MATHEMATICAL ANALYSIS OF A PARABOLIC-ELLIPTIC MODEL FOR BRAIN LACTATE KINETICS

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Abstract. Our aim in this paper is to study properties of a parabolic-elliptic system related with brain lactate kinetics. These equations are obtained from a reaction-diffusion system, when a small parameter vanishes. In particular, we prove the existence and uniqueness of nonnegative solutions and obtain error estimates on the difference of the solutions to the initial reaction-diffusion system and those to the limit one, on bounded time intervals. We also study the linear stability of the unique spatially homogeneous equilibrium.

1. Introduction

The following system of ODE's:

$$\frac{du}{dt}+\kappa(\frac{u}{k+u}-\frac{v}{k'+v})=J,\ \kappa,\ k,\ k',\ J>0, \tag{1.1}$$

$$\varepsilon\frac{dv}{dt}+Fv+\kappa(\frac{v}{k'+v}-\frac{u}{k+u})=FL,\ \varepsilon,\ F,\ L>0, \tag{1.2}$$

where ε is a small parameter, was proposed and studied as a model for brain lactate kinetics (see [5], [8], [9] and [10]; see also [4]). In this context, $u=u(t)$ and $v=v(t)$ correspond to the lactate concentrations in an interstitial (i.e., extra-cellular) domain and in a capillary domain, respectively. Furthermore, the nonlinear term $\kappa(\frac{u}{k+u}-\frac{v}{k'+v})$ stands for a co-transport through the brain-blood boundary (see [11]). Finally, J and F are forcing and input terms, respectively, assumed frozen (more generally, J depends on t and u and accounts for the interactions with a third intracellular compartment (which includes both neurons and astrocytes), while $F=F(t)$ (an applied electrical stimulus; see [7]) is piecewise linear and periodic). This model has essential applications to the therapeutic management of glioma (also called glial tumors); see [8] for thorough discussions on this issue.

Let us assume that $u(0)$ and $v(0)$ are nonnegative (recall that u and v are concentrations and are thus expected to be nonnegative). Then, noting that, if $u(0)=0$, then $\frac{du}{dt}(0)>0$ and, if $v(0)=0$, then $\frac{dv}{dt}(0)>0$, it follows from Cauchy–Lipschitz theorem that, for $t>0$ small, u and v exist and are nonnegative. This also yields that the solutions are defined and remain nonnegative on the whole interval $\mathbb{R}^+$; indeed, it is not difficult to prove that

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they are bounded on finite time intervals. Furthermore, in [5], [8], [9] and [10], questions related to the stability of the unique equilibrium were addressed. This constitutes an essential point in the modeling, since, as discussed in [8], a therapeutic perspective of such a result is to have the steady state outside the viability domain, where cell necrosis occurs. Finally, in [9], justifications for the dip and buffering which are observed in experiments (see [7]) were given, based on geometrical arguments and averaging theory on a slow manifold.

We can note that the above ODE's model does not account for spatial diffusion. Taking this into account would be relevant and desirable from a biological point of view. The simplest possible corresponding PDE's (reaction-diffusion) system, accounting for spatial diffusion, reads

$$\frac{\partial u}{\partial t} - \alpha\Delta u + \kappa(\frac{u}{k+u} - \frac{v}{k'+v}) = J,\ \alpha > 0, \tag{1.3}$$

$$\varepsilon\frac{\partial v}{\partial t} - \beta\Delta v + Fv + \kappa(\frac{v}{k'+v} - \frac{u}{k+u}) = FL,\ \beta > 0, \tag{1.4}$$

where $u = u(x,t)$ and $v = v(x,t)$, which we consider in a bounded and regular domain Ω of $\mathbb{R}^N$, $N = 1$, 2 or 3, together with Neumann boundary conditions,

$$\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = 0 \text{ on } \Gamma,$$

where $\Gamma = \partial\Omega$ and ν is the unit outer normal vector. Note that the terms $-\alpha\Delta u$ and $-\beta\Delta v$ correspond to random motions. Note however that more precise models should account for the geometry, i.e., the different compartments (interstitial, capillary), so that (1.3)-(1.4) should be viewed as a very first step towards PDE's models for brain lactate kinetics. We will consider more realistic models elsewhere.

We studied in [6] the existence, uniqueness and regularity of nonnegative solutions to (1.3)-(1.4) (note that the mathematical analysis of (1.3)-(1.4) (and, in particular, the well-posedness) appears to be challenging, due to the coupling terms, especially for negative initial data (though biologically irrelevant, this makes sense from a mathematical point of view); this is also the case for the ODE's model (1.1)-(1.2)). We further established the linear (exponential) stability of the unique spatially homogeneous equilibrium. We also mention [12] in which we proved the existence, uniqueness and regularity of the solutions to the following singular reaction-diffusion equation:

$$\frac{\partial u}{\partial t} - \Delta u + Fu + \kappa\frac{u}{k+u} = f(x,t),\ F \geq 0, \tag{1.5}$$

corresponding to the case where either u or v is known in (1.3) and (1.4); we can also think of (1.5) as an equation in each compartment, assuming that the lactate concentration is known in the other one.

Our aim in this paper is to study the limit system

$$\frac{\partial u}{\partial t} - \alpha\Delta u + \kappa(\frac{u}{k+u} - \frac{v}{k'+v}) = J, \tag{1.6}$$

$$-\beta\Delta v + Fv + \kappa(\frac{v}{k'+v} - \frac{u}{k+u}) = FL, \tag{1.7}$$

corresponding to $\varepsilon = 0$ in (1.4). We prove the existence and uniqueness of nonnegative solutions to (1.6)-(1.7). We then prove that the solutions to the initial reaction-diffusion system converge to those to the limit parabolic-elliptic one, on finite time intervals, and provide an error estimate in terms of ε. We finally study the linear stability of the unique spatially homogeneous equilibrium. We can note that a similar analysis would also be relevant in the context of the ODE's model (1.1)-(1.2). Though some of the results obtained here could apply (in a simpler way) to this system, this will be considered in more details elsewhere.

Notation: We denote by $((\cdot,\cdot))$ the usual L^2-scalar product, with associated norm $\|\cdot\|$. More generally, $\|\cdot\|_X$ denotes the norm on the Banach space X and, if X is a Hilbert space, $((\cdot,\cdot))_X$ denotes the associated scalar product.

Throughout the paper, the same letters c, c' and c'' denote positive constants which may vary from line to line. Similarly, the same letter Q denotes continuous and monotone increasing (with respect to each argument) functions which may vary from line to line.

2. The case $\varepsilon > 0$

We consider the following initial and boundary value problem:

$$\frac{\partial u}{\partial t} - \alpha\Delta u + \kappa(\frac{u}{k+u} - \frac{v}{k'+v}) = J, \tag{2.1}$$

$$\varepsilon\frac{\partial v}{\partial t} - \beta\Delta v + Fv + \kappa(\frac{v}{k'+v} - \frac{u}{k+u}) = FL,\ \varepsilon > 0, \tag{2.2}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = 0 \text{ on } \Gamma, \tag{2.3}$$

$$u|_{t=0} = u_0,\ v|_{t=0} = v_0. \tag{2.4}$$

Note that (2.1)-(2.2) are equivalent to

$$\frac{\partial u}{\partial t} - \alpha\Delta u + \kappa(\frac{k'}{k'+v} - \frac{k}{k+u}) = J, \tag{2.5}$$

$$\varepsilon\frac{\partial v}{\partial t} - \beta\Delta v + Fv + \kappa(\frac{k}{k+u} - \frac{k'}{k'+v}) = FL. \tag{2.6}$$

We assume that

$$(u_0, v_0) \in H^2_{\mathrm{N}}(\Omega)^2,\ u_0 \geq 0,\ v_0 \geq 0 \text{ a.e. } x, \tag{2.7}$$

where

$$H^2_{\mathrm{N}}(\Omega) = \{w \in H^2(\Omega),\ \frac{\partial w}{\partial \nu} = 0 \text{ on } \Gamma\}.$$

We proved in [6] the

Theorem 2.1. *We assume that* (2.7) *holds. Then,* (2.1)-(2.4) *possesses a unique strong solution* (u, v) *such that*

$$u \geq 0,\ v \geq 0 \text{ a.e. } (x, t) \tag{2.8}$$

and, $\forall T > 0$,

$$(u, v) \in L^\infty(0, T; H^2_{\mathrm{N}}(\Omega)^2) \cap L^2(0, T; H^3(\Omega)^2),$$

$$(\frac{\partial u}{\partial t}, \frac{\partial v}{\partial t}) \in L^\infty(0, T; L^2(\Omega)^2) \cap L^2(0, T; H^1(\Omega)^2).$$

Furthermore,

$$\|u(t)\|_{L^\infty(\Omega)} \leq \|u_0\|_{L^\infty(\Omega)} + (J + \kappa)t,\ t \geq 0,$$

and

$$\|v(t)\|_{L^\infty(\Omega)} \leq e^{-\frac{F}{\varepsilon}t}\|v_0\|_{L^\infty(\Omega)} + \frac{FL + \kappa}{F},\ t \geq 0.$$

Finally, if $M \geq \frac{FL+\kappa}{F}$ *and* $0 \leq v_0 \leq M$ *a.e.* x*, then* $0 \leq v \leq M$ *a.e.* (x, t)*.*

Remark 2.2. As far as the above regularity is concerned, the corresponding constants in [6] depend on ε, i.e., they are not bounded uniformly with respect to ε as this quantity goes to 0. However, it is not difficult, reading the details, to see that most constants can be made independent of ε, yielding regularity estimates on u, $\frac{\partial u}{\partial t}$ and v which are uniform with respect to ε as $\varepsilon \to 0$. Now, we have not been able to derive, at least in a straightforward way, such uniform estimates on $\frac{\partial v}{\partial t}$ which would allow us to pass to the limit in (2.2) (say, in a weak (variational) form) to deduce the existence of a solution to the limit problem corresponding to $\varepsilon = 0$ (see however Section 4). We will thus give a direct proof of existence for the limit problem which also has an interest on its own.

Remark 2.3. (i) It follows from the above that the capillary lactate concentration is uniformly (with respect to time) bounded. However, we have not been able to derive a similar upper bound on the interstitial lactate concentration u. We can note that, in the biological model, outside a bounded viability domain, cell necrosis occurs (see [8]), meaning that one expects viable trajectories to be uniformly bounded.

(ii) Multiplying (2.1) by $u + k$, integrating over Ω and by parts, we obtain

$$\frac{dE}{dt}+\alpha\|\nabla u\|^2+\kappa\|u\|_{L^1(\Omega)}\leq ((J+\frac{\kappa v}{k'+v},u+k)),$$

where

$$E=\frac{1}{2}u^2+ku.$$

Noting that v is uniformly bounded (we assume that, say, $0\leq v_0\leq \frac{FL+\kappa}{F}$), we take, for κ, J, F and L given, J small enough and k' large enough such that

$$J+\frac{\kappa v}{k'+v}<\kappa.$$

We thus deduce that

$$\frac{dE}{dt}+\alpha\|\nabla u\|^2+c\|u\|_{L^1(\Omega)}\leq c',\ c>0,$$

which yields, noting that

$$\begin{aligned}\alpha\|\nabla u\|^2+c\|u\|_{L^1(\Omega)}&\geq c'(\|\nabla u\|+\|u\|_{L^1(\Omega)})-c''\\&\geq c'\|u\|-c'',\end{aligned}$$

the differential inequality

$$\frac{dE}{dt}+c\sqrt{E}\leq c',\ c>0. \tag{2.9}$$

Set $E^*=(\frac{c'}{c})^2$, where c and c' are the same constants as in (2.9), so that

$$\frac{dE^*}{dt}+c\sqrt{E^*}=c'.$$

It then follows from comparison arguments that

$$E(t)\leq \max(E(0),E^*),\ t\geq 0, \tag{2.10}$$

and we finally deduce that the L^2-norm of u is uniformly bounded.

3. The case $\varepsilon=0$

We consider in this section the following initial and boundary value problem:

$$\frac{\partial u}{\partial t}-\alpha\Delta u+\kappa(\frac{k'}{k'+v}-\frac{k}{k+u})=J, \tag{3.1}$$

$$-\beta\Delta v+Fv+\kappa(\frac{k}{k+u}-\frac{k'}{k'+v})=FL, \tag{3.2}$$

$$\frac{\partial u}{\partial \nu}=\frac{\partial v}{\partial \nu}=0 \text{ on } \Gamma, \tag{3.3}$$

$$u|_{t=0} = u_0. \tag{3.4}$$

We assume that

$$u_0 \in H^2_{\mathrm{N}}(\Omega),\ u_0 \geq 0 \text{ a.e. } x. \tag{3.5}$$

Remark 3.1. It follows from (3.2) that

$$-\beta\Delta v(0) + Fv(0) - \frac{k'}{k' + v(0)} = FL - \frac{k}{k + u_0}.$$

We will see below that this allows to define in a unique way $v(0)$ such that $v(0) \geq 0$ a.e. x.

3.1. **Existence and uniqueness of solutions to an auxiliary problem.** We consider the following modified initial and boundary value problem:

$$\frac{\partial u}{\partial t} - \alpha\Delta u + \kappa(\frac{u}{k + |u|} - \frac{v}{k' + |v|}) = J, \tag{3.6}$$

$$-\beta\Delta v + Fv + \kappa(\frac{v}{k' + |v|} - \frac{u}{k + |u|}) = FL, \tag{3.7}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = 0 \text{ on } \Gamma, \tag{3.8}$$

$$u|_{t=0} = u_0. \tag{3.9}$$

We associate with (3.6)-(3.9) the following weak/variational formulation, for $T > 0$ given:

Find $(u, v) : [0, T] \to H^1(\Omega)^2$ such that

$$\frac{d}{dt}((u, \phi)) + \alpha((\nabla u, \nabla \phi)) + ((\varphi_k(u), \phi)) - ((\varphi_{k'}(v), \phi)) = ((J, \phi)),\ \forall \phi \in H^1(\Omega), \tag{3.10}$$

$$\beta((\nabla v, \nabla \psi)) + F((v, \psi)) + ((\varphi_{k'}(v), \psi)) - ((\varphi_k(u), \psi)) = ((FL, \psi)),\ \forall \psi \in H^1(\Omega), \tag{3.11}$$

in the sense of distributions, and

$$u(0) = u_0 \text{ in } L^2(\Omega), \tag{3.12}$$

where we have set, for $c > 0$ given,

$$\varphi_c(s) = \frac{\kappa s}{c + |s|},\ s \in \mathbb{R}.$$

We can note that φ_c is bounded (with $|\varphi_c| \leq \kappa$) and of class $\mathcal{C}^1$, with $\varphi_c'(s) = \frac{\kappa c}{(c+|s|)^2}$, so that φ_c is also Lipschitz continuous, with Lipschitz constant $\frac{\kappa}{c}$.

Let then $0 = \lambda_1 < \lambda_2 \leq \cdots$ be the eigenvalues of the minus Laplace operator associated with Neumann boundary conditions and w_1, w_2, $\cdots$ be associated eigenvectors such that the w_j's form an orthonormal in $L^2(\Omega)$ and orthogonal in $H^1(\Omega)$ basis. Setting

$$V_m = \mathrm{Span}(w_1, \cdots, w_m),\ m \in \mathbb{N},$$

we consider the following approximated problem, for $T > 0$ given:

Find $(u_m, v_m) : [0, T] \to V_m \times V_m$ such that

$$\frac{d}{dt}((u_m, \phi)) + \alpha((\nabla u_m, \nabla \phi)) + ((\varphi_k(u_m), \phi)) - ((\varphi_{k'}(v_m), \phi)) = ((J, \phi)),\ \forall \phi \in V_m, \tag{3.13}$$

$$\beta((\nabla v_m, \nabla \psi)) + F((v_m, \psi)) + ((\varphi_{k'}(v_m), \psi)) - ((\varphi_k(u_m), \psi)) = ((FL, \psi)),\ \forall \psi \in V_m, \tag{3.14}$$

in the sense of distributions, and

$$u_m(0) = u_{0m}, \tag{3.15}$$

where $u_{0m} = P_m u_0$, P_m being the orthogonal projector (for the L^2-norm) from $L^2(\Omega)$ onto V_m.

For $w \in V_m$ given, we consider the following elliptic problem:

Find $z \in V_m$ such that

$$a(z, \phi) + ((\varphi_{k'}(z), \phi)) = ((FL + \varphi_k(w), \phi)),\ \forall \phi \in V_m, \tag{3.16}$$

where

$$a(\cdot, \cdot) = \beta((\nabla \cdot, \nabla \cdot)) + F((\cdot, \cdot))$$

is bilinear, symmetric, continuous and coercive on V_m (and also on $H^1(\Omega)$). Let then $R = R_m$ be the operator defined by

$$R : V_m \to V_m,\ z \mapsto R(z),$$

where

$$((R(z), \phi))_{H^1(\Omega)} = a(z, \phi) + ((\varphi_{k'}(z), \phi)) - ((FL + \varphi_k(w), \phi)),\ \forall \phi \in V_m.$$

It is clear that this operator is well defined and continuous (since $\varphi_{k'}$ is Lipschitz continuous). Furthermore, there holds, for $z \in V_m$,

$$\begin{aligned} ((R(z), z))_{H^1(\Omega)} &= a(z, z) + ((\varphi_{k'}(z), z)) - ((FL + \varphi_k(w), z)) \\ &\geq c\|z\|^2_{H^1(\Omega)} - c'\|z\|,\ c > 0 \end{aligned}$$

(note indeed that w is given and recall that φ_k and $\varphi_{k'}$ are bounded). Therefore,

$$((R(z), z))_{H^1(\Omega)} \geq c\|z\|^2_{H^1(\Omega)} - c',$$

so that

$$((R(z), z))_{H^1(\Omega)} \geq 0 \text{ whenever } \|z\|_{H^1(\Omega)} \geq \sqrt{\frac{c'}{c}}.$$

It thus follows from the Brouwer fixed point theorem that there exists $z \in V_m$, $\|z\|_{H^1(\Omega)} \leq \sqrt{\frac{c'}{c}}$, such that

$$R(z) = 0 \text{ in } V_m$$

(see, e.g., [14]), which is equivalent to (3.16). Note that all constants here (and also below) are independent of m. This thus defines a mapping $\mathcal{F} = \mathcal{F}_m$,

$$\mathcal{F} : V_m \to V_m, \ w \mapsto z = \mathcal{F}(w).$$

Let then $(w_1, w_2) \in V_m \times V_m$ and set $z_i = \mathcal{F}(w_i)$, $i = 1, 2$. We have, setting $z = z_1 - z_2$ and $w = w_1 - w_2$,

$$a(z, \phi) + ((\varphi_{k'}(z_1) - \varphi_{k'}(z_2), \phi)) = ((\varphi_k(w_1) - \varphi_k(w_2), \phi)), \ \forall \phi \in V_m. \tag{3.17}$$

Taking $\phi = z$ and noting that $\varphi_{k'}$ is monotone increasing and φ_k is Lipschitz continuous, we obtain

$$\|z\|^2_{H^1(\Omega)} \leq c\|w\|\|z\|,$$

whence

$$\|\mathcal{F}(w_1) - \mathcal{F}(w_2)\|_{H^1(\Omega)} \leq c\|w_1 - w_2\|, \tag{3.18}$$

which yields that $\mathcal{F}$ is Lipschitz continuous on V_m (both for the L^2 and H^1-norms); this also yields that $\mathcal{F}$ is indeed a mapping, since $w_1 = w_2$ implies $z_1 = z_2$.

It follows from the above that (3.13)-(3.15) is equivalent to

Find $u_m : [0, T] \to V_m$ such that

$$\begin{aligned} \frac{d}{dt}((u_m, \phi)) + \alpha((\nabla u_m, \nabla \phi)) + ((\varphi_k(u_m), \phi)) - ((\varphi_{k'} \circ \mathcal{F}(u_m), \phi)) \\ = ((J, \phi)), \ \forall \phi \in V_m, \end{aligned} \tag{3.19}$$

in the sense of distributions,

$$u_m(0) = u_{0m} \tag{3.20}$$

and then set $v_m = \mathcal{F}(u_m)$.

Since φ_k and $\varphi_{k'}$ are Lipschitz continuous on $\mathbb{R}$ and $\mathcal{F}$ is Lipschitz continuous on V_m with respect to the L^2-norm, it is easy to prove that (3.19)-(3.20) possesses a (unique) solution $u_m \in L^\infty(0, T; L^2(\Omega)) \cap L^2(0, T; H^1(\Omega))$ (see, e.g., [13]), whence, setting $v_m = \mathcal{F}(u_m)$, the existence of a solution (u_m, v_m) to (3.13)-(3.15) such that $v_m \in L^\infty(0, T; H^1(\Omega))$. We also note that $\frac{\partial u_m}{\partial t} \in L^2(0, T; H^{-1}(\Omega))$, so that $u_m \in \mathcal{C}([0, T]; L^2(\Omega))$.

Writing $u_m(t) = \sum_{i=1}^m d_{i,m}(t) w_i$, taking $\phi = \lambda_i w_i$ in (3.19), multiplying the resulting equality by $d_{i,m}$ and summing over i, we obtain

$$\frac{1}{2}\frac{d}{dt}\|\nabla u_m\|^2 + \alpha\|\Delta u_m\|^2 - ((\varphi_k(u_m), \Delta u_m)) + ((\varphi_{k'} \circ \mathcal{F}(u_m), \Delta u_m)) = 0,$$

which yields, recalling that φ_k and $\varphi_{k'}$ are bounded,

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

whence estimates on u_m in $L^\infty(0, T; H^1(\Omega))$ and $L^2(0, T; H^2(\Omega))$. It thus follows that $\frac{\partial u_m}{\partial t} \in L^\infty(0, T; H^{-1}(\Omega)) \cap L^2(0, T; L^2(\Omega))$.

Since the above regularity estimates are uniform with respect to m, we deduce from classical Aubin–Lions compactness theorems that, at least for a subsequence which we do not relabel,

$$u_m \to u \text{ in } L^\infty(0, T; H^1(\Omega)) \text{ weak star, in } L^2(0, T; H^2(\Omega)) \text{ weak,}$$
$$\text{in } \mathcal{C}([0, T]; L^2(\Omega)) \text{ and a.e. } (x, t) \in \Omega \times (0, T),$$

$$v_m \to v \text{ in } L^\infty(0, T; H^1(\Omega)) \text{ weak star,}$$

for some functions u and v. Actually, since $v_m = \mathcal{F}(u_m)$ and $\mathcal{F}$ is Lipschitz continuous with respect to the L^2-norm, we can see that (v_m) is a Cauchy sequence in $\mathcal{C}([0, T]; L^2(\Omega))$ (note indeed that, if $m' \geq m$, then $V_m \subset V_{m'}$ and that the constant c in (3.18) is independent of m), so that

$$v_m \to v \text{ in } \mathcal{C}([0, T]; L^2(\Omega)).$$

Recalling finally that φ_k and $\varphi_{k'}$ are Lipschitz continuous, this is sufficient to pass to the limit in (3.13)-(3.15) and deduce the existence of a solution (u, v) to (3.10)-(3.12) (note that the initial condition $u_0 = u(0)$ makes sense; actually, $v(0)$ also makes sense). Indeed, we need to pass to the limit in relations of the form

$$\int_0^T [-((u_m, \phi))\theta'(t) + \alpha((\nabla u_m, \nabla\phi))\theta(t) + ((\varphi_k(u_m), \phi))\theta(t)$$
$$-((\varphi_{k'}(v_m), \phi))\theta(t) - ((J, \phi))\theta(t)]\, dt = 0$$

and

$$\int_0^T [\beta((\nabla v_m, \nabla\psi)) + F((v_m, \psi)) + ((\varphi_{k'}(v_m), \psi)) - ((\varphi_k(u_m), \psi)) - ((FL, \psi))]\theta(t)\, dt = 0,$$

for $(\phi, \psi) \in H^1(\Omega)^2$ and $\theta \in \mathcal{D}(0, T)$. More precisely, we have the

Theorem 3.2. *We assume that $u_0 \in H^1(\Omega)$. Then,* (3.10)-(3.12) *possesses a unique solution (u, v) such that, $\forall T > 0$,*

$$u \in L^\infty(0, T; H^1(\Omega)) \cap L^2(0, T; H^2(\Omega)) \cap \mathcal{C}([0, T]; L^2(\Omega)),$$

$$v \in L^\infty(0, T; H^1(\Omega)) \cap \mathcal{C}([0, T]; L^2(\Omega))$$

and

$$\frac{\partial u}{\partial t} \in L^\infty(0,T;H^{-1}(\Omega)) \cap L^2(0,T;L^2(\Omega)).$$

Proof. There remains to prove the uniqueness.

Let thus (u_1, v_1) and (u_2, v_2) be two such solutions, with initial data $u_{0,1}$ and $u_{0,2}$, respectively. We have, setting $(u, v) = (u_1 - u_2, v_1 - v_2)$ and $u_0 = u_{0,1} - u_{0,2}$,

$$\frac{d}{dt}((u,\phi)) + \alpha((\nabla u, \nabla\phi)) + ((\varphi_k(u_1) - \varphi_k(u_2), \phi)) - ((\varphi_{k'}(v_1) - \varphi_{k'}(v_2), \phi)) = 0,\ \forall \phi \in H^1(\Omega), \tag{3.21}$$

$$\beta((\nabla v, \nabla\psi)) + F((v,\psi)) + ((\varphi_{k'}(v_1) - \varphi_{k'}(v_2), \psi)) - ((\varphi_k(u_1) - \varphi_k(u_2), \psi)) = 0,\ \forall \psi \in H^1(\Omega), \tag{3.22}$$

$$u(0) = u_0. \tag{3.23}$$

Taking $\phi = u$ and $\psi = v$, we obtain, recalling that φ_k and $\varphi_{k'}$ are monotone increasing and Lipschitz continuous,

$$\frac{1}{2}\frac{d}{dt}\|u\|^2 + \alpha\|\nabla u\|^2 \leq c\|u\|\|v\| \tag{3.24}$$

and

$$\beta\|\nabla v\|^2 + F\|v\|^2 \leq c\|u\|\|v\|, \tag{3.25}$$

respectively. In particular, it follows from (3.25) that

$$\|v\| \leq c\|u\|, \tag{3.26}$$

which, injected into (3.24), yields

$$\frac{d}{dt}\|u\|^2 \leq c\|u\|^2, \tag{3.27}$$

whence, owing to Gronwall's lemma,

$$\|u(t)\| \leq e^{ct}\|u_0\|,\ t \geq 0. \tag{3.28}$$

We deduce from (3.26) and (3.28) the uniqueness, as well as the continuous dependence with respect to the initial data in the L^2-norm.

□

3.2. **Existence and uniqueness of nonnegative solutions.** We first prove additional regularity results on the solutions to (3.10)-(3.11), assuming that (3.5) holds. This can be fully justified within the Galerkin scheme considered above.

Taking $\psi = -\Delta v$ in (3.11), we have

$$\beta\|\Delta v\|^2 + F\|\nabla v\|^2 = ((\varphi_{k'}(v), \Delta v)) - ((\varphi_k(u), \Delta v)),$$

which yields, recalling that φ_k and $\varphi_{k'}$ are bounded,

$$\frac{\beta}{2}\|\Delta v\|^2 + F\|\nabla v\|^2 \le c,$$

whence estimates on v in $L^\infty(0, T; H^2(\Omega))$, $\forall T > 0$.

Taking then $\phi = \Delta^2 u$ in (3.10) and $\psi = \Delta^2 v$ in (3.11), we obtain

$$\frac{1}{2}\frac{d}{dt}\|\Delta u\|^2 + \alpha\|\nabla\Delta u\|^2 = -((\varphi_k(u), \Delta^2 u)) + ((\varphi_{k'}(v), \Delta^2 u))$$

and

$$\beta\|\nabla\Delta v\|^2 + F\|\Delta v\|^2 = -((\varphi_{k'}(v), \Delta^2 v)) + ((\varphi_k(u), \Delta^2 v)),$$

respectively. Noting that

$$|((\varphi_k(u), \Delta^2 u))| = |((\varphi_k'(u)\nabla u, \nabla\Delta u))| \le c\|\nabla u\|\|\nabla\Delta u\|,$$

we find, proceeding in a similar way for the other terms,

$$\frac{d}{dt}\|\Delta u\|^2 + \alpha\|\nabla\Delta u\|^2 \le c(\|\nabla u\|^2 + \|\nabla v\|^2)$$

and

$$\frac{\beta}{2}\|\nabla\Delta v\|^2 + F\|\Delta v\|^2 \le c(\|\nabla u\|^2 + \|\nabla v\|^2),$$

whence estimates on u and v in $L^\infty(0, T; H^2(\Omega)) \cap L^2(0, T; H^3(\Omega))$ and $L^\infty(0, T; H^3(\Omega))$, respectively, $\forall T > 0$.

Remark 3.3. This yields that $\frac{\partial u}{\partial t} \in L^\infty(0, T; L^2(\Omega)) \cap L^2(0, T; H^1(\Omega))$, $\forall T > 0$. We further note that the solution to (3.10)-(3.12) is strong, i.e., (3.6)-(3.9) are satisfied almost everywhere.

We can now prove the

Theorem 3.4. *We assume that* (3.5) *holds. Then,* (3.1)-(3.4) *possesses a unique strong solution* (u, v) *such that* $u \ge 0$, $v \ge 0$ *a.e.* (x, t) *and,* $\forall T > 0$,

$$u \in L^\infty(0, T; H^2_{\mathrm{N}}(\Omega)) \cap L^2(0, T; H^3(\Omega)),$$

$$v \in L^\infty(0, T; H^3(\Omega) \cap H^2_{\mathrm{N}}(\Omega)) \cap \mathcal{C}([0, T]; L^2(\Omega))$$

and

$$\frac{\partial u}{\partial t} \in L^\infty(0,T;L^2(\Omega)) \cap L^2(0,T;H^1(\Omega)).$$

Proof. Let (u,v) be the unique strong solution to (3.6)-(3.9). Multiplying (3.6) by $-u^-$ and (3.7) by $-v^-$, where $x^- = \max(0,-x)$, we have

$$\frac{1}{2}\frac{d}{dt}\|u^-\|^2 + \alpha\|\nabla u^-\|^2 + \kappa\int_\Omega \frac{|u^-|^2}{k+|u|}\,dx + \kappa\int_\Omega \frac{vu^-}{k'+|v|}\,dx \le 0 \tag{3.29}$$

and

$$\beta\|\nabla u^-\|^2 + F\|u^-\|^2 + \kappa\int_\Omega \frac{|v^-|^2}{k'+|v|}\,dx + \kappa\int_\Omega \frac{uv^-}{k+|u|}\,dx \le 0, \tag{3.30}$$

respectively. Writing $v = v^+ - v^-$, where $x^+ = \max(0,x)$, we deduce from (3.29) that

$$\frac{1}{2}\frac{d}{dt}\|u^-\|^2 \le \kappa\int_\Omega \frac{u^-v^-}{k'+|v|}\,dx,$$

whence

$$\frac{d}{dt}\|u^-\|^2 \le c\|u^-\|\|v^-\|. \tag{3.31}$$

Proceeding in a similar way for (3.30), we find

$$F\|v^-\|^2 \le c\|u^-\|\|v^-\|,$$

whence

$$\|v^-\| \le c\|u^-\|. \tag{3.32}$$

Injecting this into (3.31), we deduce that

$$\frac{d}{dt}\|u^-\|^2 \le c\|u^-\|^2,$$

which yields, owing to Gronwall's lemma,

$$\|u^-(t)\| \le e^{ct}\|u^-(0)\|,\ t \ge 0, \tag{3.33}$$

whence, since $u^-(0) = 0$, $u \ge 0$ a.e. (x,t). This, together with (3.32), yields that $v \ge 0$ a.e. (x,t). Consequently, (u,v) is a strong solution to (3.1)-(3.4), which finishes the proof. □

Remark 3.5. Proceeding exactly as in [6], we can prove that

$$\|u(t)\|_{L^\infty(\Omega)} \le \|u_0\|_{L^\infty(\Omega)} + (J+\kappa)t,\ t \ge 0.$$

Furthermore, it follows from (3.2) that

$$-\beta\Delta v + Fv \leq FL + \kappa. \tag{3.34}$$

Multiplying (3.34) by v^{m+1}, $m \in \mathbb{N}$, we have

$$\beta(m+1)\int_\Omega v^m|\nabla v|^2\,dx + F\|v\|^{m+2}_{L^{m+2}(\Omega)} \leq (FL+\kappa)\int_\Omega v^{m+1}\,dx,$$

which yields

$$F\|v\|^{m+2}_{L^{m+2}(\Omega)} \leq (FL+\kappa)\mathrm{Vol}(\Omega)^{\frac{1}{m+2}}\|v\|^{m+1}_{L^{m+2}(\Omega)},$$

whence

$$\|v\|_{L^{m+2}(\Omega)} \leq \frac{FL+\kappa}{F}\mathrm{Vol}(\Omega)^{\frac{1}{m+2}}. \tag{3.35}$$

Passing to the limit $m \to +\infty$ in (3.35), we finally obtain (see, e.g., [3])

$$\|v(t)\|_{L^\infty(\Omega)} \leq \frac{FL+\kappa}{F},\ t \geq 0,$$

meaning that the capillary lactate concentration is again uniformly (with respect to time) bounded. Also note that (2.10) still holds.

Remark 3.6. (i) As mentioned in the introduction (for the case $\varepsilon > 0$, but the situation is the same here), the existence of solutions for negative initial data is a challenging issue. However, we can prove the following partial result (see also [6] for the case $\varepsilon > 0$). Let δ_1 and δ_2 be two positive constants such that $k - \delta_1 > 0$ and $k' - \delta_2 > 0$ and assume that $u_0 \geq -\delta_1$ a.e. x. We then consider the following modified initial and boundary value problem:

$$\frac{\partial u}{\partial t} - \alpha\Delta u + \kappa\Big(\frac{u}{k-\delta_1+|u+\delta_1|} - \frac{v}{k'-\delta_2+|v+\delta_2|}\Big) = J, \tag{3.36}$$

$$-\beta\Delta v + Fv + \kappa\Big(\frac{v}{k'-\delta_2+|v+\delta_2|} - \frac{u}{k-\delta_1+|u+\delta_1|}\Big) = FL, \tag{3.37}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = 0 \text{ on } \Gamma, \tag{3.38}$$

$$u|_{t=0} = u_0. \tag{3.39}$$

The existence and uniqueness of the solution to (3.36)-(3.39) can be proved by arguing as above. Next, we set $\tilde{u} = u + \delta_1$ and $\tilde{v} = v + \delta_2$. These functions are solutions to

$$\frac{\partial \tilde{u}}{\partial t} - \alpha\Delta\tilde{u} + \kappa\Big(\frac{\tilde{u}}{k-\delta_1+|\tilde{u}|} - \frac{\tilde{v}}{k'-\delta_2+|\tilde{v}|}\Big) = \tilde{J}, \tag{3.40}$$

$$-\beta\Delta\tilde{v}+F\tilde{v}+\kappa(\frac{\tilde{v}}{k'-\delta_2+|\tilde{v}|}-\frac{\tilde{u}}{k-\delta_1+|\tilde{u}|})=\tilde{F}, \tag{3.41}$$

$$\frac{\partial\tilde{u}}{\partial\nu}=\frac{\partial\tilde{v}}{\partial\nu}=0 \text{ on } \Gamma, \tag{3.42}$$

$$\tilde{u}|_{t=0}=u_0+\delta_1, \tag{3.43}$$

where

$$\tilde{J}=J+\kappa(\frac{\delta_1}{k-\delta_1+|\tilde{u}|}-\frac{\delta_2}{k'-\delta_2+|\tilde{v}|})$$

and

$$\tilde{F}=F(L+\delta_2)-\kappa(\frac{\delta_1}{k-\delta_1+|\tilde{u}|}-\frac{\delta_2}{k'-\delta_2+|\tilde{v}|}).$$

Choosing δ_1 and δ_2 such that $\tilde{J}\geq 0$ and $\tilde{F}\geq 0$ (in particular, these hold when δ_1 and δ_2 are small enough) and noting that $\tilde{u}(0)\geq 0$ a.e. x, we can prove, as in the proof of Theorem 3.4, that $\tilde{u}(x,t)\geq 0$ and $\tilde{v}(x,t)\geq 0$ a.e. (x,t), so that (u,v) is solution to (3.1)-(3.4), with

$$u(x,t)\geq -\delta_1 \text{ and } v(x,t)\geq -\delta_2 \text{ a.e. } (x,t).$$

(ii) Similarly, we can prove that, if δ_1 and δ_2 are positive and small enough, with $u_0\geq\delta_1$ a.e. x, then

$$u(x,t)\geq \delta_1 \text{ and } v(x,t)\geq \delta_2 \text{ a.e. } (x,t).$$

It follows from the above that we can actually define the Lipschitz continuous (for the L^2 and H^1-norms) mapping

$$\mathcal{F}:H^1(\Omega)\to H^1(\Omega),\ w\mapsto z=\mathcal{F}(w),$$

where z is the unique solution to the following elliptic problem:

$$a(z,\phi)+((\varphi_{k'}(z),\phi))=((FL+\varphi_k(w),\phi)),\ \forall\phi\in H^1(\Omega). \tag{3.44}$$

We then have the

Proposition 3.7. *The mapping $\mathcal{F}$ is differentiable with respect to the L^2 and H^1-norms.*

Proof. Let w_0 and w belong to $H^1(\Omega)$ and set $z_0=\mathcal{F}(w_0)$ and $z=\mathcal{F}(w)$. We then have

$$a(z-z_0,\phi)+((\varphi_{k'}(z)-\varphi_{k'}(z_0),\phi))=((\varphi_k(w)-\varphi_k(w_0),\phi)),\ \forall\phi\in H^1(\Omega). \tag{3.45}$$

Taking $\phi=z-z_0$ and reacalling tht $\varphi_{k'}$ is monotone increasing, this yields

$$\|z-z_0\|_{H^1(\Omega)}\leq c\|\varphi_k(w)-\varphi_k(w_0)\|,$$

whence

$$\|z - z_0\|_{H^1(\Omega)} \leq c\|w - w_0\|. \tag{3.46}$$

Let then $Z \in H^1(\Omega)$ be the solution to the linear elliptic problem (recall that φ'_k is nonnegative)

$$a(Z, \phi) + ((\varphi'_{k'}(z_0)Z, \phi)) = ((\varphi'_k(w_0)(w - w_0), \phi)),\ \forall \phi \in H^1(\Omega). \tag{3.47}$$

Setting $h = w - w_0$, we can see that

$$\begin{aligned} a(z - z_0 - Z, \phi) &+ ((\varphi_{k'}(z) - \varphi_{k'}(z_0) - \varphi'_{k'}(z_0)Z, \phi)) \\ &= ((\varphi_k(w) - \varphi_k(w_0) - \varphi'_k(w_0)h, \phi)),\ \forall \phi \in H^1(\Omega). \end{aligned} \tag{3.48}$$

Writing

$$\varphi_{k'}(z) - \varphi_{k'}(z_0) - \varphi'_{k'}(z_0)Z = \varphi'_{k'}(z_0)(z - z_0 - Z) + o(\|z - z_0\|)$$

and

$$\varphi_k(w) - \varphi_k(w_0) - \varphi'_k(w_0)h = o(\|h\|),$$

we obtain, taking $\phi = z - z_0 - Z$ and employing (3.46) (also recall that $\varphi'_{k'} \geq 0$),

$$a(z - z_0 - Z, z - z_0 - Z) \leq |((o(\|h\|), z - z_0 - Z))|,$$

whence

$$\|z - z_0 - Z\|_{H^1(\Omega)} = o(\|h\|).$$

This yields that $\mathcal{F}$ is differentiable at w_0, with $\mathcal{F}'(w_0) \cdot h = Z$, $\mathcal{F}'$ denoting the differential of $\mathcal{F}$.

□

We deduce from Proposition 3.7 the

Corollary 3.8. *Let (u, v) be the solution to* (3.1)-(3.4) *given in Theorem 3.4. Then,* $\forall T > 0$,

$$\frac{\partial v}{\partial t} \in L^\infty(0, T; H^1(\Omega))$$

and

$$\|\frac{\partial v}{\partial t}\|_{H^1(\Omega)} \leq c\|\frac{\partial u}{\partial t}\| \text{ a.e. } t \geq 0. \tag{3.49}$$

Proof. It suffices to note that $v = \mathcal{F}(u)$, whence, owing to Proposition 3.7,

$$\frac{\partial v}{\partial t} = \mathcal{F}'(u) \cdot \frac{\partial u}{\partial t}. \tag{3.50}$$

Indeed, we can note that $u \in H^1(0, T; H^1(\Omega))$, $\forall T > 0$. Furthermore, we have

$$a(\frac{\partial v}{\partial t}, \phi) + ((\varphi'_{k'}(v)\frac{\partial v}{\partial t}, \phi)) = ((\varphi'_k(u)\frac{\partial u}{\partial t}, \phi)), \ \forall \phi \in H^1(\Omega), \tag{3.51}$$

and (3.49) follows, taking $\phi = \frac{\partial v}{\partial t}$ (also recall that $\frac{\partial u}{\partial t} \in L^\infty(0, T; L^2(\Omega))$, $\forall T > 0$). □

Remark 3.9. It follows from standard elliptic regularity results applied to (3.51) (see, e.g., [1] and [2]) that, $\forall T > 0$, $\frac{\partial v}{\partial t} \in L^\infty(0, T; H^2(\Omega)) \cap L^2(0, T; H^3(\Omega))$, with

$$\|\frac{\partial v}{\partial t}\|_{H^2(\Omega)} \le c\|\frac{\partial u}{\partial t}\| \text{ a.e. } t \ge 0$$

and

$$\|\frac{\partial v}{\partial t}\|_{L^2(0,T;H^3(\Omega))} \le Q(T, \|u_0\|_{H^1(\Omega)})\|\frac{\partial u}{\partial t}\|_{L^2(0,T;H^1(\Omega))}.$$

4. Convergence to the limit problem

All constants c and c' and functions Q in this section are independent of ε.

Let $(u^\varepsilon, v^\varepsilon)$ and (u^0, v^0) be the unique strong solutions to the initial and limit problems, respectively, as given in Theorems 2.1 and 3.4, where $v_0 = v^0(0)$, i.e.,

$$\frac{\partial u^\varepsilon}{\partial t} - \alpha\Delta u^\varepsilon + \kappa(\frac{k'}{k' + v^\varepsilon} - \frac{k}{k + u^\varepsilon}) = J, \tag{4.1}$$

$$\varepsilon\frac{\partial v^\varepsilon}{\partial t} - \beta\Delta v^\varepsilon + Fv^\varepsilon + \kappa(\frac{k}{k + u^\varepsilon} - \frac{k'}{k' + v^\varepsilon}) = FL, \tag{4.2}$$

$$\frac{\partial u^\varepsilon}{\partial \nu} = \frac{\partial v^\varepsilon}{\partial \nu} = 0 \text{ on } \Gamma, \tag{4.3}$$

$$u^\varepsilon|_{t=0} = u_0, \ v^\varepsilon|_{t=0} = v^0(0), \tag{4.4}$$

and

$$\frac{\partial u^0}{\partial t} - \alpha\Delta u^0 + \kappa(\frac{k'}{k' + v^0} - \frac{k}{k + u^0}) = J, \tag{4.5}$$

$$-\beta\Delta v^0 + Fv^0 + \kappa(\frac{k}{k + u^0} - \frac{k'}{k' + v^0}) = FL, \tag{4.6}$$

$$\frac{\partial u^0}{\partial \nu} = \frac{\partial v^0}{\partial \nu} = 0 \text{ on } \Gamma, \tag{4.7}$$

$$u^0|_{t=0} = u_0. \tag{4.8}$$

We have the

Theorem 4.1. *The following error estimates hold,* $\forall T > 0$*:*

$$\|u^\varepsilon(t) - u^0(t)\|_{H^1(\Omega)} \le Q(T, \|u_0\|_{H^1(\Omega)})\varepsilon, \ \|v^\varepsilon(t) - v^0(t)\|_{H^1(\Omega)} \le Q(T, \|u_0\|_{H^1(\Omega)})\sqrt{\varepsilon},$$

$t \in [0, T]$, *and*

$$\|u^\varepsilon - u^0\|_{L^2(0,T;H^2(\Omega))} \le Q(T, \|u_0\|_{H^1(\Omega)})\varepsilon, \ \|v^\varepsilon - v^0\|_{L^2(0,T;H^2(\Omega))} \le Q(T, \|u_0\|_{H^1(\Omega)})\varepsilon.$$

Proof. We have, setting $u = u^\varepsilon - u^0$ and $v = v^\varepsilon - v^0$,

$$\frac{\partial u}{\partial t} - \alpha \Delta u + \varphi_k(u^\varepsilon) - \varphi_k(u^0) - \varphi_{k'}(v^\varepsilon) + \varphi_{k'}(v^0) = 0, \tag{4.9}$$

$$\varepsilon \frac{\partial v}{\partial t} - \beta \Delta v + Fv + \varphi_{k'}(v^\varepsilon) - \varphi_{k'}(v^0) - \varphi_k(u^\varepsilon) + \varphi_k(u^0) = -\varepsilon \frac{\partial v^0}{\partial t}, \ \varepsilon > 0, \tag{4.10}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = 0 \text{ on } \Gamma, \tag{4.11}$$

$$u|_{t=0} = 0, \ v|_{t=0} = 0. \tag{4.12}$$

Multiplying (4.9) by u, we obtain, recalling that φ_k is monotone increasing,

$$\frac{d}{dt}\|u\|^2 + \alpha \|\nabla u\|^2 \le c\|u\|\|v\|. \tag{4.13}$$

Multiplying then (4.10) by v, we find, similarly,

$$\varepsilon \frac{d}{dt}\|v\|^2 + c\|v\|^2_{H^1(\Omega)} \le c'(\|u\|\|v\| + \varepsilon^2 \|\frac{\partial v^0}{\partial t}\|^2), \ c > 0. \tag{4.14}$$

Combining (4.13) and (4.14), we have, owing to (3.49),

$$\frac{d}{dt}(\|u\|^2 + \varepsilon\|v\|^2) + c(\|u\|^2_{H^1(\Omega)} + \|v\|^2_{H^1(\Omega)}) \le c'(\|u\|^2 + \varepsilon\|v\|^2 + \varepsilon^2 \|\frac{\partial u^\varepsilon}{\partial t}\|^2), \ c > 0, \tag{4.15}$$

from which it follows, owing to Gronwall's lemma,

$$\|u(t)\|^2 + \varepsilon\|v(t)\|^2 + c\int_0^T (\|u(s)\|^2_{H^1(\Omega)} + \|v(s)\|^2_{H^1(\Omega)})\, ds \tag{4.16}$$

$$\leq Q(T)\varepsilon^2 \|\frac{\partial u^\varepsilon}{\partial t}\|^2_{L^2(0,T;L^2(\Omega))},\ c>0,\ t\in[0,T].$$

Multiplying now (4.1) by $\frac{\partial u^\varepsilon}{\partial t}$, we obtain

$$\frac{d}{dt}\|\nabla u^\varepsilon\|^2 + c\|\frac{\partial u^\varepsilon}{\partial t}\|^2 \leq c',\ c>0,$$

whence

$$\|\frac{\partial u^\varepsilon}{\partial t}\|^2_{L^2(0,T;L^2(\Omega))} \leq Q(T, \|u_0\|_{H^1(\Omega)}). \tag{4.17}$$

We finally deduce from (4.16)-(4.17) that

$$\|u(t)\|^2 + \varepsilon\|v(t)\|^2 + c\int_0^T (\|u(s)\|^2_{H^1(\Omega)} + \|v(s)\|^2_{H^1(\Omega)})\, ds$$

$$\leq Q(T, \|u_0\|_{H^1(\Omega)})\varepsilon^2,\ c>0,\ t\in[0,T]. \tag{4.18}$$

Multiplying next (4.9) by $-\Delta u$ and (4.10) by $-\Delta v$, we find, recalling that φ_k and $\varphi_{k'}$ are Lipschitz continuous,

$$\frac{d}{dt}\|\nabla u\|^2 + c\|\Delta u\|^2 \leq c'(\|u\|^2 + \|v\|^2),\ c>0,$$

and

$$\varepsilon\frac{d}{dt}\|\nabla v\|^2 + c\|\Delta v\|^2 \leq c'(\|u\|^2 + \|v\|^2 + \varepsilon^2\|\frac{\partial v^0}{\partial t}\|^2),\ c>0,$$

respectively.

Summing these two inequalities, integrating over $[0,T]$ and proceeding as above, we have, adding the resulting inequality to (4.18),

$$\|u(t)\|^2_{H^1(\Omega)} + \varepsilon\|v(t)\|^2_{H^1(\Omega)} + c\int_0^T (\|u(s)\|^2_{H^2(\Omega)} + \|v(s)\|^2_{H^2(\Omega)})\, ds$$

$$\leq c'(\int_0^T (\|u(s)\|^2 + \|v(s)\|^2)\, ds + Q(T, \|u_0\|_{H^1(\Omega)})\varepsilon^2),\ c>0.$$

This yields, employing (4.18) to estimate the right-hand side,

$$\|u(t)\|^2_{H^1(\Omega)} + \varepsilon\|v(t)\|^2_{H^1(\Omega)} + c\int_0^T (\|u(s)\|^2_{H^2(\Omega)} + \|v(s)\|^2_{H^2(\Omega)})\, ds$$

$$\leq Q(T, \|u_0\|_{H^1(\Omega)})\varepsilon^2,\ c>0,\ t\in[0,T],$$

which finishes the proof.

□

Remark 4.2. We have similar error estimates if we assume that $\|u^\varepsilon(0) - u^0(0)\|_{H^1(\Omega)} \leq c\varepsilon$ and $\|v^\varepsilon(0) - v^0(0)\|_{H^1(\Omega)} \leq c\sqrt{\varepsilon}$.

5. A stability result

As in [6], (3.1)-(3.2) possesses a unique spatially homogeneous equilibrium $(\overline{u}, \overline{v})$ given by

$$\overline{v} = L + \frac{J}{F} > 0$$

and

$$\overline{u} = \frac{k(\frac{J}{\kappa} + \frac{\overline{v}}{k'+\overline{v}})}{1 - (\frac{J}{\kappa} + \frac{\overline{v}}{k'+\overline{v}})}.$$

Note that $\overline{u}$ is not necessarily positive. We thus assume in what follows that

$$\overline{u} > 0.$$

The linearized (around $(\overline{u}, \overline{v})$) system reads

$$\frac{\partial U}{\partial t} - \alpha \Delta U + \kappa(\frac{k}{(k+\overline{u})^2} U - \frac{k'}{(k'+\overline{v})^2} V) = 0, \tag{5.1}$$

$$-\beta \Delta V + FV + \kappa(\frac{k'}{(k'+\overline{v})^2} V - \frac{k}{(k+\overline{u})^2} U) = 0, \tag{5.2}$$

$$\frac{\partial U}{\partial \nu} = \frac{\partial V}{\partial \nu} = 0 \text{ on } \Gamma, \tag{5.3}$$

$$U|_{t=0} = U_0. \tag{5.4}$$

It is not difficult here to prove the existence, uniqueness and regularity of the solution to (5.1)-(5.4), assuming that U_0 is regular enough. Furthermore, proceeding as above, we can prove that, if $U_0 \geq 0$ a.e. x, then $U(x,t) \geq 0$ and $V(x,t) \geq 0$ a.e. (x,t).

Multiplying now (5.1) by $\frac{k}{(k+\overline{u})^2} U$ and (5.2) by $\frac{k'}{(k'+\overline{v})^2} V$, we obtain, summing the two resulting equalities,

$$\frac{1}{2} \frac{k}{(k+\overline{u})^2} \frac{d}{dt} \|U\|^2 + \frac{\alpha k}{(k+\overline{u})^2} \|\nabla U\|^2 + \frac{\beta k'}{(k'+\overline{v})^2} \|\nabla V\|^2 + \frac{Fk'}{(k'+\overline{v})^2} \|V\|^2 + \int_\Omega (\frac{k}{(k+\overline{u})^2} U - \frac{k'}{(k'+\overline{v})^2} V)^2 \, dx = 0. \tag{5.5}$$

It follows from (5.5) that

$$\frac{d}{dt} \|U\|^2 \leq 0,$$

whence

$$\|U(t)\| \leq \|U_0\|, \ t \geq 0. \tag{5.6}$$

Multiplying next (5.2) by V, we easily find

$$\|V\| \leq c\|U\|,$$

so that

$$\|V(t)\| \leq c\|U_0\|, \; t \geq 0. \tag{5.7}$$

We deduce from (5.6)-(5.7) that $(\overline{u}, \overline{v})$ is linearly stable with respect to the L^2-norm. We can also prove the linear stability with respect to the H^1-norm, proceeding in a similar way.

Now, an important question is whether we also have a linear exponential stability as in [6] for the case $\varepsilon > 0$ (see also [5], [8], [9] and [10] for the ODE's model (1.1)-(1.2)). Indeed, as mentioned in the introduction, a therapeutic perspective of such a result is to have the (spatially homogeneous) steady state outside the viability domain, where cell necrosis occurs (see [8]).

We have, in this direction, the

Theorem 5.1. *The stationary solution $(\overline{u}, \overline{v})$ is linearly exponentially stable, in the sense that all eigenvalues $s \in \mathbb{C}$ associated with the linear system* (5.1)-(5.2) *satisfy $\mathcal{R}e(s) \leq -\xi$, for a given $\xi > 0$, $\mathcal{R}e$ denoting the real part.*

Proof. We first note that it follows from (5.2) that

$$V = k_1(-\beta\Delta + (F + k_2)I)^{-1}U, \tag{5.8}$$

where $k_1 = \frac{\kappa k}{(k+\overline{u})^2}$ and $k_2 = \frac{\kappa k'}{(k'+\overline{v})^2}$. Injecting this into (5.1), we obtain

$$\frac{\partial U}{\partial t} - \alpha\Delta U + k_1 U - k_1 k_2(-\beta\Delta + (F + k_2)I)^{-1}U = 0. \tag{5.9}$$

We then look for solutions of the form

$$U(x, t) = \hat{U}(x)e^{st},$$

for $s \in \mathbb{C}$, $s = \zeta + i\eta$. Injecting this into (5.9), we find

$$-\alpha\Delta\hat{U} + (s + k_1)\hat{U} - k_1 k_2(-\beta\Delta + (F + k_2)I)^{-1}\hat{U} = 0, \tag{5.10}$$

where

$$\frac{\partial\hat{U}}{\partial\nu} = 0 \text{ on } \Gamma. \tag{5.11}$$

This yields

$$\alpha\beta\Delta^2\hat{U} - (\beta s + \alpha F + \beta k_1 + \alpha k_2)\Delta\hat{U} + ((F + k_2)s + k_1 F)\hat{U} = 0, \tag{5.12}$$

where, owing to (5.10) and (5.11),

$$\frac{\partial \hat{U}}{\partial \nu} = \frac{\partial \Delta \hat{U}}{\partial \nu} = 0 \text{ on } \Gamma. \tag{5.13}$$

Multiplying (5.12) by the conjugate of $\hat{U}$, integrating over Ω and by parts and taking the real part, we have

$$\alpha\beta \||\Delta \hat{U}|\|^2 + (\beta\zeta + \alpha F + \beta k_1 + \alpha k_2)\||\nabla \hat{U}|\|^2 + ((F + k_2)\zeta + k_1 F)\||\hat{U}|\|^2 = 0. \tag{5.14}$$

Therefore, when $\zeta \geq 0$, then, necessarily, $\hat{U} \equiv 0$. Furthermore, (5.14) can have nontrivial solutions only when

$$\beta\zeta + \alpha F + \beta k_1 + \alpha k_2 \leq 0$$

or

$$(F + k_2)\zeta + k_1 F \leq 0.$$

Therefore, necessarily,

$$\zeta \leq \max(-\frac{\alpha F + \beta k_1 + \alpha k_2}{\beta}, -\frac{k_1 F}{F + k_2}) < 0, \tag{5.15}$$

which finishes the proof.

□

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