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AN OXYGEN DRIVEN PROLIFERATIVE-TO-INVASIVE TRANSITION OF GLIOMA CELLS: AN ANALYTICAL STUDY

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Dedicated to Maurizio Grasselli on the occasion of his 60th birthday

ABSTRACT. Our aim in this paper is to analyze a model of glioma where oxygen drives cancer diffusion and proliferation. We prove the global well-posedness of the analytical problem and that, in the longtime, the illness does not disappear. Besides, the tumor dynamics increase the oxygen levels.

1. Introduction. Glioma are tumors of glial cells. Due to their location, direct approaches to the affected tissues are difficult; at the same time a large amount of data is obtained by diagnostics, like MRI and PET-scan, but their interpretation is not obvious. Two mechanisms are particularly relevant: illness invasion and proliferation interacting with nutrients dynamics; indeed, a modified energy metabolism is one of the hallmarks of cancer. In particular, low nutrient levels may starve the tumor but, at the same time, they put at risk the cell survival. On the other side, high nutrient levels feed healthy cells as well as the tumor. Analytical results may help to understand this interaction. In this paper, in particular, we analyze a glioma model proposed in [5]; there, the state variables are the tumor cells density u and a nutrient (oxygen) concentration σ ; their evolution in the brain, represented by a bounded and smooth domain $\Omega \subset \mathbb{R}^3$, is dictated by two parabolic equations: in particular, the cancer rate of change is given by the net migration and proliferation of tumor cells. The weights of these two effects are regulated by the oxygen concentration: indeed, below an oxygen threshold, invasion prevails while it is surpassed by proliferation above that threshold. Moreover, the migration mechanism is not uniform in the brain: indeed, it is faster in white matter than in grey matter. As a consequence, having normalized the carrying capacity, the tumor cells density equation is

$$\partial_t u - \operatorname{div}(D(x, \sigma) \nabla u) = h(\sigma)u(1 - u), \quad \text{in } \Omega, \quad t > 0. \quad (1)$$

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As anticipated, the diffusion coefficient of tumor cells depends on the anatomy of the brain and on the oxygen concentration: it is

$$D(x, \sigma) = D(x)B(\sigma), \quad \text{where} \quad B(\sigma) = \left[\frac{\sigma}{\beta} + \delta \left(1 - \frac{\sigma}{\beta} \right) \right], \quad (2)$$

for constants $\delta, \beta > 0$. In particular, β corresponds to the oxygen concentration in blood vessels. The function $D(x)$ is the diffusion coefficient of tumor cells in normoxic conditions and satisfies

$$0 < D_1 \leq D(x) \leq D_2, \quad \text{for any} \quad x \in \Omega,$$

where D_1 and D_2 are the diffusion coefficient in grey and white matter, respectively. Therefore, owing to the different tumor invasiveness in grey and white matters, $D_2 > D_1$. Biologically meaningful values are

$$\delta = 10 \quad \text{and} \quad 5 \leq \frac{D_2}{D_1} \leq 50.$$

In general, $\delta > 1$ since hypoxia increases migration and diffusion of tumor cells. At the same time, hypoxia reduces the tumor proliferation rate (see, e.g., [13]): in [5], oxygen's influence on cancer proliferation is regulated by the function

$$h(\sigma) = a \left[\frac{\sigma}{\beta} + b \left(1 - \frac{\sigma}{\beta} \right) \right] \quad (3)$$

with $a, b > 0$ and $b \sim 0.6 < 1$. Indeed, reasonable values of b reflect the reduced proliferation rate under hypoxia, so the condition $b < 1$ is natural. The parameter a corresponds to the proliferation rate in normoxic conditions.

The rate of change of oxygen depends on its diffusion, its uptake by tumor cells and the oxygen entering from blood vessels: oxygen evolution obeys

$$\partial_t \sigma - \Delta \sigma = -\frac{u\sigma}{1+\sigma} + \gamma(\beta - \sigma), \quad \text{in} \quad \Omega, \quad t > 0. \quad (4)$$

Here, the oxygen consumed by tumor cells is modeled by Michaelis-Menten kinetics (again some constants have been set equal to one), while the release rate of oxygen from blood vessels $\gamma > 0$ depends on vascular permeability and density.

We assume no flux boundary conditions, meaning that no tumor cells nor oxygen enter or exit the brain, namely,

$$\partial_{\mathbf{n}} u = \partial_{\mathbf{n}} \sigma = 0, \quad \text{on} \quad \partial\Omega, \quad t > 0, \quad (5)$$

being \mathbf{n} the exterior normal vector to the boundary $\partial\Omega$. Finally, we suppose that the initial tumor and oxygen configurations are known, that is,

$$u(0) = u_0, \quad \sigma(0) = \sigma_0, \quad \text{in} \quad \Omega. \quad (6)$$

This model, neglecting the dependence on the tumor diffusion coefficient on the brain anatomy and the oxygen (that is, with constant D and $\delta = 1$), has been studied in [4], where also homogeneous Dirichlet boundary conditions were considered. In this setting and for both Dirichlet and Neumann boundary conditions, less regular data were required to obtain the existence and uniqueness of solutions than those we are forced to consider here. An invariant region was devised for the dynamics, corresponding to $0 \leq u \leq 1$ and $0 \leq \sigma \leq \beta$. Moreover, in [4], tumor extinction is prevented with no flux boundary conditions, while it occurs with Dirichlet boundary conditions when invasion dominates proliferation. Otherwise, cancer permanence is shown with the same boundary conditions when proliferation prevails.

When $b = \delta = 1$, (1) amounts to the classical Fisher-Kolmogorov equation but the interesting case is when $b \in (0, 1)$ and $\delta > 1$: indeed, this renders the competition between the two effects (proliferation versus migration) dictated by the oxygen concentration and accounting for cells phenotype changes. This also translates into an analytical problem since one expects the oxygen concentration to stay below the threshold giving a *negative* diffusion, provided that this is initially the case. Thus the oxygen dependence on the diffusion coefficient introduces an analytical difficulty as the following properties should be preserved by the evolution:

- if the initial data are biologically relevant (i.e. nonnegative), the corresponding solutions stay the same; in particular,
- if the initial tumor concentration varies in the biological interval $[0, 1]$, this will happen for any time;
- if the initial oxygen concentration in the cells lies below that in blood vessels, then this will be true forever.

Since the oxygen threshold for null diffusion, $\frac{\delta}{\delta-1}\beta$, is above the oxygen concentration in blood β , one should think that, if the initial data are good, it is trivial to have migration for any time: still, from an analytical point of view, it is not obvious to prove the existence of a solution by the Galerkin method. Indeed, the projections used in this framework do not preserve the biological bounds. Thus, the existence of a solution can not be obtained directly for the original problem, due to possible singularities in the symport term and also to the possible lack of good estimates for u on account of its oxygen dependent diffusion.

This obstacle is circumvented resorting to strong solutions (and, accordingly, better initial data) and by analyzing an auxiliary problem where we tame the singularity, we use a suitable cut-off function for tumor concentration and we consider a perturbation of our problem exhibiting a further dissipation, involving a second cut-off function. Actually, a third cut-off function intervenes in tumor evolution so to avoid the boundedness of the proliferation rate h , a condition not fulfilled by (3). Galerkin method applies to this system for which the existence of a local strong solution is then proved: since the viable domain of the cells is proved to be an invariant region for the modified system, actually its solutions solve the original problem as well. In fact, this solution is unique and global on any finite time interval.

We then prove that tumor extinction does not occur, as happened with Neumann boundary conditions in [4], where the normoxic diffusion D was constant and $\delta = 1$. Actually, we can prove that the tumor grows in time and, if the minima of oxygen and tumor concentrations are strictly positive, the tumor density u tends exponentially to 1.

Moreover, as was pointed out in [5] on the base numerical simulations, the tumor appears to normalize oxygen levels: in a sense, this is confirmed by our results, since the oxygen level is proved to stay above a strictly positive trajectory, if initially this is the case.

The plan of the paper is the following: in section 2, we make precise our notations, assumptions and functional setting to be applied, in the next section, to the auxiliary problem; this is proved to be well posed and to have the aforementioned invariant region. Therefore, in section 4, we can assert the well posedness of the original problem and, in the last section, conclude with some remarks on the longtime behavior of both u and σ .

We conclude the introduction with a short review of the related literature: recently different points of view on the coupled glioma-oxygen dynamics were studied, e.g., in [7], [9], [10] and [12]. Other nutrients beyond oxygen are considered to understand metabolic changes in the tumor: in particular, essential energetic sources are glucose and lactate (see, e.g., [1], [2], [3], [8], [11]). Indeed, even with plenty of oxygen, sometimes the tumor prefers glucose as an energy source: this is the Warburg effect. In this case, lactate is a glycolysis output but it is subsequently used as an energy substrate as well. The role of lactate, and especially of lactate in the different cellular compartments of the brain, in connection with the tumor evolution, is not yet well understood.

2. The mathematical problem. As we motivated in the Introduction, we now address the initial boundary value problem

$$\begin{cases} \partial_t u - \operatorname{div}(D(x)B(\sigma)\nabla u) = h(\sigma)u(1-u), & \text{in } \Omega, \quad t > 0, \\ \partial_t \sigma - \Delta \sigma = -\frac{u\sigma}{1+\sigma} + \gamma(\beta - \sigma), & \text{in } \Omega, \quad t > 0, \\ \partial_{\mathbf{n}} u = \partial_{\mathbf{n}} \sigma = 0, & \text{on } \partial\Omega, \quad t > 0, \\ u(0) = u_0, \quad \sigma(0) = \sigma_0, & \text{in } \Omega. \end{cases} \quad (7)$$

Here $\Omega \subset \mathbb{R}^3$ is a connected and bounded domain with smooth boundary $\partial\Omega$. The functions D and h are those defined in (2) and (3). We also recall that the constants $a, b, \alpha, \beta, \gamma, \delta$ are positive.

In order to specify our assumptions, some notations are needed.

2.1. Analytical framework. We denote by $L^p(\Omega)$ the Lebesgue spaces endowed with the usual norm $\|\cdot\|_{L^p}$; in particular, $H = L^2(\Omega)$ is an Hilbert space equipped with the scalar product (\cdot, \cdot) and corresponding norm $\|\cdot\|$. The general Sobolev spaces are $W^{p,k}(\Omega)$: we will mostly deal with $H^k(\Omega) = W^{2,k}(\Omega)$ whose norm is $\|\cdot\|_{H^k}$. In the particular case $k = 1$, we set $V = H^1(\Omega)$ with norm $\|\cdot\|_V$. Then we recall that (V, H, V^*) is an Hilbert triplet, where V^* is the dual space of V and the corresponding duality pairing is denoted as $\langle \cdot, \cdot \rangle$. We also use the Hilbert spaces

$$W = H_N^2(\Omega) = \{v \in H^2(\Omega) : \partial_{\mathbf{n}} v = 0 \text{ on } \partial\Omega\}$$

and

$$Z = \{v \in H^3(\Omega) \cap H_N^2 : \nabla v \in [H_N^2(\Omega)]^3\},$$

whose norms are $\|\cdot\|_W$ and $\|\cdot\|_Z$, respectively. The solution of our problem will be time dependent with values in Banach spaces: more precisely, given a time interval I and a Banach spaces X , we recall that $L^p(I; X)$ is the space of measurable functions $f : I \rightarrow X$ such that $\|f(\cdot)\|_X \in L^p(I)$.

In the subsequent computations, we will take advantage of the 3-D Gagliardo–Nirenberg inequality:

$$\|v\|_{L^3(\Omega)} \leq c \|v\|^{\frac{1}{2}} \|v\|_V^{\frac{1}{2}}, \quad \forall v \in V. \quad (8)$$

Here c stands for a suitable positive constant; the same symbol will be used throughout the paper for any positive constant, possibly depending on the time span $T > 0$ and the structural data of the system; this constant is allowed to vary also in the same line.

Having these notations at our disposal, we can now make our assumptions precise.

2.2. Assumptions.

(H1) $D \in W^{1,6}(\Omega)$ such that $0 < D_1 \leq D(x) \leq D_2$ in Ω ;

(H2) $\delta > 1$ and $b \in (0, 1)$;

(H3) $u_0 \in V$ and $\sigma_0 \in W$ verify also $0 \leq u_0 \leq 1$ and $0 \leq \sigma_0 \leq \beta$ a.e. in Ω .

We adopted h and B as prescribed in [5] just for the sake of simplicity but our results hold for h increasing and Lipschitz continuous with $h(0) \geq 0$ and B decreasing and Lipschitz continuous with $B(\beta) > 0$.

3. An auxiliary problem. We will prove the well-posedness of an auxiliary problem obtained from the original one introducing cut-off functions and making harmless the singular term $\frac{\sigma}{1+\sigma}$. Of course, the new problem should not be too different from (7), so the changes should affect only regions ultimately escaped by biological solutions. The function B in the diffusion coefficient of the tumor will be replaced as follows: let $\mathbf{B} : \mathbb{R} \rightarrow [0, +\infty)$ be

$$\mathbf{B}(\sigma) = \begin{cases} \delta, & \text{if } \sigma \leq 0, \\ \delta + (1 - \delta)\frac{\sigma}{\beta}, & \text{if } 0 \leq \sigma \leq \beta, \\ 1, & \text{if } \sigma \geq \beta. \end{cases}$$

By definition, $\mathbf{B} \in W^{1,\infty}(\mathbb{R})$ verifies also $1 \leq \mathbf{B}(\leq \delta)$. Moreover, we see that $\mathbf{B}(\sigma) = B(\sigma)$, whenever $0 \leq \sigma \leq \beta$.

We further define the cut-off functions

$$\mathbf{h}(\sigma) = \begin{cases} h(0), & \text{if } \sigma \leq 0, \\ h(\sigma), & \text{if } 0 \leq \sigma \leq \beta, \\ h(\beta), & \text{if } \sigma \geq \beta, \end{cases} \quad \text{and} \quad \kappa(u) = \begin{cases} u(1-u), & \text{if } 0 \leq u \leq 1, \\ 0, & \text{otherwise.} \end{cases}$$

Finally, we set

$$g(\sigma) = \frac{\sigma}{1 + |\sigma|}.$$

Notice that $\mathbf{h}, \kappa \geq 0, g$ are bounded and Lipschitz continuous. Moreover, as happened with \mathbf{B} , if $0 \leq \sigma \leq \beta$ then $\mathbf{h}(\sigma) = h(\sigma)$ and $g(\sigma) = \frac{\sigma}{1 + \sigma}$. Analogously, if $0 \leq u \leq 1$, we have $\kappa(u) = u(1 - u)$.

Replacing also h by \mathbf{h} , $u(1 - u)$ by $\kappa(u)$ and introducing g in the symport term, we have our auxiliary problem as

$$\begin{cases} \partial_t \mathbf{u} - \operatorname{div}(D(x)\mathbf{B}(\mathbf{s})\nabla \mathbf{u}) = \mathbf{h}(\mathbf{s})\kappa(\mathbf{u}), & \text{in } \Omega \times (0, T), \\ \partial_t \mathbf{s} - \Delta \mathbf{s} = -\mathbf{u}g(\mathbf{s}) + \gamma(\beta - \mathbf{s}), & \text{in } \Omega \times (0, T), \\ \partial_{\mathbf{n}} \mathbf{u} = \partial_{\mathbf{n}} \mathbf{s} = 0, & \text{on } \partial\Omega \times (0, T), \\ \mathbf{u}(0) = u_0, \quad \mathbf{s}(0) = \sigma_0, & \text{in } \Omega, \end{cases} \quad (9)$$

on any finite interval $(0, T)$ for arbitrary $T > 0$.

We formally define the weak solution to the corresponding problem (9)

Definition 3.1. Given an initial datum $(u_0, \sigma_0) \in H \times V$, the pair (\mathbf{u}, \mathbf{s}) is a weak solution to (9) in $(0, T)$ if

$$\begin{aligned} \mathbf{u} &\in C([0, T]; H) \cap L^2(0, T; V) \cap H^1(0, T; V^*), \\ \mathbf{s} &\in C([0, T]; V) \cap L^2(0, T; W) \cap H^1(0, T; H), \end{aligned}$$

and if

$$\begin{cases} \langle \partial_t \mathbf{u}, v \rangle + (D(x)\mathbf{B}(\mathbf{s})\nabla \mathbf{u}, \nabla v) = (\mathbf{h}(\mathbf{s})\kappa(\mathbf{u}), v), \\ \langle \partial_t \mathbf{s}, w \rangle + (\nabla \mathbf{s}, \nabla w) = -(\mathbf{u}g(\mathbf{s}), w) + \gamma((\beta - \mathbf{s}), w), \end{cases} \quad (10)$$

for any $v, w \in V$, a.e. in $(0, T)$. Finally,

$$\mathbf{u}(0) = u_0, \quad \text{a.e. in } \Omega, \quad \text{and} \quad \mathbf{s}(0) = \sigma_0, \quad \text{a.e. in } \Omega.$$

Notice that the embedding $W^{1,6}(\Omega) \subset L^\infty(\Omega)$ justifies the above functional setting. Actually, we will be able to pass to the limit in the Galerkin scheme, and therefore to prove the existence of strong solutions, only for regular enough initial data.

Definition 3.2. Given an initial datum $(u_0, \sigma_0) \in V \times W$, the pair (\mathbf{u}, \mathbf{s}) is a strong solution to (9) in $(0, T)$ if

$$\begin{aligned} \mathbf{u} &\in C([0, T]; V) \cap L^2(0, T; W) \cap H^1(0, T; H), \\ \mathbf{s} &\in C([0, T]; W) \cap L^2(0, T; Z) \cap H^1(0, T; V), \end{aligned}$$

and if

$$\begin{cases} \partial_t \mathbf{u} - \operatorname{div}(D(x)\mathbf{B}(\mathbf{s})\nabla \mathbf{u}) = \mathbf{h}(\mathbf{s})\kappa(\mathbf{u}), & \text{a.e. in } \Omega \times (0, T), \\ \partial_t \mathbf{s} - \Delta \mathbf{s} = -\mathbf{u}g(\mathbf{s}) + \gamma(\beta - \mathbf{s}), & \text{a.e. in } \Omega \times (0, T). \end{cases}$$

Finally,

$$\mathbf{u}(0) = u_0, \quad \text{a.e. in } \Omega, \quad \text{and} \quad \mathbf{s}(0) = \sigma_0, \quad \text{in } \Omega.$$

The study of the auxiliary problem (9) is justified by the fact that any weak solution to (9) originating from initial data (u_0, σ_0) , with $0 \leq u_0 \leq 1$ and $0 \leq \sigma_0 \leq \beta$ a.e. in Ω , preserves these conditions in its evolution so that it is a weak solution to (7) as well. Indeed,

Lemma 3.3. *Let (\mathbf{u}, \mathbf{s}) be a weak solution to (9) originating from $(u_0, \sigma_0) \in H \times V$ satisfying $0 \leq u_0 \leq 1$ and $0 \leq \sigma_0 \leq \beta$ a.e. in Ω . Then $0 \leq \mathbf{u} \leq 1$ and $0 \leq \mathbf{s} \leq \beta$ a.e. in $\Omega \times [0, T]$.*

Proof. Testing the first equation in (10) by $-\mathbf{u}^- \in V$, where $\mathbf{u}^- = \max(0, -\mathbf{u})$, we obtain

$$\frac{1}{2} \frac{d}{dt} \|\mathbf{u}^-\|^2 + \int_{\Omega} D\mathbf{B}(\mathbf{s}) |\nabla \mathbf{u}^-|^2 dx = - \int_{\Omega} \mathbf{h}(\mathbf{s})\kappa(\mathbf{u})\mathbf{u}^- dx = 0.$$

Since, by definition of \mathbf{B} and (H1),

$$\int_{\Omega} D\mathbf{B}(\mathbf{s}) |\nabla \mathbf{u}^-|^2 dx \geq D_1 \|\nabla \mathbf{u}^-\|^2 \geq 0,$$

we are lead to

$$\frac{1}{2} \frac{d}{dt} \|\mathbf{u}^-\|^2 \leq 0.$$

Being $\|\mathbf{u}^-(0)\|^2 = 0$ owing to $0 \leq u_0 \leq 1$ a.e. in Ω , then $\|\mathbf{u}^-(t)\|^2 = 0$ follows for every t so that $\mathbf{u} \geq 0$ a.e. in $\Omega \times (0, T)$.

Testing the second equation in (10) by $-\mathbf{s}^- \in V$ and recalling the definition of g , we get

$$\frac{1}{2} \frac{d}{dt} \|\mathbf{s}^-\|^2 + \|\nabla \mathbf{s}^-\|^2 = - \int_{\Omega} \frac{\mathbf{u}|\mathbf{s}^-|^2}{1 + |\mathbf{s}^-|} + \gamma \int_{\Omega} (\beta + \mathbf{s}^-)(-\mathbf{s}^-).$$

Having already proved $\mathbf{u} \geq 0$, then the above right-hand side is less than or equal to zero. Integrating over $[0, t]$ the inequality $\frac{d}{dt} \|\mathbf{s}^-\|^2 \leq 0$, we have

$$\|\mathbf{s}^-(t)\|^2 \leq \|\mathbf{s}^-(0)\|^2$$

for all times, yielding $s \geq 0$ a.e. in $\Omega \times (0, T)$.

In order to obtain the upper bounds, we write the equation for $w = s - \beta$, that is,

$$\partial_t w - \Delta w = -\frac{us}{1+|s|} - \gamma w,$$

and we test it by $w^+ \in V$, where $w^+ = \max(w, 0)$:

$$\frac{1}{2} \frac{d}{dt} \|w^+\|^2 + \|\nabla w^+\|^2 = - \int_{\Omega} \frac{usw^+}{1+|s|} + \gamma \int_{\Omega} -|w^+|^2.$$

Since the right-hand side is ≤ 0 , we deduce from the Gronwall Lemma that, if $\|w^+(0)\| = 0$, then $\|w^+(t)\| = 0$ for every t , proving $s \leq \beta$ a.e. in $\Omega \times (0, T)$. Similarly, $v = u - 1$ satisfies

$$\partial_t v - \operatorname{div}(DB(s)\nabla v) = h(s)\kappa(u).$$

Testing this equation by $v^+ \in V$ and exploiting (H1), we find

$$\frac{1}{2} \frac{d}{dt} \|v^+\|^2 \leq \frac{1}{2} \frac{d}{dt} \|v^+\|^2 + D_1 \|\nabla v^+\|^2 \leq 0.$$

Being $v^+(0) = (u_0 - 1)^+ = 0$, it is straightforward to obtain that $v^+(t) = (u(t) - 1)^+ = 0$ for all t so that $u \leq 1$ a.e. in $\Omega \times (0, T)$ is accomplished as well. \square

Lemma 3.4. *For any (u_0, σ_0) satisfying (H3), there exists a local strong solution to (9).*

Proof. In order to prove the local existence of a weak solution to (9), we introduce the Galerkin approximation of the problem. Thus, let $0 = \lambda_1 < \lambda_2 \leq \dots$ be the eigenvalues of the minus Laplace operator associated with Neumann boundary conditions and e_1, e_2, \dots be associated eigenvectors such that $\{e_j\}_{j=1}^{\infty}$ forms an orthonormal basis in H which is also orthogonal in V . We set $V_n = \operatorname{Span}\{e_1, \dots, e_n\}$ and denote by \mathbb{P}_n the corresponding projection.

Now, for any fixed $n \in \mathbb{N}$ we consider the following approximated problem: Find $t_n > 0$ and $a_j, b_j \in C^1([0, t_n])$ such that

$$u_n(t) = \sum_{j=1}^n a_j(t)e_j \quad \text{and} \quad \sigma_n(t) = \sum_{j=1}^n b_j(t)e_j \in C^1([0, t_n], V_n)$$

satisfy

$$\begin{cases} \langle \partial_t u_n, v \rangle + (D(x)B(\sigma_n)\nabla u_n, \nabla v) = (h(\sigma_n)\kappa(u_n), v), & \forall v \in V_n, \\ \langle \partial_t \sigma_n, w \rangle + (\nabla \sigma_n, \nabla w) = -(u_n g(\sigma_n), w) + \gamma((\beta - \sigma_n), w), & \forall w \in V_n, \end{cases} \quad (11)$$

together with

$$u_n(0) = \mathbb{P}_n u_0, \quad \sigma_n(0) = \mathbb{P}_n \sigma_0, \quad \text{in a.e. } \Omega.$$

The existence and uniqueness for any $n \in \mathbb{N}$ of $(u_n, \sigma_n) \in C^1([0, t_n]; V_n)$ follows from Cauchy-Lipschitz Theorem, where the maximal existence time $t_n \in (0, T]$ depends on n .

In order to acquire estimates for (u_n, σ_n) uniform with respect to n , we multiply the first equation in (11) by u_n and the second by σ_n , then adding the results we

obtain

$$\begin{aligned} & \frac{1}{2} \frac{d}{dt} (\|u_n\|^2 + \|\sigma_n\|^2) + \int_{\Omega} DB(\sigma_n) |\nabla u_n|^2 dx + \|\nabla \sigma_n\|^2 + \gamma \|\sigma_n\|^2 \\ &= \int_{\Omega} h(\sigma_n) \kappa(u_n) u_n dx - \int_{\Omega} u_n g(\sigma_n) \sigma_n dx + \gamma \beta \int_{\Omega} \sigma_n dx. \end{aligned}$$

Here h , κ and g are bounded functions hence the rhs is bounded by

$$c(1 + \|u_n\|^2 + \|\sigma_n\|^2),$$

where the constant c is independent of $n \in \mathbb{N}$, although it may possibly be influenced by T and the structural data of the problem. In turn, due to the definition of B and the lower bound for D , the second term on the lefthand side is

$$\int_{\Omega} DB(\sigma_n) |\nabla u_n|^2 dx \geq D_1 \|\nabla u_n\|^2$$

so that we are lead to the differential inequality

$$\frac{1}{2} \frac{d}{dt} (\|u_n\|^2 + \|\sigma_n\|^2) + D_1 \|\nabla u_n\|^2 + \|\nabla \sigma_n\|^2 + \gamma \|\sigma_n\|^2 \leq c(1 + \|u_n\|^2 + \|\sigma_n\|^2).$$

By Gronwall's lemma, we deduce that

$$\|u_n(t)\| + \|\sigma_n(t)\| \leq c, \quad \forall t \in [0, t_n], \quad \forall n \in \mathbb{N},$$

therefore there exists $\tau > 0$ independent of n such that

$$\|u_n\|_{L^\infty(0, \tau; H)} + \|\sigma_n\|_{L^\infty(0, \tau; H)} + \|u_n\|_{L^2(0, \tau; V)} + \|\sigma_n\|_{L^2(0, \tau; V)} \leq c. \quad (12)$$

Next we take the product of the second equation in (11) with $-\Delta \sigma_n$, obtaining

$$\begin{aligned} \frac{1}{2} \frac{d}{dt} \|\nabla \sigma_n\|^2 + \|\Delta \sigma_n\|^2 + \gamma \|\nabla \sigma_n\|^2 &= -\gamma \beta \int_{\Omega} \Delta \sigma_n dx + \int_{\Omega} u_n g(\sigma_n) \Delta \sigma_n dx \\ &= \int_{\Omega} u_n g(\sigma_n) \Delta \sigma_n dx \leq \frac{1}{2} \|\Delta \sigma_n\|^2 + \frac{1}{2} \|u_n\|^2, \end{aligned}$$

being $|g(r)| < 1$ for any $r \in \mathbb{R}$. It is therefore straightforward to see that, by Gronwall lemma and (12), we have

$$\|\sigma_n\|_{L^\infty(0, \tau; V)} + \|\sigma_n\|_{L^2(0, \tau; W)} \leq c. \quad (13)$$

Unfortunately, the estimates obtained so far do not allow to pass to the limit in the Galerkin approximations (see the subsequent formula (17)), making necessary further computations and to resort to strong solutions.

We test the second equation in (11) with $\Delta^2 \sigma_n$, obtaining

$$\begin{aligned} & \frac{1}{2} \frac{d}{dt} \|\Delta \sigma_n\|^2 + \|\nabla \Delta \sigma_n\|^2 + \gamma \|\Delta \sigma_n\|^2 \\ &= \int_{\Omega} g(\sigma_n) \nabla u_n \nabla \Delta \sigma_n dx + \int_{\Omega} u_n g'(\sigma_n) \nabla \sigma_n \nabla \Delta \sigma_n dx. \end{aligned}$$

Owing again to the bound $|g(r)| < 1$ for any $r \in \mathbb{R}$, the first contribution is easily dealt with as

$$\int_{\Omega} g(\sigma_n) \nabla u_n \nabla \Delta \sigma_n dx \leq \|\nabla u_n\| \|\nabla \Delta \sigma_n\| \leq \|u_n\|_V \|\nabla \Delta \sigma_n\|.$$

For the second addendum, we observe that $|g'(r)| < 1$ as well, then we use Hölder inequality with exponents 6, 3 and 2

$$\begin{aligned} \int_{\Omega} u_n g'(\sigma_n) \nabla \sigma_n \nabla \Delta \sigma_n dx &\leq \|u_n\|_{L^6} \|\nabla \sigma_n\|_{L^3} \|\nabla \Delta \sigma_n\| \\ &\leq \|u_n\|_V \|\nabla \sigma_n\|^{\frac{1}{2}} \|\sigma_n\|_W^{\frac{1}{2}} \|\nabla \Delta \sigma_n\| \\ &\leq c \|u_n\|_V (1 + \|\Delta \sigma_n\|) \|\nabla \Delta \sigma_n\|, \end{aligned}$$

in view of (8), (13) and Young's inequality. Collecting these estimates, the above righthand side is controlled as

$$\begin{aligned} &\int_{\Omega} g(\sigma_n) \nabla u_n \nabla \Delta \sigma_n dx + \int_{\Omega} u_n g'(\sigma_n) \nabla \sigma_n \nabla \Delta \sigma_n dx \\ &\leq \|u_n\|_V \|\nabla \Delta \sigma_n\| + c \|u_n\|_V (1 + \|\Delta \sigma_n\|) \|\nabla \Delta \sigma_n\| \\ &\leq \frac{1}{2} \|\nabla \Delta \sigma_n\|^2 + \|u_n\|_V^2 + c \|u_n\|_V^2 (1 + \|\Delta \sigma_n\|^2) \\ &\leq \frac{1}{2} \|\nabla \Delta \sigma_n\|^2 + c \|u_n\|_V^2 (1 + \|\Delta \sigma_n\|^2), \end{aligned}$$

in view of (8). Then the differential inequality turns into

$$\frac{1}{2} \frac{d}{dt} \|\Delta \sigma_n\|^2 + \frac{1}{2} \|\nabla \Delta \sigma_n\|^2 + \gamma \|\Delta \sigma_n\|^2 \leq c \|u_n\|_V^2 + c \|u_n\|_V^2 \|\Delta \sigma_n\|^2$$

so that, by (12), the Gronwall lemma gives

$$\|\sigma_n\|_{L^\infty(0,\tau;W)} + \|\sigma_n\|_{L^2(0,\tau;Z)} \leq c. \quad (14)$$

Finally, we consider the product of the first equation in (11) by $-\Delta u_n$, obtaining

$$\begin{aligned} &\frac{1}{2} \frac{d}{dt} \|\nabla u_n\|^2 + \int_{\Omega} D\mathbf{B}(\sigma_n) |\Delta u_n|^2 dx \\ &= - \int_{\Omega} \mathbf{B}(\sigma_n) \nabla D \nabla u_n \Delta u_n dx - \int_{\Omega} D\mathbf{B}'(\sigma_n) \nabla \sigma_n \nabla u_n \Delta u_n dx - \int_{\Omega} \mathbf{h}(\sigma_n) \kappa(u_n) \Delta u_n dx. \end{aligned}$$

Here, the first term on the rhs is controlled as

$$\begin{aligned} - \int_{\Omega} \mathbf{B}(\sigma_n) \nabla D \nabla u_n \Delta u_n dx &\leq c \|\nabla D\|_{L^6} \|\nabla u_n\|_{L^3} \|\Delta u_n\| \\ &\leq c \|\nabla u_n\|^{\frac{1}{2}} \|u_n\|_{H^2}^{\frac{3}{2}} \\ &\leq \frac{D_1}{6} \|\Delta u_n\|^2 + c(1 + \|\nabla u_n\|^2), \end{aligned}$$

owing to (H1), (8), Young's inequality with exponents 4 and 4/3 and (12). Recalling $\mathbf{B} \in W^{1,\infty}(\mathbb{R})$, we deduce for the second term

$$\begin{aligned} - \int_{\Omega} D\mathbf{B}'(\sigma_n) \nabla \sigma_n \nabla u_n \Delta u_n dx &\leq c D_2 \|\nabla \sigma_n\|_{L^6} \|\nabla u_n\|_{L^3} \|\Delta u_n\| \\ &\leq c \|\sigma_n\|_{H^2} \|\nabla u_n\|^{\frac{1}{2}} \|u_n\|_{H^2}^{\frac{3}{2}} \\ &\leq c \|\nabla u_n\|^{\frac{1}{2}} \|u_n\|_{H^2}^{\frac{3}{2}} \\ &\leq \frac{D_1}{6} \|\Delta u_n\|^2 + c(1 + \|\nabla u_n\|^2), \end{aligned}$$

having exploited also (8), (12), (14) and Young's inequality with exponents 4 and 4/3. Being the last term easily controlled thanks to the boundedness of \mathbf{h} and κ as

$$-\int_{\Omega} \mathbf{h}(\sigma_n) \kappa(u_n) \Delta u_n dx \leq c \|\Delta u_n\| \leq \frac{D_1}{6} \|\Delta u_n\|^2 + c,$$

then, by (H1) and the definition of \mathbf{B} , we are lead to

$$\frac{d}{dt} \|\nabla u_n\|^2 + D_1 \|\Delta u_n\|^2 \leq c \|\nabla u_n\|^2 + c,$$

so that Gronwall's lemma entails

$$\|u_n\|_{L^\infty(0,\tau;V)} + \|u_n\|_{L^2(0,\tau;W)} \leq c. \quad (15)$$

Finally, we read from the equations of (11) that

$$\|\partial_t u_n\|_{L^2(0,\tau;H)} + \|\partial_t \sigma_n\|_{L^2(0,\tau;H)} \leq c. \quad (16)$$

In view of this last control together with (12)–(16), we deduce that, up to a subsequence,

$$\begin{aligned} u_n &\rightharpoonup \mathbf{u} \quad \text{weakly-}^* \text{ in } L^\infty(0,\tau;V), \\ u_n &\rightharpoonup \mathbf{u} \quad \text{weakly in } L^2(0,\tau;W), \\ u_n &\rightarrow \mathbf{u} \quad \text{strongly in } L^2(0,\tau;V), \\ \sigma_n &\rightharpoonup \mathbf{s} \quad \text{weakly-}^* \text{ in } L^\infty(0,\tau;W), \\ \sigma_n &\rightharpoonup \mathbf{s} \quad \text{weakly in } L^2(0,\tau;Z), \\ \sigma_n &\rightarrow \mathbf{s} \quad \text{strongly in } L^2(0,\tau;W) \quad \text{and} \quad C([0,\tau];V). \end{aligned}$$

We now see that (\mathbf{u}, \mathbf{s}) is a weak solution to (9) on $[0, \tau]$ since we can pass to the limit in (11) as $n \rightarrow \infty$. To prove this, it suffices to consider the three nonlinear terms appearing in the equations. Indeed, for any $w \in V$, $\phi \in C_0^\infty(0, t)$ where $t \leq \tau$, we first examine

$$\begin{aligned} &\int_0^t \int_{\Omega} D[\mathbf{B}(\sigma_n) \nabla u_n - \mathbf{B}(\mathbf{s}) \nabla \mathbf{u}] \nabla w \phi dx \\ &= \int_0^t \int_{\Omega} D[\mathbf{B}(\sigma_n) - \mathbf{B}(\mathbf{s})] \nabla u_n \nabla w \phi dx + \int_0^t \int_{\Omega} D\mathbf{B}(\mathbf{s}) \nabla (u_n - \mathbf{u}) \nabla w \phi dx. \end{aligned}$$

Recalling that, by definition, \mathbf{B} is Lipschitz continuous,

$$\begin{aligned} &\int_0^t \int_{\Omega} D[\mathbf{B}(\sigma_n) - \mathbf{B}(\mathbf{s})] \nabla u_n \nabla w \phi dx \\ &\leq c \int_0^t \int_{\Omega} |\sigma_n - \mathbf{s}| |\nabla u_n| |\nabla w| |\phi| dx ds \\ &\leq c \|\phi\|_{L^\infty(0,t)} \|w\|_V \int_0^t \|\sigma_n - \mathbf{s}\|_{L^\infty} \|u_n\|_V ds \\ &\leq c \|\phi\|_{L^\infty(0,t)} \|w\|_V \|\sigma_n - \mathbf{s}\|_{L^2(0,t;W)} \|u_n\|_{L^2(0,t;V)} \rightarrow 0, \end{aligned}$$

having exploited also (H1) and the inclusion $H^2(\Omega) \subset L^\infty(\Omega)$. This embedding with the definition of \mathbf{B} and assumption (H1) yield

$$\begin{aligned} & \int_0^t \int_{\Omega} D\mathbf{B}(\mathbf{s}) \nabla(u_n - \mathbf{u}) \nabla w \phi \, dx \\ & \leq c \int_0^t \int_{\Omega} (1 + |\mathbf{s}|) |\nabla(u_n - \mathbf{u})| |\nabla w| |\phi| \, dx ds \\ & \leq c \|\phi\|_{L^\infty(0,t)} \|w\|_V (1 + \|\mathbf{s}\|_{L^2(0,T;W)}) \|u_n - \mathbf{u}\|_{L^2(0,T;V)} \rightarrow 0 \end{aligned} \quad (17)$$

as $n \rightarrow \infty$. We now turn to the second nonlinear term that decomposes in the following sum

$$\begin{aligned} & \int_0^t \int_{\Omega} [\mathbf{h}(\sigma_n) \kappa(u_n) - \mathbf{h}(\mathbf{s}) \kappa(\mathbf{u})] w \phi \, dx ds \\ & = \int_0^t \int_{\Omega} [\mathbf{h}(\sigma_n) - \mathbf{h}(\mathbf{s})] \kappa(u_n) w \phi \, dx ds + \int_0^t \int_{\Omega} \mathbf{h}(\mathbf{s}) [\kappa(u_n) - \kappa(\mathbf{u})] w \phi \, dx ds. \end{aligned}$$

Here, due to the boundedness of κ and the Lipschitz continuity of \mathbf{h} , we see that

$$\begin{aligned} \int_0^t \int_{\Omega} [\mathbf{h}(\sigma_n) - \mathbf{h}(\mathbf{s})] \kappa(u_n) w \phi \, dx ds & \leq c \|\phi\|_{L^\infty(0,t)} \int_0^t \int_{\Omega} |\sigma_n - \mathbf{s}| |w| \, ds \\ & \leq c \sqrt{t} \|\phi\|_{L^\infty(0,t)} \|w\|_V \|\sigma_n - \mathbf{s}\|_{L^2(0,t;H)} \end{aligned}$$

while, by the boundedness of \mathbf{h} and the Lipschitz continuity of κ , it follows

$$\begin{aligned} \int_0^t \int_{\Omega} \mathbf{h}(\mathbf{s}) [\kappa(u_n) - \kappa(\mathbf{u})] w \phi \, dx ds & \leq c \|\phi\|_{L^\infty(0,t)} \int_0^t \int_{\Omega} |u_n - \mathbf{u}| |w| \, ds \\ & \leq c \sqrt{t} \|\phi\|_{L^\infty(0,t)} \|w\|_V \|u_n - \mathbf{u}\|_{L^2(0,t;H)}. \end{aligned}$$

It is therefore straightforward to pass to the limit in the second nonlinear term. Finally, owing to the boundedness and Lipschitz continuity of g as well as $\|\mathbf{u}\|_{L^2(0,t;V)} \leq c$, we handle the last contribution as

$$\begin{aligned} & \int_0^t \int_{\Omega} [u_n g(\sigma_n) - \mathbf{u} g(\mathbf{s})] w \phi \, dx ds \\ & = \int_0^t \int_{\Omega} (u_n - \mathbf{u}) g(\sigma_n) w \phi \, dx ds + \int_0^t \int_{\Omega} \mathbf{u} [g(\sigma_n) - g(\mathbf{s})] w \phi \, dx ds \\ & \leq c \int_0^t \int_{\Omega} |u_n - \mathbf{u}| |w| |\phi| \, dx ds + c \int_0^t \int_{\Omega} |\mathbf{u}| |\sigma_n - \mathbf{s}| |w| |\phi| \, dx ds \\ & \leq c \|\phi\|_{L^\infty(0,t)} \|w\|_V (\sqrt{t} \|u_n - \mathbf{u}\|_{L^2(0,t;H)} + \|\mathbf{u}\|_{L^2(0,t;V)} \|\sigma_n - \mathbf{s}\|_{L^2(0,t;H)}). \end{aligned}$$

We can therefore conclude that (\mathbf{u}, \mathbf{s}) is indeed a local weak solution to (9) on $[0, \tau]$. Actually, the solution is strong on account of the regularity of the initial data and of the above computations. \square

Another consequence of the bounds for any strong solution is their global existence, namely,

Lemma 3.5. *For any $T > 0$ and any (u_0, σ_0) verifying (H3), any strong solution to (9) originating from (u_0, σ_0) is global in time on $[0, T]$.*

Proof. This proof goes exactly as in [4]; we just report it for the reader's convenience.

Let us define

$\bar{t} = \sup\{t \geq 0 : \exists (\mathbf{u}, \mathbf{s}) \in [0, 1] \times [0, \beta]$ strong solution on $[0, t]$ departing from $(u_0, \sigma_0)\}$.

We know that there exists a solution $(\mathbf{u}, \mathbf{s}) \in [0, 1] \times [0, \beta]$ defined on $[0, \tau]$, hence $\bar{t} \geq \tau > 0$ and

$$\|\mathbf{u}(t)\|^2 + \|\mathbf{s}(t)\|^2 \leq (1 + \beta)|\Omega| \quad \forall t \in [0, \bar{t}].$$

This implies that $\bar{t} = T$: indeed, the uniform bounds of the H -norms tell that $\lim_{t \rightarrow \bar{t}} \mathbf{u}(t)$ and $\lim_{t \rightarrow \bar{t}} \mathbf{s}(t)$ exist in H (at least for a subsequence). Now we can consider a solution to the Cauchy problem with initial datum $(\mathbf{u}(\bar{t}), \mathbf{s}(\bar{t}))$, which is defined on an interval $[\bar{t}, \bar{t} + \eta]$, for some $\eta > 0$ (see also the extension theorem [6, Lemma 3.1, p. 13]). In this way we contradict the definition of \bar{t} . \square

4. Well posedness of the original problem.

Lemma 4.1. *For any $T > 0$ and any (u_0, σ_0) verifying (H3), there exists a global strong solution to (7) originating from (u_0, σ_0) .*

Indeed, owing to Lemma 3.4, a local strong solution (\mathbf{u}, \mathbf{s}) to (9) originating from (u_0, σ_0) satisfying (H3) do exist. Actually, from Lemma 3.3, we learn that

$$0 \leq \mathbf{u} \leq 1 \quad \text{and} \quad 0 \leq \mathbf{s} \leq \beta, \quad \text{a.e. in } \Omega \times [0, \tau].$$

Two consequences follow: first, (\mathbf{u}, \mathbf{s}) is global in time, thanks to Lemma 3.5. Moreover,

$$B(\mathbf{u}) = B(u), \quad h(\mathbf{u}) = h(u), \quad \kappa(\mathbf{u}) = u(1 - u) \quad \text{and} \quad g(\mathbf{s}) = \frac{\mathbf{s}}{1 + \mathbf{s}}.$$

Thus (\mathbf{u}, \mathbf{s}) is in fact a strong global solution to (7).

Lemma 4.2. *Given a pair of initial data (u_{0i}, σ_{0i}) satisfying (H3), denoting as (u_i, σ_i) a strong solution to (7) on $(0, T)$ originating from (u_{0i}, σ_{0i}) ($i = 1, 2$), there exists a positive constant c , depending on T , such that*

$$\begin{aligned} \|u_1 - u_2\|_{C([0, T]; H) \cap L^2(0, T; V)}^2 + \|\sigma_1 - \sigma_2\|_{C([0, T]; V) \cap L^2(0, T; W)}^2 \\ \leq c(\|u_{01} - u_{02}\|^2 + \|\sigma_{01} - \sigma_{02}\|_V^2). \end{aligned} \quad (18)$$

In particular, for any (u_0, σ_0) satisfying (H3), the corresponding strong solution to (7) is unique.

Proof. The same arguments applied in the proof of Lemma 4.1 give

$$0 \leq u_i \leq 1 \quad \text{and} \quad 0 \leq \sigma_i \leq \beta, \quad \text{a.e. in } \Omega \times (0, T),$$

therefore we may take advantage of the notations $u_i(u_i - 1) = \kappa(u_i)$ and $\frac{\sigma_i}{1 + \sigma_i} = g(\sigma_i)$. We also observe that $h(u_i)$ and $\kappa(u_i)$ are bounded and Lipschitz continuous with respect to u_i while the same is true for $B(\sigma_i)$ and $g(\sigma_i)$ with respect to σ_i . Finally, we recall that

$$\|u_i\|_{L^\infty(0, T; V)} \leq c, \quad i = 1, 2. \quad (19)$$

Then it is readily seen that the differences

$$u = u_1 - u_2 \quad \text{and} \quad \sigma = \sigma_1 - \sigma_2$$

satisfy the equations

$$\partial_t u - \operatorname{div}(DB(\sigma_1)\nabla u_1 - DB(\sigma_2)\nabla u_2) = h(\sigma_1)\kappa(u_1) - h(\sigma_2)\kappa(u_2), \quad (20)$$

$$\partial_t \sigma - \Delta \sigma + \gamma \sigma = -u_1 g(\sigma_1) + u_2 g(\sigma_2), \quad (21)$$

supplemented with homogenous Neumann boundary conditions and with the initial conditions

$$u(0) = u_{01} - u_{02} \quad \text{and} \quad \sigma(0) = \sigma_{01} - \sigma_{02}.$$

We test (20) by u and (21) by $\sigma - \Delta \sigma$ then we add the results, obtaining

$$\begin{aligned} & \frac{1}{2} \frac{d}{dt} (\|u\|^2 + \|\sigma\|^2 + \|\nabla \sigma\|^2) + \int_{\Omega} DB(\sigma_1) |\nabla u|^2 dx + \|\Delta \sigma\|^2 + (1 + \gamma) \|\nabla \sigma\|^2 + \gamma \|\sigma\|^2 \\ &= - \int_{\Omega} D[B(\sigma_1) - B(\sigma_2)] \nabla u_2 \nabla u dx + \int_{\Omega} [h(\sigma_1) - h(\sigma_2)] \kappa(u_1) u dx \\ &+ \int_{\Omega} h(\sigma_2) [\kappa(u_1) - \kappa(u_2)] u dx - \int_{\Omega} u g(\sigma_1) (\sigma - \Delta \sigma) dx - \int_{\Omega} u_2 [g(\sigma_1) - g(\sigma_2)] (\sigma - \Delta \sigma) dx. \end{aligned}$$

By (H1) and the definition of B , the lhs is larger than

$$\frac{1}{2} \frac{d}{dt} (\|u\|^2 + \|\sigma\|^2 + \|\nabla \sigma\|^2) + D_1 \|\nabla u\|^2 + \|\Delta \sigma\|^2 + (1 + \gamma) \|\nabla \sigma\|^2 + \gamma \|\sigma\|^2.$$

These same assumptions, together with Agmon's inequality and (19), allow to control

$$\begin{aligned} - \int_{\Omega} D[B(\sigma_1) - B(\sigma_2)] \nabla u_2 \nabla u dx &\leq c \int_{\Omega} |\sigma| |\nabla u_2| |\nabla u| dx \\ &\leq c \|\sigma\|_{L^\infty} \|\nabla u_2\| \|\nabla u\| dx \\ &\leq c \|\sigma\|_{V}^{\frac{1}{2}} \|\sigma\|_{W}^{\frac{1}{2}} \|\nabla u\| \\ &\leq \frac{1}{2} \|\nabla u\|^2 + \frac{1}{4} \|\Delta \sigma\|^2 + c \|\sigma\|_{V}^2. \end{aligned}$$

Then the Lipschitz continuity and the boundedness on bounded intervals of h and κ justify

$$\begin{aligned} \int_{\Omega} [h(\sigma_1) - h(\sigma_2)] \kappa(u_1) u dx + \int_{\Omega} h(\sigma_2) [\kappa(u_1) - \kappa(u_2)] u dx &\leq c \int_{\Omega} (|u| |\sigma| + |u|^2) dx \\ &\leq c (\|u\|^2 + \|\sigma\|^2). \end{aligned}$$

Analogous arguments apply to g and we also recall $0 \leq u_2 \leq 1$, so that

$$\begin{aligned} - \int_{\Omega} u g(\sigma_1) (\sigma - \Delta \sigma) dx - \int_{\Omega} u_2 [g(\sigma_1) - g(\sigma_2)] (\sigma - \Delta \sigma) dx \\ \leq \int_{\Omega} (|u| + |\sigma|) (|\sigma| + |\Delta \sigma|) dx \\ \leq \frac{1}{4} \|\Delta \sigma\|^2 + c (\|u\|^2 + \|\sigma\|^2). \end{aligned}$$

Having introduced $\Lambda(t) = \|u(t)\|^2 + \|\sigma(t)\|_{V}^2$, the above computations lead to

$$\frac{d}{dt} \Lambda + (\|\nabla u\|^2 + \|\Delta \sigma\|^2) \leq c \Lambda,$$

hence, by Gronwall's lemma and an integration in time, we obtain (18). In particular, when the initial data are the same, the uniqueness of the strong solution is straightforward. \square

Remark 1. We observe that, when $(u_0, \sigma_0) \in H \times H$ verify $0 \leq u_0 \leq 1$ and $0 \leq \sigma_0 \leq \beta$ and the diffusion coefficient is constant (that is, when $D(x)$ is constant and $\delta = 1$), the model is exactly that of [4]. Here we prove that the same results on the global existence of a unique weak solution can be achieved without the assumption that h is bounded but just under (H2).

5. Asymptotic behavior and further remarks. We now compare the longtime tumor evolution in our model, where the diffusion coefficient depends on the position and the oxygen concentration, with the particular case analyzed in [4] when this coefficient is constant. The prognosis is still bad: this is not surprising in view of the lower bound

$$D(x)B(\sigma) \geq D_1, \quad (22)$$

following from (H1) and $0 \leq \sigma \leq \beta$. Therefore, even in our more general case, no illness extinction occurs. This can be seen as in [4]: fix an initial datum (u_0, σ_0) satisfying (H3) together with $0 < u_0 \leq 1$ and such that $0 < \|u_0 - 1\| < \|1\|$. Denoting as (u, σ) the corresponding strong solution to (7), we see that $v = u - 1$ solves

$$\begin{cases} \partial_t v - \operatorname{div}(DB(\sigma)\nabla v) = -h(\sigma)uv, & \text{in } \Omega, \quad t > 0, \\ \partial_{\mathbf{n}} v = 0, & \text{in } \partial\Omega, \quad t > 0, \\ v(0) = u_0 - 1 \leq 0, & \text{in } \Omega. \end{cases}$$

Testing the differential equation with v , from (22) we deduce

$$\frac{1}{2} \frac{d}{dt} \|v\|^2 + D_1 \|\nabla v\|^2 \leq - \int_{\Omega} h(\sigma)uv^2 dx \leq 0, \quad (23)$$

so that

$$\|v(t)\| = \|u(t) - 1\| \leq \|v(0)\| = \|u_0 - 1\|.$$

Therefore, the inequality

$$\|1\| - \|u(t) - 1\| \geq \|1\| - \|u_0 - 1\| > 0,$$

holding for any positive time, entails

$$\|u(t)\| \geq \|1\| - \|u(t) - 1\| > 0, \quad \forall t > 0,$$

preventing the tumor extinction.

We are actually able to prove that the tumor tends to grow, in the sense that the distance of the tumor density from 1 decreases in time. Indeed, if we go back to (23), we see that

$$\|u(t) - 1\| \leq \|u_0 - 1\|, \quad \forall t > 0,$$

for any u_0 such that $0 \leq u_0 \leq 1$. Actually, if we assume that the minimum oxygen level is $\underline{\sigma} > 0$ and that $\underline{u} > 0$ is the minimum tumor density, then (23) implies

$$\frac{1}{2} \frac{d}{dt} \|u - 1\|^2 + h(\underline{\sigma})\underline{u}\|u - 1\|^2 \leq 0,$$

leading to

$$\|u(t) - 1\|^2 \leq \|u_0 - 1\|^2 e^{-h(\underline{\sigma})\underline{u}t}, \quad \forall t > 0.$$

Finally, we observe that the oxygen levels may not be too small. Indeed, if the initial oxygen level σ_0 is strictly positive, then in its evolution σ will be greater than a strictly positive function ψ : more precisely, ψ is a spatially homogeneous solution to the oxygen equation corresponding to $u = 1$. Indeed, assume that in the pair

(u_0, σ_0) verifying (H3) the second component is such that $0 < \sigma_0 \leq \beta$ in Ω . Since $\sigma_0 \in C(\bar{\Omega})$, then $\psi_0 = \min_{\bar{\Omega}} \sigma_0 \in (0, \beta]$. We now consider the Cauchy problem

$$\begin{cases} \psi' + \gamma\psi = \gamma\beta - g(\psi), \\ \psi(0) = \psi_0, \end{cases} \quad (24)$$

whose solution ψ exists and is unique globally in time. Since $\psi_0 \in (0, \beta]$, we easily see that $0 \leq \psi(t) \leq \beta$ for any $t > 0$. Actually, it is not possible that there exists $\tau > 0$ such that $\psi(\tau) = 0$. Indeed, if this were the case, let

$$\tilde{t} = \sup\{\tau > 0 : \psi(t) > 0 \text{ in } [0, \tau)\};$$

if $\tilde{t} \in (0, +\infty)$ then we have $\psi(\tilde{t}) = 0$ while $\psi(t) > 0$ in $[0, \tilde{t})$. At the same time, from the equation we read $\psi'(\tilde{t}) = \gamma\beta > 0$, contradicting the definition of \tilde{t} . Thus $\psi(t) > 0$ for any positive time. We now can see that if σ is the oxygen component of a solution (u, σ) originating from (u_0, σ_0) as above, then $\sigma(t) \geq \psi(t)$ for any $t > 0$.

Indeed, $w = \sigma - \psi$ solves the problem

$$\begin{cases} \partial_t w - \Delta w + \gamma w = -ug(\sigma) + g(\psi), & \text{in } \Omega \times \mathbb{R}^+, \\ \partial_n w = 0, & \text{on } \partial\Omega \times \mathbb{R}^+, \\ w(0) = \sigma_0 - \psi_0, & \text{in } \Omega, \end{cases} \quad (25)$$

so that $w(0) > 0$ in Ω entails $w^-(0) = 0$. We test the differential equation in (25) with $-w^-$, obtaining

$$\begin{aligned} & \frac{1}{2} \frac{d}{dt} \|w^-\|^2 + \|\nabla w^-\|^2 + \gamma \|w^-\|^2 \\ &= \int_{\Omega} u[g(\sigma) - g(\psi)]w^- dx - \int_{\Omega} (1-u)g(\psi)w^- dx \leq 0 \end{aligned}$$

because, by definition of g and due to $u \geq 0$,

$$\int_{\Omega} u[g(\sigma) - g(\psi)]w^- dx = \int_{\Omega} u \frac{\sigma - \psi}{(1+\sigma)(1+\psi)} w^- dx = - \int_{\Omega} u \frac{(w^-)^2}{(1+\sigma)(1+\psi)} dx \leq 0,$$

whereas $u \leq 1$ and $g(\psi) > 0$ yield

$$- \int_{\Omega} (1-u)g(\psi)w^- dx \leq 0.$$

Therefore

$$\|w^-(t)\|^2 \leq \|w^-(0)\|^2 = 0, \quad \forall t > 0,$$

meaning that $w(t) = \sigma(t) - \psi(t) \geq 0$ for any time.

This oxygen behavior complies with the observation made in [5] that the tumor tends to normalize oxygen levels.

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REFERENCES

- [1] A. Aubert and R. Costalat. Interaction between astrocytes and neurons studied using a mathematical model of compartmentalized energy metabolism, *J. Cereb. Blood Flow Metab.*, **25** (2005), 1476–1490.
- [2] A. Aubert, R. Costalat, P. Magistretti, J. Pierre and L. Pellerin. Brain lactate kinetics: modeling evidence for neuronal lactate uptake upon activation, *Proc. National Acad. Sci. USA* **102**, (2005), 16448–16453.
- [3] L. Cherfils, S. Gatti, A. Miranville, R. Guillevin. Analysis of a model for tumor growth and lactate exchanges in a glioma, *Discrete Contin. Dyn. Syst. Ser. S*, **14**, (2021), 2729–2749.
- [4] M. Conti, S. Gatti, A. Miranville. Mathematical analysis of a model for proliferative-to-invasive transition of hypoxic glioma cells, *Nonlinear Analysis*, **189**, (2019), 111572, 17 pp.
- [5] H. Gomez. Quantitative analysis of the proliferative-to-invasive transition of hypoxic glioma cells, *Integr. Biol.* **9**, (2017), 257–262.
- [6] P. Hartman. Ordinary differential equation. Corrected reprint of the second (1982) edition, Society for Industrial and Applied Mathematics (SIAM), Philadelphia, PA, 2002.
- [7] L. Li. On a coupled Cahn-Hilliard/Cahn-Hilliard model for the proliferative-to-invasive transition of hypoxic glioma cells, *Commun. Pure Appl. Anal.* **20**, (2021), 1545–1557.
- [8] L. Li, A. Miranville, R. Guillevin. Cahn–Hilliard Models for Glial Cells, *Appl. Math. Optim.* **84**, (2021), 1821–1842.
- [9] L. Li, L. Cherfils, A. Miranville, R. Guillevin. A Cahn-Hilliard model with a proliferation term for the proliferative-to-invasive transition of hypoxic glioma cells, *Communications in Mathematical Science* **19**, (2021), 1509–1532.
- [10] L. Li, A. Miranville, R. Guillevin. A coupled Cahn-Hilliard model for the proliferative-to-invasive transition of hypoxic glioma cells, *Quart. Appl. Math.*, **79**, (2021), 383–394.
- [11] B. Mendoza-Juez, A. Martínez-González, G.F. Calvo and V.M. Pérez-García. A mathematical model for the glucose-lactate metabolism of in vitro cancer cells, *Bull. Math. Biol.* **74** (2012), 1125–1142.
- [12] A. Miranville, E. Rocca, G. Schimperna. On the long time behavior of a tumor growth model, *J. Differential Equations* **267**, (2019), 2616–2642.
- [13] B. Muz, P. de la Puente, F. Azab, A.K. Azab. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy, *Hypoxia* **3**, (2015), 83–92.

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