ANALYSIS OF A MODEL FOR TUMOR GROWTH AND LACTATE EXCHANGES IN A GLIOMA

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Abstract. Our aim in this paper is to study a mathematical model for tumor growth and lactate exchanges in a glioma. We prove the existence of nonnegative (i.e. biologically relevant) solutions and, under proper assumptions, the uniqueness of the solution. We also state the permanence of the tumor when necrosis is not taken into account in the model and obtain linear stability results. We end the paper with numerical simulations.

1. Introduction. It is well known that tumors influence the energy metabolism and sources: in particular, for brain tumors and, among them, for the most common gliomas, it is difficult to carefully measure the production, consumption or transport of a nutrient, so that one resorts to mathematical models. In particular, among the nutrients, we focus here on the lactate production, consumption and transport in the brain when a glioma occurs. Therefore we address a model proposed by [1] and [6] (see also [8]) to describe at the same time the evolution of the tumor cell density

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u and the lactate concentrations in the intracellular and in the capillary domains, respectively, \( \varphi \) and \( \psi \).

The resulting problem is given by a reaction-diffusion equation for \( u \) coupled with two parabolic nonlinear equations for the lactates, involving in particular co-transport terms. More precisely, it reads

\[
\partial_t u - \text{div}(D \nabla u) = a(\varphi, \psi) u(\gamma - u) - u g(\varphi, \psi),
\]

\[
\partial_t \varphi - \alpha \Delta \varphi + k \left( \frac{\varphi}{K + \varphi} - \frac{\psi}{K' + \psi} \right) = J(t, \varphi, u),
\]

\[
\varepsilon \partial_t \psi - \beta \Delta \psi + k \left( \frac{\psi}{K' + \psi} - \frac{\varphi}{K + \varphi} \right) + F \psi = F L.
\]

Dealing with a biomedical system, our first concern is to show that a biologically relevant solution originates from any biologically meaningful initial datum: therefore, considering density and concentrations, the solutions are expected to stay non-negative if they depart from biological data. This is a crucial issue also on account of the possibly singular co-transport terms for the lactate concentrations. Then, we prove the existence of a weak solution on any finite time interval by the Galerkin method and further a priori estimates, which requires a careful management of the nonlinearities. Since the tumor proliferation rate is in general non-constant and it actually depends on the lactate concentrations, the uniqueness of the solution is not obvious. Indeed, this will be proved under suitable assumptions.

The boundedness of the solutions on any finite time interval is another desirable feature: such a task can be accomplished provided that the initial data are smooth enough. We conclude with some forecasts: we see that the illness is not extinguished when we neglect necrosis. Also, assuming a constant balance sheet for lactate, as far as production, consumption and export are concerned, under suitable conditions we observe two stationary solutions sharing the same fixed lactate concentrations, whose linear stability can be investigated. While the most favorable occurrence, corresponding to the absence of tumor is unstable, the other one is stable provided that suitable assumptions hold true.

In our model, the equation for the tumor cell density is a reaction-diffusion equation in which the proliferation rate \( a \) depends on both lactate concentrations: for fixed concentrations, the tumor cells increase their density till they reach their maximal capacity \( \gamma > 0 \). We also take into account the tumor cells necrosis whose rate is represented by the function \( g(\varphi, \psi) \). The equations governing the evolution of extracellular and capillary lactates are both diffusion equations (the terms \( -\alpha \Delta \varphi \) and \( -\beta \Delta \psi \) correspond to random motions) and contain nonlinear co-transport terms through the brain-blood boundary, where \( k \) is the maximum transport rate between the blood and the cell, while \( K > 0 \) and \( K' > 0 \) are the Michaelis-Menten constants for the intracellular and the capillary lactate, respectively. Concerning the extracellular lactate, we also keep into account a forcing term \( J \), depending on time, the tumor cell density and the extracellular lactate seen as regulatory terms. The function \( J \) represents the balance sheet of the production, consumption or export of lactate by the cell. In the equation for capillary lactate, the model also accounts for the volume separating these two compartments, \( \varepsilon > 0 \), and the blood flow contribution both from arterial and venous lactate; in particular, \( L > 0 \) corresponds to the arterial lactate concentration and \( F \) to the cerebral blood flow.
The sole lactate kinetics has been investigated in [3, 4, 7]. In particular, well-posedness, bounds on the solutions and stability of the unique spatially homogeneous equilibrium have been obtained.

We also mention related models, also including diffusion and tumor growth ([5]) and different phenotypes of the tumor cells ([6]). These works account for glucose-lactate dynamics (see also [8] in which diffusion is neglected).

The plan of the paper is as follows. In the next Section, we make precise our assumptions and introduce the proper functional setting, as well as the main tools that we employ. In Section 3, we prove the global in time existence of a weak solution, first addressing a modified problem where the symport terms are tamed so to be no longer singular. This further system is useful, since, for positive initial data, its solutions and those to the original problem coincide. Hence, having shown the local in time existence of a weak solution to the nonsingular problem by the Galerkin method, we are then able to prove that such a solution exists globally, owing to a priori estimates which are uniform in time. In order to tackle the uniqueness issue, we first devise suitable $L^\infty$– upper bounds on the solutions when the initial data are smooth enough and we neglect necrosis. These, or the reduction to two-space dimensions, allow us to properly handle the tumor proliferation rate when it is not constant, so that the uniqueness of the solution can be shown in three different cases. Finally, in the last section, we make some remarks on the asymptotic behavior of the solutions. Namely, without necrosis, permanence of the tumor is shown. Another case when we can infer something on the longtime behavior is when $J$ is constant. Under suitable assumptions, two stationary solutions exist and are linearly unstable and stable, respectively.

2. Mathematical setting. We consider the following initial and boundary value problem:

\[
\begin{aligned}
\partial_t u - \text{div}(D\nabla u) &= a(\varphi, \psi) u(\gamma - u) - u g(\varphi, \psi), \quad \text{in } \Omega_T = \Omega \times (0, T), \\
\partial_t \varphi - \alpha \Delta \varphi + k \left( \frac{\varphi}{K + \varphi} - \frac{\psi}{K' + \psi} \right) &= J(t, \varphi, u), \quad \text{in } \Omega_T, \\
\varepsilon \partial_t \psi - \beta \Delta \psi + k \left( \frac{\psi}{K' + \psi} - \frac{\varphi}{K + \varphi} \right) + F \psi &= FL, \quad \text{in } \Omega_T, \\
D \nabla u \cdot n &= \partial_n \varphi = \partial_n \psi = 0, \quad \text{on } \partial \Omega \times (0, T), \\
u(0) = u_0, \quad \varphi(0) = \varphi_0, \quad \psi(0) = \psi_0, \quad \text{in } \Omega,
\end{aligned}
\]

where $\Omega$ is a bounded and regular domain of $\mathbb{R}^N$ with $N = 1, 2, 3$, unless otherwise stated. We recall that $\varepsilon, \alpha, \beta, \gamma, k, K, K', F, L$ are positive constants related with the biological mechanisms in the glioma, as described in the introduction.

We next assume that

(H1) $0 < a_1 \leq a(\varphi, \psi) \leq a_2$, and there exists $c > 0$ such that

$$|a(s_1, t_1) - a(s_2, t_2)| \leq c(|s_1 - s_2| + |t_1 - t_2|) \quad \forall s_1, s_2, t_1, t_2 \in \mathbb{R}.$$

(H2) $g \in C(\mathbb{R}^2)$, $0 \leq g \leq G$ and there exists a positive constant $C$ such that

$$|g(s_1, t_1) - g(s_2, t_2)| \leq C(|s_1 - s_2| + |t_1 - t_2|), \quad \forall s_1, s_2, t_1, t_2 \in \mathbb{R}.$$
(H3) \( J \in C(\mathbb{R}^+ \times \mathbb{R}^2) \) is such that \( 0 \leq J_1 \leq J(t, \varphi, u) \leq J_2 \) for any \((t, \varphi, u) \in \mathbb{R}^+ \times \mathbb{R}^2 \)
and
\[ \exists l > 0 : |J(t,s_1,t_1) - J(t,s_2,t_2)| \leq l(|s_1-s_2| + |t_1-t_2|) \quad \forall t \geq 0, \quad \forall s_1, s_2, t_1, t_2 \in \mathbb{R}. \]

(H4) The matrix \( D \) is symmetric and there exists \( d > 0 \) such that \( (D\xi, \xi) \geq d|\xi|^2 \),
\[ \forall \xi \in \mathbb{R}^3, \quad \xi \neq 0. \]

We set \( H = L^2(\Omega) \) with inner product denoted by \( \langle \cdot, \cdot \rangle \) and corresponding norm \( \| \cdot \| \).
We also set \( V = H^1(\Omega) \) equipped with the norm \( \|u\|^2_V = \|u\|^2 + \|\nabla u\|^2 \),
and \( V' \) its dual space, the symbol \( \langle \cdot, \cdot \rangle \) standing for the corresponding duality pairing.
The proper phase space for biologically meaningful solutions is
\[ \mathcal{H}^+ = [H^+]^3 \quad \text{where} \quad H^+ = \{ v \in H : v \geq 0 \ \text{a.e. in} \ \Omega \}. \]

We recall the classical Gagliardo-Nirenberg inequalities:
\[ \|u\|_{L^3} \leq C\|u\|^{1/2}_V \|u\|^{1/2}, \quad \forall u \in V, \quad (2) \]
and, depending on the space dimension \( N \),
\[ \|u\|_{L^4} \leq C\|u\|^{1/2}_V \|u\|^{1/2}, \quad \forall u \in V \quad (N \leq 2) \]
\[ \|u\|_{L^4} \leq C\|u\|^{3/4}_V \|u\|^{1/4}, \quad \forall u \in V \quad (N = 3). \]

Throughout the paper, the letters \( c \) and \( C_T \) denote generic positive constants
which may vary from line to line. In particular, \( C_T \) depends on the time interval \([0, T]\).

3. **Existence.** In order to justify the existence of weak solutions, which requires
in particular to ensure the meaningfulness of the symport terms, we first study the modified problem
\[
\begin{aligned}
\partial_t u - \text{div}(D\nabla u) &= a(\varphi, \psi)(u(\gamma-u) - ug(\varphi, \psi)), \quad \text{in} \ \Omega_T = \Omega \times (0, T), \\
\partial_t \varphi - \alpha \Delta \varphi + k \left( \frac{\varphi}{K + |\varphi|} - \frac{\psi}{K' + |\psi|} \right) &= J(t, \varphi, u), \quad \text{in} \ \Omega_T, \\
\varepsilon \partial_t \psi - \beta \Delta \psi + k \left( \frac{\psi}{K' + |\psi|} - \frac{\varphi}{K + |\varphi|} \right) + F\psi &= FL, \quad \text{in} \ \Omega_T, \\
D\nabla u \cdot n &= 0, \quad \partial_n \varphi = 0 = \partial_n \psi, \quad \text{on} \ \partial \Omega \times (0, T), \\
u(0) = u_0, \quad \varphi(0) = \varphi_0, \quad \psi(0) = \psi_0, \quad \text{in} \ \Omega,
\end{aligned}
\]
\[ (4) \]
where \((u_0, \varphi_0, \psi_0) \in \mathcal{H}^+. \)

Now, for \( T > 0 \) fixed, \((u, \varphi, \psi)\) is a weak solution to (4) if
\[ (u, \varphi, \psi) \in [L^\infty(0, T; H) \cap L^2(0, T; V)]^3, \quad (\partial_t u, \partial_t \varphi, \partial_t \psi) \in [L^2(0, T; V')]^3 \]
and there hold
\[
\begin{aligned}
\langle \partial_t u, v \rangle + (D\nabla u, \nabla v) &= (a(\varphi, \psi)(u(\gamma-u), v) - (ug(\varphi, \psi), v), \\
\langle \partial_t \varphi, w \rangle + \alpha (\nabla \varphi, \nabla w) + k \left( \frac{\varphi}{K + |\varphi|} - \frac{\psi}{K' + |\psi|} \right), w) &= (J(t, \varphi, u), w), \\
\varepsilon \langle \partial_t \psi, \omega \rangle + \beta (\nabla \psi, \nabla \omega) + k \left( \frac{\psi}{K' + |\psi|} - \frac{\varphi}{K + |\varphi|} \right), \omega) &= F((\psi-L), \omega) = 0,
\end{aligned}
\]
\[ (5) \]
Lemma 3.1. Any weak solution to (4) departing from \((u_0, \varphi_0, \psi_0) \in H^+\) remains nonnegative.

Proof. We recall that any \(x \in \mathbb{R}\) can be written as \(x = x^+ - x^-\), with \(x^+ = \max(x, 0)\) and \(x^- = \max(-x, 0)\). To accomplish our task, we test the second equation of (5) by \(-\varphi^-\). Then, recalling that \(\psi = \psi^+ - \psi^-\), after standard transformations, we get:

\[
\frac{1}{2} \frac{d}{dt} \|\varphi^-\|^2 + \alpha \|\nabla \varphi^-\|^2 + k \int_{\Omega} \frac{\varphi^-}{K + |\varphi|} \, dx = -k \int_{\Omega} \frac{\psi^\varphi^-}{K^\varphi + |\psi|} \, dx - \int_{\Omega} J(t, \varphi, u) \varphi^- \, dx \\
\leq k \int_{\Omega} \frac{\psi^-}{K^\varphi + |\psi|} \, dx \\
\leq \alpha \|\varphi^-\|^2 + c \|\psi^-\|^2,
\]

in view of (H3). Analogously, testing the third equation of (5) by \(-\psi^-\) yields

\[
\frac{1}{2} \frac{d}{dt} (\varepsilon \|\psi^-\|^2 + F \|\psi^-\|^2 + k \int_{\Omega} \frac{(\psi^-)^2}{K^\varphi + |\psi|} \, dx = -k \int_{\Omega} \frac{\varphi^\psi^-}{K^\psi + |\psi|} \, dx - \int_{\Omega} F L \psi^- \, dx \\
\leq \alpha \varepsilon \|\psi^-\|^2 + c \|\psi^-\|^2,
\]

which, together with the previous inequality, provides

\[
\frac{d}{dt} (\|\varphi^-\|^2 + \varepsilon \|\psi^-\|^2) \leq c(\|\varphi^-\|^2 + \varepsilon \|\psi^-\|^2).
\]

Recalling the initial conditions, by Gronwall’s Lemma we conclude that \(\varphi(t) \geq 0\) and \(\psi(t) \geq 0 \quad \forall t \geq 0\).

Now, testing the first equation of (5) by \(-u^-\), by (H1)–(H2) and the interpolation inequality (2), we obtain

\[
\frac{1}{2} \frac{d}{dt} \|u^-\|^2 + (D \nabla u^-, \nabla u^-) \leq a_2 \gamma \|u^-\|^2 + a_2 \|u^-\|_{L^3}^2 - \int_{\Omega} (u^-)^2 g(\varphi, \psi) \, dx \\
\leq c(\|u^-\|^2 + \|u^-\|_{L^2}^2 \|u^-\|^2).
\]

Adding to both sides of the equation \(d \|u^-\|^2\) and taking into account (H4), we get

\[
\frac{1}{2} \frac{d}{dt} \|u^-\|^2 + d \|u^-\|_{V^*}^2 \leq \frac{1}{2} \|u^-\|_{V^*}^2 + c(\|u^-\|^6 + \|u^-\|^2).
\]

After simplifications, we obtain:

\[
\frac{d}{dt} \|u^-\|^2 + d \|u^-\|_{V^*}^2 \leq c(1 + \|u^-\|^4) \|u^-\|^2.
\]

Since \(u \in C([0, T]; H)\) guarantees the continuity of \(c(1 + \|u^-\|^4)\), an application of the Gronwall Lemma, in view of \(u^-(0) = 0\), leads to \(u^-(t) = 0\), hence \(u(t) \geq 0\) \(\forall t \geq 0\).
3.1. Local existence of a weak solution to (4). In order to prove the local existence of a weak solution to (4), we introduce the Galerkin approximation of the problem. Thus, let $0 = \lambda_1 < \lambda_2 \leq \cdots$ be the eigenvalues of the minus Laplace operator associated with Neumann boundary conditions and $e_1, e_2, \cdots$ be associated eigenvectors such that $\{e_j\}_{j=1}^{\infty}$ forms an orthonormal basis in $H$ which is also orthogonal in $V$. We set $V_n = \text{Span}\{e_1, \ldots, e_n\}$ and denote by $P_n$ the corresponding projection.

Now, for any fixed $n \in \mathbb{N}$ we consider the following approximated problem: Find $t_n > 0$ and $(u_n, \varphi_n, \psi_n) : [0, t_n] \to (V_n)^3$ such that
\[
\begin{cases}
\partial_t u_n + (D\nabla u_n, \nabla v) = (a(\varphi_n, \psi_n)u_n(\gamma - u_n), v) - (u_n g(\varphi_n, \psi_n), v), \\
(\partial_t \varphi_n, w) + \alpha(\nabla \varphi_n, \nabla w) + k\left(\frac{\varphi_n}{K + |\varphi_n|} - \frac{\psi_n}{K' + |\psi_n|}\right), w) = (J(\cdot, \varphi_n, u_n), w), \\
\varepsilon(\partial_t \psi_n, \omega) + \beta(\nabla \psi_n, \nabla \omega) + k\left(-\frac{\varphi_n}{K + |\varphi_n|} + \frac{\psi_n}{K' + |\psi_n|}\right), \omega) + F((\psi_n - L), \omega) = 0,
\end{cases}
\]
for any $v, w, \omega \in V_n$, a.e. in $(0, t_n)$. Moreover, $u_n(0) = P_n u_0$, $\varphi_n(0) = P_n \varphi_0$, $\psi_n(0) = P_n \psi_0$ a.e. in $\Omega$.

Remark 1. The initial datum $(P_n u_0, P_n \varphi_0, P_n \psi_0)$ of the $n$–th approximated problem does not necessarily preserve the positivity of $(u_0, \varphi_0, \psi_0)$. Therefore the maximum principle stated in Lemma 3.1 does not apply to $(u_n, \varphi_n, \psi_n)$ and we have to deal with the modified system.

Thanks to the Cauchy Lipschitz theorem, for any $n \in \mathbb{N}$ there exists a unique solution $(u_n, \varphi_n, \psi_n) \in C^1([0, t_n], V_n)$ to (6). Now in order to pass to the limit, we choose $v = u_n$ in the first equation of (6).
\[
\frac{1}{2} \frac{d}{dt} \|u_n\|^2 + (D\nabla u_n, \nabla u_n) = \int_{\Omega} a(\varphi_n, \psi_n)(\gamma u_n^2 - u_n^3) \, dx - \int_{\partial \Omega} g(\varphi_n, \psi_n)u_n^2 \, dx
\leq c(\|u_n\|^2 + \|u_n\|_2^3)
\leq \frac{d}{2} \|\nabla u_n\|^2 + c(\|u_n\|^2 + \|u_n\|^6),
\]
owing to (H1)–(H2), and having exploited (2) and the Young inequality. Here and throughout this proof, the constant $c$ is independent of $n$ but it is allowed to depend on $T$. Therefore, denoting by $\Lambda(t) = \|u_n(t)\|^2$, the assumption (H4) on $D$ gives
\[
\frac{d}{dt} \Lambda + d\|\nabla u_n\|^2 \leq h(\Lambda), \quad \text{where} \quad h(s) = c(1 + s + s^3),
\]
for some $c$ still independent of $n$. Arguing as in [2, Section 4], that is, by comparison with the solution to a suitable Cauchy problem for ODEs, we deduce that
\[
\|u_n\|_{L^\infty(0, \tau; H)} \leq c,
\]
for some $0 < \tau \leq t_n$ and $c$ both independent of $n$. Integrating the above differential inequality over $(0, \tau)$, we deduce that
\[
\|u_n\|_{L^2(0, \tau; V')} \leq c,
\]
so that, by comparison,
\[
\|\partial_t u_n\|_{L^2(0, \tau; V')} \leq c.
\]
Now, testing the second equation of (6) by $\varphi_n$ yields:
\[
\frac{1}{2} \frac{d}{dt} \|\varphi_n\|^2 + \alpha\|\nabla \varphi_n\|^2 + k \int_{\Omega} \frac{(\varphi_n)^2}{K + |\varphi_n|} \, dx - k \int_{\Omega} \frac{\varphi_n^3}{K' + |\psi_n|} \, dx = \int_{\Omega} J(t, \varphi_n, u_n) \varphi_n \, dx.
\]
Since \( \left| \frac{s}{K^2 + |n|} \right| \leq 1 \) and, by (H3), noting that \( 0 \leq J(\cdot, \cdot, \cdot) \leq J_2 \), we get

\[
\frac{1}{2} \frac{d}{dt} \| \varphi_n \|^2 + \alpha \| \nabla \varphi_n \|^2 \leq c(\| \varphi_n \|^2 + 1),
\]

so that, as above

\[
\| \varphi_n \|_{L^\infty(0, \tau; H)} + \| \varphi_n \|_{L^2(0, \tau; V)} + \| \partial_t \varphi_n \|_{L^2(0, \tau; V')} \leq c.
\]

The third component \( \psi_n \) is analogously controlled, that is, we test the third equation of (6) by \( \psi_n \), obtaining

\[
\frac{1}{2} \frac{d}{dt} (\varepsilon \| \psi_n \|^2) + \beta \| \nabla \psi_n \|^2 + F \| \psi_n \|^2 + k \int_\Omega \frac{\psi_n^2}{K^2 + |\psi_n|} dx - k \int_\Omega \frac{\psi_n \varphi_n}{K + |\varphi_n|} dx = FL \int_\Omega \psi_n dx.
\]

Arguing as above, this leads to:

\[
\frac{1}{2} \frac{d}{dt} (\varepsilon \| \psi_n \|^2) + \beta \| \nabla \psi_n \|^2 + F \| \psi_n \|^2 \leq c(1 + \| \psi_n \|^2)
\]

and a further application of Gronwall’s lemma followed by an integration in time yields

\[
\| \psi_n \|_{L^\infty(0, \tau; H)} + \| \psi_n \|_{L^2(0, \tau; V)} + \| \partial_t \psi_n \|_{L^2(0, \tau; V')} \leq c.
\]

Thus we conclude that, up to a subsequence,

\[
(u_n, \varphi_n, \psi_n) \to (u, \varphi, \psi) \quad \text{weakly-} * \text{ in} \quad L^\infty(0, \tau; H^2),
\]

\[
(u_n, \varphi_n, \psi_n) \to (u, \varphi, \psi) \quad \text{weakly} \quad L^2(0, \tau; V^3),
\]

\[
(u_n, \varphi_n, \psi_n) \to (u, \varphi, \psi) \quad \text{strongly} \quad L^2(0, \tau; H^3).
\]

Moreover, since the previous a priori bounds and the interpolation inequality (2) lead to the uniform boundedness of \( u_n \) in \( L^3(\Omega \times (0, \tau)) \), we have

\[
\| u \|_{L^3(\Omega \times (0, \tau))} \leq c.
\]

(7)

In order to prove that \( (u, \varphi, \psi) \) is indeed a weak solution to (4), we want to pass to the limit in the nonlinear terms in (6). Let \( w \in V \) and \( \phi \in C_c^\infty(0, \tau) \) be arbitrary and \( t \leq \tau \). We only discuss the difficult terms, namely,

\[
\int_0^t \int_\Omega [a(\varphi_n, \psi_n)u_n^2 - a(\varphi, \psi)u^2] w \phi dx\, ds
\]

\[
= \int_0^t \int_\Omega a(\varphi_n, \psi_n)(u_n^2 - u^2) w \phi dx\, ds + \int_0^t \int_\Omega (a(\varphi_n, \psi_n) - a(\varphi, \psi)) u^2 w \phi dx\, ds.
\]

The first term on the right-hand side is managed, thanks to (H1), the H"older inequality and (7), as

\[
\int_0^t \int_\Omega a(\varphi_n, \psi_n)(u_n^2 - u^2) w \phi dx\, ds
\]

\[
\leq a_2 \| \phi \|_{L^\infty(0, \tau)} \int_0^t \int_\Omega |u_n - u| (|u_n| + |u|) |w| dx\, ds
\]

\[
\leq a_2 \| \phi \|_{L^\infty(0, \tau)} \| w \| \| \tau \| \int_0^t |u_n - u| (\| u_n \|_{L^3} + \| u \|_{L^3}) ds
\]

\[
\leq c \| \phi \|_{L^\infty(0, \tau)} \| w \| \| \tau \| (\| u_n \|_{L^2(0, t; V)} + \| u \|_{L^3(\Omega \times (0, t))}) \| u_n - u \|_{L^2(0, t; H)} \to 0 \quad \text{as} \quad n \to \infty.
\]
In order to show that also the second contribution tends to zero, we preliminarily observe that by (H1)
\[
\|a(\varphi, \psi) - a(\varphi_n, \psi_n)\|_{L^3}^3 = \left( \int_\Omega |a(\varphi_n, \psi_n) - a(\varphi, \psi)|^6 \, dx \right)^{1/2} \\
\leq c \left( \int_\Omega |a(\varphi_n, \psi_n) - a(\varphi, \psi)|^2 \, dx \right)^{1/2} \\
\leq c \left( \|\varphi_n - \varphi\| + \|\psi_n - \psi\| \right)
\]
on account of the boundedness and the Lipschitz continuity of \(a\). Therefore
\[
\int_0^t \int_\Omega [a(\varphi_n, \psi_n) - a(\varphi, \psi)] w \phi \, dx \, ds \\
\leq c \|\phi\|_{L^\infty(0, t)} \int_0^t \|a(\varphi_n, \psi_n) - a(\varphi, \psi)\|_{L^\infty} \|u\|_{L^3}^2 \|w\|_{L^3} \, ds \\
\leq c \|\phi\|_{L^\infty(0, t)} \|w\|_{V} \left( \int_0^t \|a(\varphi_n, \psi_n) - a(\varphi, \psi)\|_{L^3}^2 \, ds \right)^{1/3} \left( \int_0^t \|u\|_{L^3}^2 \, ds \right)^{2/3} \\
\leq c \|\phi\|_{L^\infty(0, t)} \|w\|_{V} \left( \int_0^t (\|\varphi_n - \varphi\| + \|\psi_n - \psi\|) \, ds \right)^{1/3} \|u\|_{L^3(\Omega \times (0, t))} \\
\leq c \|\phi\|_{L^\infty(0, t)} \|w\|_{V} (\|\varphi_n - \varphi\|_{L^2(0, t;H)} + \|\psi_n - \psi\|_{L^2(0, t;H)}^{1/3} \to 0 \quad \text{as} \quad n \to \infty,
\]
having exploited (7). It is easier to tackle
\[
\int_0^t \int_\Omega [a(\varphi_n, \psi_n)u_n - a(\varphi, \psi)u] w \phi \, dx \, ds \\
= \int_0^t \int_\Omega a(\varphi_n, \psi_n)(u_n - u) w \phi \, dx \, ds + \int_0^t \int_\Omega [a(\varphi_n, \psi_n) - a(\varphi, \psi)] u w \phi \, dx \, ds \\
\leq c \|\phi\|_{L^\infty(0, t)} \int_0^t \left\{ \int_\Omega |u_n - u| \, dx + \int_\Omega (|\varphi_n - \varphi| + |\psi_n - \psi|) |u| \, dx \right\} \, ds \\
\leq c \|\phi\|_{L^\infty(0, t)} \|w\|_{V} \left\{ \|u_n - u\|_{L^2(0, t;H)} + \|\varphi_n - \varphi\|_{L^2(0, t;H)} + \|\psi_n - \psi\|_{L^2(0, t;H)} \right\} \|u\|_{L^3(\Omega \times (0, t))}
\]
whose limit as \(n \to \infty\) vanishes. Due to (H2)-(H3), we deal analogously with the terms
\[
\int_0^t \int_\Omega [g(\varphi_n, \psi_n)u_n - g(\varphi, \psi)u] w \phi \, dx \, ds \quad \text{and} \quad \int_0^t \int_\Omega [J(s, \varphi_n, u_n) - J(s, \varphi, u)] w \phi \, dx \, ds.
\]
The source nonlinear terms are easily treated thanks to the Lipschitz continuity of the map \(\frac{s}{\mu + |s|}\) for any \(\mu > 0\). For the reader’s convenience we just show the first one,
\[
k \int_0^t \int_\Omega \left( \frac{\varphi_n - \varphi}{K + |\varphi_n|} \right) w \phi \, dx \, ds \\
\leq c \|\phi\|_{L^\infty(0, t)} \int_0^t \int_\Omega |\varphi_n - \varphi| |w| \, dx \, ds \\
\leq c \|\phi\|_{L^\infty(0, t)} \|w\|_{V} \|\varphi_n - \varphi\|_{L^2(0, t;H)} \to 0
\]
as \(n \to +\infty\).

We can now prove the global in time existence of the weak solutions to (1) issuing from nonnegative initial data.

**Lemma 3.2.** Let \(T > 0\) be fixed and \((u_0, \varphi_0, \psi_0) \in \mathcal{H}^+\). Then any weak solution to (1) is defined on \([0, T]\).
Proof. Owing to Lemma 3.1 we learn that \( u(t), \varphi(t), \psi(t) \geq 0 \) whenever defined. Therefore, multiplying the first equation of (1) by \( u \), thanks to (H1), (H2) and (H4), we get:

\[
\frac{1}{2} \frac{d}{dt} \|u\|^2 + d\|\nabla u\|^2 + a_1\|u\|_{L^2}^2 \leq a_2\gamma\|u\|^2 \leq \frac{a_1}{2}\|u\|_{L^2}^3 + c.
\]

Since \( \frac{a_1}{2}\|u\|_{L^2}^3 \geq d\|u\|_{L^2}^2 - c \), we obtain:

\[
\frac{1}{2} \frac{d}{dt} \|u\|^2 + d\|u\|_{L^2}^2 \leq c,
\]

hence the dissipative estimate and the integral inequality

\[
\|u(t)\|^2 \leq e^{-2dt}\|u_0\|^2 + c \quad \text{and} \quad \int_0^t \|u(s)\|_{L^2}^2 ds \leq C_T, \quad t \in [0, T],
\]

with \( C_T \) depending on \( T \).

The product of the second equation of (1) by \( \varphi \) yields:

\[
\frac{1}{2} \frac{d}{dt} \|\varphi\|^2 + a\|\nabla \varphi\|^2 + k \int_{\Omega} \frac{\varphi^2}{K+\varphi} dx - k \int_{\Omega} \frac{\varphi \psi}{K^r+\psi} dx = \int_{\Omega} J(t, \varphi, u) \varphi dx.
\]

Since \( \frac{\psi}{K^r+\psi} \leq 1 \), and \( J(t, \varphi, u) \leq J_2 \) due to (H3), we get

\[
\frac{1}{2} \frac{d}{dt} \|\varphi\|^2 + a\|\nabla \varphi\|^2 \leq c(\|\varphi\|^2 + 1),
\]

showing that no dissipation occurs for \( \varphi \) as

\[
\|\varphi(t)\|^2 \leq e^{ct}\|\varphi_0\|^2 + c, \quad t \in [0, T].
\]

Multiplying the third equation of (1) by \( \psi \), we obtain:

\[
\frac{1}{2} \frac{d}{dt} (\varepsilon\|\psi\|^2) + \beta\|\nabla \psi\|^2 + F\|\psi\|^2 + k \int_{\Omega} \frac{\psi^2}{K^r+\psi} dx - k \int_{\Omega} \frac{\psi \varphi}{K^r+\psi} dx = FL \int_{\Omega} \psi dx,
\]

leading to:

\[
\frac{1}{2} \frac{d}{dt} (\varepsilon\|\psi\|^2) + \beta\|\nabla \psi\|^2 + F\|\psi\|^2 \leq k \int_{\Omega} \frac{\psi \varphi}{K^r+\psi} dx + FL \int_{\Omega} \psi dx \leq c \int_{\Omega} \psi dx \leq \frac{F}{2}\|\psi\|^2 + c.
\]

Thus we conclude that

\[
\frac{1}{2} \frac{d}{dt} (\varepsilon\|\psi\|^2) + \beta\|\nabla \psi\|^2 + F\|\psi\|^2 \leq c,
\]

which implies the dissipative estimate

\[
\varepsilon\|\psi(t)\|^2 \leq \varepsilon\|\psi_0\|^2 e^{-\frac{ct}{\varepsilon}} + c, \quad t \in [0, T].
\]

4. \( L^\infty \)-upper bounds on the solutions.

**Lemma 4.1.** Denoting by \( (u, \varphi, \psi) \) any solution departing from \( (u_0, \varphi_0, \psi_0) \in H^+ \) with \( u_0 \in L^\infty(\Omega) \), we have \( \|u(t)\|_{L^\infty} \leq \max\{\gamma, \|u_0\|_{L^\infty}\} \) for almost any \( t \geq 0 \).

**Proof.** We first consider the case when \( u_0 \leq \gamma \) a.e. in \( \Omega \). Then it is readily seen that \( \xi = u - \gamma \) is solution to:

\[
\partial_t \xi - \text{div}(D\nabla \xi) = -\xi a(\varphi, \psi) - ug(\varphi, \psi),
\]

complemented with homogeneous Neumann boundary conditions and with \( \xi(0) = u_0 - \gamma \leq 0 \) a.e. in \( \Omega \). Multiplying the equation by \( \xi^+ \), we infer:

\[
\frac{1}{2} \frac{d}{dt} \|\xi^+\|^2 + (D\nabla \xi^+, \nabla \xi^+) = -\int_{\Omega} (\xi^+)^2 a(\varphi, \psi) dx - \int_{\Omega} u\xi^+ g(\varphi, \psi) dx \leq 0.
\]
Hence, since \( \xi^+(0) = 0 \), it follows \( \xi^+(t) = 0 \; \forall t \geq 0 \), i.e.
\[
u(t) \leq \gamma \; \forall t \geq 0.
\]

If instead \( \|u_0\|_{L^\infty} > \gamma \), arguing as in [2], we compare \( u \) with the solution to the Cauchy problem
\[
\begin{cases}
y'(t) = a_1 \Phi(y), \\
y(0) = \|u_0\|_{L^\infty}
\end{cases}
\]
where \( \Phi(y) = y(\gamma - y) \).
For this, there exists a unique solution \( \lambda(t) \) for \( t \geq 0 \) with \( \gamma < \lambda(t) \leq \|u_0\|_{L^\infty} \), for any \( t \geq 0 \). Therefore, \( w = \lambda - u \) solves
\[
\begin{cases}
\partial_t w - \text{div}(D \nabla w) = a_1 \Phi(\lambda) - a(\varphi, \psi)\Phi(u) + u g(\varphi, \psi), \\
w(0) = \|u_0\|_{L^\infty} - u_0 \geq 0.
\end{cases}
\]
In particular,
\[
\partial_t w - \text{div}(D \nabla w) \geq a(\varphi, \psi)[\Phi(\lambda) - \Phi(u)] + u g(\varphi, \psi)
\]
\[
= a(\varphi, \psi) \frac{\Phi(\lambda) - \Phi(u)}{\lambda - u} w + u g(\varphi, \psi),
\]
so that, taking the product by \( -w^- \), we obtain
\[
\frac{1}{2} \frac{d}{dt} \|w^-\|^2 + d \|\nabla w^-\|^2 \leq \int_{\Omega^-} a(\varphi, \psi) \frac{\Phi(\lambda) - \Phi(u)}{\lambda - u} (w^-)^2 dx,
\]
where \( \Omega^- = \{ x \in \Omega : \lambda(t) \leq u(x, t) \} \). Hence, by definition of \( \Omega^- \), we have \( u \geq \lambda \) and, since \( \Phi \) is monotone decreasing on \( (\gamma, +\infty) \),
\[
\frac{\Phi(\lambda) - \Phi(u)}{\lambda - u} \leq 0 \; \text{in} \; \Omega^-.
\]
As a consequence,
\[
\frac{1}{2} \frac{d}{dt} \|w^-\|^2 + d \|\nabla w^-\|^2 \leq 0
\]
and we can conclude that \( w^- = 0 \), hence \( u \leq \lambda \), which, in particular, entails \( \|u(t)\|_{L^\infty} \leq \|u_0\|_{L^\infty}, \; \forall t \geq 0 \). \( \square \)

For more regular initial data, we can devise \( L^\infty \)-upper bounds on finite time intervals for both lactate concentrations, namely,

**Lemma 4.2.** Let \((u_0, \varphi_0, \psi_0) \in \mathcal{H}^+ \cap [V \times H^2(\Omega) \times H^2(\Omega)]\) be arbitrary. Then, for any given \( T > 0 \), there exists \( C_T > 0 \) such that
\[
\varphi(t) \leq C_T \quad \text{and} \quad \psi(t) \leq C_T, \; \text{a.e. in} \; \Omega \times [0, T].
\]

**Proof.** We multiply the first equation of (1) by \(-\text{div}(D \nabla u)\). This yields
\[
\frac{1}{2} \frac{d}{dt} (D \nabla u, \nabla u) + \|\text{div}(D \nabla u)\|^2
\]
\[
= \int_{\Omega} a(\varphi, \psi) u^2 \text{div}(D \nabla u) dx - \gamma \int_{\Omega} a(\varphi, \psi) u \text{div}(D \nabla u) dx + \int_{\Omega} g(\varphi, \psi) u \text{div}(D \nabla u) dx.
\]
We handle the first term in the right-hand side employing (3) for $N \leq 3$ and recalling (8),

$$
\int_{\Omega} \alpha(\varphi, \psi) u^2 \text{div}(D \nabla u) dx \leq a_2 \|u\|_{L^2}^2 \|\text{div}(D \nabla u)\| \leq \frac{1}{\beta}\|\text{div}(D \nabla u)\|^2 + c\|u\|_{L^2}^3
$$

$$
\leq \frac{1}{\beta}\|\text{div}(D \nabla u)\|^2 + c\|u\|^2 + c\|u\|^3
$$

The other terms can be handled in the same way. Therefore,

$$
\frac{1}{2} \frac{d}{dt} \|D \nabla u, \nabla u\| + \frac{1}{2} \|\text{div}(D \nabla u)\|^2 \leq c\|u\|_V + 1)(D \nabla u, \nabla u) + c,
$$

on account of $d\|\nabla u\|^2 \leq (D \nabla u, \nabla u)$. By Gronwall’s lemma, we conclude that

$$
\|u(t)\|_V \leq C_T \quad \forall t \in [0, T].
$$

We next multiply the second equation of (1) by $-\Delta \varphi$. It yields:

$$
\frac{1}{2} \frac{d}{dt} \|\nabla \varphi\|^2 + \alpha\|\Delta \varphi\|^2 - k \int_{\Omega} \frac{\varphi}{K + \varphi} \Delta \varphi dx + k \int_{\Omega} \frac{\psi}{K + \psi} \Delta \varphi dx = - k \int_{\Omega} J(t, \varphi, u) \Delta \varphi dx.
$$

By (H3), we find

$$
\frac{1}{2} \frac{d}{dt} \|\nabla \varphi\|^2 + \alpha\|\Delta \varphi\|^2 \leq c\|\Delta \varphi\| \leq \frac{\alpha}{2}\|\Delta \varphi\|^2 + c,
$$

so that

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

and we conclude that $\|\nabla \varphi(t)\|^2 \leq C_T$ and $\int_0^t \|\Delta \varphi(s)\|^2 ds \leq C_T \quad \forall t \in [0, T].$

Now, the product of the third equation of (1) by $-\Delta \psi$ yields

$$
\frac{1}{2} \frac{d}{dt} (\epsilon \|\nabla \psi\|^2) + \beta\|\Delta \psi\|^2 + F\|\nabla \psi\|^2 - k \int_{\Omega} \frac{\psi}{K + \psi} \Delta \psi dx + k \int_{\Omega} \frac{\varphi}{K + \varphi} \Delta \psi dx = 0.
$$

Again, we conclude that

$$
\frac{1}{2} \frac{d}{dt} (\epsilon \|\nabla \psi\|^2) + \frac{\beta}{2}\|\Delta \psi\|^2 + F\|\nabla \psi\|^2 \leq c,
$$

so that, by Gronwall’s lemma,

$$
\|\nabla \psi(t)\|^2 \leq \|\nabla \psi_0\|^2 e^{-\frac{\beta t}{2}} + c, \quad \forall t \in [0, T].
$$

We then multiply the second equation of (1) by $\partial_t \varphi$, getting

$$
\|\partial_t \varphi\|^2 + \frac{\alpha}{2} \frac{d}{dt}\|\nabla \varphi\|^2 + k \int_{\Omega} \frac{\varphi}{K + \varphi} \partial_t \varphi dx - k \int_{\Omega} \frac{\psi}{K + \psi} \partial_t \varphi dx = \int_{\Omega} J(t, \varphi, u) \partial_t \varphi dx.
$$

Owing to (H3),

$$
\|\partial_t \varphi\|^2 + \frac{\alpha}{2} \frac{d}{dt}\|\nabla \varphi\|^2 \leq c\|\partial_t \varphi\| \leq \frac{1}{2}\|\partial_t \varphi\|^2 + c,
$$

yielding to

$$
\|\partial_t \varphi\|^2 + \frac{\alpha}{2} \frac{d}{dt}\|\nabla \varphi\|^2 \leq c
$$

so that, integrating in time,

$$
\int_0^t \|\partial_t \varphi(s)\|^2 ds \leq C_T, \quad \forall t \in [0, T]. \tag{9}
$$

We rewrite the third equation of (1) in the following equivalent form:

$$
\epsilon \partial_t \psi - \beta \Delta \psi + k \left(\frac{K}{K + \varphi} - \frac{K'}{K' + \psi}\right) + F \psi = FL,
$$
and differentiate this equation with respect to time. This yields:

\[
\begin{cases}
\varepsilon \partial_t^2 \psi - \beta \Delta \partial_t \psi + F \partial_t \psi + \frac{kK'}{(K' + \psi)^2} \partial_t \psi - \frac{kK}{(K + \varphi)^2} \partial_t \varphi = 0, & \text{in } \Omega \times (0, T), \\
\partial_n \partial_t \psi = 0, & \text{on } \partial \Omega \times (0, T), \\
\partial_t \psi(0) = \frac{1}{\varepsilon} \left( \beta \Delta \psi_0 - \frac{kK}{K + \varphi_0} + \frac{kK'}{K' + \psi_0} - F \psi_0 + FL \right) \in H & \text{in } \Omega.
\end{cases}
\]

(10)

Multiplying this equation by \( \partial_t \psi \), we obtain:

\[
\frac{1}{2} \frac{d}{dt} \left( \varepsilon \| \partial_t \psi \|^2 \right) + \beta \| \nabla (\partial_t \psi) \|^2 + F \| \partial_t \psi \|^2 + kK' \int_\Omega \frac{(\partial_t \psi)^2}{(K' + \psi)^2} \, dx = kK \int_\Omega \frac{\partial_t \varphi \partial_t \psi}{(K + \varphi)^2} \, dx.
\]

Since the right hand side can be handled in the following way

\[
kK \int_\Omega \frac{\partial_t \varphi \partial_t \psi}{(K + \varphi)^2} \, dx \leq c \| \partial_t \varphi \|^2 + \frac{F}{2} \| \partial_t \psi \|^2,
\]

we obtain:

\[
\frac{1}{2} \frac{d}{dt} \left( \varepsilon \| \partial_t \psi \|^2 \right) + \beta \| \nabla (\partial_t \psi) \|^2 + \frac{F}{2} \| \partial_t \psi \|^2 \leq c \| \partial_t \varphi \|^2.
\]

A further application of Gronwall’s lemma, on account of (9), yields

\[
\| \partial_t \psi(t) \|^2 \leq \| \partial_t \psi(0) \|^2 e^{-\frac{F}{2} t} + C_T, \quad t \in [0, T].
\]

Since (1) can be written as

\[-\beta \Delta \psi = -\varepsilon \partial_t \psi - k \left( \frac{\psi}{K' + \psi} - \frac{\varphi}{K + \varphi} \right) + FL - F \psi,
\]

we conclude that \( \| \psi(t) \|_{H^2} \leq C_T \) for \( t \in [0, T] \). By Agmon inequality, it follows that \( \| \psi(t) \|_{L^\infty} \leq C_T \quad \forall \ 0 \leq t \leq T \).

To prove that \( \| \varphi(t) \|_{L^\infty} \leq C_T \), first notice that \( J(t, \varphi, u) + \frac{k\varphi}{K' + \psi} \leq J_2 + k =: C_2 \), where \( C_2 > 0 \) is an absolute constant. Consider then the solution \( z \) to

\[
\begin{cases}
\partial_t z - \alpha \Delta z + \frac{kz}{K + z} = C_2, \\
\partial_n z |_{\partial \Omega} = 0, \\
z(0) = \varphi_0.
\end{cases}
\]

(11)

It is easy to check that \( z \geq 0 \). Next, we prove that \( \| z(t) \|_{H^2} \leq C_T \quad \forall t \in [0, T] \), then that \( 0 \leq \varphi(x, t) \leq z(x, t) \). Taking the product of the first equation of (11) by \( z \), we obtain

\[
\frac{1}{2} \frac{d}{dt} \| z \|^2 \leq \frac{1}{2} \frac{d}{dt} \| z \|^2 + \alpha \| \nabla z \|^2 + k \int_\Omega \frac{z^2}{K + z} \, dx = C_2 \int_\Omega z \, dx \leq c \| z \|,
\]

thus, \( \| z(t) \| \leq C_T, \quad \forall t \in [0, T] \). We now test (11) with \(-\Delta z\), obtaining

\[
\frac{1}{2} \frac{d}{dt} \| \nabla z \|^2 + \alpha \| \Delta z \|^2 = -C_2 \int_\Omega \Delta z \, dx + k \int_\Omega \frac{z \Delta z}{K + z} \, dx \leq \frac{\alpha}{2} \| \Delta z \|^2 + c.
\]

Hence we get \( \| \nabla z(t) \| \leq C_T, \quad \forall t \in [0, T] \). We then differentiate (11) in time,

\[
\begin{cases}
\partial_{tt}^2 z - \alpha \Delta \partial_t z + \frac{kK}{(K + z)^2} \partial_t z = 0, \\
\partial_n \partial_t z |_{\partial \Omega} = 0, \\
\partial_t z(0) = \alpha \Delta \varphi_0 - \frac{k \varphi_0}{K + \varphi_0} + C_2,
\end{cases}
\]

and prove that \( \| \Delta z(t) \| \leq C_T, \quad \forall t \in [0, T] \).
and multiply the resulting equation by $\partial_t z$. We obtain:

$$\frac{1}{2} \frac{d}{dt} \|\partial_t z\|^2 \leq \frac{1}{2} \frac{d}{dt} \|\partial_t z\|^2 + \alpha \|\nabla \partial_t z\|^2 + k K \int_\Omega \frac{(\partial_t z)^2}{(K + z)^2} \, dx = 0,$$

so that $\|\partial_t z(t)\|^2 \leq \|\partial_t z(0)\|^2 \forall t \in [0, T]$. Then we deduce from the first equation of (11) that

$$\|\Delta z(t)\| \leq C_T, \quad \text{so that} \quad \|z(t)\|_{H^2} \leq C_T \quad \forall t \in [0, T]$$

and, by Agmon’s inequality,

$$\|z(t)\|_{L^\infty} \leq C_T \quad \forall t \in [0, T].$$

In order to compare $\varphi$ with $z$, let $w = \varphi - z$. We can see that $w$ solves

$$\begin{cases}
\partial_t w - \alpha \Delta w + k \left( \frac{\varphi}{K + \varphi} - \frac{z}{K + z} \right) = J(t, \varphi, u) + \frac{k \psi}{K' + \psi} - C_2 \leq 0, \\
\partial_n w |_{\partial \Omega} = 0, \\
w(0) = 0.
\end{cases} \tag{12}$$

Multiplying the equation in (12) by $w^+$ and using the fact that $\frac{\varphi}{K + \varphi} - \frac{z}{K + z} = \frac{K w}{(K + \varphi)(K + z)}$, we obtain:

$$\frac{1}{2} \frac{d}{dt} \|w^+\|^2 + \alpha \|\nabla w^+\|^2 = -k K \int_\Omega \frac{(w^+)^2}{(K + \varphi)(K + z)} \, dx \leq 0.$$

We conclude that $\|w^+(t)\|^2 \leq \|w^+(0)\|^2 = 0$, which implies that $\varphi(t) \leq z(t) \leq C_T$ a.e. in $\Omega \times [0, T]$. \qed

5. Uniqueness.

**Theorem 5.1.** The weak solution to (1) departing from any datum $(u_0, \varphi_0, \psi_0) \in H^+$ is unique if one of the following conditions is met:

1. $a$ is constant;
2. $\Omega \subset \mathbb{R}^2$, that is, $N = 2$;
3. $u_0 \in L^\infty(\Omega)$.

**Proof.** Assume that $(u_1, \varphi_1, \psi_1)$ and $(u_2, \varphi_2, \psi_2)$ are two weak solutions issuing from the same arbitrarily fixed initial datum $(u_0, \varphi_0, \psi_0) \in H^+$. Then the triplet $(u, \varphi, \psi)$ defined as

$$u = u_1 - u_2, \quad \varphi = \varphi_1 - \varphi_2, \quad \psi = \psi_1 - \psi_2$$

solves

$$\begin{cases}
\partial_t u - \text{div}(D \nabla u) = a_1 u_1 (\gamma - u_1) - a_2 u_2 (\gamma - u_2) - u_1 g_1 + u_2 g_2, & \text{in } \Omega_T, \\
\partial_t \varphi - \alpha \Delta \varphi, & \text{in } \Omega_T, \\
\partial_t \psi - \beta \Delta \psi + F \psi = \frac{k K \varphi}{(K + \varphi_1)(K + \varphi_2)} - \frac{k K' \psi}{(K' + \psi_1)(K' + \psi_2)}, & \text{in } \Omega_T, \\
\varepsilon \partial_t \psi - \beta \Delta \psi + F \psi = \frac{k K \varphi}{(K + \varphi_1)(K + \varphi_2)} - \frac{k K' \psi}{(K' + \psi_1)(K' + \psi_2)}, & \text{in } \Omega_T, \\
D \nabla u \cdot n = \partial_n \varphi = \partial_n \psi = 0, & \text{on } \partial \Omega_T, \\
u(0) = 0, \quad \varphi(0) = 0, \quad \psi(0) = 0., & \text{in } \Omega, 
\end{cases} \tag{13}$$
having set, for the sake of brevity, \( a_i = a(\varphi_i, \psi_i) \), \( g_i = g(\varphi_i, \psi_i) \) and \( J_i = J(t, \varphi_i, u_i) \) for \( i = 1, 2 \).

Multiplying the second equation in (13) by \( \varphi \) and recalling the definition of \( J_i \), we have
\[
\frac{1}{2} \frac{d}{dt} \| \varphi \|^2 + \alpha \| \nabla \varphi \|^2
= \int_{\Omega} \left[ J(t, \varphi_2, u_2) - J(t, \varphi_2, u_2) \right] \varphi \, dx - \int_{\Omega} \frac{kK\varphi^2}{(K + \varphi_1)(K + \varphi_2)} \, dx + \int_{\Omega} \frac{kK'\varphi}{(K' + \varphi_2)(K' + \psi_2)} \, dx
\leq \int_{\Omega} \left[ J(t, \varphi_1, u_1) - J(t, \varphi_1, u_2) \right] \varphi \, dx + \int_{\Omega} \frac{kK\varphi^2}{(K + \varphi_1)(K + \varphi_2)} \, dx
\leq c(\| \varphi \|^2 + \| \varphi \|^2).
\]
on account of the Lipschitz continuity of \( J \) stated in (H3). Next the product of the third equation in (13) by \( \psi \) gives
\[
\frac{1}{2} \frac{d}{dt}(\beta \| \nabla \psi \|^2) = \int_{\Omega} \left[ \frac{kK\varphi\psi}{(K + \varphi_1)(K + \varphi_2)} - \frac{kK'\psi}{(K' + \varphi_2)(K' + \psi_2)} \right] \, dx
\leq \int_{\Omega} \frac{kK\varphi\psi}{(K + \varphi_1)(K + \varphi_2)} \, dx \leq c(\| \varphi \|^2 + \| \psi \|^2).
\]
We take the product in \( H \) of the first equation in (13) by \( u \), so that, recalling the definition of \( a_i \) and \( g_i \), we deduce that
\[
\frac{1}{2} \frac{d}{dt} \| u \|^2 + (D\nabla u, \nabla u)
= \int_{\Omega} [a(\varphi_1, \psi_1) - a(\varphi_2, \psi_2)] (\gamma u - u_1^2) u \, dx + \int_{\Omega} a(\varphi_2, \psi_2) [\gamma u^2 - (u_1 + u_2)u^2] \, dx
- \int_{\Omega} [g(\varphi_1, \psi_1) - g(\varphi_2, \psi_2)] u_1 u \, dx - \int_{\Omega} g(\varphi_2, \psi_2) u^2 \, dx
= - \int_{\Omega} [a(\varphi_1, \psi_1) - a(\varphi_2, \psi_2)] u_1^2 u \, dx + \int_{\Omega} [\gamma a(\varphi_2, \psi_2) - g(\varphi_2, \psi_2)] u^2 \, dx
+ \int_{\Omega} [\gamma [a(\varphi_1, \psi_1) - a(\varphi_2, \psi_2)] - [g(\varphi_1, \psi_1) - g(\varphi_2, \psi_2)]] u_1 u \, dx = \sum_{i=1}^{3} I_i.
\]
The assumptions on \( a \) and \( g \) easily yield
\[
I_2 \leq c\| u \|^2,
\]
owing to (H1)-(H2), and
\[
I_3 \leq c \int_{\Omega} (\| \varphi \| + \| \psi \|) |u_1| \| u \| \, dx \leq c(\| \varphi \| + \| \psi \|) \| u \|_{L^3} \| u \|_{L^6}
\leq \frac{d}{2} \| u \|^2 + c\| u_1 \|^2 (\| \varphi \|^2 + \| \psi \|^2),
\]
on account of the Lipschitz continuity. Therefore, adding together the previous inequalities, we are left to consider
\[
\frac{d}{dt} (\| u \|^2 + \| \varphi \|^2 + \epsilon \| \psi \|^2) + d\| \nabla u \|^2 + 2\alpha \| \nabla \varphi \|^2 + 2\beta \| \nabla \psi \|^2
\leq c(1 + \| u_1 \|^2) (\| u \|^2 + \| \varphi \|^2 + \epsilon \| \psi \|^2) + 2|I_1|.
\]
In the first case, we take a constant, so that \( I_1 \) vanishes and we can conclude thanks to (8).
In the second one, we may take advantage of (3) for \( N \leq 2 \), so that
\[
2|I_1| \leq 2 \int_{\Omega} |a(\varphi_1, \psi_1) - a(\varphi_2, \psi_2)| |u_1|^2 |u| dx \leq c ||a(\varphi_1, \psi_1) - a(\varphi_2, \psi_2)||_L^2 \|u_1\|^2 \|u\|_L^4.
\]
\[
\leq c \left( ||\varphi||_{L^4} + ||\psi||_{L^4} \right) ||u_1||_{L^4}^2 \|u\|_L^4.
\]
\[
\leq \frac{c}{2} \left( ||\varphi||^{1/2} ||\varphi||^{1/2} + ||\psi||^{1/2} ||\psi||^{1/2} \right) ||u_1|| ||u_1|| \|\varphi\|^{1/2} \|\varphi\|^{1/2}
\]
\[
\leq d ||\nabla u||^2 + 2a ||\nabla \varphi||^2 + 2b ||\nabla \psi||^2 + c(1 + ||u_1||^2)(||u||^2 + ||\varphi||^2 + \varepsilon ||\psi||^2).
\]
Since this yields
\[
\frac{d}{dt} \left( ||u||^2 + ||\varphi||^2 + \varepsilon ||\psi||^2 \right) \leq c \left(1 + ||u_1||^2 \right) \left( ||u||^2 + ||\varphi||^2 + \varepsilon ||\psi||^2 \right)
\]
the uniqueness easily follows from (8).

In case \( u_0 \in L^\infty(\Omega) \), then we know from Lemma 4.1 that
\[
\sup_{t \geq 0} \|u_1(t)\|_{L^\infty} \leq \max \{\gamma, \|u_0\|_{L^\infty} \}.
\]
Therefore
\[
2|I_1| \leq c \sup_{t \geq 0} \|u_1(t)\|_{L^\infty}^2 \left( ||\varphi|| + ||\psi|| \right) \|u\| \leq c(1 + ||u_1||^2)(||u||^2 + ||\varphi||^2 + \varepsilon ||\psi||^2).
\]
We finally conclude that
\[
\frac{d}{dt} \left( ||u||^2 + ||\varphi||^2 + \varepsilon ||\psi||^2 \right) \leq c \left(1 + ||u_1||^2 \right) \left( ||u||^2 + ||\varphi||^2 + \varepsilon ||\psi||^2 \right),
\]
hence the uniqueness due to (8).

6. **Permanence of the illness and linear stability.** As far as the longterm dynamics is concerned, we will be able to prove that, when the function \( g \) vanishes, then there is permanence of the illness. In turn, when \( J \) is constant then, provided suitable conditions hold true, there exist two stationary states whose linear stability can be investigated: the former one is unstable, while the latter is stable.

6.1. **Permanence of the tumor when \( g = 0 \).** Let us assume that the initial datum satisfies \( u_0 > 0 \) and \( 0 < ||u_0 - \gamma|| < ||\gamma|| \).

We set \( v = u - \gamma \). Then \( v \) is solution to the equation:
\[
\partial_t v - \text{div}(D \nabla v) = -a(\varphi, \psi) uv.
\]
Multiplying this equation by \( v \), we obtain, since \( a(\varphi, \psi) > 0 \) and \( u \geq 0 \),
\[
\frac{1}{2} \frac{d}{dt} \|v\|^2 + (D \nabla v, \nabla v) = -\int_\Omega a(\varphi, \psi) u v^2 dx \leq 0.
\]
Hence \( \|v(t)\| = \|v(0)\| = \|v(t)\| \leq \|v(0)\| = \|u_0 - \gamma\| \). Therefore, \( \|\gamma\| - \|u(t) - \gamma\| \geq \|\gamma\| - \|u_0 - \gamma\| > 0 \) and, since \( \|u(t)\| \geq \|\gamma\| - \|u(t) - \gamma\| \), we deduce that
\[
\|u(t)\| \geq \|\gamma\| - \|u_0 - \gamma\| > 0 \quad \forall t \geq 0,
\]
meaning that extinction cannot occur.
6.2. Stability analysis when $J$ is constant. When $J$ is constant, there exist two spatially homogeneous stationary states $(0, \bar{\varphi}, \bar{\psi})$ and $(\tilde{u}, \tilde{\varphi}, \tilde{\psi})$, where
\[
\tilde{\varphi} = K \frac{k\bar{\psi} + J(K' + \psi)}{kK' - J(K + \psi)}, \quad \tilde{\psi} = L + \frac{J}{F'}, \quad \tilde{\psi} = -\frac{\bar{g}}{\bar{a}} + \gamma
\]
while $\bar{a} = a(\bar{\varphi}, \bar{\psi})$ and $\bar{g} = g(\bar{\varphi}, \bar{\psi})$. We assume $\tilde{\varphi} > 0$ together with $\tilde{\psi} > 0$ (i.e. $\bar{g} < \bar{a} \gamma$).

The system linearized around the first equilibrium $(0, \bar{\varphi}, \bar{\psi})$ reads
\[
\begin{cases}
\partial_t \tilde{u} - \text{div}(D\nabla \tilde{u}) = (\bar{a} \gamma - \bar{g}) \tilde{u}, & \text{in } \Omega \times (0, \infty), \\
\partial_t \tilde{\varphi} - \alpha \Delta \tilde{\varphi} = -\frac{kK \tilde{\varphi}}{(K + \bar{\varphi})^2} + \frac{kK' \tilde{\psi}}{(K' + \psi)^2}, & \text{in } \Omega \times (0, \infty), \\
\varepsilon \partial_t \tilde{\psi} - \beta \Delta \tilde{\psi} + F \tilde{\psi} = \frac{kK \tilde{\varphi}}{(K + \bar{\varphi})^2} - \frac{kK' \tilde{\psi}}{(K' + \psi)^2}, & \text{in } \Omega \times (0, \infty), \\
D \nabla \tilde{u} \cdot n = 0, & \text{on } \partial \Omega \times (0, \infty), \\
\tilde{u}(0) = \tilde{u}_0, & \tilde{\varphi}(0) = \bar{\varphi}_0, \quad \tilde{\psi}(0) = \bar{\psi}_0, & \text{in } \Omega, \\
\end{cases}
\] (14)

whereas, linearizing around $(\tilde{u}, \tilde{\varphi}, \tilde{\psi})$, the first equation reads
\[
\partial_t \tilde{u} - \text{div}(D\nabla \tilde{u}) + (\bar{a} \gamma - \bar{g}) \tilde{u} = \tilde{u} \left( \frac{\bar{g}}{\bar{a}} \frac{\partial a}{\partial \varphi}(\tilde{\varphi}, \tilde{\psi}) - \frac{\partial g}{\partial \varphi}(\tilde{\varphi}, \tilde{\psi}) \right) \tilde{\varphi} + \tilde{u} \left( \frac{\bar{g}}{\bar{a}} \frac{\partial a}{\partial \psi}(\tilde{\varphi}, \tilde{\psi}) - \frac{\partial g}{\partial \psi}(\tilde{\varphi}, \tilde{\psi}) \right) \tilde{\psi}. \tag{15}
\]

Lemma 6.1. When $J$ is constant and $\bar{u}, \tilde{\psi} > 0$ then

(I) the stationary solution $(0, \bar{\varphi}, \bar{\psi})$ is linearly unstable in $H^+;$

(II) the stationary solution $(\tilde{u}, \tilde{\varphi}, \tilde{\psi})$ is linearly stable in $H^+$, provided that
\[
\frac{\partial a}{\partial \varphi}(\tilde{\varphi}, \tilde{\psi}), \frac{\partial a}{\partial \psi}(\tilde{\varphi}, \tilde{\psi}) \leq 0 \quad \text{and} \quad \frac{\partial g}{\partial \varphi}(\tilde{\varphi}, \tilde{\psi}), \frac{\partial g}{\partial \psi}(\tilde{\varphi}, \tilde{\psi}) \geq 0.
\]

Proof. Since the stability for $\tilde{\varphi}$ and $\tilde{\psi}$ can be handled exactly as in [3], we focus on the first variable $u$.

(I) In order to prove that $(0, \bar{\varphi}, \bar{\psi})$ is unstable, we prove that the solution originating from a constant in space initial datum does not approach zero as time progresses. Fix $\bar{u}_0 > 0$ and consider the ODE
\[
\begin{cases}
\dot{\bar{u}}' - (\bar{a} \gamma - \bar{g}) \bar{u} = 0, \\
\bar{u}(0) = \bar{u}_0.
\end{cases}
\]
This ODE can be explicitly solved, yielding
\[
\bar{u}(t) = \bar{u}_0 e^{(\bar{a} \gamma - \bar{g}) t}, \quad t \geq 0,
\]
so that
\[
\|\bar{u}(t)\| \to +\infty \quad \text{as} \quad t \to +\infty.
\]

(II) Now, we deal with the stability of $(\tilde{u}, \tilde{\varphi}, \tilde{\psi})$. We can easily prove that $\tilde{\varphi}, \tilde{\psi}$ and $\tilde{\psi}$ are positive. So we just observe that, under our assumptions, the product of (15) by $\tilde{u}$ in $H$ gives
\[
\frac{1}{2} \frac{d}{dt} \|\tilde{u}\|^2 + d \|\nabla \tilde{u}\|^2 + (\bar{a} \gamma - \bar{g}) \|\tilde{u}\|^2 \leq 0,
\]
yielding $\|\tilde{u}(t)\| \leq \|\bar{u}_0\|, \quad \forall t \geq 0$. \qed
Remark 2. When \( g = 0 \) and \( J \) is constant, the stability analysis complies with the aforementioned permanence of the disease for solutions departing from a biologically meaningful initial datum.

7. Numerical simulations. In the numerical simulations presented below, \( \Omega \) is an ellipse parametrized by \( x = 6 \cos \theta, \ y = 8 \sin \theta, \ \theta \in [0, 2\pi] \). The tumor is initialized as \( u_0(x, y) = 0.1e^{-10(x^2+(y-2.5)^2)} \) and is centered at the point \((0; 2.5)\). We assume, as far as the lactate concentrations are concerned, that, far from the tumor area, the initial concentrations \( \varphi_0 \) and \( \psi_0 \) are close to the equilibrium values \( \bar{\varphi} \) and \( \bar{\psi} \) and, in the tumor area, the initial lactate concentrations correspond to a spike (see Figure 1 and Figure 5).

7.1. Grompertz growth of the brain lactate concentration.

Concerning the first test, we take for the lactate equations the parameters values given in \([4]\), Section 5, for patient 1, namely, \( \varphi_0 = 0.025mM, \ \psi_0 = 0.329mM, \ J(t, \varphi, u) = 0.026mM.d^{-1}, \ \kappa = 0.001mM.s^{-1}, \ K = 3.5mM, \ K' = 3.5mM, \ L = 0.3mM, \ F = 0.0272s^{-1}, \ \varepsilon = 0.1s^{-1} \). We also used \( \alpha = 0.05, \ \beta = 0.02, \ D = \begin{pmatrix} 0.01 & 0 \\ 0 & 0.005 \end{pmatrix} \), \( a(\varphi, \psi) = 0.5 + \tanh(\frac{\varphi+\psi}{2}) \) and \( g(\varphi, \psi) = 0.06\varphi + 0.03\psi, \ \gamma = 1.2 \). This particular case leads to \( \bar{\varphi} \sim 3.854, \ \bar{\psi} \sim 1.256 \) (hence \( \bar{\varphi} + \bar{\psi} \sim 5.11 \)) and \( \bar{u} \sim 1.019 \).

We can see in Figure 2 that the tumor spreads and the concentration increases with respect to time, up to its equilibrium value. Moreover the lactate concentrations in the tumor area tend to return to their equilibrium values.

![Tumor and lactate concentrations](image)

**Figure 1.** Tumor (left) and sum of the lactate concentrations \( \varphi + \psi \) (right) at time \( t = 0 \). \( u_0(x, y) = 0.1e^{-10(x^2+(y-2.5)^2)} \), \( \varphi_0 = 0.025mM \) inside and \( \bar{\varphi}_0 = 3.854 \) outside the tumor area, \( \psi_0 = 0.329mM \) inside and \( \psi_0 = 1.256mM \) outside the tumor area.

7.2. Lactate decrease of the brain tumor. We now take initial lactate concentrations corresponding to patient 5 in \([4]\), i.e. \( \varphi_0 = 1.817mM, \ \psi_0 = 2.291mM, \ J(t, \varphi, u) = 0.007mM.d^{-1} \), the other parameters being unchanged. This particular value of \( J \) leads to \( \bar{\varphi} \sim 0.915, \ \bar{\psi} \sim 0.557 \) (hence \( \bar{\varphi} + \bar{\psi} \sim 1.472 \)) and \( \bar{u} = 1.136 \). We can see in Figure 6 that the tumor spreads and the concentration increases with respect to time, up to its equilibrium value. Meanwhile the lactate concentrations inside the tumor decrease, tending to return to their equilibrium values.
Figure 2. Tumor (left) and sum of the lactate concentrations $\varphi + \psi$ (right) at time $t = 10$.

Figure 3. Evolution of the tumor concentration (left) and the lactate concentrations (right) with respect to time at the center of the tumor (point $(0; 2.5)$). Evolution of the tumor diameter (below) with respect to time.

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Concerning the tumor (left), intracellular lactate (right) and capillary lactate (below), comparison between the concentrations at the center of the tumor (green) and at the point (0.8; 2.5), initially outside the tumor (blue).

Tumor (left) and sum of the lactate concentrations $\varphi + \psi$ (right) at time $t = 0$. $(u_0(x, y) = 0.1e^{-10(x^2+(y-2.5)^2)}$, $\varphi_0 = 1.817mM$ inside and $\varphi_0 = 0.915mM$ outside the tumor area, $\psi_0 = 2.291mM$ inside and $\psi_0 = 0.557mM$ outside the tumor area.)

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Figure 6. Tumor (left) and sum of the lactate concentrations $\varphi + \psi$ (right) at time $t = 10$.

Figure 7. Evolution of the tumor concentration (left) and the lactate concentrations (right) with respect to time at the center of the tumor (point $(0; 2.5)$). Evolution of the tumor diameter (below) with respect to time.

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