ and } \ \beta^{(\tau)} \rightharpoonup \beta' \text{ weakly in } L^2\left(0,T;H^1(\Omega)\right) \tag{42}$$

and according to (39), (40) and (43), we derive that $\alpha' = \alpha$ and $\beta' = \beta$. To conclude that (α, β) is a weak solution of (1)-(3) it is sufficient to prove that

$$\alpha^{(\tau)} \rightarrow \alpha \ \text{ and } \ \beta^{(\tau)} \rightarrow \beta \text{ strongly in } L^2(Q_T). \tag{43}$$

To this end we observe that

$$\begin{aligned}
\|\alpha^{(\tau)}-\alpha\|_{L^2(Q_T)} &\leq \|\tilde{\alpha}^{(\tau)}-\alpha^{(\tau)}\|_{L^2(Q_T)}+\|\tilde{\alpha}^{(\tau)}-\alpha\|_{L^2(Q_T)}\\
&\leq \|\tilde{\alpha}^{(\tau)}-\alpha^{(\tau)}\|^{\frac{1}{2}}_{L^2(0,T;H^1(\Omega))}\,\|\tilde{\alpha}^{(\tau)}-\alpha^{(\tau)}\|^{\frac{1}{2}}_{L^2\left(0,T;(H^1(\Omega))'\right)}\\
&\quad +\|\tilde{\alpha}^{(\tau)}-\alpha\|_{L^2(Q_T)}.
\end{aligned}$$

Using (36), (37), (39) and (41), it is straightforward to deduce that $\alpha^{(\tau)}\to\alpha$ strongly in $L^2(Q_T)$. Analogously, we obtain that $\beta^{(\tau)}\to\beta$ strongly in $L^2(Q_T)$.
Finally, since $H^1(0,T;(H^1(\Omega))')\cap L^2(0,T;H^1(\Omega))\subset\mathcal{C}^0([0,T];L^2(\Omega))$, the initial conditions are satisfied and thus (α,β) is a weak solution of (1)-(3) in the sense of definition 1. This ends the proof of theorem 1.

Remark 1 *All the results proved in this work remain valid if we replace the assumption* $(\mathbf{A_1})$ *by*
$(\mathbf{A1_1})$ $\frac{8}{7}\max(\lambda,\mu)\leq P_0\leq\frac{18}{7}(\lambda+\mu),\ \ \theta=0$
or
$(\mathbf{A1_2})$ $\frac{2}{3}\max(\lambda,\mu)\leq P_0\leq\frac{8}{7}\min(\lambda,\mu),\ \ \theta=0.$
Indeed direct calculations show that in these cases, (13) becomes

$$(-2\mu\beta-2\lambda\alpha+2P_0)^2\leq\frac{9}{4}\left(2\lambda(1-\alpha)+P_0\right)\left(2\mu(1-\beta)+P_0\right)$$

6 Appendices

6.1 Proof of lemma 3

(23) is equivalent to say that

$$\Big[\mathbf{D}^{\varepsilon}_{12}(r,s)(1+2\varepsilon e^{-r})+\mathbf{D}^{\varepsilon}_{21}(r,s)(1+2\varepsilon e^{-s})\Big]^2\leq$$

$$4\Big[\mathbf{D}^{\varepsilon}_{11}(r,s)\left(1+2\varepsilon e^{-r}\right)-\varepsilon^2\Big]\Big[\mathbf{D}^{\varepsilon}_{22}(r,s)\left(1+2\varepsilon e^{-s}\right)-\varepsilon^2\Big] \tag{44}$$

and we have

$$\Big[(\mathbf{D}^{\varepsilon}_{12}(r,s)(1+2\varepsilon e^{-r})+\mathbf{D}^{\varepsilon}_{21}(r,s)(1+2\varepsilon e^{-s})\Big]^2=$$

$$e^{2(r+s)}(e^r+e^s-1)^2+4\varepsilon^2e^{2r}(e^r-\frac{1}{2})^2+4\varepsilon^2e^{2s}(e^s-\frac{1}{2})^2+8\varepsilon^2e^{r+s}(e^r-\frac{1}{2})(e^s-\frac{1}{2})$$

$$+4\varepsilon e^{2r+s}(e^r-\frac{1}{2})(e^r+e^s-1)+4\varepsilon e^{r+2s}(e^s-\frac{1}{2})(e^r+e^s-1)=\sum_{k=1}^{6}I_k$$

I_k denoting the successive terms of the equality. We split the proof into two cases
Case 1- We suppose that $e^r+e^s\leq 1$ so that

$$\mathbf{D}^{\varepsilon}_{11}(r,s)\left(1+2\varepsilon e^{-r}\right)-\varepsilon^2=e^{2r}(\frac{3}{2}-e^r)+\varepsilon e^r+2\varepsilon e^r(\frac{3}{2}-e^r)+\varepsilon^2$$

$$\mathbf{D}^{\varepsilon}_{22}(r,s)\left(1+2\varepsilon e^{-s}\right)-\varepsilon^2=e^{2s}(\frac{3}{2}-e^s)+\varepsilon e^s+2\varepsilon e^s(\frac{3}{2}-e^s)+\varepsilon^2.$$

To handle I_1, we use (13) to see that

$$I_1 \le [e^{2(r)}(\frac{3}{2} - e^r)]\ [e^{2s}(\frac{3}{2} - e^s)].$$

Now to estimate I_2, I_3, ..., I_6 we make use of the fact that for $a = e^r$ or e^s

$$|a - \frac{1}{2}| \le \frac{1}{2} \le (\frac{3}{2} - a)$$

to have

$$I_2 \le 2\varepsilon^2[e^{2r}(\frac{3}{2} - e^r)^2], \quad I_3 \le 2\varepsilon^2[e^{2s}(\frac{3}{2} - e^s)^2], \quad I_4 \le \varepsilon e^r[2\varepsilon e^s(\frac{3}{2} - e^s)]$$

$$I_5 \le 4[e^{2r}(\frac{3}{2} - e^r)]\ [\varepsilon e^s], \quad I_6 \le 4[\varepsilon e^r]\ [e^{2s}(\frac{3}{2} - e^s)]$$

which concludes the proof in the first case.
Case 2- We suppose that $e^r + e^s > 1$ therefore

$$\mathbf{D}^{\varepsilon}_{11}(r,s)\left(1 + 2\varepsilon e^{-r}\right) - \varepsilon^2 =$$

$$e^{2r}(\frac{1}{2} + e^s) + e^{2r+s}(e^r + e^s - 1) + \varepsilon e^r + 5e^r(e^r + e^s - 1)(e^s + e^r) +$$

$$2\varepsilon e^r(\frac{1}{2} + e^s) + 2\varepsilon e^{r+s}(e^r + e^s - 1) + 10\varepsilon(e^r + e^s - 1)(e^r + e^s) + \varepsilon^2$$

and

$$\mathbf{D}^{\varepsilon}_{22}(r,s)\left(1 + 2\varepsilon e^{-s}\right) - \varepsilon^2 =$$

$$e^{2s}(\frac{1}{2} + e^r) + e^{r+2s}(e^r + e^s - 1) + \varepsilon e^s + 5e^s(e^r + e^s - 1)(e^s + e^r) +$$

$$2\varepsilon e^s(\frac{1}{2} + e^r) + 2\varepsilon e^{r+s}(e^r + e^s - 1) + 10\varepsilon(e^r + e^s - 1)(e^r + e^s) + \varepsilon^2.$$

First using (15) we get

$$I_1 \le \frac{9}{4}\ [e^{2r}(\frac{1}{2} + e^s) + e^{2r+s}(e^r + e^s - 1)]\ [e^{2s}(\frac{1}{2} + e^r) + e^{r+2s}(e^r + e^s - 1)].$$

Now to estimate I_2, we distinguish two cases

- If $e^r \le \frac{1}{2} + \frac{1}{\sqrt{2}}$ then $(e^r - \frac{1}{2})^2 \le \frac{1}{2} \le \frac{1}{2} + e^s$ and

$$I_2 \le 4\varepsilon^2\ [e^{2r}(\frac{1}{2} + e^s)]$$

- If $e^r > \frac{1}{2} + \frac{1}{\sqrt{2}}$ then $e^r - \frac{1}{2} \le 6(e^r + e^s - 1)$ and

$$I_2 \le \frac{36}{25}\ [10\varepsilon(e^r + e^s - 1)(e^r + e^s)]^2.$$

Notice that I_3 can be estimated in the same way.
Now for I_4, taking into account that $(e^r - \frac{1}{2})(e^s - \frac{1}{2}) \leq (e^r + \frac{1}{2})(e^s + \frac{1}{2})$, we see that

$$I_4 \leq 4\ [2\varepsilon e^r(\frac{1}{2} + e^r)]\ [2\varepsilon e^s(\frac{1}{2} + e^s)].$$

To estimate I_5, we consider two cases
• If $e^r \leq \frac{3}{2}$ we have

$$|I_5| \leq \frac{4}{5}\ \varepsilon e^r\ [5e^s(e^r + e^s - 1)(e^r + e^s)]$$

• If $e^r > \frac{3}{2}$, the inequality $e^r - \frac{1}{2} < 6(e^r + e^s - 1)$ leads to

$$I_5 \leq 24\varepsilon e^s(e^r + e^s)^2(e^r + e^s - 21)^2 \leq \frac{12}{25}\ [10\varepsilon(e^r + e^s - 1))(e^r + e^s)]\ [5e^s(e^r + e^s - 1))(e^r + e^s)].$$

I_6 can be estimated along the same lines as I_5 and we get the result.

6.2 Derivation of the model

Rapid tumor cells proliferation in some areas may outstrip the rate of new blood vessel growth and this may also cause hypoxic areas (low oxygen tension) to form, see [5]. Well oxygenated tumor cells are markedly more responsive to radiotherapy than their hypoxic counterparts, chemotherapy agents only kill tumor cells if they are rapidly proliferating so the non proliferative hypoxic fractions of tumor are relatively resistant to their effects. While in hypoxia, non proliferative state, tumor cells are also known to secrete cytokines and enzymes to induce the growth of new blood vessels within the tumor, providing thereby oxygen and nutrients for tumor growth. Because these hypoxic areas are relatively inaccessible to conventional anticancer drugs and gene vectors (due to the absence of a blood supply), recent research has focused on the development of novel drug/gene vectors capable of penetrating these regions in tumors [17]. Macrophages are the mature form in tissue of a type of white blood cells known as monocytes. They are present in all tissues. It has been established that the majority of malignant tumors contain numerous macrophages. These macrophages are referred as tumor associated macrophages (from now on abbreviated by TAMs); they are able to kill (lyse) mutant cells. Tumor cells and TAMs both release factors which can affect each other's activity and so, the details of this regulation can have important consequences for the survival of tumors. It was thought that the main function of TAMs was to exert direct cytotoxic effect on tumor cells. However, several authors recently suggested that these cells can also promote tumor growth and metastasis and play an important role in promoting angiogenesis (the development of new blood vessels from an existing vascular network) which ensures the adequate supply of oxygen and nutrients for tumor cells. TAMs are also attracted into and/or immobilized in avascular and necrotic hypoxic areas of vascularized tumors. Then it has been suggested that given their propensity for hypoxic areas, macrophages could be used as delivery vehicles to target hypoxia-regulated gene therapy to such sites.

For the convenience of the reader, we derive following [2], [3], [7], [14] and [18], the model discussed in this paper.

The vascular tumor is viewed as a mixture of three constituents: tumor cells, TAMs and blood vessels. We denote their respective volume fractions by α, β and γ. We note that microscopic changes in the oxygen tension in the tumor mass between blood vessels can be averaged out. Thus the local average oxygen tension can be characterized by the functional blood vessels volume fraction so that we do not explicitly include oxygen tension as a dependent variable [4]. We suppose that the mixture is satured so we take

$$\alpha + \beta + \gamma = 1. \tag{45}$$

We associate with each phase a velocity, a pressure and a spatial stress (the force that the phase exerts on itself): they are denoted by (v_1, P_1, σ_1) for the tumor cells, (v_2, P_2, σ_2) for the TAMs and (v_3, P_3, σ_3) for the blood vessels. We formulate conservation of mass equations for the three volume fractions, under the assumption that each phase has the same constant density ($\rho_1 = \rho_2 = \rho_3$). In one dimensional case, the equations read

$$\alpha_t + (\alpha v_1)_x = q_1(\alpha, \beta, \gamma) \ , \ \beta_t + (\beta v_2)_x = q_2(\alpha, \beta, \gamma) \text{ and } \gamma_t + (\gamma v_3)_x = q_3(\alpha, \beta, \gamma) \tag{46}$$

where q_1, q_2 and q_3 are the rates of production related to each phase. We assume that the momentum is conserved and that the motion of cells and blood vessels are so slow that inertial terms can be neglected, so we can write

$$(\alpha\sigma_1)_x + F_1 = 0 \ , \ \ (\beta\sigma_2)_x + F_2 = 0, \ \ (\gamma\sigma_3)_x + F_3 = 0 \tag{47}$$

where F_1, F_2 and F_3 are the momentum supply related to each phase. Equations (46) and (47) are closed by introducing suitable constitutive relations for q_1, q_2 , q_3, σ_1, σ_2, σ_3, F_1, F_2 and F_3.

Rates of production. Let k_i , $i = 1, ..., 11$ be non-negative rate constants.
We assume that the *tumor cells* proliferate only if the level of oxygen is sufficient, in other words in the presence of blood vessels. The death of tumor cells can be either natural (apoptosis) or programmed due to low oxygen tension (necrosis) or caused by TAMs. Then we can choose

$$q_1 = k_1\alpha\gamma - k_2\alpha - k_3\,(1-\gamma)\,\alpha - k_4\alpha\beta. \tag{48}$$

The *tumor associated macrophages* proliferate proportionally to the volume fraction. In addition, there is an influx from capillaries which increases with the decrease of tumor cells and blood vessels. They die, but the presence of tumor cells promotes TAMs survival and become inactivated when they lyse tumor cells. Thus we write

$$q_2 = k_5\beta + k_6\beta\,(1 - \sigma\,(\alpha+\gamma)) - k_7\beta\,(1-\alpha) - k_8\alpha\beta. \tag{49}$$

The volume fraction of *blood vessels* increases by angiogenesis which can be stimulated either by TAMs or by tumor cells. Blood vessels become dysfunctional when the local pressure exerted on them by tumor cells (αP_1) exceeds a critical pressure P^*. Then we choose

$$q_3 = k_9\beta\gamma + k_{10}\alpha\gamma - k_{11}\gamma H\,(\alpha P_1 - P^*)\,. \tag{50}$$

Partial stress tensors. We neglect viscous effect and we assume

$$\sigma_1 = -P_1 = -\,(P + \Sigma_1) \ \ , \sigma_2 = -P_2 = -\,(P + \Sigma_2) \ \text{ and } \sigma_3 = -P_3 \tag{51}$$

where P is assumed to be common pressure and Σ_1 and Σ_2 represent the pressures due to cell-cell interactions (compression) exerted on tumor cells and macrophages. We assume that the pressure on macrophages increases as its volume fraction increases and that the presence of tumor cells generates an additional stress in the macrophages, so we write

$$\Sigma_2 = \mu\, \beta\, (1 + \theta\alpha) \tag{52}$$

where μ and θ are nonnegative constants. Now we turn our attention to Σ_1. The assumption that the TAMs have the ability to migrate into hypoxic areas of tumor mass and to accumulate in large numbers in such areas, allows us to suppose that the tumor cells are insensitive to the effects of the presence of TAMs in the well oxygenated areas. Furthermore, TAMs are immobilized in hypoxic areas, see [11], hence the tumor cells are insensitive to the effects of TAMs in the hypoxic areas. In summary we choose Σ_1 to be independent of β

$$\Sigma_1 = \lambda\alpha \tag{53}$$

where λ is a nonnegative constant. It remains to choose P_3. We suppose that the tumor undergoes one-dimensional growth, parallel to the x-axis, by occupying the region

$$l_1(t) \leq x \leq l_2(t)$$

at time t. Under this assumption we can choose

$$P_3 = P + P_0, \tag{54}$$

where P_0 is the externally set pressure constant.

Momentum source terms. We suppose that there are momentum source due to interfacial pressures or interaction between two phases. We set

$$\begin{aligned} F_1 = &\quad P\alpha_x + d_1\alpha\beta\,(v_2 - v_1) + d_2\alpha\gamma\,(v_3 - v_1) &(55)\\ F_2 = &\quad P\beta_x - d_1\alpha\beta\,(v_2 - v_1) + d_3\beta\gamma(v_3 - v_2) &(56)\\ F_3 = &\quad P\gamma_x - d_2\alpha\gamma\,(v_3 - v_1) - d_3\beta\gamma\,(v_3 - v_2)\,. &(57)\end{aligned}$$

In the following, we can proceed as in [2], [3], [7] and [14] and we introduce

$$v_{mix} = \alpha v_1 + \beta v_2 + \gamma v_3. \tag{58}$$

Summing the three continuity equations (46) and the three momentum equations (47), we get

$$(v_{mix})_x = q_1 + q_2 + q_3 \tag{59}$$

$$(\alpha\sigma_1)_x + (\beta\sigma_2)_x + (\gamma\sigma_3)_x = 0$$

which give using (51)

$$P_x = -\left(\alpha\Sigma_1 + \beta\Sigma_2 + \gamma P_0\right)_x. \tag{60}$$

Moreover using (58) and (55), the first equation of (47) reduces, in the case $d_1 = d_2 = d_3 = d$, to give either $\alpha = 0$, which we reject because it can be only transient, or

$$P_x + \frac{1}{\alpha}\,(\alpha\Sigma_1)_x = -dv_1 + dv_{mix},$$

this, after the use of (60), means that

$$v_1 = v_{mix} + \frac{1}{d}\left((\alpha\Sigma_1 + \beta\Sigma_2 + \gamma P_0)_x - \frac{1}{\alpha}(\alpha\Sigma_1)_x \right). \tag{61}$$

Using (51), (52), (53) and the fact that P_0 is constant, (61) can be rewritten as follows

$$v_1 = v_{mix} + \frac{1}{d}\left(\alpha_x\left(2\lambda\alpha + \mu\theta\beta^2 - P_0 - 2\lambda\right) + \beta_x\left(2\mu\beta\left(1+\theta\alpha\right) - P_0\right)\right). \tag{62}$$

Similarly using (58) and (56), the second equation of (47) reduces to

$$v_2 = v_{mix} + \frac{1}{d}\left(\alpha_x\left(2\lambda\alpha + \mu\theta\beta^2 - P_0 - \mu\theta\beta\right) + \beta_x\left(2\mu\left(\beta-1\right)\left(1+\theta\alpha\right) - P_0\right)\right). \tag{63}$$

Substituting the relations (62) and (63) in (46), the resulting equations for α and β are given by

$$\alpha_t + (\alpha v_{mix})_x - \frac{1}{d}\left(\left(2\lambda\alpha\left(1-\alpha\right) - \mu\theta\alpha\beta^2 + P_0\alpha\right)\alpha_x + \left(-2\mu\beta\alpha\left(1+\theta\alpha\right) + P_0\alpha\right)\beta_x\right)_x = q_1$$

$$\beta_t + (\beta v_{mix})_x - \frac{1}{d}\left(\left(-2\lambda\alpha\beta + \mu\theta\beta^2\left(1-\beta\right) + P_0\beta\right)\alpha_x + \left(2\mu\beta\left(1-\beta\right)\left(1+\theta\alpha\right) + P_0\beta\right)\beta_x\right)_x = q_2.$$

Here the nonlinear diffusion is due to cell-cell interactions and the externally set pressure. In the case $P_0 = 0$, the above system has been obtained by Jackson and Byrne in [14]. They presented therein a mathematical modeling framework to describe the growth, encapsulation and transcapsular spread of solid tumors. To derive the boundary conditions, we limit ourselves to a non symmetric situation in which the tumor grows only on the right side. This allows us to take $l_1(t) = 0$ for all $t \geq 0$. Then we suppose that the free boundary of the tumor moves at the same speed as the tumor cells so

$$\frac{\partial l_2}{\partial t} = v_1|_{x=l_2(t)}. \tag{64}$$

For simplicity, we suppose that

$$q_1 + q_2 + q_3 = 0. \tag{65}$$

We complement the system with the following initial and boundary conditions. At $t = 0$, we set

$$l_2 = l > 0\ ,\ \ \alpha = \alpha_0 \geq 0\ ,\ \ \beta = \beta_0 \geq 0 \text{ and } \ \gamma = 1 - \alpha_0 - \beta_0 \geq 0 \tag{66}$$

and at $x = 0$, we suppose that $\alpha = \alpha^1$, $\beta = \beta^1$, with $0 < \alpha_1, \beta_1, \alpha_1 + \beta_1 \leq 1$.
Now at the free boundary $x = l_2(t)$, we impose the no flux boundary conditions

$$v_1 = v_2 = v_3 = 0 \tag{67}$$

which implies with (64), that $\frac{\partial}{\partial t}(l_2) = v_1|_{x=l_2(t)} = 0$ i.e. $l_2(t) = l$ for all $t \geq 0$.
Moreover, combining (59), (65), (58) and (67), we obtain

$$v_{mix} = 0 \ \text{ for all } t > 0\ ,\ \ x \in (0, l). \tag{68}$$

Thus, if $\theta = 0$ and $\lambda = \mu$, inserting (68) and (67) into (62) and (63), we see that

$$\alpha_x = \beta_x = 0 \text{ at } x = l \tag{69}$$

In summary, we have obtained the model (1)-(3).

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