Global existence of classical solutions to a combined chemotaxis–haptotaxis model with logistic source

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1. Introduction

Recently, there is an increasing biological interest in mathematical modelling of cancer invasion (see [2,3,9,18,21,22]), and the qualitative analysis of cancer invasion models is mathematically and biologically interesting and challenging (see [7,16,21,23,27]).

Cancer invasion is associated with the degradation of the extracellular matrix (ECM), which is degraded by matrix degrading enzymes (MDEs) secreted by tumor cells. The degradation creates spatial gradients which direct the migration of invasive cells either by a mechanism termed chemotaxis (cellular locomotion directed in response to a concentration gradient of the diffusible MDE) or by a mechanism termed haptotaxis (cellular locomotion directed in response to a concentration gradient of the non-diffusible adhesive molecules within extracellular matrix). Chaplain and Lolas [2,3] proposed a PDE model describing interactions between tumor cells, matrix degrading enzymes and the host tissue (ECM). The model considers the competition between the following three biological mechanisms: chemotaxis, haptotaxis and logistic cell growth.

The classical chemotaxis model may be first proposed in 1970 by Keller and Segel (see [13]) and it has been greatly extended and studied in the last two decades (see [4,5,8,12,17,19,24–26] and the references cited therein). The interesting feature of Keller–Segel types of models is the possibility of blow-up of solutions in finite time, which strongly depends on the space dimension (see [10,11,20], for instance). Some recent studies show that the large nonlinear diffusion function (see [14]), the nonlinear chemotactic sensitivity function (see [12]) and the logistic growth term (see [26]) may prevent the blow-up of solutions. The classical chemotaxis model has also been extended by Chaplain and Lolas [2,3] to a chemotaxis–haptotaxis model describing tumor invasion of tissue.

In qualitative analysis of the model, the $L^p$-estimate techniques for the haptotactic term and the chemotactic term are quite different (see [23,27]), since ECM density satisfies an ODE whereas MDE concentration satisfies a PDE. Therefore, the
2. Mathematical model

The mathematical model of cancer invasion is involved in the following three key physical variables: the cancer cell density \( c(x, t) \), the extracellular matrix density \( v(x, t) \) and the matrix degrading enzyme concentration \( u(x, t) \). The equations describing the dynamics of each variable read as follows [2,3,23]:

\[
\frac{\partial c}{\partial t} = \nabla \cdot (D_c \nabla c) - \nabla \cdot (\chi c \nabla v) - \nabla \cdot (\xi c \nabla v) + \mu c(1 - c - v),
\]

(2.1)

\[
\frac{\partial v}{\partial t} = - \delta uv, \quad \text{proteolysis}
\]

(2.2)

\[
\frac{\partial u}{\partial t} = \nabla \cdot (D_u \nabla u) + \alpha c - \beta u, \quad \text{production-decay}
\]

(2.3)

where \( D_c, \delta, D_u, \alpha \) and \( \beta \) are assumed to be positive constants, and \( \chi, \xi \) and \( \mu \) are assumed to be non-negative constants. In Eq. (2.1), the migration of cancer cells is assumed to be governed by random motion, chemotaxis and haptotaxis; cancer cell proliferation satisfies a logistic law accounting for the competition for space. In Eq. (2.2), since ECM is “static”, we neglect any diffusion and focus solely on its degradation by MDEs upon contact; for simplicity, we assume that no remodelling of the ECM takes place, as done in [22,23,27]. In Eq. (2.3), the MDE concentration is assumed to be influenced by diffusion, production and decay; specifically, MDE is produced by cancer cells, diffuses throughout ECM, and undergoes decay through simple degradation.

The equations are considered on some bounded domain \( \Omega \subset \mathbb{R}^d \) (\( d = 1, 2, \text{or } 3 \)) with boundary \( \partial \Omega \). To close the system of equations, we need to impose boundary and initial conditions.

**Boundary conditions:** Guided by the in vitro experimental protocol in which invasion takes place within an isolated system, we assumed that there is no-flux of cancer cells or MDEs across the boundary of the domain,

\[
-D_c \frac{\partial c}{\partial v} + \chi c \frac{\partial u}{\partial v} + \xi c \frac{\partial v}{\partial v} = 0 \quad \text{on } \partial \Omega \times (0, T),
\]

(2.4)

\[
\frac{\partial u}{\partial v} = 0 \quad \text{on } \partial \Omega \times (0, T),
\]

(2.5)

where \( v \) is the outward normal vector to \( \partial \Omega \).

**Initial conditions:** We prescribe the initial data

\[
c(x, 0) = c_0(x), \quad v(x, 0) = v_0(x), \quad u(x, 0) = u_0(x), \quad x \in \Omega.
\]

(2.6)

For any \( 0 < T \leq \infty \) we set

\[
\Omega_T = \Omega \times [0, T), \quad \partial \Omega_T = \partial \Omega \times [0, T).
\]

To simplify the formulæ, throughout this paper we suppose

\[
D_c = \delta = D_u = \alpha = \beta = 1.
\]

However, we will keep the model parameters \( \chi, \xi \) and \( \mu \), since our analysis will focus on dealing with the chemotactic term, the haptotactic term and the logistic growth term. Introduce the variable transformation:

\[
a = ce^{-\xi v}.
\]

(2.7)

In terms of the variables \( a, v \) and \( u \), Eqs. (2.1)–(2.6) take the following form [23]:

Lemma 3.1. Then there holds

\[
\frac{\partial a}{\partial t} = e^{\varepsilon y} \nabla \cdot (e^{\varepsilon y} \nabla a) - e^{\varepsilon y} \nabla \cdot (\chi e^{\varepsilon y} a \nabla u) + \varepsilon a u v + \mu a (1 - e^{\varepsilon y} a - v) \quad \text{in } \Omega_T,
\]

(2.8)

\[
\frac{\partial v}{\partial t} = -uv \quad \text{in } \Omega_T,
\]

(2.9)

\[
\frac{\partial u}{\partial t} = \Delta u + e^{\varepsilon y} a - u \quad \text{in } \Omega_T,
\]

(2.10)

\[
\frac{\partial a}{\partial t} = \frac{\partial u}{\partial v} = 0 \quad \text{on } \partial \Omega_T,
\]

(2.11)

where \(a(0, \Omega) \geq 0, \quad u(0, \Omega) \geq 0, \quad 0 \leq v(0, \Omega) \leq 1, \quad \partial \Omega \in C^{2+\sigma}, \quad \sigma = 1/5, \quad a_0(\Omega), u_0(\Omega), v_0(\Omega) \in C^2(\overline{\Omega}), \quad \frac{\partial a_0(\Omega)}{\partial v} = \frac{\partial a_0(\Omega)}{\partial v} = 0 \quad \text{on } \partial \Omega.
\]

We hereby have the following local existence result [23]:

Theorem 2.1. Under assumption (2.13), there exists a unique solution \((a, v, u) \in C^{2+\sigma}(\Omega_T)\) of the system (2.8)–(2.12) for some small \(T > 0\) which depends on \(\|u_0(\Omega), v_0(\Omega), u_0(\Omega)\|_{C^{2+\sigma}(\Omega)}\).

3. Global existence in 2 dimensions

For convenience of notations, throughout this paper we denote various constants which are independent of \(T\) by \(A_0\).

We shall need the following Gagliardo–Nirenberg’s interpolation inequality [6,12]:

\[
\|u\|_{L^p(\Omega)} \leq A_0 \|u\|_{H^1(\Omega)}^{\theta} \|u\|_{L^1(\Omega)}^{1-\theta} \quad \text{for } u \in H^1(\Omega),
\]

where \(p, q \geq 1, \quad p(d-q) < dq, \quad r \in (0, p)\) and

\[
\theta = \frac{d}{p} - \frac{d}{q} + \frac{d}{r} \in (0, 1).
\]

We shall also need the following interpolation inequality proved by Biler et al. [1]:

\[
\|u\|_{L^3(\Omega)}^3 \leq e \|u\|_{H^1(\Omega)}^2 \left( (u+1) \log(u+1) \right) \|u\|_{L^1(\Omega)} + p(e^{-1}) \|u\|_{L^1(\Omega)}
\]

for \(u \geq 0\) and \(u \in H^1(\Omega), \) where \(e > 0\) is any number, and \(p(\cdot)\) is some increasing function.

To continue the local solution established in Theorem 2.1 to all \(t > 0\), we need to establish some \textit{a priori} estimates.

Lemma 3.1. (See [23].) There hold

\[
a \geq 0, \quad u \geq 0, \quad 0 \leq v \leq 1.
\]

Lemma 3.2. (See [23].) There hold

\[
\|a\|_{L^1(\Omega)} \leq \max(\|c_0\|_{L^1(\Omega)}, |\Omega|),
\]

(3.2)

\[
\|u\|_{L^1(\Omega)} \leq \|u_0\|_{L^1(\Omega)} + \max(\|c_0\|_{L^1(\Omega)}, |\Omega|),
\]

(3.3)

where \(|\Omega|\) denotes the Lebesgue measure of the domain \(\Omega\).

Up to now we have had the \(L^1(\Omega)\)-estimate of solutions. In the following we shall raise the regularity estimate to \(L^3(\Omega_T)\).

Lemma 3.3. Assume that \(d = 2\). Moreover,

\[
\mu > 0.
\]

Then there holds

\[
\|c\|_{L^3(\Omega_T)} \leq A.
\]

(3.4)
Proof. The proof is divided into the following six steps.

Step 1: Estimate $\|c\|_{L^2(\Omega_T)}^2$. Integrate Eq. (2.1) in $\Omega \times [0, t]$ $(t \leq T)$ and use the no-flux boundary condition (2.4). One obtains

$$\int_\Omega c \, dx - \int_\Omega c_0 \, dx = \mu \int_0^t \int_\Omega c^2 \, dx \, ds - \mu \int_0^t \int_\Omega cv \, dx \, ds.$$

Further, using assumption (3.4) and estimates (3.1) and (3.2), one obtains

$$\int_0^t \|c(s)\|_{L^2}^2 \, ds \leq A. \quad (3.5)$$

Step 2: Estimate $\|\Delta_1 u\|_{L^2(\Omega_T)}^2$. Multiply Eq. (2.3) by $\Delta_1 u$, integrate the product in $\Omega$, and use the no-flux boundary condition (2.5). Then

$$\frac{1}{2} \frac{d}{dt} \int_\Omega |\nabla u|^2 \, dx + \frac{1}{2} \int_\Omega |\Delta_1 u|^2 \, dx + \int_\Omega |\nabla u|^2 \, dx = - \int_\Omega c \Delta_1 u \, dx.$$

Cauchy’s inequality allows to write

$$\frac{1}{2} \frac{d}{dt} \int_\Omega |\nabla u|^2 \, dx + \frac{1}{2} \int_\Omega |\Delta_1 u|^2 \, dx + \int_\Omega |\nabla u|^2 \, dx \leq \frac{1}{2} \int_\Omega |c(t)|_{L^2}^2. \quad (3.6)$$

which gives

$$\frac{1}{2} \frac{d}{dt} \int_\Omega |\nabla u|^2 \, dx + \int_\Omega |\nabla u|^2 \, dx \leq \frac{1}{2} \|c(t)\|_{L^2}^2.$$

This, together with Gronwall’s lemma and estimate (3.5), yields

$$\int_\Omega |\nabla u(t)|^2 \, dx \leq A. \quad (3.7)$$

Similarly, multiplying Eq. (2.3) by $u$, and integrating the product in $\Omega$, one obtains

$$\int_\Omega |u(t)|^2 \, dx \leq A. \quad (3.8)$$

Integrating both sides of inequality (3.6) in $[0, t]$ $(t \leq T)$, and using estimates (3.5) and (3.7), one obtains

$$\int_0^t \|\Delta u(s)\|_{L^2}^2 \, ds \leq A. \quad (3.9)$$

Step 3: Estimate $\|\Delta v\|_{L^2(\Omega_T)}^2$. Note that Eq. (2.2) can be rewritten as

$$v(x, t) = v_0(x)e^{-\int_0^t u(x, s) \, ds} \quad (3.10)$$

and therefore

$$\nabla v = e^{-\int_0^t u(x, s) \, ds} \nabla v_0 = v_0(x)e^{-\int_0^t u(x, s) \, ds} \int_0^t \nabla u \, ds, \quad (3.11)$$

$$\Delta v = e^{-\int_0^t u(x, s) \, ds} \Delta v_0 - 2e^{-\int_0^t u(x, s) \, ds} \int_0^t \nabla u \cdot \nabla v_0 \, ds + v_0(x)e^{-\int_0^t u(x, s) \, ds} \left( \int_0^t \nabla u \, ds \right)^2$$

$$- v_0(x)e^{-\int_0^t u(x, s) \, ds} \int_0^t \Delta u \, ds. \quad (3.12)$$

Using estimates (3.1) and (3.7), one obtains from (3.11) that
\[
\int_{\Omega} |\nabla v(t)|^2 \, dx \leq A. \tag{3.13}
\]

Applying the aforementioned Gagliardo–Nirenberg’s inequality with \( p = 4, \, q = r = d = 2 \) and \( \theta = 1/2 \), and using estimate (3.7), one obtains
\[
\|\nabla u\|_{L^4(\Omega)} \leq A_0 \|u\|_{H^1(\Omega)}^{1/2} \|\nabla u\|_{L^2(\Omega)}^{1/2} \leq A \|u\|_{H^1(\Omega)}^{1/2}.
\]

This, together with Gronwall’s lemma and estimates (3.5), (3.9) and (3.15), yields
\[
\int_0^t \|\nabla u(s)\|_{L^4}^4 \, ds \leq A \int_0^t \|u(s)\|_{H^1}^2 \, ds \leq A. \tag{3.14}
\]

Finally, using estimates (3.1), (3.7), (3.9) and (3.14), one derives from (3.12) that
\[
\int_0^t \|\Delta v(s)\|_{L^2}^2 \, ds \leq A. \tag{3.15}
\]

**Step 4: Estimate \( \| (c + 1) \log (c + 1) \|_{L^1(\Omega)} \).** Multiply Eq. (2.1) by \( \log (c + 1) \), integrate the product in \( \Omega \) and use the no-flux boundary condition (2.4). One obtains
\[
\frac{d}{dt} \int_\Omega \left[ (c + 1) \log (c + 1) - c \right] \Delta u \, dx + \int_\Omega \frac{1}{c + 1} |\nabla c|^2 \, dx = \chi \int_\Omega \frac{1}{c + 1} \nabla v \cdot \nabla u \, dx + \xi \int_\Omega \frac{c}{c + 1} \nabla c \cdot \nabla v \, dx + \mu \int_\Omega c(1 - c - v) \log (c + 1) \, dx. \tag{3.16}
\]

Here, one observes that
\[
\int_\Omega \frac{c}{c + 1} \nabla c \cdot \nabla u \, dx = \int_\Omega \left[ \log (c + 1) - c \right] \Delta u \, dx, \tag{3.17}
\]
\[
\int_\Omega \frac{c}{c + 1} \nabla c \cdot \nabla v \, dx = \int_\Omega \left[ \log (c + 1) - c \right] \Delta v \, dx, \tag{3.18}
\]
in which we have used the boundary condition (2.5) and \( \frac{\partial u}{\partial n} |_{\partial \Omega} = 0 \) (which is derived from Eq. (3.11), the boundary condition (2.5) and \( \frac{\partial v}{\partial n} |_{\partial \Omega} = 0 \) in assumption (2.13)). On the other hand, one observes that
\[
\int_\Omega \left[ \log (c + 1) - c \right] \Delta u \, dx \leq A_0 \left( \| \Delta u(t) \|_{L^2}^2 + \| c(t) \|_{L^2}^2 \right), \tag{3.19}
\]
\[
\int_\Omega \left[ \log (c + 1) - c \right] \Delta v \, dx \leq A_0 \left( \| \Delta v(t) \|_{L^2}^2 + \| c(t) \|_{L^2}^2 \right), \tag{3.20}
\]
\[
\int_\Omega c(1 - c - v) \log (c + 1) \, dx \leq \int_\Omega c \log (c + 1) \, dx \leq \int_\Omega \left[ (c + 1) \log (c + 1) - c \right] \, dx + \| c \|_{L^1(\Omega)}
\]
\[
\leq \int_\Omega \left[ (c + 1) \log (c + 1) - c \right] \, dx + A_0, \tag{3.21}
\]
in which we have used the basic inequality: \( \log (1 + c) \leq c \) for any \( c \geq 0 \) in derivation of estimates (3.19) and (3.20), and we have used estimates (3.1) and (3.2) in derivation of estimate (3.21). Taking into account all above estimates, one obtains from (3.16) that
\[
\frac{d}{dt} \int_\Omega \left[ (c + 1) \log (c + 1) - c \right] \, dx + \int_\Omega \frac{1}{c + 1} |\nabla c|^2 \, dx \leq \int_\Omega \left[ (c + 1) \log (c + 1) - c \right] \, dx + A_0 \left( \| \Delta u(t) \|_{L^2}^2 + \| \Delta v(t) \|_{L^2}^2 + \| c(t) \|_{L^2}^2 \right) + A_0. \tag{3.22}
\]

This, together with Gronwall’s lemma and estimates (3.5), (3.9) and (3.15), yields
\[
\int_\Omega \left[ (c + 1) \log (c + 1) - c \right] \, dx \leq A. \tag{3.23}
\]

Here we should note that \( (c + 1) \log (c + 1) - c \geq 0 \) for any \( c \geq 0 \).
Step 5: Estimate $\|\nabla c\|_{L^2(\Omega^T)}$. Multiply Eq. (2.1) by $c$, integrate the product in $\Omega$ and use the no-flux boundary condition (2.4). One obtains

$$\frac{1}{2} \frac{d}{dt} \int_{\Omega} c^2 dx + Dc \int_{\Omega} |\nabla c|^2 dx = \chi \int_{\Omega} c \nabla c \cdot \nabla u dx + \xi \int_{\Omega} c \nabla c \cdot \nabla v dx + \mu \int_{\Omega} c^2 (1 - c - v) dx. \quad (3.24)$$

Note that

$$\int_{\Omega} c \nabla c \cdot \nabla u dx = - \frac{1}{2} \int_{\Omega} c^2 \Delta u dx \quad (3.25)$$

by the boundary condition (2.5). This boundary condition, together with Eq. (3.11) and the assumption $\frac{\partial v_0(x)}{\partial n}|_{\partial \Omega} = 0$ in (2.13), yields the following boundary condition of $v$:

$$\frac{\partial v}{\partial n} \bigg|_{\partial \Omega_T} = 0,$$

and therefore

$$\int_{\Omega} c \nabla c \cdot \nabla v dx = - \frac{1}{2} \int_{\Omega} c^2 \Delta v dx. \quad (3.26)$$

We shall need the following interpolation inequality [6]

$$\|\Delta u\|_{L^1(\Omega^T)} \leq A_0 \|u\|_{H^3(\Omega)}^{2/3} \|u\|_{H^1(\Omega)}^{1/3} \quad \text{ for } u \in H^3(\Omega), \quad (3.27)$$

where $H^q(\Omega) := W^{q,2}(\Omega)$. Now we estimate $\int_{\Omega} c^2 \Delta u dx$:

$$\left| \int_{\Omega} c^2 \Delta u dx \right| \leq A_0 \|c\|_{L^3(\Omega)}^2 \|\Delta u\|_{L^1(\Omega)} \quad \text{(by Hölder’s inequality)}$$

$$\leq A_0 \|c\|_{L^3(\Omega)}^2 \|u\|_{H^1(\Omega)}^{2/3} \|u\|_{H^1(\Omega)}^{1/3} \quad \text{(by interpolation inequality (3.27))}$$

$$\leq A \|c\|_{L^3(\Omega)}^2 \|u\|_{H^1(\Omega)}^{2/3} \quad \text{(by estimates (3.7) and (3.8))}$$

$$\leq A \left[ \varepsilon \|c\|_{H^1(\Omega)}^2 + (c + 1) \log(c + 1) \right] \|c\|_{L^1(\Omega)} + p(\varepsilon^{-1}) \|c\|_{L^1(\Omega)}^2 \|u\|_{H^1(\Omega)} \quad \text{(by Biler et al. interpolation inequality)}$$

$$\leq A \left[ \varepsilon \|c\|_{H^1(\Omega)}^2 + p(\varepsilon^{-1}) \right]^{2/3} \|u\|_{H^1(\Omega)}^{2/3} \quad \text{(by estimates (3.23) and } \|c\|_{L^1(\Omega)} \leq A_0)$$

$$\leq \varepsilon \|u\|_{H^1(\Omega)}^2 + A \varepsilon^{-1/2} \|c\|_{H^1(\Omega)} \|u\|_{H^1(\Omega)} + p(\varepsilon^{-1}) \quad \text{(by the Young’s inequality)}$$

$$= \varepsilon \|u\|_{H^1(\Omega)}^2 + A \varepsilon^{-1/2} \|c\|_{H^1(\Omega)}^2 + A \varepsilon^{-1/2} p(\varepsilon^{-1}). \quad (3.28)$$

Similarly, one has

$$\left| \int_{\Omega} c^2 \Delta v dx \right| \leq \varepsilon \|v\|_{H^1(\Omega)}^2 + A \varepsilon^{1/2} \|c\|_{H^1(\Omega)}^2 + A \varepsilon^{-1/2} p(\varepsilon^{-1}). \quad (3.29)$$

On the other hand, by Young’s inequality,

$$\int_{\Omega} c^2 dx \leq \varepsilon \int_{\Omega} c^2 dx + A_0(\varepsilon)|\Omega|. \quad (3.30)$$

Taking into account all above estimates (3.24)–(3.30) and using assumption $\mu > 0$, one has

$$\frac{1}{2} \frac{d}{dt} \int_{\Omega} c^2 dx + Dc \int_{\Omega} |\nabla c|^2 dx \leq \varepsilon \left( \|u\|_{H^1(\Omega)}^2 + \|v\|_{H^1(\Omega)}^2 \right) + A \varepsilon^{-1/2} p(\varepsilon^{-1}) + A_0$$

$$\leq \varepsilon \left( \|\nabla u\|_{L^2(\Omega)}^2 + \|\nabla v\|_{L^2(\Omega)}^2 \right) + A \varepsilon^{-1/2} p(\varepsilon^{-1}) + A \quad (3.31)$$

for sufficiently small $\varepsilon > 0$. Here we used the facts that
\[ \|u\|_{H^1(\Omega)} \leq A_0(\|\nabla \Delta u\|_{L^2(\Omega)} + \|u\|_{H^1(\Omega)}) \quad \text{(for } u \in H^3(\Omega) \text{ with } \frac{\partial u}{\partial \nu} \bigg|_{\partial \Omega} = 0) \]

and that
\[ \|v\|_{H^1(\Omega)} \leq A_0\|\nabla \Delta v\|_{L^2(\Omega)} + A \quad \text{(for } v \in H^3(\Omega) \text{ with } \frac{\partial v}{\partial \nu} \bigg|_{\partial \Omega} = 0). \]

Next, multiply Eq. (2.3) by \( \Delta u \) and integrate the products. Using integral by parts, one obtains
\[ \frac{1}{2} \frac{d}{dt} \int_{\Omega} |\Delta u|^2 \, dx + \int_{\Omega} \nabla \Delta u \cdot \nabla u \, dx = -\int_{\Omega} \nabla c \cdot \nabla \Delta u \, dx \]
\[ \leq \frac{1}{2} \int_{\Omega} |\nabla \Delta u|^2 \, dx + \frac{1}{2} \int_{\Omega} |\nabla c|^2 \, dx. \] (3.32)

Here we used the following compatible condition
\[ \frac{\partial \Delta u}{\partial \nu} \bigg|_{\partial \Omega} = 0. \] (3.33)

We note that by Eq. (2.3),
\[ \frac{\partial \nabla u}{\partial t} = \nabla (\Delta u) + \nabla c - \nabla u, \]
and the compatible condition on the boundary \( \partial \Omega \) should be
\[ \frac{\partial \Delta u}{\partial \nu} = \nabla (\Delta u) \cdot \nu = \frac{\partial}{\partial t} \left( \frac{\partial u}{\partial \nu} \right) - \frac{\partial c}{\partial \nu} + \frac{\partial u}{\partial \nu}. \] (3.34)

As aforementioned,
\[ \frac{\partial u}{\partial \nu} \bigg|_{\partial \Omega} = \frac{\partial v}{\partial \nu} \bigg|_{\partial \Omega} = 0. \] (3.35)

This, together with the boundary condition (2.4), yields
\[ \frac{\partial c}{\partial \nu} \bigg|_{\partial \Omega} = 0. \] (3.36)

Hence, we conclude from Eqs. (3.34)-(3.36) that the condition (3.33) holds.

We are now in a position to consider \( \|\nabla \Delta v\|_{L^2(\Omega)} \). We derive from (3.12) that
\[ \nabla \Delta v = e^{-\int_0^t u(x,s) \, ds} \left[ \nabla \Delta v_0 - \int_0^t \nabla u \, ds \nabla v_0 + 2 \int_0^t \nabla u \cdot \nabla v_0 \, ds - 2 \int_0^t \nabla (\nabla u \cdot \nabla v_0) \, ds \right. \]
\[ + \nabla v_0 \left( \int_0^t \nabla u \, ds \right)^2 + 3 v_0(\mathbf{x}) \int_0^t \nabla u \, ds \int_0^t \nabla u \, ds - v_0(\mathbf{x}) \int_0^t \nabla u \, ds \int_0^t \nabla u \, ds \int_0^t \nabla u \, ds \int_0^t \nabla u \, ds \right] \]
\[ \left. - \nabla v_0 \int_0^t \nabla u \, ds - v_0(\mathbf{x}) \int_0^t \nabla u \, ds \right]. \] (3.37)

This, together with assumption \( v_0(\mathbf{x}) \in C^2(\bar{\Omega}) \) (see (2.13)), estimate \( u \geq 0 \) (see (3.1)), and estimates (3.7), (3.9) and (3.14), yields
\[ \|\nabla \Delta v\|_{L^2(\Omega)}^2 \leq A + A \int_0^t |\nabla \Delta u|^2 \, dx \, ds. \] (3.38)

We now add inequality (3.32) to inequality (3.31) multiplied by \( 2/D_c \), use estimate (3.38) and take \( \varepsilon > 0 \) sufficiently small. One obtains
\[
\frac{d}{dt} \int_\Omega \left( \frac{1}{D_c} \partial_c^2 + \frac{1}{2} |\Delta u|^2 \right) dx + \frac{1}{4} \int_\Omega \left( |\nabla c|^2 + |\nabla \Delta u|^2 \right) dx \leq A \varepsilon \int_0^t \int_\Omega |\nabla \Delta u|^2 dx ds + A \varepsilon^{-1/2} p(\varepsilon^{-1}) + A. \tag{3.39}
\]

Integrating with respect to variable \( t \) in both sides of above inequality, one obtains

\[
\int_\Omega \left( \frac{1}{D_c} \partial_c^2 + \frac{1}{2} |\Delta u|^2 \right) dx + \frac{1}{4} \int_0^T \int_\Omega |\nabla c|^2 dx dt + \left( \frac{1}{4} - AT \varepsilon \right) \int_0^T \int_\Omega |\nabla \Delta u|^2 dx dt \leq A \varepsilon^{-1/2} p(\varepsilon^{-1}) + A. \tag{3.40}
\]

Taking \( \varepsilon > 0 \) sufficiently small such that \( \left( \frac{1}{4} - AT \varepsilon \right) \geq 0 \), one derives from inequality (3.40) that

\[
\int_0^T \int_\Omega |\nabla c|^2 dx dt \leq A. \tag{3.41}
\]

**Step 6: Estimate \( \|c\|_{L^1(\Omega_T)} \).** Applying the aforementioned Gagliardo–Nirenberg’s inequality with \( p = 3, q = d = 2, r = 1 \) and \( \theta = 2/3 \), and using estimate (3.2), one obtains

\[
\|c(t)\|_{L^1(\Omega_T)} \leq A_0 \|c(t)\|_{W^{1,2}(\Omega)}^{2/3} \|c(t)\|_{L^1(\Omega_T)}^{1/3} \leq A_0 \|c(t)\|_{W^{1,2}(\Omega)}^{2/3}.
\]

Thus, using estimate (3.5) and (3.41), one obtains

\[
\int_0^T \|c(s)\|_{L^1(\Omega_T)} ds \leq A_0 \int_0^T \|c(t)\|_{W^{1,2}(\Omega)}^{2} ds \leq A.
\]

This completes the proof of Lemma 3.3. \( \square \)

**Lemma 3.4.** Assume that \( d = 2 \) and \( \mu > 0 \). Then there holds

\[
\|(a, v, u)\|_{C^{1+\sigma, 1+\sigma/2}_{x, t} (\Omega_T)} \leq A
\]

where \( \sigma = 1/5 \).

**Proof.** Eq. (2.10) can be rewritten as

\[
\frac{\partial u}{\partial t} - \Delta u + u = c,
\]

where by Lemma 3.3 we have

\[
\|c\|_{L^3(\Omega_T)} \leq A. \tag{3.43}
\]

Using estimate (3.43) and proceeding as in the proof of Lemma 4.4 in [23], we can further raise the regularity estimate of \( c \) from \( L^3(\Omega_T) \) to \( L^4(\Omega_T) \), and then to \( L^5(\Omega_T) \); \( \|u\|_{W^{2,1}_s(\Omega_T)} \leq A \). Therefore, by the parabolic \( L^p \) estimates [15] we have

\[
\|u\|_{W^{2,1}_s(\Omega_T)} \leq A. \tag{3.44}
\]

By (2.9) and (2.12) we get

\[
v(x, t) = v_0(x)e^{-\int_0^t u(x, \tau) d\tau}.
\]

Using assumption (2.13), estimates (3.1) and (3.44), we obtain from (3.45) that

\[
\|v\|_{W^{2,1}_s(\Omega_T)} \leq A. \tag{3.46}
\]

By the Sobolev imbedding theorem (see [15, Lemma 3.3, p. 80]), we derive from estimates (3.44) and (3.46) that

\[
\|\nabla u\|_{C^{\sigma, \sigma/2}_{x, t} (\Omega_T)}, \quad \|\nabla v\|_{C^{\sigma, \sigma/2}_{x, t} (\Omega_T)} \leq A, \tag{3.47}
\]

where \( \sigma = 1 - \frac{d+2}{2} = 1/5 \), and therefore

\[
\|\nabla u\|_{L^\infty(\Omega_T)}, \quad \|\nabla v\|_{L^\infty(\Omega_T)} \leq A. \tag{3.48}
\]
Now, Eq. (2.8) can be rewritten as in the following non-divergence form:

\[
\frac{\partial a}{\partial t} - \Delta a - (\xi \nabla v - \chi \nabla u) \cdot \nabla a + \left[ \chi \xi \nabla u \cdot \nabla v + \chi \Delta u - \xi uv - \mu (1 - c - v) \right] a = 0,
\]  
(3.49)

where

\[
\|\xi \nabla v - \chi \nabla u\|_{L^\infty(\Omega_T)} \leq A, 
(3.50)
\]

\[
\|\chi \xi \nabla u \cdot \nabla v + \chi \Delta u - \xi uv - \mu (1 - c - v)\|_{L^5(\Omega_T)} \leq A
(3.51)
\]

by estimates (3.1), (3.43), (3.44) and (3.48). By Eq. (3.49), estimates (3.50), (3.51) and the parabolic \(L^p\) estimates we then have

\[
\|a\|_{W^{2,1(\Omega_T)}} \leq A.
(3.52)
\]

By estimate (3.52) and the Sobolev imbedding theorem,

\[
\|a\|_{C^{\sigma,\sigma/2(x,t)}}(\Omega_T) \leq A.
(3.53)
\]

Also, the Sobolev imbedding theorem, together with estimates (3.44) and (3.46), yields

\[
\|u\|_{C^{\sigma,\sigma/2(x,t)}}(\Omega_T) \leq A, \quad \|v\|_{C^{\sigma,\sigma/2(x,t)}}(\Omega_T) \leq A.
(3.54)
\]

Now, from Eqs. (2.10)–(2.12), estimates (3.53) and (3.54) and the parabolic Schauder estimates we have

\[
\|u\|_{C^{2+\sigma,1+\sigma/2(x,t)}}(\Omega_T) \leq A,
(3.55)
\]

and therefore, by Eq. (3.45),

\[
\|v\|_{C^{2+\sigma,1+\sigma/2(x,t)}}(\Omega_T) \leq A
(3.56)
\]

Finally, we conclude from Eq. (3.49), estimates (3.53), (3.55) and (3.56), Eqs. (2.11), (2.12) and the parabolic Schauder estimates that

\[
\|a\|_{C^{2+\sigma,1+\sigma/2(x,t)}}(\Omega_T) \leq A.
(3.57)
\]

This completes the proof of Lemma 3.4. \(\square\)

A priori estimate (3.42) allows us to continue the local solution in Theorem 2.1 step-by-step to all \(t > 0\), as done in [7,23]. Thus, we have the following theorem:

**Theorem 3.5.** Assume that \(d = 2\) and \(\mu > 0\). Then there exists a unique global solution \((a, v, u) \in C^{2+\sigma,1+\sigma/2}(\Omega_\infty)\) of the system (2.8)–(2.13).

4. Summary

In this paper we have studied global existence and uniqueness of classical solutions to a combined chemotaxis–haptotaxis model describing cancer invasion of tissue. On this taxis model, we have the following analytical results:

(i) In 1 dimension, there exists a unique global classical solution for \(\mu \geq 0\) (see [23]);
(ii) In 2 dimensions, there exists a unique global classical solution for \(\mu > 0\), which has just been proven by this paper;
(iii) In 3 dimensions, there exists a unique global classical solution for large \(\mu\) (compared with the chemotactic coefficient \(\chi\)) (see [23]).

Note that the solution might blow up for \(\mu = 0\) in 2 dimensions (see [23]). Therefore, the analytical result of this paper shows that the logistic growth term prevents the blow-up of solutions in 2 dimensions. The \(L^p\)-estimate techniques developed in this paper are quite different from those in [23], and this paper improved greatly our previous results in [23] in 2 dimensions. Since our analysis strongly depends on space dimensions, the following problem is very interesting and challenging:

**Open problem.** Study the global existence or blow-up of solutions to the model (2.1)–(2.6) for small \(\mu > 0\) in 3 dimensions.
References