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# ON A REACTION-DIFFUSION SYSTEM ASSOCIATED WITH BRAIN LACTATE KINETICS

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Abstract. Our aim in this article is to study properties of a reaction-diffusion system which is related with brain lactate kinetics, when spatial diffusion is taken into account. In particular, we prove the existence and uniqueness of nonnegative solutions and obtain linear stability results. We also derive $L^\infty$-bounds on the solutions. These results give insights on the therapeutic management of glioma.

## 1. Introduction

Glioma (also called glial tumors) appear to be the most frequent primary brain tumors. In particular, the so-called grade-II low-grade glioma take a significant place, as they inevitably evolve to anaplastic transformation, with a very poor prognosis. We can note that delay and kinetics of this transformation are highly variable and the occurrence of commutation into anaplastic glioma is a decisive factor. The prediction of this moment constitutes a challenge and is a deciding factor for therapeutic management. Though currently unpredictable by clinical data and morphological medical imaging, some data concerning glioma metabolism are accessible noninvasively by magnetic resonance imaging. Furthermore, we can obtain metabolite concentrations, such as creatine and lactate, by means of magnetic resonance spectroscopy. A major challenge is to explain the variations of magnetic resonance data observed during the transformation of low grade glioma and suggest new therapies. We refer the interested readers to [7] and the references therein for more details.

In view of this, the system of ODE's

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

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

where $\epsilon$ is a small parameter, was proposed and studied as a model for brain lactate kinetics (see [5, 7, 8, 9]). 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

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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 [10]). Finally, $J$ and $F$ are forcing and input terms, respectively, assumed frozen. In particular, the model has a unique stationary point which is asymptotically stable. This is consistent with clinical observations which suggest that, within a short time scale from minutes to days, metabolite concentrations within the tumor are nearly constant. Furthermore, as discussed in [7], a therapeutic perspective of such a result is to have the stationary point outside the viability domain, where cell necrosis occurs.

Now, it is reasonable to expect that the lactate concentrations vary according to the position in the brain, meaning that, in view of more precise models, one should consider a PDE's system. Furthermore, spatial diffusion, meaning that the lactates spread (note that there is a flux into different compartments), should also be taken into account. This suggests reaction-diffusion models to describe the lactate kinetics.

The simplest possible corresponding PDE's (reaction-diffusion) system, accounting for spatial diffusion, reads (see also [12])

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

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

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

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

where $\Gamma = \partial\Omega$ and $\nu$ is the unit outer normal vector.

Actually, more precise models should also account for the geometry, i.e., the different compartments (interstitial, capillary). In the simplified model (1.3)-(1.4), even if, initially, meaning in the initial conditions, the two compartments are separated, $u$ and $v$ diffuse in each of them: the total lactate concentration should thus be seen as the sum $u + v$. Finally, although we kept here, at first approximation, the same nonlinear terms as in (1.1)-(1.2), this should be further investigated in view of more realistic PDE's models; this paper can thus be seen as a first step to understand the mathematical difficulties related with reaction-diffusion systems with such nonlinearities/such a coupling. We will address more elaborate models elsewhere.

A first step, to validate the model, is to show that it still satisfies the important (in view of therapeutic management) properties of the ODE's system. More precisely, two major issues are the boundedness of the lactate concentrations (related with the viability domain of the glial tumors) and the stability of the unique (spatially homogeneous in the case of the PDE's system) steady state (related with therapeutic protocols).

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).

In [13], the well-posedness of the following singular reaction-diffusion equation was studied:

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

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.

In this paper, we prove the existence and uniqueness of regular nonnegative solutions to (1.3)-(1.4), for nonnegative initial data. We also derive $L^\infty$-bounds on these solutions. We then study the linear stability of the unique spatially homogeneous steady state. We can note that this spatially homogeneous equilibrium is the same as the unique equilibirum for (1.1)-(1.2), meaning that (1.3)-(1.4) contains important and relevant features of the original ODE's model.

**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 $X$.

Throughout the paper, the same letters $c$ and $c'$ denote (generally positive) constants which may vary from line to line.

## 2. Existence, uniqueness and regularity of nonnegative solutions

We consider the initial and boundary value problem

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

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

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

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

Note that (2.1)-(2.2) are equivalent to (1.3)-(1.4). We assume that

$$(u_0, v_0) \in (H^3(\Omega) \cap H^2_{\rm N}(\Omega))^2, \quad u_0 \geq 0,\ v_0 \geq 0 \text{ a.e. } x, \tag{2.5}$$

where

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

**Theorem 2.1.** *We assume that* (2.5) *holds. Then,* (2.1)-(2.4) *possesses a unique solution* $(u,v)$ *such that*

$$u \geq 0, \quad v \geq 0 \quad a.e.\ (x,t) \tag{2.6}$$

*and, for all* $T > 0$*,*

$$(u,v) \in L^\infty(0,T;(H^3(\Omega)\cap H^2_{\rm N}(\Omega))^2) \cap L^2(0,T;H^4(\Omega)^2),$$

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

*Proof.* (a) Uniqueness: Let $(u_1,v_1)$ and $(u_2,v_2)$ be two such solutions to (2.1)-(2.3) with initial data $(u_{0,1},v_{0,1})$ and $(u_{0,2},v_{0,2})$, respectively. We set $(u,v) = (u_1-u_2, v_1-v_2)$ and $(u_0,v_0) = (u_{0,1}-u_{0,2}, v_{0,1}-v_{0,2})$ and have

$$\frac{\partial u}{\partial t} - \alpha\Delta u + \kappa\Big(\frac{ku}{(k+u_1)(k+u_2)} - \frac{k'v}{(k'+v_1)(k'+v_2)}\Big) = 0, \tag{2.7}$$

$$\epsilon\frac{\partial v}{\partial t}-\beta\Delta v+Fv+\kappa(\frac{k'v}{(k'+v_1)(k'+v_2)}-\frac{ku}{(k+u_1)(k+u_2)})=0, \tag{2.8}$$

$$\frac{\partial u}{\partial \nu}=\frac{\partial v}{\partial \nu}=0 \quad \text{on } \Gamma, \tag{2.9}$$

$$u|_{t=0}=u_0, \quad v|_{t=0}=v_0. \tag{2.10}$$

We multiply (2.7) by $u$ and (2.8) by $v$ and integrate over $\Omega$ and by parts. Summing the two resulting equalities, we easily obtain, noting that $u_i \geq 0$, $v_i \geq 0$ a.e. $(x,t)$, $i=1,2$, so that

$$0 \leq \frac{k}{(k+u_1)(k+u_2)} \leq \frac{1}{k}, \quad 0 \leq \frac{k'}{(k'+v_1)(k'+v_2)} \leq \frac{1}{k'} \quad \text{a.e. } (x,t),$$

the differential inequality

$$\frac{1}{2}\frac{d}{dt}(\|u\|^2+\epsilon\|v\|^2) \leq \kappa(\frac{1}{k}+\frac{1}{k'})|((u,v))|.$$

This yields

$$\frac{d}{dt}(\|u\|^2+\epsilon\|v\|^2) \leq c(\|u\|^2+\epsilon\|v\|^2), \tag{2.11}$$

whence, owing to Gronwall's lemma,

$$\begin{aligned}&\|u_1(t)-u_2(t)\|^2+\epsilon\|v_1(t)-v_2(t)\|^2\\ &\leq e^{ct}(\|u_{0,1}-u_{0,2}\|^2+\epsilon(\|v_{0,1}-v_{0,2}\|^2), \quad t \geq 0.\end{aligned} \tag{2.12}$$

This yields the uniqueness, as well as the continuous dependence with respect to the initial data in the $L^2$-norm.

(b) Regularity estimates: We assume that (2.1)-(2.4) possesses a solution $(u,v)$ such that (2.6) is satisfied and the estimates below are justified.

We multiply (2.1) by $u$ and (2.2) by $v$ and find, summing the two resulting equalities,

$$\frac{1}{2}\frac{d}{dt}(\|u\|^2+\epsilon\|v\|^2)+\alpha\|\nabla u\|^2+\beta\|\nabla v\|^2 \leq (J+\kappa)\int_\Omega u\,dx+(FL+\kappa)\int_\Omega v\,dx,$$

which yields

$$\frac{d}{dt}(\|u\|^2+\epsilon\|v\|^2)+c(\|\nabla u\|^2+\|\nabla v\|^2) \leq c'(\|u\|^2+\epsilon\|v\|^2)+c'', \ c>0, \tag{2.13}$$

whence estimates on $u$ and $v$ in $L^\infty(0,T;L^2(\Omega))$ and $L^2(0,T;H^1(\Omega))$, for all $T>0$.

**Remark 2.2.** Multiplying (2.2) by $v$ gives

$$\frac{\epsilon}{2}\frac{d}{dt}\|v\|^2+\beta\|\nabla v\|^2+F\|v\|^2 \leq c\|v\|,$$

which yields

$$\epsilon\frac{d}{dt}\|v\|^2+F\|v\|^2 \leq c,$$

whence, owing to Gronwall's lemma,

$$\|v(t)\|^2 \leq e^{-\frac{F}{\epsilon}t}\|v_0\|^2+c, \ t \geq 0,$$

so that the estimate on $v$ in $L^2(\Omega)$ is global in time and even dissipative (in the sense that it is independent of time and bounded sets of initial data, at least for large times). We can also note that this estimate only depends on the initial datum for $v$.

Next, we multiply (2.1) by $-\Delta u$ and (2.2) by $-\Delta v$ and have, summing the two resulting equalities,

$$\frac{1}{2}\frac{d}{dt}(\|\nabla u\|^2+\epsilon\|\nabla v\|^2)+\alpha\|\Delta u\|^2+\beta\|\Delta v\|^2\le c(\|\Delta u\|+\|\Delta v\|),$$

owing again to (2.6), which yields

$$\frac{d}{dt}(\|\nabla u\|^2+\epsilon\|\nabla v\|^2)+c(\|\Delta u\|^2+\|\Delta v\|^2)\le c',\quad c>0, \tag{2.14}$$

and we obtain estimates on $u$ and $v$ in $L^\infty(0,T;H^1(\Omega))$ and $L^2(0,T;H^2(\Omega))$, for all $T>0$.

We then differentiate (2.1) and (2.2) with respect to time to have

$$\frac{\partial}{\partial t}\frac{\partial u}{\partial t}-\alpha\Delta\frac{\partial u}{\partial t}+\kappa(\frac{k}{(k+u)^2}\frac{\partial u}{\partial t}-\frac{k'}{(k'+v)^2}\frac{\partial v}{\partial t})=0, \tag{2.15}$$

$$\epsilon\frac{\partial}{\partial t}\frac{\partial v}{\partial t}-\beta\Delta\frac{\partial v}{\partial t}+F\frac{\partial v}{\partial t}+\kappa(\frac{k'}{(k'+v)^2}\frac{\partial v}{\partial t}-\frac{k}{(k+u)^2}\frac{\partial u}{\partial t})=0, \tag{2.16}$$

$$\frac{\partial}{\partial\nu}\frac{\partial u}{\partial t}=\frac{\partial}{\partial\nu}\frac{\partial v}{\partial t}=0\quad\text{on }\Gamma, \tag{2.17}$$

where the initial data

$$\frac{\partial u}{\partial t}(0)=J+\alpha\Delta u_0+\kappa(\frac{k}{k+u_0}-\frac{k'}{k'+v_0}), \tag{2.18}$$

$$\frac{\partial v}{\partial t}(0)=\frac{1}{\epsilon}(FL+\beta\Delta v_0-Fv_0+\kappa(\frac{k'}{k'+v_0}-\frac{k}{k+u_0})) \tag{2.19}$$

belong to $H^1(\Omega)$.

We multiply (2.15) by $\frac{\partial u}{\partial t}$ and (2.16) by $\frac{\partial v}{\partial t}$ and obtain, summing the two resulting equalities and owing once more to (2.6),

$$\frac{d}{dt}(\|\frac{\partial u}{\partial t}\|^2+\epsilon\|\frac{\partial v}{\partial t}\|^2)+c(\|\nabla\frac{\partial u}{\partial t}\|^2+\|\nabla\frac{\partial v}{\partial t}\|^2)\le c'(\|\frac{\partial u}{\partial t}\|^2+\epsilon\|\frac{\partial v}{\partial t}\|^2),\ c>0, \tag{2.20}$$

whence estimates on $\frac{\partial u}{\partial t}$ and $\frac{\partial v}{\partial t}$ in $L^\infty(0,T;L^2(\Omega))$ and $L^2(0,T;H^1(\Omega))$, for all $T>0$.

We also multiply (2.15) by $-\Delta\frac{\partial u}{\partial t}$ and (2.16) by $-\Delta\frac{\partial v}{\partial t}$ and find

$$\begin{aligned}&\frac{d}{dt}(\|\nabla\frac{\partial u}{\partial t}\|^2+\epsilon\|\nabla\frac{\partial v}{\partial t}\|^2)+c(\|\Delta\frac{\partial u}{\partial t}\|^2+\|\Delta\frac{\partial v}{\partial t}\|^2)\\&\le c'(\|\frac{\partial u}{\partial t}\|+\|\frac{\partial v}{\partial t}\|)(\|\Delta\frac{\partial u}{\partial t}\|+\|\Delta\frac{\partial v}{\partial t}\|),\end{aligned}$$

which yields

$$\frac{d}{dt}(\|\nabla\frac{\partial u}{\partial t}\|^2+\epsilon\|\nabla\frac{\partial v}{\partial t}\|^2)+c(\|\Delta\frac{\partial u}{\partial t}\|^2+\|\Delta\frac{\partial v}{\partial t}\|^2)\le c'(\|\frac{\partial u}{\partial t}\|^2+\|\frac{\partial v}{\partial t}\|^2), \tag{2.21}$$

with $c>0$, whence estimates on $\frac{\partial u}{\partial t}$ and $\frac{\partial v}{\partial t}$ in $L^\infty(0,T;H^1(\Omega))$ and $L^2(0,T;H^2(\Omega))$, for all $T>0$. We now rewrite (2.1)-(2.2) as an elliptic system, for $t>0$ fixed,

$$-\alpha\Delta u=g(x,t),\quad\frac{\partial u}{\partial\nu}=0\quad\text{on }\Gamma, \tag{2.22}$$

$$-\beta\Delta v=h(x,t),\ \frac{\partial v}{\partial\nu}=0\quad\text{on }\Gamma, \tag{2.23}$$

where

$$g = J - \frac{\partial u}{\partial t} - \kappa(\frac{k'}{k'+v} - \frac{k}{k+u}), \tag{2.24}$$

$$h = FL - \epsilon\frac{\partial v}{\partial t} - Fv - \kappa(\frac{k}{k+u} - \frac{k'}{k'+v}) \tag{2.25}$$

belong to $L^\infty(0,T;L^2(\Omega))$ and $L^2(0,T;H^1(\Omega))$, $\forall T>0$. Indeed, note that

$$\frac{\partial}{\partial x_i}\frac{1}{k+u} = -\frac{1}{(k+u)^2}\frac{\partial u}{\partial x_i}, \quad \frac{\partial}{\partial x_i}\frac{1}{k'+v} = -\frac{1}{(k'+v)^2}\frac{\partial v}{\partial x_i}, \quad i=1,\dots,n.$$

It thus follows from standard elliptic regularity results (see, e.g., [1] and [2]) that $(u,v)\in L^\infty(0,T;H^2(\Omega)^2)\cap L^2(0,T;H^3(\Omega)^2)$, for all $T>0$. This, in turn, yields that $g$ and $h$ belong to $L^\infty(0,T;H^1(\Omega))$ and $L^2(0,T;H^2(\Omega))$, for all $T>0$. Indeed, note that

$$\frac{\partial^2}{\partial x_i\partial x_j}\frac{1}{k+u} = \frac{2}{(k+u)^3}\frac{\partial u}{\partial x_i}\frac{\partial u}{\partial x_j} - \frac{1}{(k+u)^2}\frac{\partial^2 u}{\partial x_i\partial x_j}, \; i,\; j=1,\dots,n,$$

and

$$\begin{aligned}\|\frac{\partial^2}{\partial x_i\partial x_j}\frac{1}{k+u}\| &\le c(\|\frac{\partial u}{\partial x_i}\frac{\partial u}{\partial x_j}\| + \|\frac{\partial^2 u}{\partial x_i\partial x_j}\|)\\ &\le c(\|\frac{\partial u}{\partial x_i}\|_{L^4(\Omega)}\|\frac{\partial u}{\partial x_j}\|_{L^4(\Omega)} + \|\frac{\partial^2 u}{\partial x_i\partial x_j}\|)\\ &\le c(\|u\|^2_{H^2(\Omega)}+1),\end{aligned}$$

where $i,j=1,\dots,n$, owing to the continuous embedding $H^1(\Omega)\subset L^4(\Omega)$. We proceed in a similar way for $v$. Again, standard elliptic regularity results yield that $(u,v)\in L^\infty(0,T;H^3(\Omega)^2)\cap L^2(0,T;H^4(\Omega)^2)$, for all $T>0$.

(c) Existence of nonnegative solutions: We consider the initial and boundary value problem

$$\frac{\partial u}{\partial t} - \alpha\Delta u + \kappa(\frac{u}{k+|u|} - \frac{v}{k'+|v|}) = J, \tag{2.26}$$

$$\epsilon\frac{\partial v}{\partial t} - \beta\Delta v + Fv + \kappa(\frac{v}{k'+|v|} - \frac{u}{k+|u|}) = FL, \tag{2.27}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = 0 \quad \text{on } \Gamma, \tag{2.28}$$

$$u|_{t=0} = u_0, \quad v|_{t=0} = v_0. \tag{2.29}$$

Noting that $f(s)=\frac{s}{c+|s|}$, $c>0$ given, is of class $\mathcal{C}^1$, where $f'(s)=\frac{c}{(c+|s|)^2}$ is bounded on $\mathbb{R}$, so that $f$ is also Lipschitz continuous, we can prove the existence and uniqueness of the weak (i.e., variational) solution to (2.26)-(2.29) (we refer the interested reader to, e.g., [11], [14] and [15] for developments on reaction-diffusion equations and systems). Furthermore, this solution satisfies regularity estimates which are similar to those derived above and is thus strong (i.e., it satisfies (2.26)-(2.29) a.e. $(x,t)$). This, together with the existence of a solution, can be done by considering a standard Galerkin scheme, taking a spectral basis associated with the spectrum of the minus Laplace operator, with Neumann boundary conditions, as Galerkin basis.

We then multiply (2.26) by $-u^-$, where $u^- = \min(0, -u)$, and have

$$\frac{1}{2}\frac{d}{dt}\|u^-\|^2 + \alpha\|\nabla u^-\|^2 + \kappa\int_\Omega \frac{|u^-|^2}{k+|u|}\,dx + \kappa\int_\Omega \frac{vu^-}{k'+|v|}\,dx \le 0. \tag{2.30}$$

Noting that $v = v^+ - v^-$, where $v^+ = \max(0, v)$, and $u^-$ and $v^+$ are nonnegative, it follows that

$$\frac{d}{dt}\|u^-\|^2 \le 2\kappa\int_\Omega \frac{v^- u^-}{k'+|v|}\,dx, \tag{2.31}$$

whence

$$\frac{d}{dt}\|u^-\|^2 \le c(\|u^-\|^2 + \epsilon\|v^-\|^2). \tag{2.32}$$

Similarly, multiplying (2.27) by $-v^-$, we obtain

$$\epsilon\frac{d}{dt}\|v^-\|^2 \le c(\|u^-\|^2 + \epsilon\|v^-\|^2). \tag{2.33}$$

Summing (2.32) and (2.33), we find

$$\frac{d}{dt}(\|u^-\|^2 + \epsilon\|v^-\|^2) \le c(\|u^-\|^2 + \epsilon\|v^-\|^2). \tag{2.34}$$

Gronwall's lemma finally yields

$$\|u^-(t)\|^2 + \epsilon\|v^-(t)\|^2 \le e^{ct}(\|u_0^-\|^2 + \epsilon\|v_0^-\|^2), \tag{2.35}$$

whence $u^- = v^- = 0$ (recall that $u_0 \ge 0$ and $v_0 \ge 0$ a.e. $x$) and $u \ge 0$ and $v \ge 0$ a.e. $(x,t)$. This means that $(u, v)$ is solution to (2.1)-(2.4) and the regularity estimates derived above are now fully justified. □

**Remark 2.3.** (i) Actually, the biologically relevant quadrant $\{u \ge 0,\ v \ge 0\}$ is an invariant region (see [14]) for both systems (2.1)-(2.2) and (2.26)-(2.27), meaning that solutions starting from this region cannot leave it. We chose however to give a proof of the nonnegativity of the solutions, also having in mind more elaborate models which we will study in forthcoming papers.

(ii) We now assume that

$$u_0 \ge -\delta_1 \quad \text{and} \quad v_0 \ge -\delta_2 \quad \text{a.e. } x, \tag{2.36}$$

where $\delta_1$ and $\delta_2$ are positive (and are intended to be small). We then consider the modified initial and boundary value problem

$$\frac{\partial u}{\partial t} - \alpha\Delta u + \kappa\Big(\frac{u}{k-\delta_1+|u+\delta_1|} - \frac{v}{k'-\delta_2+|v+\delta_2|}\Big) = J, \tag{2.37}$$

$$\epsilon\frac{\partial v}{\partial t} - \beta\Delta v + Fv + \kappa\Big(\frac{v}{k'-\delta_2+|v+\delta_2|} - \frac{u}{k-\delta_1+|u+\delta_1|}\Big) = FL, \tag{2.38}$$

$$\frac{\partial u}{\partial \nu} = \frac{\partial v}{\partial \nu} = 0 \quad \text{on } \Gamma, \tag{2.39}$$

$$u|_{t=0} = u_0, \quad v|_{t=0} = v_0, \tag{2.40}$$

where $\delta_1$ and $\delta_2$ are chosen such that $k - \delta_1 > 0$ and $k' - \delta_2 > 0$. The existence and uniqueness of the solution to (2.37)-(2.40) is straightforward. Next, we set $\tilde{u} = u + \delta_1$ and $\tilde{v} = v + \delta_2$. These functions are solutions to

$$\frac{\partial \tilde{u}}{\partial t} - \alpha\Delta\tilde{u} + \kappa\Big(\frac{\tilde{u}}{k-\delta_1+|\tilde{u}|} - \frac{\tilde{v}}{k'-\delta_2+|\tilde{v}|}\Big) = \tilde{J}, \tag{2.41}$$

$$\epsilon\frac{\partial\tilde{v}}{\partial t}-\beta\Delta\tilde{v}+F\tilde{v}+\kappa(\frac{\tilde{v}}{k'-\delta_2+|\tilde{v}|}-\frac{\tilde{u}}{k-\delta_1+|\tilde{u}|})=\tilde{F}, \tag{2.42}$$

$$\frac{\partial\tilde{u}}{\partial\nu}=\frac{\partial\tilde{v}}{\partial\nu}=0\quad\text{on }\Gamma, \tag{2.43}$$

$$\tilde{u}|_{t=0}=u_0+\delta_1,\quad \tilde{v}|_{t=0}=v_0+\delta_2, \tag{2.44}$$

where

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

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

Choosing $\delta_1$ and $\delta_2$ such that $\tilde{J}\geq 0$ and $\tilde{F}\geq 0$ (in particular, these hold when $\delta_1$ and $\delta_2$ are small enough) and noting that $\tilde{u}(0)\geq 0$ and $\tilde{v}(0)\geq 0$ a.e. $x$, we can prove, as in the proof of Theorem 2.1, 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 (2.1)-(2.3) (here, the quadrant $\{u\geq -\delta_1,\ v\geq -\delta_2\}$ is an invariant region). For general negative initial data however, the existence of a global in time solution is much more involved.

**Theorem 2.4.** *Under the assumptions of Theorem 2.1, the solution $(u,v)$ to (2.1)-(2.4) such that (2.6) holds satisfies*

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

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

*Proof.* We note that, owing to (2.6),

$$\frac{\partial u}{\partial t}-\alpha\Delta u\leq J+\kappa, \tag{2.45}$$

$$\epsilon\frac{\partial v}{\partial t}-\beta\Delta v+Fv\leq FL+\kappa. \tag{2.46}$$

We multiply (2.45) by $u^{m+1}$, $m\in\mathbb{N}$, and have

$$\frac{1}{m+2}\frac{d}{dt}\|u\|^{m+2}_{L^{m+2}(\Omega)}+\alpha(m+1)\int_\Omega u^m|\nabla u|^2\,dx\leq (J+\kappa)\int_\Omega u^{m+1}\,dx,$$

which yields

$$\|u\|^{m+1}_{L^{m+2}(\Omega)}\frac{d}{dt}\|u\|_{L^{m+2}(\Omega)}\leq (J+\kappa)\mathrm{Vol}(\Omega)^{\frac{1}{m+2}}\|u\|^{m+1}_{L^{m+2}(\Omega)}. \tag{2.47}$$

Therefore, $\|u(t)\|_{L^{m+2}(\Omega)}=0$ or $\|u(t)\|_{L^{m+2}(\Omega)}>0$ and

$$\frac{d}{dt}\|u\|_{L^{m+2}(\Omega)}\leq (J+\kappa)\mathrm{Vol}(\Omega)^{\frac{1}{m+2}}. \tag{2.48}$$

In the later case (note that it follows from the regularity given in Theorem 2.1 that $u$ is continuous, both in space and time), for $t>0$ given, either $\|u(s)\|_{L^{m+2}(\Omega)}>0$, for all $s\in(0,t]$, in which case

$$\|u(t)\|_{L^{m+2}(\Omega)}\leq\|u_0\|_{L^{m+2}(\Omega)}+(J+\kappa)\mathrm{Vol}(\Omega)^{\frac{1}{m+2}}t, \tag{2.49}$$

or there exists $t_0\in(0,t]$ such that $\|u(t_0)\|_{L^{m+2}(\Omega)}=0$ and $\|u(s)\|_{L^{m+2}(\Omega)}>0$, for all $s\in(t_0,t]$, in which case

$$\|u(t)\|_{L^{m+2}(\Omega)}\leq (J+\kappa)\mathrm{Vol}(\Omega)^{\frac{1}{m+2}}(t-t_0),$$

so that (2.49) again holds. Noting that (2.49) also holds when $\|u(t)\|_{L^{m+2}(\Omega)} = 0$, we obtain, passing to the limit $m \to +\infty$ (see, e.g., [3]),

$$\|u(t)\|_{L^\infty(\Omega)} \le \|u_0\|_{L^\infty(\Omega)} + (J+\kappa)t, \quad t \ge 0. \tag{2.50}$$

Proceeding in a similar way for (2.46), we find

$$\epsilon \frac{d}{dt}\|v\|_{L^{m+2}(\Omega)} + F\|v\|_{L^{m+2}(\Omega)} \le (FL+\kappa)\mathrm{Vol}(\Omega)^{\frac{1}{m+2}}. \tag{2.51}$$

Employing Gronwall's lemma, we deduce from (2.51) that

$$\|v(t)\|_{L^{m+2}(\Omega)} \le e^{-\frac{F}{\epsilon}t}\|v_0\|_{L^{m+2}(\Omega)} + \frac{FL+\kappa}{F}\mathrm{Vol}(\Omega)^{\frac{1}{m+2}}, \quad t \ge 0. \tag{2.52}$$

Passing to the limit $m \to +\infty$, we finally have

$$\|v(t)\|_{L^\infty(\Omega)} \le e^{-\frac{F}{\epsilon}t}\|v_0\|_{L^\infty(\Omega)} + \frac{FL+\kappa}{F},\ t \ge 0, \tag{2.53}$$

which completes the proof. □

**Remark 2.5.** (i) In particular, from (2.53) (which is a dissipative estimate) it follows that if $\|v_0\|_{L^\infty(\Omega)} \le R$ and $\delta > 0$ is given, then there exists $t_0 = t_0(R,\delta) > 0$ such that

$$\|v(t)\|_{L^\infty(\Omega)} \le \frac{FL+\kappa}{F} + \delta, \quad t \ge t_0. \tag{2.54}$$

Let now $M$ be such that $F(L-M)+\kappa \le 0$, i.e., $M \ge \frac{FL+\kappa}{F}$, and $v_0$ be such that $0 \le v_0 \le M$ a.e. $x$. Setting $\tilde{v} = v - M$, we obtain

$$\epsilon\frac{\partial \tilde{v}}{\partial t} - \beta\Delta\tilde{v} + F\tilde{v} \le 0, \tag{2.55}$$

$$\frac{\partial \tilde{v}}{\partial \nu} = 0 \quad \text{on } \Gamma, \tag{2.56}$$

where $\tilde{v}(0) \le 0$. Multiplying (2.55) by $\tilde{v}^+$, we easily find

$$\frac{d}{dt}\|\tilde{v}^+\|^2 \le 0,$$

whence $\tilde{v}^+ = 0$ and $0 \le v \le M$ a.e. $(x,t)$ (compare with (2.54)), meaning that the capillary lactate concentration is uniformly bounded (or ultimately uniformly bounded in (2.54)). Now, 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 [7]), meaning that one expects viable trajectories to be uniformly bounded.

(ii) Multiplying (1.3) by $u+k$, integrating over $\Omega$ and by parts, we obtain

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

where

$$E = \frac{1}{2}\|u\|^2 + k\|u\|_{L^1(\Omega)}.$$

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

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

We thus deduce that

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

which yields, noting that

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

the differential inequality

$$\frac{dE}{dt} + c\sqrt{E} \le c', \quad c > 0. \tag{2.57}$$

Set $E^* = (c'/c)^2$, where $c$ and $c'$ are the same constants as in (2.57), so that

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

It then follows from comparison arguments that

$$E(t) \le \max(E(0), E^*), \quad t \ge 0, \tag{2.58}$$

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

We finally have

**Theorem 2.6.** *We further assume that $J \ge \kappa$, $FL \ge \kappa$ and $u_0 > 0$ and $v_0 > 0$ a.e. $x$. Let $(u, v)$ be the solution to* (2.1)-(2.4) *such that* (2.6) *holds. Then, $u > 0$ and $v > 0$ a.e. $(x, t)$ and*

$$u(x,t) \ge \frac{1}{\|\frac{1}{u_0}\|_{L^\infty(\Omega)}}, \quad v(x,t) \ge \frac{e^{-\frac{F}{\epsilon}t}}{\|\frac{1}{v_0}\|_{L^\infty(\Omega)}} \quad \text{a.e. } (x,t).$$

*Proof.* We first note that from (2.1)-(2.2) it follows that

$$\frac{\partial u}{\partial t} - \alpha\Delta u \ge J - \kappa, \tag{2.59}$$

$$\epsilon\frac{\partial v}{\partial t} - \beta\Delta v + Fv \ge FL - \kappa. \tag{2.60}$$

Multiplying (2.59) by $-\frac{1}{u}$, we have

$$\frac{d}{dt}\int_\Omega \ln\frac{1}{u}\,dx \le 0,$$

whence

$$\int_\Omega \ln\frac{1}{u(t)}\,dx \le \int_\Omega \ln\frac{1}{u_0}\,dx, \quad t \ge 0,$$

and $u(x,t) > 0$ a.e. $(x,t)$. We proceed in a similar way to prove that $v(x,t) > 0$ a.e. $(x,t)$.

Next, we multiply (2.59) by $-\frac{1}{u^{m+1}}$, $m \in \mathbb{N}$, and find that

$$\frac{1}{m}\frac{d}{dt}\|\frac{1}{u}\|^m_{L^m(\Omega)} + \alpha(m+1)\int_\Omega \frac{|\nabla u|^2}{u^{m+2}}\,dx \le 0,$$

whence

$$\|\frac{1}{u(t)}\|_{L^m(\Omega)} \le \|\frac{1}{u_0}\|_{L^m(\Omega)}, \quad t \ge 0. \tag{2.61}$$

Passing to the limit $m \to +\infty$, we deduce that

$$\|\frac{1}{u(t)}\|_{L^\infty(\Omega)} \le \|\frac{1}{u_0}\|_{L^\infty(\Omega)}, \quad t \ge 0. \tag{2.62}$$

Multiplying (2.60) by $-\frac{1}{v^{m+1}}$, $m \in \mathbb{N}$, we have

$$\frac{\epsilon}{m}\frac{d}{dt}\|\frac{1}{v}\|^m_{L^m(\Omega)} \le F\|\frac{1}{v}\|^m_{L^m(\Omega)},$$

which yields

$$\epsilon\frac{d}{dt}\|\frac{1}{v}\|_{L^m(\Omega)} \le F\|\frac{1}{v}\|_{L^m(\Omega)}, \tag{2.63}$$

whence, employing Gronwall's lemma,

$$\|\frac{1}{v(t)}\|_{L^m(\Omega)} \le \|\frac{1}{v_0}\|_{L^m(\Omega)} e^{\frac{F}{\epsilon}t}, \quad t \ge 0. \tag{2.64}$$

Passing to the limit $m \to +\infty$, we deduce that

$$\|\frac{1}{v(t)}\|_{L^\infty(\Omega)} \le \|\frac{1}{v_0}\|_{L^\infty(\Omega)} e^{\frac{F}{\epsilon}t}, \quad t \ge 0, \tag{2.65}$$

which completes the proof. □

**Remark 2.7.** Proceeding as in the proof of Theorem 2.1 (see also Remark 2.3, (ii)), we can prove that, if

$$u_0 \ge \delta_1 \quad \text{and} \quad v_0 \ge \delta_2 \quad \text{a.e. } x,$$

where $\delta_1$ and $\delta_2$ are positive and small enough, then

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

**Remark 2.8.** It is interesting to note that, as far as the $L^\infty$-estimates are concerned, the system behaves as if it were uncoupled.

## 3. A stability result

As shown in [5, 7, 8, 9], (2.1)-(2.3) possesses a unique spatially homogeneous stationary solution $(u,v) = (\overline{u},\overline{v})$ given by

$$\overline{v} = L + \frac{J}{F} > 0, \tag{3.1}$$

$$\overline{u} = \frac{k(\frac{J}{\kappa} + \frac{\overline{v}}{k'+\overline{v}})}{1 - (\frac{J}{\kappa} + \frac{\overline{v}}{k'+\overline{v}})}. \tag{3.2}$$

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

$$\overline{u} > 0. \tag{3.3}$$

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

$$\frac{\partial U}{\partial t} - \alpha\Delta U + \kappa(\frac{k}{(k+\overline{u})^2}U - \frac{k'}{(k'+\overline{v})^2}V) = 0, \tag{3.4}$$

$$\epsilon\frac{\partial V}{\partial t} - \beta\Delta V + FV + \kappa(\frac{k'}{(k'+\overline{v})^2}V - \frac{k}{(k+\overline{u})^2}U) = 0, \tag{3.5}$$

$$\frac{\partial U}{\partial \nu} = \frac{\partial V}{\partial \nu} = 0 \quad \text{on } \Gamma, \tag{3.6}$$

$$U|_{t=0} = U_0, \quad V|_{t=0} = V_0. \tag{3.7}$$

Noting that (3.4)-(3.5) is a linear system, it is not difficult to prove the following result.

**Theorem 3.1.** *We assume that* $(U_0, V_0) \in L^2(\Omega)^2$. *Then* (3.4)-(3.7) *possesses a unique weak solution* $(U, V)$ *such that, for all* $T > 0$,

$$(U, V) \in L^\infty(0, T; L^2(\Omega)^2) \cap L^2(0, T; H^1(\Omega)^2).$$

*If we further assume that* $(U_0, V_0) \in H^1(\Omega)^2$, *then, for all* $T > 0$,

$$(U, V) \in L^\infty(0, T; H^1(\Omega)^2) \cap L^2(0, T; H^2(\Omega)^2).$$

*Finally, if* $(U_0, V_0) \in H^2_{\rm N}(\Omega)^2$, *then, for all* $T > 0$,

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

*and the solution is strong.*

**Remark 3.2.** It is easy to prove that, if $U_0 \geq 0$ and $V_0 \geq 0$ a.e. $x$, then $U \geq 0$ and $V \geq 0$ a.e. $(x, t)$.

**Theorem 3.3.** *The stationary solution* $(\overline{u}, \overline{v})$ *is linearly stable in* $L^2(\Omega)^2$.

*Proof.* We multiply (3.4) by $\frac{k}{(k+\overline{u})^2} U$ and (3.5) by $\frac{k'}{(k'+\overline{v})^2} V$ and obtain, summing the two resulting equalities,

$$\begin{aligned} &\frac{1}{2}\frac{d}{dt}\Big(\frac{k}{(k+\overline{u})^2}\|U\|^2 + \epsilon\frac{k'}{(k'+\overline{v})^2}\|V\|^2\Big) \\ &+ \frac{\alpha k}{(k+\overline{u})^2}\|\nabla U\|^2 + \frac{\beta k'}{(k'+\overline{v})^2}\|\nabla V\|^2 + \frac{Fk'}{(k'+\overline{v})^2}\|V\|^2 \\ &+ \kappa\Big(\frac{k^2}{(k+\overline{u})^4}\|U\|^2 + \frac{k'^2}{(k'+\overline{v})^4}\|V\|^2 - \frac{2kk'}{(k+\overline{u})^2(k'+\overline{v})^2}\int_\Omega UV\,dx\Big) = 0. \end{aligned} \tag{3.8}$$

Noting that

$$\begin{aligned} &\frac{k^2}{(k+\overline{u})^4}\|U\|^2 + \frac{k'^2}{(k'+\overline{v})^4}\|V\|^2 - \frac{2kk'}{(k+\overline{u})^2(k'+\overline{v})^2}\int_\Omega UV\,dx \\ &= \int_\Omega \Big(\frac{k}{(k+\overline{u})^2}U - \frac{k'}{(k'+\overline{v})^2}V\Big)^2\,dx \geq 0, \end{aligned}$$

we deduce from (3.8) that

$$\frac{d}{dt}\Big(\frac{k}{(k+\overline{u})^2}\|U\|^2 + \epsilon\frac{k'}{(k'+\overline{v})^2}\|V\|^2\Big) \leq 0, \tag{3.9}$$

whence

$$\frac{k}{(k+\overline{u})^2}\|U(t)\|^2 + \epsilon\frac{k'}{(k'+\overline{v})^2}\|V(t)\|^2 \leq \frac{k}{(k+\overline{u})^2}\|U_0\|^2 + \epsilon\frac{k'}{(k'+\overline{v})^2}\|V_0\|^2 \tag{3.10}$$

and the result follows. □

**Remark 3.4.** Similarly, multiplying (3.4) by $-\frac{k}{(k+\overline{u})^2}\Delta U$ and (3.5) by $-\frac{k'}{(k'+\overline{v})^2}\Delta V$, we obtain the linear stability of the stationary solution $(\overline{u}, \overline{v})$ in $H^1(\Omega)^2$.

Actually, we can do better and prove the following result.

**Theorem 3.5.** *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* (3.4)-(3.6) *satisfy* $\mathcal{R}e(s) \leq -\xi$, *for a given* $\xi > 0$, $\mathcal{R}e$ *denoting the real part.*

*Proof.* We look for solutions of the form

$$U(x,t) = \hat{U}(x)e^{st}, \quad V(x,t) = \hat{V}(x)e^{\frac{s}{\epsilon}t}, \tag{3.11}$$

for $s \in \mathbb{C}$. Inserting this into (3.4)-(3.6), we have

$$-\alpha\Delta\hat{U} + s\hat{U} + \kappa(\frac{k}{(k+\overline{u})^2}\hat{U} - \frac{k'}{(k'+\overline{v})^2}\hat{V}) = 0, \tag{3.12}$$

$$-\beta\Delta\hat{V} + (s+F)\hat{V} + \kappa(\frac{k'}{(k'+\overline{v})^2}\hat{V} - \frac{k}{(k+\overline{u})^2}\hat{U}) = 0, \tag{3.13}$$

$$\frac{\partial\hat{U}}{\partial\nu} = \frac{\partial\hat{V}}{\partial\nu} = 0 \quad \text{on } \Gamma. \tag{3.14}$$

Summing (3.12) and (3.13), we obtain

$$-\Delta(\alpha\hat{U} + \beta\hat{V}) + \frac{s+F}{\beta}(\alpha\hat{U} + \beta\hat{V}) + (s - \frac{\alpha(s+F)}{\beta})\hat{U} = 0, \tag{3.15}$$

$$\frac{\partial}{\partial\nu}(\alpha\hat{U} + \beta\hat{V}) = 0 \quad \text{on } \Gamma, \tag{3.16}$$

so that

$$\hat{V} = \frac{\alpha F + (\alpha-\beta)s}{\beta^2}(-\Delta + \frac{s+F}{\beta}I)^{-1}\hat{U} - \frac{\alpha}{\beta}\hat{U}. \tag{3.17}$$

Inserting this into (3.12), we find

$$-\alpha\Delta\hat{U} + \delta\hat{U} - \gamma(-\Delta + \frac{s+F}{\beta}I)^{-1}\hat{U} = 0, \tag{3.18}$$

where

$$\delta = s + \frac{\kappa k}{(k+\overline{u})^2} + \frac{\kappa k'\alpha}{\beta(k'+\overline{v})^2},$$
$$\gamma = \frac{\kappa k'(\alpha F + (\alpha-\beta)s)}{\beta^2(k'+\overline{v})^2}.$$

This yields

$$\alpha\Delta^2\hat{U} - (\frac{\alpha(s+F)}{\beta} + \delta)\Delta\hat{U} + (\frac{\delta(s+F)}{\beta} - \gamma)\hat{U} = 0, \tag{3.19}$$

where, in view of (3.14) and (3.18),

$$\frac{\partial\hat{U}}{\partial\nu} = \frac{\partial\Delta\hat{U}}{\partial\nu} = 0 \quad \text{on } \Gamma. \tag{3.20}$$

We further note that, setting

$$k_1 = \frac{\kappa k}{(k+\overline{u})^2}, \quad k_2 = \frac{\kappa k'}{(k'+\overline{v})^2},$$

we have

$$\frac{\alpha(s+F)}{\beta} + \delta = (1 + \frac{\alpha}{\beta})s + k_1 + \frac{\alpha k_2}{\beta} + \frac{\alpha F}{\beta}, \tag{3.21}$$

$$\frac{\delta(s+F)}{\beta} - \gamma = \frac{1}{\beta}(s^2 + (k_1 + k_2 + F)s + k_1 F). \tag{3.22}$$

Thus to study the stability of $(\overline{u},\overline{v})$, we need to study the eigenvalues/eigenvectors of problem (3.19)-(3.20).

We first assume that $s \in \mathbb{R}$. Then, when $s \geq 0$, noting that $\frac{\alpha(s+F)}{\beta} + \delta > 0$ and $\frac{\delta(s+F)}{\beta} - \gamma > 0$, we easily prove that the only solution to (3.19)-(3.20) is the trivial one, $\hat{U} \equiv 0$. Furthermore, (3.19)-(3.20) can have nontrivial solutions only when

$$s \in \big[ -\frac{b+\sqrt{\theta}}{2}, -\frac{b-\sqrt{\theta}}{2}\big], \quad -\frac{b-\sqrt{\theta}}{2} < 0,$$

where

$$\theta = (k_1 + k_2 + F)^2 - 4k_1F = (k_1 - F)^2 + k_2^2 + 2k_1k_2 + 2k_2F > 0$$

and $b = k_1 + k_2 + F$, or

$$\frac{\alpha(s+F)}{\beta} + \delta \leq 0,$$

i.e.,

$$s \leq -\frac{1}{1+\frac{\alpha}{\beta}}(\frac{\alpha F}{\beta} + k_1 + \frac{\alpha k_2}{\beta}) < 0.$$

Therefore, necessarily,

$$s \leq \max\big( -\frac{b-\sqrt{\theta}}{2}, -\frac{1}{1+\frac{\alpha}{\beta}}(\frac{\alpha F}{\beta} + k_1 + \frac{\alpha k_2}{\beta})\big) < 0. \tag{3.23}$$

We now assume that $s \in \mathbb{C}\backslash\mathbb{R}$. Setting $s = \zeta + i\eta$, $\eta \in \mathbb{R}\backslash\{0\}$, we obtain, multiplying (3.19) by the conjugate of $\hat{U}$, integrating over $\Omega$ and by parts and taking the imaginary part,

$$\eta(1 + \frac{\alpha}{\beta})\||\nabla \hat{U}|\|^2 + \frac{\eta(k_1 + k_2 + F) + 2\zeta\eta}{\beta}\||\hat{U}|\|^2 = 0. \tag{3.24}$$

Therefore, when $\zeta \geq 0$, then, necessarily, $\hat{U} \equiv 0$. Furthermore, (3.24) can have nontrivial solutions only when

$$\zeta \leq -\frac{k_1 + k_2 + F}{2} < 0, \tag{3.25}$$

which completes the proof. □

**Remark 3.6.** (i) In [5, 7, 8, 9], it was proved that $(\overline{u}, \overline{v})$ is a node for the linearized system associated with (1.1)-(1.2), meaning that it is linearly exponentially stable.

(ii) 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 [7]).

(iii) An important question is whether there are other (not spatially homogeneous) equilibria. This will be addressed elsewhere.

## 4. Concluding remarks

Possible extensions of our results are the following ones.

(i) We can consider a time dependent electrical stimulus $F = F(t)$, where $F$ is continuous and satisfies

$$0 < F_1 \leq F(t) \leq F_2,\ t \geq 0.$$

In particular, these assumptions are satisfied by the continuous piecewise linear stimulus considered in experiments (see [6]), where $F(0) = F_0 > 0$, $F(t) = F_1t$, $t \in [t_0, t_1]$, $F_1 > 0$, and $F(t) = F_0$, $t \geq t_f$. In that case, the well-posedness and some regularity results (here, we cannot differentiate the equations with respect to time) obtained in this paper still hold, with minor modifications.

(ii) We can also consider a forcing term $J = J(x,t,u)$ (such a forcing term accounts for the interactions with a third intracellular compartment (which includes both neurons and astrocytes)) such that $J$ is continuous on $\mathbb{R} \times \mathbb{R}^+ \times \mathbb{R}$, of class $\mathcal{C}^1$ with respect to $t$, $0 \le J(x,t,s) \le J_1$, $|\frac{\partial J}{\partial t}(x,t,s)| \le J_2$, $(x,t,s) \in \mathbb{R} \times \mathbb{R}^+ \times \mathbb{R}$, and $J$ is Lipschitz continuous with respect to $s$, uniformly in $x$ and $t$,

$$|J(x,t,s_1) - J(x,t,s_2)| \le c|s_1 - s_2|, \quad x \in \mathbb{R},\ t \in \mathbb{R}^+,\ s_1, s_2 \in \mathbb{R}.$$

In that case, the well-posedness and regularity results obtained in this paper still hold, with minor modifications.

(iii) An interesting problem is to study the limit as $\epsilon$ goes to 0 in (1.4). This will be addressed elsewhere.

(iv) A more general ODE's model for brain lactate kinetics reads

$$\begin{gathered}
\frac{du}{dt} + \kappa_1\Big(\frac{u}{k+u} - \frac{p}{k_n+p}\Big) + \kappa_2\Big(\frac{u}{k+u} - \frac{q}{k_a+q}\Big) + \kappa\Big(\frac{u}{k+u} - \frac{v}{k'+v}\Big) = J_0, \\
\frac{dp}{dt} + \kappa_1\Big(\frac{p}{k_n+p} - \frac{u}{k+u}\Big) = J_1, \\
\frac{dq}{dt} + \kappa_2\Big(\frac{q}{k_a+q} - \frac{u}{k+u}\Big) + \kappa_a\Big(\frac{q}{k_a+q} - \frac{v}{k'+v}\Big) = J_2, \\
\epsilon\frac{dv}{dt} + Fv + \kappa\Big(\frac{v}{k'+v} - \frac{u}{k+u}\Big) + \kappa_a\Big(\frac{v}{k'+v} - \frac{q}{k_a+q}\Big) = FL,
\end{gathered}$$

where all the constants are nonnegative. In this model, the intracellular compartment splits into neurons and astrocytes. It also includes transports through cell membranes and a direct transport from capillary to intracellular astrocytes. We refer the reader to [4] for more details. It would also be interesting to construct and study corresponding PDE's models.

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