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BOUNDEDNESS OF SOLUTIONS OF A HAPTOTAXIS MODEL

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In this paper we prove the existence of global solutions of the haptotaxis model of cancer invasion for arbitrary non-negative initial conditions. Uniform boundedness of the solutions is shown using the method of bounded invariant rectangles applied to the reformulated system of reaction-diffusion equations in divergence form with a diagonal diffusion matrix. Moreover, the analysis of the model shows how the structure of kinetics of the model is related to the growth properties of the solutions and how this growth depends on the ratio of the sensitivity function (describing the size of haptotaxis) and the diffusion coefficient. One of the implications of our analysis is that in the haptotaxis model with a logistic growth term, cell density may exceed the carrying capacity, which is impossible in the classical logistic equation and its reaction-diffusion extension.

Keywords: Haptotaxis; chemotaxis model; boundedness of solutions.

AMS Subject Classification: 35B30, 35B45, 35B35, 35K55, 35Q80

1. Introduction

Recently, a number of studies were published concerning mathematical models for cancer invasion, see for example Refs. 1, 2, 4, 5, 18, 32 and 28. Many of these papers examine the spread of cancer cells using systems of partial differential equations with cancer cell migration governed by random motility, i.e. diffusion, and the directed response of the cells to extracellular matrix (ECM) gradients, i.e. haptotaxis. In such model it is usually assumed that haptotaxis occurs when cells respond to gradients of non-diffusible molecules and migrate towards their higher concentrations. The ECM gradients are assumed to be created when the ECM is degraded by the matrix degrading enzymes (MDEs) secreted by cancer cells.

The generic mathematical model of this process has the form:

$$\partial_t u = D_u \Delta u - \nabla \cdot (\chi(v) u \nabla v) + F_1(u, v, m), \tag{1.1}$$

$$\partial_t v = F_2(v, m), \tag{1.2}$$

$$\partial_t m = D_m \Delta m + F_3(u, v, m) \tag{1.3}$$

with $(t, x) \in (0, T) \times \Omega$, non-negative initial conditions and zero-flux boundary conditions.

This system was proposed by Anderson and colleagues,[1] to model the interactions between the cancer cells and the surrounding tissue in the initial, avascular stage of growth of a solid tumor. The three partial differential equations describe the evolution in time and space of cancer cell density (denoted by u), the extracellular matrix protein density (denoted by v) and the matrix degrading enzyme concentration (denoted by m). The two key factors governing migration of cancer cells during invasion are random motion and haptotaxis. In addition to migration, the model includes a term describing cell growth (proliferation and death) expressed by a kinetics function F_1.

Function χ is called the sensitivity function and describes the sensitivity of the cancer cells to the gradient of the ECM (strength of haptotaxis). The rate of haptotaxis is assumed to depend on the density of the ECM and is generally chosen as a decreasing positive function reflecting the observation that sensitivity is lower for higher densities of the ECM, which is a saturation effect. Using the derivation based on kinetic analysis of a model mechanism for binding dynamics of the extracellular ligand to a cell-surface receptor, Sherratt,[30] proposed the following sensitivity function:

$$\chi(v) = \frac{\chi}{(\alpha_0 + \beta_0 v)^2}, \tag{1.4}$$

where $\chi \geq 0$ and $\alpha_0, \beta_0 > 0$.

The dynamics of the ECM is modeled using an ordinary differential equation, assuming that there is neither spatial transport of the ECM nor its remodeling and that the ECM is degraded upon contact with the matrix degrading enzyme (MDE) secreted by the cancer cells at the rate $F_2(v, m) = -\alpha v m$. The spatio-temporal evolution of the concentration of the MDE is assumed to occur through diffusion, production depending on interaction between cancer cells and the ECM, and loss through simple degradation, $F_3(u, v, m) = -\delta_m m + \mu_m u v$.

This model belongs to the wide class of the so-called chemotaxis models (for review see Refs. 13, 12 and references therein). There exists a vast literature concerning mathematical analysis of different reaction-diffusion-taxis models. In the case of chemotaxis the cells follow the gradient of the diffusible chemical, which is produced by themselves, as it is the case in classical Keller–Segel model, or by the external source, see e.g. Ref. 16. It is well known that in the classical chemotaxis model solutions may exhibit singularities in finite time, such as explosions, see e.g. Refs. 15 and 25.

In the case of haptotaxis the movement of cells follows the gradient of the non-diffusible molecules, which is degraded by cells. In the model of haptotaxis numerical simulations indicate the existence of bounded solutions, see e.g. Ref. 32. The aim of this work is to check if indeed the solutions of the model of haptotaxis are uniformly bounded and how these bounds depend on the reaction terms.

System of a similar structure, however with linear kinetics of the ECM, $F_3(u, v, m) = -\alpha m + \beta u$, constant sensitivity function χ, and considering only spatial transport of cancer cells, i.e. $F_1(u, v) = 0$, was studied by Morales-Rodrigo in Ref. 23. Local existence and uniqueness of the model solutions in Hölder spaces were shown using the Schauder fix-point theory.

Simplified system of two equations with cell kinetics $F_1(u, v) = 0$ was also analyzed by Corrias, Perthame and Zaag,[7,8] who derived L^p estimates and proved the existence of global weak solutions under the assumption that initial data are sufficiently small. In Ref. 33, a model with nonlocal cell kinetics $F_1(u, v)$, given by an integral term, was studied and the existence of global solutions was shown without imposing any smallness conditions on the initial data. Models similar to (1.1)−(1.3) have also been studied in Refs. 3, 17 and 24.

In this paper we study the model (1.1)−(1.3) with nonzero cell kinetics F_1 in the form of a logistic growth law accounting for the competition for space, i.e. $F_1(u, v) = \mu_u u(1 - u - v)$, as it was proposed for the modeling of cancer invasion in Ref. 1 and follow-up papers. We show that due to the structure of the kinetics system, the solutions of the model are uniformly bounded for arbitrary non-negative initial conditions. For non-negative initial conditions, we show the existence of a local weak solution, which is non-negative. Following a change of variables, we reformulate the model as a system of reaction-diffusion equations in divergence form with a diagonal diffusion matrix. Showing *a priori* estimates for the supremum norm and applying the method of bounded invariant rectangles to the reformulated system, we prove uniform boundedness of the model solution and the existence of the global solution. In addition, we show L^p regularity of the model solution, which implies uniqueness. The paper also includes the proof of higher regularity of the solutions. Analysis of the model shows how the structure of kinetics of the haptotaxis model is related to the growth properties of the model solution. Similar analysis can be performed for a simplified system consisting of two equations. In this case a proof of boundedness of model solutions in a two-dimensional domain is also presented.

2. Problem Setting

We consider a rescaled system of equations,

$$\partial_t u = D_u \Delta u - \nabla \cdot (\chi(v) u \nabla v) + \mu_u u(1 - u - v), \tag{2.1}$$

$$\partial_t v = -\alpha m v, \tag{2.2}$$

$$\partial_t m = D_m \Delta m - \delta_m m + \mu_m u v, \tag{2.3}$$

defined in a bounded domain $(0, T) \times \Omega$ with $\partial\Omega \subset C^2$, $n = \dim \Omega \leq 3$, with initial conditions

$$u(0, x) = u_0(x), \quad v(0, x) = v_0(x), \quad m(0, x) = m_0(x), \tag{2.4}$$

and boundary conditions

$$\begin{aligned} (D_u \nabla u - \chi(v) u \nabla v) \cdot \nu = 0, \\ D_m \nabla m \cdot \nu = 0. \end{aligned} \tag{2.5}$$

In the remainder of this work we assume that the diffusion coefficients $D_u > 0$, $D_m > 0$ and rates of reaction terms $\mu_u > 0$, $\alpha > 0$, $\mu_m \geq 0$ and $\delta_m > 0$ are constant.

Remark 2.1. The results of this paper can be extended to the model with space and time dependent parameters fulfilling certain regularity assumptions.

Definition 2.1. The triple (u, v, m) is called a weak solution of the model (2.1)–(2.3) with initial conditions (2.4) and boundary conditions (2.5), if $u, v, m \in L^2(0, T; H^1(\Omega))$, $u, v \in L^\infty((0, T) \times \Omega)$, $u_t, v_t, m_t \in L^2((0, T) \times \Omega)$ such that

$$\int_0^T \int_\Omega (u_t \varphi_1 + D_u \nabla u \cdot \nabla \varphi_1 - \chi(v) u \nabla v \cdot \nabla \varphi_1)\, dx dt = \int_0^T \int_\Omega \mu_u u(1 - u - v) \varphi_1 \, dx dt,$$

$$\int_0^T \int_\Omega (v_t \varphi_2 + \alpha m v \varphi_2)\, dx dt = 0,$$

$$\int_0^T \int_\Omega (m_t \varphi_3 + D_u \nabla m \cdot \nabla \varphi_3 + \delta_m m \varphi_3)\, dx dt = \int_0^T \int_\Omega \mu_m u v \varphi_3 \, dx dt$$

for all $\varphi_1 \in L^2(0, T; H^1(\Omega))$, $\varphi_2 \in L^2((0, T) \times \Omega)$, $\varphi_3 \in L^2(0, T; H^1(\Omega))$, and u, v, m satisfy initial conditions (2.4), i.e. $u \to u_0$, $v \to v_0$, $m \to m_0$ in $L^2(\Omega)$ as $t \to 0$.

To investigate the existence and boundedness of model solutions, we change the variables so that we obtain an equivalent system with the first equation expressed in a divergence form with a diagonal diffusion matrix, similar as in Ref. 7. Substituting $s = \frac{u}{\phi(v)}$, where $\phi(v)$ is a function such that for all $v > 0$, $D_u \phi' = \phi(v)\chi(v)$ and $\phi(0) = 1$, we rewrite system (2.1)–(2.5) in the following form:

$$\phi(v) \partial_t s = D_u \nabla \cdot (\phi(v) \nabla s) + s\phi(v) \left(\alpha \frac{\chi(v)}{D_u} v m + \mu_u - \mu_u s \phi(v) - \mu_u v \right), \tag{2.6}$$

$$\partial_t v = -\alpha m v, \tag{2.7}$$

$$\partial_t m = D_m \Delta m - \delta_m m + \mu_m s \phi(v) v, \tag{2.8}$$

$$s(0, x) = s_0(x) = u_0/\phi(v_0), \quad v(0, x) = v_0(x), \quad m(0, x) = m_0(x), \tag{2.9}$$

$$D_u \phi(v) \nabla s \cdot \nu = 0, \quad D_m \nabla m \cdot \nu = 0. \tag{2.10}$$

Function $\phi(v)$ can be explicitly computed and is given by

$$\phi(v) = \exp\left(\frac{1}{D_u} \int_0^v \chi(v') dv' \right). \tag{2.11}$$

From (2.11) follows that $\phi(v) \geq 1$ for all $v \geq 0$.

A system of two equations of similar structure as (2.6) and (2.7), i.e. consisting of a nonlinear parabolic equation and an ordinary differential equation, was considered in Ref. 10, where the existence of a unique global solution in $L^\infty(0,T;W^{2,p}(\Omega))$ was shown under the assumption that the solution was bounded. In addition, L^p estimates similar to those for chemotaxis equations in Ref. 7 were derived. In the next step we show the existence of local weak solutions of the system (2.6)–(2.10) in the following sense:

Definition 2.2. The triple (s, v, m) is called a weak solution of the model (2.6)–(2.8) with initial conditions (2.9) and boundary conditions (2.10), if $s, v, m \in L^2(0,T;H^1(\Omega))$, $v \in L^\infty((0,T)\times\Omega)$, $s_t, v_t, m_t \in L^2((0,T)\times\Omega)$ such that

$$\begin{aligned}\int_0^T\int_\Omega (\phi(v)\partial_t s\varphi_1 + D_u\phi(v)\nabla s\cdot\nabla\varphi_1)\,dxdt \\ = \int_0^T\int_\Omega s\phi(v)\alpha\frac{\chi(v)}{D_u}vm\varphi_1\,dxdt \\ + \int_0^T\int_\Omega s\phi(v)\mu_u(1-s\phi(v)-v)\varphi_1\,dxdt,\end{aligned} \tag{2.12}$$

$$\int_0^T\int_\Omega (\partial_t v\varphi_2 + \alpha m v\varphi_2)\,dxdt = 0, \tag{2.13}$$

$$\int_0^T\int_\Omega (\partial_t m\varphi_3 + D_m\nabla m\cdot\nabla\varphi_3 + \delta_m m\varphi_3)\,dxdt = \int_0^T\int_\Omega \mu_m s\phi(v)v\varphi_3\,dxdt \tag{2.14}$$

for all $\varphi_1 \in L^2(0,T;H^1(\Omega))$, $\varphi_2 \in L^2((0,T)\times\Omega)$, $\varphi_3 \in L^2(0,T;H^1(\Omega))$, and s, v, m satisfy initial conditions (2.9), i.e. $s \to s_0$, $v \to v_0$, $m \to m_0$ in $L^2(\Omega)$ as $t \to 0$.

Notice that the assumption $s \in L^2(0,T;H^1(\Omega))$ implies that $D_u\nabla u - \chi(v)u\nabla v \in L^2((0,T)\times\Omega)$. Moreover, if u and v are bounded, then the existence of weak solutions of the reformulated system in the sense of Definition 2.2 is equivalent to the existence of weak solutions of the original system in the sense of Definition 2.1.

3. Main Results

In this section the main theorems of the paper are formulated. First, using Schauder fix-point theorem we prove a local existence of solutions of (2.6)–(2.10).

Theorem 3.1. *For $s_0 \geq 0$, $m_0 \geq 0$, $v_0 \geq 0$, $s_0, v_0, m_0 \in H^1(\Omega)$, $v_0 \in L^\infty(\Omega)$ and a continuous and positive χ, there exists a local in time, non-negative weak solution of the system (2.6)–(2.10) (in the sense of Definition 2.2).*

Next, we show global existence and uniform boundedness of solutions using the method of bounded invariant rectangles.

Theorem 3.2. *For non-negative and bounded initial data, $u_0, v_0, m_0 \in H^1(\Omega)$ and a continuous and positive function χ, there exists a global solution of the system* (2.1)–(2.5), *in the sense of Definition* 2.1. *The solution is uniformly bounded.*

After showing additional regularity of global solutions of the system (2.1)–(2.5), i.e. $m \in L^q(0,T;W^{1,q}(\Omega))$ and $v \in L^\infty(0,T;W^{1,q}(\Omega))$, $q \geq n = \dim(\Omega)$, the uniqueness result is obtained.

Theorem 3.3. *Assume that*

(i) *the sensitivity function χ is a positive and continuous function on $[0,\infty)$ and is locally Lipschitz-continuous,*
(ii) *initial conditions satisfy $u_0, v_0, m_0 \in L^\infty(\Omega)$, $\nabla v_0, \nabla m_0 \in L^q(\Omega)$, where $q \geq n$, $n = \dim(\Omega)$, $\nabla u_0 \in L^2(\Omega)$ and $u_0 \geq 0$, $v_0 \geq 0$, $m_0 \geq 0$.*

Then, a weak solution of problem (2.1)–(2.5) *is unique. In addition, $v \in L^\infty(0,T;W^{1,q}(\Omega))$, $m \in L^q(0,T,W^{1,q}(\Omega))$, where $q \geq n = \dim(\Omega)$.*

Computations in the proofs of *a priori* estimates are carried for classical solutions of the regularized system. For details about regularization see the Appendix. Due to the lower semicontinuity of norms and density arguments on the data, *a priori* estimates also hold for the weak solutions of the original system.

4. Existence of a Local Solution

Local existence of solutions of the model is shown using a fix-point theorem. First, we show *a priori* estimates for solutions s and m of system (2.6)–(2.10).

Lemma 4.1. *For a continuous and positive χ, $\|v\|_{L^\infty((0,T)\times\Omega)} \leq C$, $v \geq 0$, $s \geq 0$, $s_0 \in L^2(\Omega)$, and $m_0 \in L^2(\Omega)$ the following estimates hold*:

$$\sup_{(0,T)} \|s\|^2_{L^2(\Omega)} + \|\nabla s\|^2_{L^2((0,T)\times\Omega)} + \|s\|^3_{L^3((0,T)\times\Omega)} \leq C\exp(C(\|v\|_{L^\infty((0,T)\times\Omega)})(T + \|m\|^4_{L^8(0,T;L^2(\Omega))}T^{\frac{1}{2}}))\|s_0\|^2_{L^2(\Omega)}, \tag{4.1}$$

$$\sup_{(0,T)} \|m\|^2_{L^2(\Omega)} + \|\nabla m\|^2_{L^2((0,T)\times\Omega)} \leq C\|m_0\|^2_{L^2(\Omega)} + C\left(\sup_{(0,T)\times\Omega} v\right)\|s\|^2_{L^2((0,T)\times\Omega)}. \tag{4.2}$$

Proof. Testing Eqs. (2.6) and (2.8) with s and m respectively, we obtain

$$\begin{aligned} &\frac{1}{2}\int_\Omega \partial_t(\phi(v)|s|^2)\,dx + \int_\Omega D_u\phi(v)\nabla s\nabla s\,dx \\ &\quad= \frac{1}{2}\int_\Omega \phi'\partial_t v|s|^2\,dx + \int_\Omega s^2\phi(v)\bigg(\alpha\frac{\chi(v)}{D_u}vm \\ &\qquad + \mu_u - \mu_u s\phi(v) - \mu_u v\bigg)\,dx, \\ &\frac{1}{2}\int_\Omega \partial_t|m|^2\,dx + \int_\Omega D_m\nabla m\nabla m\,dx + \int_\Omega \delta_m m^2\,dx \\ &\quad= \int_\Omega \mu_m s\phi(v)vm\,dx. \end{aligned} \tag{4.3}$$

Due to the boundedness of v, $\phi(v)$ is also bounded and s can be used as a test function in (2.6). Equation (2.7) and non-negativity of s and v yield

$$\begin{aligned}
\frac{1}{2}\int_\Omega \partial_t(\phi(v)|s|^2)\,dx &+ \int_\Omega D_u\phi(v)|\nabla s|^2\,dx + \int_\Omega \mu_u\phi(v)(s^3\phi(v)+s^2v)\,dx \\
&\le C\sup_\Omega |v|\int_\Omega \mu_u|s|^2\,dx + \frac{1}{2}\int_\Omega \alpha\phi(v)\frac{\chi(v)}{D_u}vs^2|m|\,dx \\
&\le C\sup_\Omega |v|\int_\Omega \mu_u|s|^2\,dx + \frac{\alpha}{D_u}C\sup_\Omega |v|\left(\int_\Omega |s|^3\,dx\right)^{1/3} \\
&\quad\times\left(\int_\Omega |s|^6\,dx\right)^{1/6}\left(\int_\Omega |m|^2\,dx\right)^{1/2}. \qquad (4.4)
\end{aligned}$$

Applying Sobolev inequalities (see for example Ref. 9, Sec. 5.6),

$$\|s\|_{L^3(\Omega)} \le C\|s\|^{1/2}_{H^1(\Omega)}\|s\|^{1/2}_{L^2(\Omega)}$$

and

$$\|s\|_{L^6(\Omega)} \le C\|s\|_{H^1(\Omega)}$$

for $\dim(\Omega)\le 3$, and using the inequality $ab \le 3\delta_0 a^{4/3}/4 + b^4/(4\delta_0^3)$, satisfied by any $\delta_0 > 0$, we obtain the estimate

$$\begin{aligned}
\int_\Omega \partial_t(\phi(v)|s|^2)\,dx &+ \int_\Omega D_u\phi(v)|\nabla s|^2\,dx + \int_\Omega \mu_u\phi(v)(s^3\phi(v)+s^2v)\,dx \\
&\le C\sup_\Omega |v|\Bigg(\int_\Omega \mu_u|s|^2\,dx + \delta_0\int_\Omega (|\nabla s|^2+|s|^2)\,dx \\
&\quad + \frac{1}{\delta_0^3}\int_\Omega |s|^2\,dx\left(\int_\Omega |m|^2\,dx\right)^2\Bigg).
\end{aligned}$$

Choosing δ_0 such that $D_u - C(\sup_{(0,T)\times\Omega} v)\delta_0 \ge d_1 > 0$, and integrating equations in (4.3) with respect to t over $(0,\tau)$ for any $\tau\in[0,T]$ leads to

$$\begin{aligned}
\frac{1}{2}\int_\Omega \phi(v)|s|^2\,dx &+ \int_0^\tau\int_\Omega (d_1|\nabla s|^2 + \mu_u\phi(v)(s^3\phi(v)+s^2v))\,dxdt \\
&\le \frac{1}{2}\int_\Omega \phi(v_0)|s_0|^2\,dx + C\left(\sup_{(0,\tau)\times\Omega} v\right)\int_0^\tau\int_\Omega |s|^2\left(1+\left(\int_\Omega |m|^2\,dx\right)^2\right)dxdt, \\
\frac{1}{2}\int_\Omega |m|^2\,dx &+ \int_0^\tau\int_\Omega (D_m|\nabla m|^2 + \delta_m m^2)\,dxdt \\
&\le \frac{1}{2}\int_\Omega |m_0|^2\,dx + \frac{\mu_m}{2}\int_0^\tau\int_\Omega |m|^2\,dxdt + \frac{\mu_m}{2}\int_0^\tau\int_\Omega |v\phi(v)|^2|s|^2\,dxdt.
\end{aligned}$$

Using the Gronwall inequality (see Ref. 9, Chap. B2), and the fact that $\phi(v) \geq 1$ we conclude that

$$\sup_{(0,T)} \int_\Omega |s|^2\, dx + \int_0^T \int_\Omega (|\nabla s|^2 + |s|^3)\, dxdt$$
$$\leq C \exp\left(C \left(\sup_{(0,T)\times\Omega} v \right) (T + \|m\|^4_{L^8(0,T;L^2(\Omega))} T^{\frac{1}{2}}) \right) \int_\Omega |s_0|^2\, dx,$$
$$\sup_{(0,T)} \int_\Omega |m|^2\, dx + \int_0^T \int_\Omega (|\nabla m|^2 + |m|^2)\, dxdt$$
$$\leq C \int_\Omega |m_0|^2\, dx + C \sup_{(0,T)\times\Omega} v \int_0^T \int_\Omega |s|^2\, dxdt.$$

Using the *a priori* estimates we prove the local existence theorem. □

Proof of Theorem 3.1. Non-negativity of solutions for non-negative initial conditions $s_0 \geq 0$, $v_0 \geq 0$, and $m_0 \geq 0$ is a consequence of the maximum principle. In order to apply the maximum principle, we consider a regularization of the equation for v. For details see the Appendix.

The existence of a solution will be proved by showing the existence of a fix-point of an operator K defined on $L^8(0,T;L^2(\Omega))$ by $m = K(\bar{m})$ with m being a solution of

$$\phi(v)\partial_t s = D_u \nabla \cdot (\phi(v)\nabla s) + s\phi(v) \left(\alpha \frac{\chi(v)}{D_u} v\bar{m} + \mu_u - \mu_u s\phi(v) - \mu_u v \right), \tag{4.5}$$

$$\partial_t v = -\alpha \bar{m} v, \tag{4.6}$$

$$\partial_t m = D_m \Delta m - \delta_m m + \mu_m s\phi(v)v. \tag{4.7}$$

Existence and boundedness of v is a straightforward consequence of Eq. (4.6). Indeed, for a given $\bar{m} \in L^8(0,T;L^2(\Omega))$ a solution $v(\bar{m})$ of the problem

$$\partial_t v = -\alpha \bar{m} v,$$
$$v(0) = v_0(x)$$

has the form

$$v(t,x) = v_0(x) e^{-\alpha \int_0^t \bar{m}(\tau,x)d\tau} \tag{4.8}$$

and we conclude that $0 \leq v \leq \sup_\Omega v_0$ for $\bar{m} \geq 0$ and $v_0 \geq 0$.

For $\bar{m} \in L^8(0,T;L^2(\Omega))$, using estimate (4.1) from Lemma 4.1 and the Galerkin method, we obtain a solution $s(\bar{m}) \in L^2(0,T;H^1(\Omega)) \cap L^\infty(0,T;L^2(\Omega))$ of Eq. (4.5) (see Ref. 19). Moreover,

$$\|s\|^2_{L^2(\Omega)}(\tau) \leq \exp\left(C \left(\sup_\Omega v_0 \right) (\tau + \|\bar{m}\|^4_{L^8(0,\tau;L^2(\Omega))} \tau^{1/2}) \right) \|s_0\|^2_{L^2(\Omega)}$$

for any $\tau \in [0,T]$. Estimate (4.2) in Lemma 4.1 and the Galerkin method also imply the existence of $m \in L^2(0,T;H^1(\Omega)) \cap L^\infty(0,T;L^2(\Omega))$ (see Ref. 19). Using $\partial_t m$ as a test function for Eq. (4.7) and the regularity of m_0 we obtain

$$\int_0^T\int_\Omega |\partial_t m|^2\,dx + \frac{D_m}{2}\sup_{0\le t\le T}\int_\Omega |\nabla m|^2\,dx \le \frac{D_m}{2}\int_\Omega |\nabla m_0|^2\,dx$$
$$+ C\int_0^T\int_\Omega \left(\delta_0|\partial_t m|^2 + \frac{\delta_m^2}{\delta_0}|m|^2 + \frac{1}{\delta_0}\sup_{(0,T)\times\Omega} v|s|^2\right)dxdt. \qquad (4.9)$$

In conclusion, $m \in H^1(0,T;L^2(\Omega)) \cap L^\infty(0,T;H^1(\Omega))$.

A priori estimates for m and s guarantee that, for a time T^* small enough, the operator K satisfies $K: B_R \to B_R$ and also $K : L^8(0,T;L^2(\Omega)) \to L^\infty(0,T; H^1(\Omega)) \cap H^1(0,T;L^2(\Omega)) \subset L^8(0,T;L^2(\Omega))$. Since $L^\infty(0,T;H^1(\Omega)) \cap H^1(0,T; L^2(\Omega)) \subset L^8(0,T;L^2(\Omega))$ is a compact embedding (see Ref. 21), we apply Schauder fix-point theorem and obtain the existence of a solution for $t \in [0,T^*]$.

To show that the solution has the regularity required by Definition 2.2, we apply $\partial_t s$ as test function in Eq. (4.5) and obtain

$$\int_0^{T^*}\int_\Omega |\partial_t s|^2\,dxdt + \sup_{(0,T^*)}\int_\Omega (D_u\phi(v)|\nabla s|^2 + \mu_u s^3\phi^2(v))\,dx$$
$$+ \int_0^{T^*}\int_\Omega \frac{\phi(v)\chi(v)}{D_u}\alpha m|\nabla s|^2\,dxdt$$
$$\le C\int_\Omega (\phi(v_0)|\nabla s_0|^2 + \phi^2(v_0)s_0^3)\,dx$$
$$+ C\left(\sup_{(0,T^*)\times\Omega}|v|\right)\int_0^{T^*}\int_\Omega\left(\delta_0|\partial_t s|^2 + \frac{1}{\delta_0}|s|^2\right)dxdt$$
$$+ \|s\|^2_{L^2(0,T^*;L^4(\Omega))} + \|m\|^2_{L^\infty(0,T^*;L^4(\Omega))}$$
$$- C\int_0^{T^*}\int_\Omega s^3\phi^2(v)mv\,dxdt. \qquad (4.10)$$

The Sobolev Embedding Theorem for $\dim(\Omega) \le 4$ (see Ref. 9) yields

$$\|s\|_{L^2(0,T^*;L^4(\Omega))} \le C\|s\|_{L^2(0,T^*;H^1(\Omega))},$$
$$\|m\|_{L^\infty(0,T^*;L^4(\Omega))} \le C\|m\|_{L^\infty(0,T^*;H^1(\Omega))}.$$

Since the last integral in (4.10) is nonpositive, estimates obtained above for s and m imply boundedness of $\partial_t s$ in $L^2((0,T^*)\times\Omega)$ and ∇s in $L^\infty(0,T^*;L^2(\Omega))$.

Boundedness of $\partial_t v$ in $L^2((0,T^*)\times\Omega)$ directly follows from Eq. (4.6) using $\partial_t v$ as a test function and taking into account that $v \le \sup_\Omega v_0$ and $\|m\|_{L^2((0,T^*)\times\Omega)} \le C$. The regularity $v \in L^2(0,T^*;H^1(\Omega))$ is obtained using (4.8) and the regularity of $v_0 \in H^1(\Omega)$ and $m \in L^2(0,T^*;H^1(\Omega))$. □

Remark 4.1. Existence of a local weak solution of (2.6)–(2.10) with $s, m \in L^\infty(0,T^*;H^1(\Omega))$ implies also the existence of a local solution of (2.1)–(2.5) such that $v, m \in L^2(0,T^*;H^1(\Omega))$, $D_u\nabla u - \chi(v)u\nabla v \in L^2((0,T^*)\times\Omega)$, $u, v, m \in H^1(0,T^*;L^2(\Omega))$.

5. Boundedness and Existence of a Global Solution

Theorem 5.1. *For non-negative and bounded initial conditions and a positive and continuous sensitivity function* χ, *the solutions of the problem* (2.1)–(2.5) *are uniformly bounded.*

In the proof of this theorem we will use the following result on the regularity of m.

Lemma 5.1. *Suppose that* $m_0, s_0, v_0 \in L^\infty(\Omega)$, $m_0 \geq 0, s_0 \geq 0, v_0 \geq 0$, *and* χ *is positive and continuous, then the solution* m *of the system* (2.6)–(2.8) *satisfies,*

$$m \in L^1(0,T;C^{0,\gamma}(\bar{\Omega})), \quad p > n, \quad \gamma = \left[\frac{n}{p}\right] + 1 - \frac{n}{p} \quad \text{for all } T \in (0,\infty),$$

$$\int_0^t \|m\|_{C^{0,\gamma}(\bar{\Omega})} d\tau \leq C\Big(t + \sup_\Omega u_0 + \sup_\Omega m_0\Big)^\gamma,$$

where C *and* γ *are some positive constants.*

Proof. In the proof we use the fact that solutions s, v, m are non-negative. Integration of Eq. (2.6) yields

$$\partial_t \int_\Omega s\phi(v)\,dx + \mu_u \int_\Omega s^2\phi(v)^2\,dx + \mu_u \int_\Omega s\phi(v)v\,dx = \mu_u \int_\Omega s\phi(v)\,dx.$$

Then, the integration with respect to t, $v \leq \sup_\Omega v_0$, $1 \leq \phi(v) \leq C$, the boundedness of the domain Ω and Young inequality imply

$$\int_\Omega s\,dx \leq \int_\Omega s\phi(v)\,dx \leq C_1 t + \int_\Omega s_0\phi(v_0)\,dx \quad \text{for all } t \in [0,\infty).$$

For $s \in L^\infty(0,T;L^\sigma(\Omega))$ due to the regularity theory for parabolic equations, see Ref. 14, and Eq. (2.8), we obtain

$$\begin{aligned}
&\|m\|_{W^{1,q}(\Omega)} \leq c_1(\|m_0\|_{L^1(\Omega)} + \|s\|_{L^\infty(0,t;L^\sigma(\Omega))}) \\
&\qquad \text{for } t \in (0,T], \quad q < \frac{n\sigma}{n-\sigma}, \quad \sigma \in [1,n], \\
&\|m\|_{L^r(\Omega)} \leq c_2(\|m_0\|_{L^r(\Omega)} + \|s\|_{L^\infty(0,t;L^\sigma(\Omega))}) \\
&\qquad \text{for } t \in [0,T], \quad r < \frac{n\sigma}{n-2\sigma}, \quad \sigma \in [1,n/2].
\end{aligned}$$

Testing Eq. (2.6) with ps_μ^{p-1}, where $s_\mu = s + \mu$, $\mu > 0$, for $1 < p < 2$ and $s_\mu = s$ for $p \geq 2$, and using Gagliardo–Nirenberg inequality we obtain

$$\begin{aligned}
&\partial_t \int_\Omega \phi(v)s_\mu^p\,dx + \int_\Omega \phi(v)\left(\frac{4(p-1)D_u}{p}|\nabla(s_\mu^{\frac{p}{2}})|^2 + \mu_u p\phi(v)s_\mu^{p+1}\right)dx \\
&\quad \leq C\int_\Omega s_\mu^p\phi(v)\,dx + \frac{\alpha(p-1)}{D_u}\int_\Omega \phi(v)\chi(v)vms_\mu^p\,dx \\
&\quad \leq C_1\left(\int_\Omega m^{r'}\,dx\right)^{\frac{1}{r'}}\left(\int_\Omega s_\mu^{pr}\,dx\right)^{\frac{1}{r}} + C\int_\Omega s_\mu^p\phi(v)\,dx
\end{aligned}$$

$$\leq C_1\left(\int_\Omega m^{r'}\,dx\right)^{\frac{1}{r'}}\left(\int_\Omega s_\mu^\sigma\,dx\right)^{\frac{(r-1)p}{r\sigma}}\left(\int_\Omega (s_\mu^p+|\nabla(s_\mu^{\frac{p}{2}})|^2)\,dx\right)^{\frac{1}{r}}$$
$$+C\int_\Omega s_\mu^p\phi(v)\,dx$$
$$\leq C_\delta\left(\int_\Omega m^{r'}\,dx\right)\left(\int_\Omega s_\mu^\sigma\,dx\right)^{\frac{p}{\sigma}}+C_2\delta\int_\Omega (s_\mu^p+|\nabla(s_\mu^{\frac{p}{2}})|^2)\,dx$$
$$+C\int_\Omega s_\mu^p\phi(v)\,dx.$$

Here

$$p\in(\sigma,2\sigma]\quad\text{such that}\quad \frac{np}{np+2\sigma}<\frac{1}{r}<1+\frac{2}{n}-\frac{1}{\sigma},\qquad \frac{1}{r}+\frac{1}{r'}=1.$$

Choosing $\sigma=1$ and limit $\mu\to 0$, following integration with respect to time and using the Lebesgue Theorem, we obtain

$$\int_\Omega \phi(v)s^p\,dx\leq Ct\left(C_1t+\int_\Omega u_0\,dx+\sup_\Omega m_0\right)^{r'}\left(C_1t+\int_\Omega u_0\,dx\right)^p$$
$$+Ct+\int_\Omega \phi(v_0)s_0^p\,dx$$

for all $t\in[0,T]$, with $1<p<\frac{4}{3}$ and $\frac{3}{2}<r<1+\frac{2}{3p}$ for $n=3$,

$$1<p\leq 2\quad\text{and}\quad 1<r<1+\frac{1}{p}\quad\text{for } n=2.$$

Iterating over p and σ and using the regularity results from the semigroup theory, we conclude that $m\in L^1(0,T;W^{1,p}(\Omega))$ and for p such that $p>n$, using the Sobolev Embedding Theorem, we obtain

$$\int_0^t \|m\|_{C^{0,\alpha}(\bar\Omega)}\,d\tau\leq C\left(t+\sup_\Omega u_0+\sup_\Omega m_0\right)^\gamma$$

for some positive constant γ.

Proof of Theorem 5.1. We consider the equivalent formulation (2.6)–(2.8) and rewrite Eq. (2.6) in the form

$$\partial_t s=D_u\Delta s+D_u\frac{\phi'(v)}{\phi(v)}\nabla v\nabla s+s\left(\alpha\frac{\chi(v)}{D_u}vm+\mu_u-\mu_u s\phi(v)-\mu_u v\right).\qquad(5.1)$$

Now, using the framework of invariant rectangles (see Ref. 31 for $\Omega\subset\mathcal{R}^1$ and Ref. 6 for $\Omega\subset\mathcal{R}^n$) we show that solutions of the system (2.6)–(2.10) are uniformly bounded. The theory of bounded invariant rectangles can be applied to this problem using a regularization argument (for details see the Appendix).

First, we solve the equation for v and obtain

$$v = \psi(t, x, m) = v_0(x)e^{-\alpha\int_0^t m(\tau,x)d\tau}.$$

Non-negativity of m implies that v is uniformly bounded by $\bar{v} = \sup_\Omega v_0(x)$. We introduce a set

$$\Sigma = \{(s, m) : 0 \le s \le \bar{s},\ 0 \le m \le \bar{m}\}. \tag{5.2}$$

Let F_s and F_m denote the kinetics of the system (2.6)–(2.8), i.e. $F_s(s, m, t) = s(\alpha\frac{\chi(\psi)}{D_u}\psi m + \mu_u - \mu_u s\phi(\psi) - \mu_u\psi)$ and $F_m(s, m, t) = -\delta_m m + \mu_m s\phi(\psi)\psi$. To show that there exist constants $\bar{s}$ and $\bar{m} < \infty$ such that $s(t, x) \le \bar{s}$, $m(t, x) \le \bar{m}$, for every $t \ge 0$, $x \in \Omega$, and an initial condition $(s_0, m_0) \in \Sigma$, we check that there exist constants $\bar{s}, \bar{m}$ such that for $s \le \bar{s}$, $m \le \bar{m}$, the vector field $[F_s, F_m]$ does not point outwards Σ, i.e. $F_s(s, m, t)|_{s=\bar{s}} \le 0$ and $F_m(s, m, t)|_{m=\bar{m}} \le 0$.

In turn, since $s \ge 0$, the condition for boundedness of s, $F_s(s, m, t)|_{s=\bar{s}} \le 0$, is satisfied if there exists a constant $\bar{s}$ such that

$$\begin{aligned}\bar{s} &\ge \frac{\alpha/D_u\chi(\psi)\psi m + \mu_u - \mu_u\psi}{\mu_u\phi(\psi)}\\ &= \frac{1}{\phi(\psi)} + \frac{\alpha/D_u\chi(\psi)\psi m - \mu_u\psi}{\mu_u\phi(\psi)} \quad \text{for all } t \ge 0, \quad x \in \bar{\Omega}.\end{aligned} \tag{5.3}$$

Properties of the function χ imply that $0 \le \chi(\psi) \le B$. Moreover, $\phi(\psi)$ is always bounded away from 0. Thus, to find $\bar{s}$ satisfying (5.3), it is enough to show that the product $m(t, x)\psi(t, m(t, x))$ is uniformly bounded. For this we consider a function of m given by

$$f(m) = m\psi = v_0 m e^{-\alpha\int_0^t m d\tau} \quad \text{for all } t \ge 0, \quad x \in \bar{\Omega}.$$

We show that $f(m)$ is an eventually nonincreasing function.

First, we show that the solutions of the model (2.6)–(2.8) can be estimated by the solutions of the ODEs system with the kinetics corresponding to the supremum over space of the original zeroth-order terms calculated in the proceeding time points. The proof is based on the considerations similar to those used in the proof of Theorem 14.16 in Ref. 31.

Lemma 5.2. *Let $S(t)$ and $M(t)$ be solutions of the following equations*:

$$\begin{aligned}\frac{dS}{dt} &= S\left(\alpha\sup_\Omega\left(\frac{\chi(v)}{D_u}v\right)\sup_\Omega m(t, x) + \mu_u\right),\\ S(0) &= \sup_\Omega s_0(x),\\ \frac{dM}{dt} &= \mu_m S\sup_\Omega(\phi(v)v),\\ M(0) &= \sup_\Omega m_0(x)\end{aligned}$$

with m and v given by system (2.6)–(2.8). Then, the solutions of the system (2.6)–(2.8) satisfy $s(t,x) \le S(t)$ and $m(t,x) \le M(t)$ for every $x \in \bar{\Omega}$ and $t \in [0,T]$.

Proof of Lemma 5.2. Notice that $S(t)$, $M(t)$ are also solutions of

$$\begin{aligned}
\partial_t S &= D_u \Delta S + D_u \frac{\phi'(v)}{\phi(v)} \nabla v \nabla S + S\left(\alpha \sup_\Omega \left(\frac{\chi(v)}{D_u} v\right) \sup_\Omega m(t,x) + \mu_u\right),\\
S(0) &= \sup_\Omega s_0(x), \quad D_u \nabla S \cdot \nu = 0,\\
\partial_t M &= D_m \Delta M + \mu_m S \sup_\Omega (\phi(v)v),\\
M(0) &= \sup_\Omega m_0(x), \quad D_m \nabla M \cdot \nu = 0.
\end{aligned}$$

For $\sigma(t,x) = s(t,x) - S(t)$ and $\omega(t,x) = m(t,x) - M(t)$ we obtain

$$\begin{aligned}
\partial_t \sigma &= D_u \Delta \sigma + D_u \frac{\phi'(v)}{\phi(v)} \nabla v \nabla \sigma + \sigma\left(\alpha \sup_\Omega \left(\frac{\chi(v)}{D_u} v\right) \sup_\Omega m(t,x) + \mu_u\right)\\
&\quad - \alpha s\left(\sup_\Omega \left(\frac{\chi(v)}{D_u} v\right) \sup_\Omega m(t,x) - \frac{\chi(v)}{D_u} v m(t,x)\right) - \mu_u s(s\phi(v) + v),\\
\partial_t \omega &= D_m \Delta \omega + \mu_m \sigma \sup_\Omega (\phi(v)v) - s\left(\sup_\Omega (\phi(v)v) - \phi(v)v\right) - \delta_m m.
\end{aligned}$$

To show that $\sigma \le 0$ and $\omega \le 0$ we have to check that (i) $F_\sigma \le 0$ for $\sigma = 0$, $\omega \le 0$ and (ii) $F_\omega \le 0$ for $\omega = 0$, $\sigma \le 0$, where F_σ and F_ω are zeroth-order terms of the equations for σ and ω respectively.

These conditions are fulfilled, since $s \ge 0$, $v \ge 0$ and $m \ge 0$. Thus, applying Theorem 14.11, Ref. 31 we obtain that $s(t,x) \le S(t)$ and $m(t,x) \le M(t)$ for all $(t,x) \in [0,T] \times \bar{\Omega}$.

Using Lemmas 5.2 and 5.1 we show that m exists globally. Indeed, solving equations for S and M results in the estimate

$$m(x,t) \le M(t) \le C_1 t \exp\left(C_2 \int_0^t \sup_{x \in \bar{\Omega}} m(\tau,x) d\tau + C_3 t\right), \tag{5.4}$$

for every $x \in \bar{\Omega}$, and C_1, C_2 some positive constants depending on the model parameters and initial conditions.

In turn, using the regularity of m given by Lemma 5.1 and the inequality (5.4) we conclude that m is bounded for every finite time point t. Therefore, in every $x \in \bar{\Omega}$, m is uniformly bounded or $\int_0^t m(\tau,x)d\tau$ is growing. In the latter case, for a given constant α there exists $t^* \in (0,\infty)$ such that $\int_0^{t^*} m(\tau,x)d\tau \ge 1/\alpha$. If $\int_0^{t^*} m(\tau,x)d\tau \ge 1/\alpha$, then the function $f(m)$ is monotone nonincreasing for every $t \ge t^*$. Moreover, there exists a constant A such that

$$m\psi \le A \quad \text{for } m \ge 0, \quad t \ge 0, \quad x \in \bar{\Omega}.$$

This allows us to conclude that there exists $\bar{s}$ such that the inequality (5.3) is fulfilled for all $t \ge 0$.

To show that there exists a constant $\bar{m}$ such that $F_m(s, m, t)|_{m=\bar{m}} \leq 0$, we have to show that there exists $\bar{m}$ such that

$$\bar{m} \geq \mu_m \psi \phi(\psi) s / \delta_m. \tag{5.5}$$

For $s \leq \bar{s}$ and $v \leq \bar{v}$, the right-hand side of the inequality (5.5) can be estimated from above by $\frac{\mu_m}{\delta_m} \bar{v} \phi_{\max} \bar{s}$ and therefore any

$$\bar{m} \geq \frac{\mu_m}{\delta_m} \bar{v} \phi_{\max} \bar{s}$$

fulfills the inequality (5.5).

Finally, we conclude that for $\bar{s}$, $\bar{m}$ large enough, the vector field $[F_s, F_m]$ does not point outwards to Σ, and, therefore, Σ is invariant for system (2.6)–(2.10).

Since $\bar{s}$, $\bar{m}$ can be chosen arbitrarily large, we also conclude that the solutions of the system (2.6)–(2.8) with non-negative initial conditions are uniformly bounded. Boundedness of s and v imply boundedness of u. Hence we conclude that the solutions of the original system (2.1)–(2.5) are uniformly bounded for all $t \in [0, \infty)$. □

Remark 5.1. Inequality (5.3) yields the following estimate for $u = s\phi(v)$,

$$u \leq 1 + \bar{v} \left(\frac{\alpha \bar{m}}{\mu_u} \frac{\sup \chi(v)}{D_u} - 1 \right).$$

This shows the dependence of the bound of the solution on the diffusion parameter D_u and the sensitivity function χ. In particular, the above inequality indicates that increasing value of $\frac{\chi(v)}{D_u}$ may lead to the increase of bounds for $u + v$.

Using the boundedness of the solutions, the global existence theorem can be shown.

Proof of Theorem 3.2. For $u, v \in L^\infty((0, T) \times \Omega)$, Definitions 2.1 and 2.2 are equivalent. Thus, the existence of global solutions of system (2.1)–(2.5) is equivalent to the existence of global solution of (2.6)–(2.10). The latter results from a standard argument based on the theory of bounded invariant rectangles,[31] which provides *a priori* L^∞ estimates for the solutions of the system. □

5.1. *Uniqueness of solutions*

For the proof of uniqueness of solutions of the system considered, we need more regularity of v. Therefore, we prove the following:

Lemma 5.3. *For $m \geq 0$, $m \in L^q(0, T; W^{1,q}(\Omega))$, and $v_0 \in W^{1,q}(\Omega)$ where $2 \leq q < \infty$ the following estimate is fulfilled*

$$\sup_{(0,T)} \|\nabla v\|^q_{L^q(\Omega)} \leq C \|\nabla v_0\|^q_{L^q(\Omega)} + C \sup_{(0,T)\times\Omega} v \int_0^T \int_\Omega |\nabla m|^q \, dx dt.$$

Proof. To obtain the estimate, we differentiate the equation for v with respect to x_i, $1 \leq i \leq n = \dim(\Omega)$, use $|v_{x_i}|^{q-2} v_{x_i}$ as a test function, and integrate over t in the interval $(0,\tau)$ for any $\tau \in [0,T]$. We obtain

$$\int_\Omega |v_{x_i}|^q \le \int_\Omega |v_{0,x_i}|^q\,dx + \int_0^\tau\!\!\int_\Omega \frac{\alpha}{q}|v|\,|m_{x_i}|^q\,dxdt$$
$$+ \int_0^\tau\!\!\int_\Omega \frac{q-1}{q}\alpha|v|\,|v_{x_i}|^q\,dxdt - \alpha\int_0^\tau\!\!\int_\Omega |v_{x_i}|^q m\,dxdt.$$

Since $0 \le v \le \sup_\Omega v_0$ for $m \ge 0$, and also the last integral is non-negative, the Gronwall inequality yields the estimate for v_{x_i} for all $1 \le i \le n$. □

Proof of Theorem 3.3. Lemma 5.1 and Theorem 3.2 imply the existence of a weak bounded solution of the system (2.1)−(2.5). To show uniqueness we assume that there exist two solutions of (2.1)−(2.5) denoted by (u_1, v_1, m_1) and (u_2, v_2, m_2). The differences $\tilde{u} = u_1 - u_2$, $\tilde{v} = v_1 - v_2$, $\tilde{m} = m_1 - m_2$ satisfy

$$\int_0^T\!\!\int_\Omega (\partial_t\tilde{u}\varphi_1 + D_u\nabla\tilde{u}\nabla\varphi_1 - \chi(v_1)u_1\nabla\tilde{v}\nabla\varphi_1 + (\chi(v_1)u_1 - \chi(v_2)u_2)\nabla v_2\nabla\varphi_1)\,dxdt$$
$$= \int_0^T\!\!\int_\Omega (\mu_u\tilde{u}(1-u_1-v_1) - \mu_u u_2(\tilde{u}+\tilde{v}))\varphi_1\,dxdt, \tag{5.6}$$

$$\int_0^T\!\!\int_\Omega (\partial_t\tilde{v} + \alpha\tilde{m}v_1 + \alpha m_2\tilde{v})\varphi_2\,dxdt = 0, \tag{5.7}$$

$$\int_0^T\!\!\int_\Omega (\partial_t\tilde{m}\varphi_3 + D_m\nabla\tilde{m}\nabla\varphi_3 + \delta_m\tilde{m}\varphi_3)\,dxdt$$
$$= \int_0^T\!\!\int_\Omega (\mu_m\tilde{u}v_1 + \mu_m u_2\tilde{v})\varphi_3\,dxdt \tag{5.8}$$

for $\varphi_1, \varphi_3 \in L^2(0,T;H^1(\Omega))$, $\varphi_2 \in L^2((0,T)\times\Omega)$. Using $\tilde{u}$, $\tilde{v}$, $\tilde{m}$ as test functions in Eqs. (5.6)−(5.8) respectively, we obtain, for any $\tau \in [0,T]$,

$$\frac{1}{2}\int_\Omega |\tilde{u}|^2\,dx + \int_0^\tau\!\!\int_\Omega D_u|\nabla\tilde{u}|^2\,dxdt$$
$$\le \int_0^\tau\!\!\int_\Omega \chi(v_1)u_1\nabla\tilde{v}\nabla\tilde{u}\,dxdt + \int_0^\tau\!\!\int_\Omega (\chi(v_1)u_1 - \chi(v_2)u_2)\nabla v_2\nabla\tilde{u}\,dxdt$$
$$+ C\int_0^\tau\!\!\int_\Omega (|\tilde{u}|^2 + |\tilde{v}|^2 + |\tilde{u}|^2)\,dxdt, \tag{5.9}$$

$$\int_\Omega |\tilde{v}|^2\,dx \le C\int_0^\tau\!\!\int_\Omega (|\tilde{m}|^2 + |\tilde{v}|^2)\,dxdt, \tag{5.10}$$

$$\frac{1}{2}\int_\Omega |\tilde{m}|^2\,dx + \int_0^\tau\!\!\int_\Omega (D_m|\nabla\tilde{m}|^2 + \delta_m|\tilde{m}|^2)\,dxdt$$
$$\le C\int_0^\tau\!\!\int_\Omega (|\tilde{m}|^2 + |\tilde{u}|^2 + |\tilde{v}|^2)\,dxdt. \tag{5.11}$$

We estimate

$$\begin{aligned}\int_0^\tau\!\!\int_\Omega (\chi(v_1)u_1 - \chi(v_2)u_2)\nabla v_2 \nabla \tilde{u}\, dxdt \\ \le (\|u_1 - u_2\|_{L^{2,p}((0,T)\times\Omega)} + \|v_1 - v_2\|_{L^{2,p}((0,T)\times\Omega)}) \\ \times \|\nabla v_2\|_{L^{\infty,p'}((0,T)\times\Omega)} \|\nabla \tilde{u}\|_{L^2((0,T)\times\Omega)},\end{aligned}$$

where $\frac{1}{p} + \frac{1}{p'} = \frac{1}{2}$ and $p = \frac{2n}{n-2}$ for $n = \dim(\Omega) > 2$, $p < \infty$ for $n = 2$, and $p = \infty$ for $n = 1$.

Applying the Sobolev Embedding Theorem,[9] we conclude that

$$\begin{aligned}\|u_1 - u_2\|_{L^2(0,\tau;L^p(\Omega))} \le C\|\tilde{u}\|_{L^2(0,\tau;H^1(\Omega))}, \\ \|v_1 - v_2\|_{L^2(0,\tau;L^p(\Omega))} \le C\|\tilde{v}\|_{L^2(0,\tau;H^1(\Omega))}.\end{aligned}$$

For a bounded solution (u, v, m), the semigroup theory (see Theorem 3.6 in Ref. 26, Chap. 7, p. 215) yields that $m \in L^q(0, T; W^{1,q}(\Omega))$ for any $1 < q < \infty$. Thus, using the estimate in Lemma 5.3 we conclude that $\|\nabla v_2\|_{L^{\infty,p'}((0,T)\times\Omega)} \le C$.

Remark 5.2. The regularity of m can be shown directly using *a priori* estimates, as it is done in Sec. 5.2.

Differentiating equation for $\tilde{v}$ with respect to x_i, $1 \le i \le n$, and using $\partial_{x_i}\tilde{v}$ as a test function, we obtain for $\tau \in [0, T]$

$$\begin{aligned}\int_0^\tau\!\!\int_\Omega \partial_t|\partial_{x_i}\tilde{v}|^2\, dx &\le C\int_0^\tau\!\!\int_\Omega (|\partial_{x_i}\tilde{m}||\partial_{x_i}\tilde{v}| + |\tilde{m}||\partial_{x_i}v_1||\partial_{x_i}\tilde{v}| \\ &\quad + |\partial_{x_i}m_2||\tilde{v}||\partial_{x_i}\tilde{v}|)\, dxdt + \int_0^\tau\!\!\int_\Omega |m_2||\delta_{x_i}\tilde{v}|^2\ dxdt \\ &\le C\int_0^\tau\!\!\int_\Omega \left(\delta_0|\partial_{x_i}\tilde{m}|^2 + \frac{3}{\delta_0}|\partial_{x_i}\tilde{v}|^2\right) dxdt \\ &\quad + \delta_0\|\tilde{m}\|^2_{L^2(0,\tau;L^p(\Omega))}\|\partial_{x_i}v_1\|^2_{L^\infty(0,\tau;L^{p'}(\Omega))} \\ &\quad + \delta_0\|\partial_{x_i}m_2\|^2_{L^2(0,\tau;L^{p'}(\Omega))}\|\tilde{v}\|^2_{L^\infty(0,\tau;L^p(\Omega))}.\end{aligned}$$

The Sobolev Embedding Theorem yields

$$\begin{aligned}\|\tilde{m}\|_{L^2(0,\tau;L^p(\Omega))} \le C\|\tilde{m}\|_{L^2(0,\tau;H^1(\Omega))}, \\ \|\tilde{v}\|_{L^\infty(0,\tau;L^p(\Omega))} \le C\|\tilde{v}\|_{L^\infty(0,\tau;H^1(\Omega))}.\end{aligned}$$

Thus, using that $\|\nabla m_2\|^2_{L^2(0,\tau;L^{p'}(\Omega))} \le C$ and $\|\nabla v_1\|^2_{L^\infty(0,\tau;L^{p'}(\Omega))} \le C$ we obtain

$$\begin{aligned}\sup_{0\le t\le\tau}\int_\Omega |\partial_{x_i}\tilde{v}|^2\, dx &\le C\int_0^\tau\!\!\int_\Omega \delta_0|\partial_{x_i}\tilde{m}|^2\, dxdt + C\delta_0 \sup_{0\le t\le\tau}\int_\Omega |\tilde{v}|^2\, dx \\ &\le \int_0^\tau\!\!\int_\Omega \delta_0|\partial_{x_i}\tilde{m}|^2\, dxdt + C\delta_0\int_0^\tau\!\!\int_\Omega |\tilde{m}|^2\, dxdt.\end{aligned}$$

Adding inequalities (5.9)–(5.11) and using the Gronwall inequality we obtain

$$\sup_{0\le t\le T}\int_\Omega (|\tilde{u}|^2 + |\tilde{v}|^2 + |\tilde{m}|^2)\, dx \le 0,$$

which proves the uniqueness of solutions.

5.2. $W^{2,q}$ *regularity*

In this section we show higher regularity of the model solutions.

Lemma 5.4. *For* $m \geq 0$, $m \in L^q(0,T;W^{2,q}(\Omega))$, *and* $v_0 \in W^{2,q}(\Omega)$ *the following estimate holds*:

$$\|\nabla^2 v\|^q_{L^q(\Omega)} \leq \|\nabla^2 v_0\|^q_{L^q(\Omega)} + C \sup_{(0,T)\times\Omega} |v| \int_0^T\int_\Omega (|\nabla v|^{2q} + |\nabla m|^{2q} + |\nabla^2 m|^q)\, dxdt.$$

Proof. Differentiating the equation for v with respect to x_i and x_j and testing the obtained equation with $|v_{x_ix_j}|^{q-2}v_{x_ix_j}$ yields, for any $\tau \in [0,T]$,

$$\begin{aligned}\frac{1}{2}\int_\Omega |v_{x_ix_j}|^q\, dx \leq{}& \frac{1}{2}\int_\Omega |v_{0,x_ix_j}|^q\, dx + \alpha\frac{q-1}{q}\int_0^\tau\int_\Omega \left(1 + \sup_{(0,\tau)\times\Omega}|v|\right)|v_{x_ix_j}|^q\, dxdt \\ &+ \int_0^\tau\int_\Omega \frac{\alpha}{2q}(|v_{x_i}|^{2q} + |v_{x_j}|^{2q} + |m_{x_i}|^{2q} + |m_{x_j}|^{2q})\, dxdt \\ &+ \frac{\alpha}{q}\sup_{(0,T)\times\Omega}|v|\int_0^\tau\int_\Omega |m_{x_ix_j}|^q\, dxdt - \alpha\int_0^\tau\int_\Omega m|v_{x_ix_j}|^q\, dxdt.\end{aligned}$$

Since the last integral is nonpositive, applying the Gronwall inequality provides the required estimate. □

Lemma 5.5. *Under the assumptions of Theorem* 3.2 *and* $s_0, m_0 \in W^{2,q}(\Omega)$, *the following estimates hold*

$$\begin{aligned}\sup_{(0,T)}\int_\Omega |s_t|^q\, dx \leq{}& C\left(\sup_{(0,T)\times\Omega}\{v,m,s\}, \|s_0\|_{W^{2,q}(\Omega)}\right) \\ &+ C\left(\sup_{(0,T)\times\Omega}\{v,m\}\right)\int_0^T\int_\Omega |\nabla s|^q\, dxdt,\end{aligned}$$

$$\begin{aligned}\sup_{(0,T)}\int_\Omega |m_t|^q\, dx \leq{}& C\left(\sup_{(0,T)\times\Omega}\{v,s,m\}, \|s_0\|_{W^{2,q}(\Omega)}\right) \\ &+ C\left(\sup_{(0,T)\times\Omega} v\right)\int_0^T\int_\Omega |s_t|^q\, dxdt.\end{aligned}$$

Proof. Differentiating Eqs. (2.6) and (2.8) with respect to t, we obtain

$$\begin{aligned}\phi(v)\partial_t^2 s ={}& D_u\nabla\cdot(\phi(v)\partial_t\nabla s) + D_u\nabla(\phi'(v)\partial_t v\nabla s) - \partial_t s\phi'(v)\partial_t v \\ &+ (\partial_t s\phi(v) + s\phi(v)'\partial_t v)\left(\alpha\frac{\chi(v)}{D_u}vm + \mu_u - \mu_u s\phi(v) - \mu_u v\right) \\ &+ s\phi(v)\left(\frac{\alpha}{D_u}(\chi'(v)\partial_t vvm + \chi(v)(\partial_t vm + v\partial_t m))\right. \\ &\left. - \mu_u(\partial_t s\phi(v) + s\phi'(v)\partial_t v) - \mu_u\partial_t v\right) \qquad (5.12)\end{aligned}$$

and

$$\partial_t^2 m = D_m \Delta \partial_t m - \delta_m \partial_t m + \mu_m \partial_t s \phi(v) v + \mu_m s \phi'(v) \partial_t v v + \mu_m s \phi(v) \partial_t v. \qquad (5.13)$$

Testing Eq. (5.12) using a test function $|\partial_t s|^{q-2} \partial_t s$ yields, for $\tau \in [0, T]$,

$$\begin{aligned}
\int_0^\tau \int_\Omega & \left(\frac{1}{q} \partial_t (\phi(v) |\partial_t s|^q) + (q-1) D_u \phi(v) |\nabla \partial_t s|^2 |\partial_t s|^{q-2} \right) dx dt \\
&= - \int_0^\tau \int_\Omega D_u \phi'(v) \partial_t v \nabla s |\partial_t s|^{q-2} \partial_t \nabla s dx dt \\
&\quad + \int_0^\tau \int_\Omega \left(\frac{1}{q} - 1 \right) \phi'(v) \partial_t v |\partial_t s|^q \, dx dt \\
&\quad + \int_0^\tau \int_\Omega (|\partial_t s|^q \phi(v) + s |\partial_t s|^{q-2} \partial_t s \phi'(v) \partial_t v) \\
&\quad \times \left(\frac{\alpha \chi(v)}{D_u} v m + \mu_u (1 - s\phi(v) - v) \right) dx dt \\
&\quad + \int_0^\tau \int_\Omega s |\partial_t s|^{q-2} \partial_t s \phi(v) \frac{\alpha}{D_u} (\chi'(v) \partial_t v v m + \chi(v) (\partial_t v \, m + v \partial_t m)) \, dx dt \\
&\quad - \int_0^\tau \int_\Omega s |\partial_t s|^{q-2} \partial_t s \, \phi(v) \mu_u (\partial_t s \, \phi(v) + s \phi'(v) \partial_t v + \partial_t v) \, dx dt.
\end{aligned}$$

We estimate

$$\begin{aligned}
\int_0^\tau \int_\Omega & \left(\frac{1}{q} \partial_t (\phi(v) |\partial_t s|^q) + (q-1)(D_u \phi(v) - \delta_0 D_u |\phi' \partial_t v|) |\nabla \partial_t s|^2 |\partial_t s|^{q-2} \right) dx dt \\
&\quad + \int_0^\tau \int_\Omega \mu_u |s_t|^q \phi(v) (2\phi(v) s + v) \, dx dt \\
&\le \int_0^\tau \int_\Omega \frac{\alpha \phi(v) \chi(v)}{\delta_0 (q-1)} v m \left(\frac{q-2}{q} |s_t|^q + \frac{2}{q} |\nabla s|^q \right) dx dt \\
&\quad + \int_0^\tau \int_\Omega |s_t|^q \phi(v) \left(C \frac{q-1}{q} + \alpha \frac{\chi(v)}{D_u} v \left(\frac{q+1}{q} m + s \right) \right. \\
&\quad \left. + \mu_u (1 + 2 s \phi(v) + v) \right) dx dt \\
&\quad + \frac{1}{q} \int_0^\tau \int_\Omega (\alpha s \phi(v) m v)^q \left(\frac{\alpha}{D_u} \left(\frac{\chi^2(v)}{D_u} v m + \chi'(v) v m + \chi(v) m \right) \right)^q dx dt \\
&\quad + \frac{1}{q} \int_0^\tau \int_\Omega (\alpha s \phi(v) m v)^q \left(\mu_u \left(1 + \frac{\chi(v)}{D_u} (1 + s + s\phi(v) + v) \right) \right)^q dx dt \\
&\quad + \frac{1}{q} C \int_0^\tau \int_\Omega |s| |v| |\chi(v)| |\phi(v)| |m_t|^q \, dx dt.
\end{aligned}$$

In turn, testing Eq. (5.13) with a test function $|\partial_t m_t|^{q-2}\partial_t m$ yields

$$\int_0^\tau\int_\Omega \left(\frac{1}{q}\partial_t|m_t|^q + D_m(q-1)|\nabla m_t|^2|m_t|^{q-2} + \delta_m|m_t|^q\right)dxdt$$
$$\leq \int_0^\tau\int_\Omega \left(\frac{c}{\delta_0}|v||s_t|^q + \delta_0|m_t|^q + s(\phi'(v)\,v+\phi(v))\partial_t v|m_t|^{q-1}\right)dxdt$$
$$\leq \int_0^\tau\int_\Omega C_1\left(\sup_{(0,T)\times\Omega} v\,|s_t|^q + |m_t|^q + \sup_{(0,T)\times\Omega}\{s,v\}\,|m|^q\right)dxdt.$$

Combining both inequalities and using the Gronwall inequality supplies the estimates in the lemma. The boundedness of $\|s_t(0)\|_{L^q(\Omega)}$ and $\|m_t(0)\|_{L^q(\Omega)}$ follows from regularity of s_0 and m_0. □

Lemma 5.6. *Under the assumptions of Theorem 3.2, the following estimates hold*

$$\sup_{(0,T)}\|\nabla s\|^{2q}_{L^{2q}} \leq C\left(\sup_{(0,T)\times\Omega}\{v,m,s\}\right)\left(1+\sup_{(0,T)}\|\nabla v\|^{2q}_{L^{2q}} + \sup_{(0,T)}\|s_t\|^q_{L^q}\right),$$
$$\sup_{(0,T)}\|\Delta s\|^{q}_{L^{q}} \leq C\left(\sup_{(0,T)\times\Omega}\{v,m,s\}\right)\left(1+\sup_{(0,T)}\|\nabla v\|^{2q}_{L^{2q}} + \sup_{(0,T)}\|s_t\|^q_{L^q}\right),$$
$$\sup_{(0,T)}\|\nabla m\|^{2q}_{L^{2q}} \leq C\left(\sup_{(0,T)\times\Omega}\{v,m,s\}\right)\left(1+\sup_{(0,T)}\|m_t\|^q_{L^q}\right),$$
$$\sup_{(0,T)}\|\Delta m\|^{q}_{L^{q}} \leq C\left(\sup_{(0,T)\times\Omega}\{v,m,s\}\right)\left(1+\sup_{(0,T)}\|m_t\|^q_{L^q}\right).$$

Proof. From Eq. (2.6) we obtain

$$\int_\Omega|\Delta s|^q\,dx \leq C\int_\Omega\left(|\partial_t s|^q + \frac{\phi'(v)^q}{\phi(v)^q}|\nabla v|^q|\nabla s|^q\right)dx$$
$$+C\int_\Omega|s|^q\left(\left(\frac{\alpha}{D_u}\right)^q(\chi(v)vm)^q + \mu_u^q(1+s\phi(v)+v)^q\right)dx.$$

Using boundedness of the solution we obtain

$$\int_\Omega|\Delta s|^q\,dx \leq C\left(\|\partial_t s\|^q_{L^q(\Omega)} + \frac{\phi'(v)^q}{\phi(v)^q}\|\nabla v\|^q_{L^{2q}(\Omega)}\|\nabla s\|^q_{L^{2q}(\Omega)}\right)$$
$$+C\left(\sup_{(0,T)\times\Omega}\{v,m,s\}\right). \tag{5.14}$$

Then, using the Gagliardo−Nirenberg inequality (e.g. Ref. 9, Sec. 5.6.1) provides the estimate,

$$\|\nabla s\|^q_{L^{2q}} \leq \sup_{(0,T)\times\Omega}|s|^{q/2}\|s\|^{q/2}_{W^{2,q}(\Omega)} \leq C\left(\sup_{(0,T)\times\Omega}|s|\right)(\|s\|^{q/2}_{L^q(\Omega)} + \|\Delta s\|^{q/2}_{L^q(\Omega)}).$$

Thus, inequality (5.14) yields

$$\|\Delta s\|^q_{L^q(\Omega)} \leq C\|\partial_t s\|^q_{L^q(\Omega)} + C\left(\sup_{(0,T)\times\Omega}\{v,s\}\right)\|\nabla v\|^q_{L^{2q}(\Omega)}(\|\Delta s\|^{q/2}_{L^q(\Omega)} + \|s\|^{q/2}_{L^q(\Omega)})$$
$$+ C\left(\sup_{(0,T)\times\Omega}\{v,m,s\}\right).$$

Furthermore,

$$\|\Delta s\|^{q/2}_{L^q(\Omega)}$$
$$\leq C\left(\sup_{(0,T)\times\Omega}\{v,s\}\right)\|\nabla v\|^q_{L^{2q}(\Omega)} + C\sup_{(0,T)\times\Omega}\{v,s\}$$
$$\times\left(\|\nabla v\|^{2q}_{L^{2q}(\Omega)} + \|\nabla v\|^q_{L^{2q}(\Omega)} + \|\nabla v\|^q_{L^{2q}(\Omega)} + \|\partial_t s\|^q_{L^q(\Omega)} + \sup_{(0,T)\times\Omega} m\right)^{1/2}$$

and from the Gagliardo–Nirenberg inequality

$$\|\nabla s\|^{2q}_{L^{2q}(\Omega)} \leq C\sup_{(0,T)\times\Omega}\{|v|,|s|\}(\|\nabla v\|^{2q}_{L^{2q}(\Omega)} + \|\partial_t s\|^q_{L^q(\Omega)})$$
$$+ C\sup_{(0,T)\times\Omega}\{|v|,|m|,|s|\}.$$

The equation for m yields

$$|\Delta m|^q \leq C(|\partial_t m|^q + \delta_m^q|m|^q + \mu_m^q|v\phi(v)s|^q).$$

Using again the Gagliardo–Nirenberg inequality results in estimates for m

$$\|\nabla m\|^{2q}_{L^{2q}(\Omega)} \leq C(\|m\|^q_{L^q(\Omega)} + \|\Delta m\|^q_{L^q(\Omega)})$$
$$\leq C\|\partial_t m\|^q_{L^q(\Omega)} + C\left(\sup_{(0,T)\times\Omega}\{s,v,m\}\right)^q. \qquad \square$$

Iterating the estimates in Lemmas 5.3–5.6 in respect to q, we obtain the $L^\infty(0,T; W^{2,q}(\Omega))$ regularity of the solutions.

6. Boundedness of the Solutions of a Reduced Model

In several modeling cases system (2.1)–(2.5) was reduced to the two-equation system. Here we show that boundedness results hold also for the reduced system. Let us assume that the matrix degrading enzyme has only a local influence on the tissue, i.e. $D_m = 0$, and its dynamics is faster than that of cancer cells and of the ECM. This leads to reduction of the model to

$$\partial_t u = D_u\Delta u + \nabla(\chi u\nabla v) + \mu_u u(1-u-v),$$
$$\partial_t v = -\alpha u v^2.$$

A model of this form was examined by several authors (see for example Refs. 7, 22 and 27). Changing variables, as in three-equation model, leads to a reformulated model of the form

$$\partial_t s = D_u \Delta s - D \frac{\phi'(v)}{\phi(v)} \nabla v \nabla s + s(\alpha\phi'(v) s v^2 + \mu_u - \mu_u s\phi(v) - \mu_u v), \tag{6.1}$$

$$\partial_t v = -\alpha s \phi(v) v^2. \tag{6.2}$$

Equation (6.1) differs from Eq. (2.6) only in the form of the zero-order terms.

First we show the regularity of the solution s. Here we assume that Ω is a two-dimensional domain.

Lemma 6.1. *Assume* $n = 2$, $s_0, v_0 \in L^\infty(\Omega)$, $s_0, v_0 \in H^1(\Omega)$, s_0, v_0 *non-negative and* χ *continuous and positive. Then, it holds*

$$\sup_{(0,t)\times\Omega} s \le C\left(\sup_{\Omega} s_0 + (t+1)\left(f(t)\left(1 + \int_0^t (f^2(\tau) + f(\tau))d\tau\right) + 1\right)^{\gamma}\right), \quad t \in [0, \infty),$$

where $0 < \gamma \le 8$, $f(t) = \|s_0^2 \phi(v_0)\|_{L^1(\Omega)} \exp(c_1 t^2 + c_2 t)$, *and* s *is a solution of the model* (6.1)–(6.2).

Proof. Due to the maximum principle, the solutions are non-negative for nonnegative initial conditions. Then, the equation for v provides $v(x,t) \le \sup_\Omega v_0(x)$.

The Gagliardo–Nirenberg interpolation inequality for $n = 2$ implies

$$\|s\|_{L^4(\Omega)} \le c\|s\|^{1/2}_{H^1(\Omega)} \|s\|^{1/2}_{L^2(\Omega)}. \tag{6.3}$$

From equation for s and since $\phi(v) \ge 1$ we obtain that

$$\int_\Omega s\, dx \le \int_\Omega u_0\, dx + Ct, \qquad \int_0^t\int_\Omega s^2\, dxdt \le t\int_\Omega u_0\, dx + \frac{C}{2}t^2.$$

Using s as a test function in Eq. (6.1), the fact that $\phi(v)$ is bounded for a bounded v, $\phi'(v) = \chi(v)\phi(v)/D_u$, and the estimate (6.3) we obtain

$$\begin{aligned}
\partial_t \int_\Omega \phi(v) s^2\, dx &+ \int_\Omega D_u \phi(v) |\nabla s|^2\, dx + \mu_u \int_\Omega \phi(v)^2 s^3\, dx \\
&\le \frac{\alpha}{2D_u}\int_\Omega \chi(v)\phi^2(v) v^2 s^3\, dx + \mu_u \int_\Omega \phi(v) s^2\, dx \\
&\le c_1\left(\int_\Omega \phi(v) s^2\, dx\right)^{1/2}\left(\int_\Omega s^4\, dx\right)^{1/2} + \mu_u\int_\Omega \phi(v)s^2\, dx \\
&\le c_2 \frac{1}{\delta}\left(\int_\Omega \phi(v)s^2\, dx\right)^2 + c_4\delta\int_\Omega |\nabla s|^2\, dx + \mu_u \int_\Omega \phi(v)s^2\, dx.
\end{aligned}$$

The last estimate with $c_4\delta < D_u$ implies

$$\partial_t \int_\Omega \phi(v)s^2\,dx \le C_\delta\left(\int_\Omega \phi(v)s^2\,dx\right)^2 + \mu_u \int_\Omega \phi(v)s^2\,dx.$$

For $y = \int_\Omega \phi(v)s^2\,dx$ we obtain

$$\frac{dy}{y} \le C(y+1)dt \quad \text{and} \quad y \le y(0)e^{(C\int_0^t (y+1)dt)} = y(0)e^{(C_1t^2+C_2t)} = f(t).$$

Thus

$$\begin{aligned}\int_\Omega |s|^2\,dx + \int_0^t\int_\Omega (|\nabla s|^2 + |s|^3)\,dxd\tau \\ \le c_1\int_0^t (f^2(\tau)+f(\tau))d\tau + c_2\int_\Omega \phi(v_0)s_0^2\,dx.\end{aligned} \tag{6.4}$$

Testing Eq. (6.1) with $\partial_t s$ and using (6.3) we obtain

$$\begin{aligned}\int_\Omega \phi(v)|\partial_t s|^2\,dx + \frac{1}{2}\partial_t\int_\Omega D_u\phi(v)|\nabla s|^2\,dx + \frac{\alpha}{2}\int_\Omega D_u\phi'(v)\phi(v)v^2 s|\nabla s|^2\,dx \\ + \frac{\mu_u}{3}\int_\Omega \partial_t(\phi(v)^2 s^3)\,dx + \frac{2\mu_u\alpha}{3}\int_\Omega \phi'(v)\phi^2(v)v^2s^4\,dx \\ \le \frac{\alpha}{D_u}\int_\Omega \chi(v)\phi^2(v)v^2s^2\partial_t s\,dx + \mu_u\int_\Omega \phi(v)s\partial_t s dx \\ \le c_1\delta\int_\Omega |\partial_t s|^2\,dx + C_{3,\delta}\int_\Omega s^2\,dx\int_\Omega |\nabla s|^2\,dx + C_{2,\delta}\int_\Omega \phi(v)s^2\,dx.\end{aligned}$$

Integration with respect to t and estimate (6.4) imply

$$\begin{aligned}\int_0^t\int_\Omega \phi(v)|\partial_t s|^2\,dxd\tau + \int_\Omega (D_u\phi(v)|\nabla s|^2 + \phi(v)^2s^3)\,dx \\ + \int_0^t\int_\Omega \phi^3(v)\frac{\chi(v)}{D_u}v^2s^4\,dxd\tau \\ \le Cf(t)\left(1 + \int_0^t (f^2(\tau)+f(\tau))d\tau\right) \\ + \int_\Omega D_u\phi(v_0)|\nabla s_0|^2\,dx + \int_\Omega \phi(v_0)^2 s_0^3\,dx.\end{aligned}$$

Using similar approach as in Ref. 20 we show the estimate for $\sup_{(0,t)\times\Omega} s$. Choosing $\varphi = \eta(s)(s-k)_+$ with $k \ge \sup_\Omega s_0$ as a test function, where

$$0 \le \frac{\eta'(s)(s-k)}{\eta(s)} \le k_1, \qquad \int_k^s \eta(r)(r-k)dr \ge \frac{1}{2+k_1}\eta(s)(s-k)^2 \quad \text{for } s \ge k,$$

we obtain

$$\begin{aligned}
\partial_t \int_\Omega \phi(v) \int_0^s \eta(r)(r-k)_+ \, drdx + \alpha \int_\Omega \phi'(v)\, v^2 \, \phi(v)\, s \int_0^s \eta(r)(r-k)_+ \, drdx \\
+ \int_\Omega D_u \phi(v)\eta(s)\nabla s \nabla s \, dx + \int_\Omega D_u \phi(v)\eta'(s)(s-k)_+ \nabla s \nabla s \, dx \\
+ \mu_u \int_\Omega s^2 \phi^2(v)\eta(s)(s-k)_+ \, dx + \mu_u \int_\Omega s\phi(v) v\eta(s)(s-k)_+ \, dx \\
= \alpha \int_\Omega \phi'(v)\phi(v) v^2 s(s-k+k)\eta(s)(s-k)_+ \, dx + \mu_u \int_\Omega \phi(v)\, s\eta(s)(s-k)_+ \, dx.
\end{aligned}$$

The first term on the right-hand side can be estimated using the Gagliardo−Nirenberg inequality

$$\begin{aligned}
&\alpha \int_\Omega \phi'(v)\phi(v) v^2 s\eta(s)(s-k)^2 \, dx \\
&\quad \le C_1 \left(\int_\Omega s^3 \, dx \right)^{1/3} \left(\int_\Omega (((s-k)_+)^2 \eta(s))^{3/2} \, dx \right)^{2/3} \\
&\quad \le C \left(\int_\Omega s^3 \, dx \right)^{1/3} \left(\int_\Omega s^2 \eta(s) \, dx \right)^{2/3} \\
&\qquad \times \left(\int_\Omega (|\nabla((s-k)_+ \eta^{1/2}(s))|^2 + \eta(s) s^2) \, dx \right)^{1/3} \\
&\quad \le C\delta \int_\Omega (\eta(s)|\nabla s|^2 + s^2 \eta(s)) \, dx + C_\delta (k_1 + 1) \\
&\qquad \times \left(\int_\Omega s^3 \, dx \right)^{1/2} \left(\int_\Omega s^2 \eta(s) \, dx \right).
\end{aligned}$$

For $\eta(s) = s^{2q-2}((1-\frac{k}{s})_+)^{(n+2)q-n-2}$ and $h(s) = s^q(((1-\frac{k}{s})_+)^{(n+2)q-n})^{1/2}$ we obtain

$$\begin{aligned}
&\sup_{(0,t)} \int_\Omega h^2 \, dx + \int_0^t \int_\Omega |\nabla h|^2 \, dx d\tau \\
&\quad \le C q^4 \left(\sup_{(0,t)} \|s\|^{\frac{3}{2}}_{L^3(\Omega)} + 1 \right) \int_0^t \int_\Omega |h|^2 \left(\left(1 - \frac{k}{s} \right)_+ \right)^{-2} dx d\tau.
\end{aligned}$$

The Sobolev Embedding Theorem implies for $\kappa = (n+2)/n$

$$\left(\int_0^t \int_\Omega |w|^{\kappa q} d\mu \right)^{1/(\kappa q)} \le \left(C_1 q^4 \sup_{(0,t)} \|s\|^{\frac{3}{2}}_{L^3(\Omega)} + C_2 q^4 \right)^{1/q} \left(\int_0^t \int_\Omega |w|^q d\mu \right)^{1/q},$$

where $w = s^2(1-\frac{k}{s})^{n+2}$, $d\mu = ((1-\frac{k}{s})_+)^{-n-2} \, dx d\tau$. Choosing $q = 1, \kappa, \kappa^2, \ldots, \kappa^j, \ldots$ and letting $j \to \infty$ we obtain, for some constant $0 < \gamma \le 8$,

$$\begin{aligned}
&\sup_{(0,t)\times\Omega} s^2((1-k/s)_+)^{n+2} \\
&\quad \le C_1 \left(f(t) \left(1 + \int_0^t (f^2(\tau) + f(\tau)) d\tau \right) + C_2 \right)^\gamma \int_0^t \int_\Omega s^2 \, dx d\tau.
\end{aligned}$$

Thus

$$\sup_{(0,t)\times\Omega} s \le 2k + C\Big(f(t)\Big(1+\int_0^t (f^2(\tau)+f(\tau))d\tau\Big)+C\Big)^{\gamma}\|s\|_{L^2((0,t)\times\Omega)}$$
$$\le 2\sup_{\Omega} s_0 + C(C_1 t + C_2)\Big(f(t)\Big(1+\int_0^t (f^2(\tau)+f(\tau))d\tau\Big)+C\Big)^{\gamma}. \qquad \square$$

We solve ordinary differential equation for v, i.e. $v(t,x)=\psi(t,x,s)$, and obtain

$$\partial_t s = D_u\Delta s - D_u\frac{\phi'(\psi)}{\psi}\nabla\psi\nabla s + s(\alpha\phi'(\psi)s\psi^2 + \mu_u - \mu_u s\phi(\psi) - \mu_u\psi).$$

To show uniform boundedness of solutions for this system, we have to ensure that there exists $\bar{s}$ such that

$$\bar{s}(\alpha\phi'(v)\bar{s}\psi^2 + \mu_u - \mu_u\bar{s}\phi(\psi) - \mu_u\psi) \le 0 \quad \text{for all } t\ge 0, \quad x\in\bar{\Omega}.$$

Using expression for $\phi'(\psi)$ and positivity of $\bar{s}$, we obtain an equivalent inequality,

$$\Big(\frac{\alpha}{D_u}\phi(\psi)\chi(\psi)\bar{s}\psi^2 + \mu_u - \mu_u\bar{s}\phi(\psi) - \mu_u\psi\Big) \le 0,$$

which can be rewritten as

$$\bar{s}\phi(\psi)\Big(\mu_u - \frac{\alpha}{D}\chi(\psi)\psi^2\Big) \ge \mu_u(1-\psi).$$

Since ψ is positive, it is enough to show that there exists $\bar{s}$ such that

$$\bar{s}\phi(\psi)\Big(\mu_u - \frac{\alpha}{D}\chi(\psi)\psi^2\Big) \ge \mu_u. \tag{6.5}$$

Using Eq. (6.2) we obtain

$$\partial_t v = -\alpha s v^2\phi(v) \le -\alpha s v^2,$$

that yields

$$\psi(t,x,s) = v(t,x) \le \frac{v_0(x)}{1+v_0(x)\alpha\int_0^t s(\tau,x)d\tau}.$$

The estimate of Lemma 6.1 implies that s is bounded in any finite time point t and therefore, s is uniformly bounded or $\int_0^t s(\tau,x)d\tau$ is growing with respect to time t. Boundedness of $0\le\chi\le B$ (see assumptions on χ, Theorem 3.1) implies that for every point $x\in\bar{\Omega}$ there exists $t^*\in(0,\infty)$ such that

$$\mu_u - \frac{\alpha}{D}\chi v^2 \ge \mu_u - \frac{\alpha}{D}B\frac{v_0^2}{(1+v_0\alpha\int_0^{t^*} s(\tau,x)\,d\tau)^2} \ge \delta,$$

for some $\delta>0$. In turn, the last inequality yields that there exists $\bar{s}$ such that inequality (6.5) is fulfilled. This proves the boundedness of the solution (u,v) of the reduced system.

7. Discussion

In this paper we have shown global existence of the solutions of a model of cancer invasion given in the form of a nonlinear reaction-diffusion-taxis equation coupled with an ordinary differential equation and a reaction-diffusion equation. The model was proposed by Anderson and colleagues,[1] to describe cancer cell proliferation, diffusion and movement along the gradient of the density of adhesive components of extracellular matrix. lt includes key features of the growth and invasion of a solid tumor in its avascular stage, i.e. cell proliferation, random motility, haptotaxis and extracellular matrix degradation. The model, or its discrete counterpart, were applied by many authors to study different aspects of cancer invasion.[2,4,5,32,33,28]

We have shown that the solutions of the model are non-negative and uniformly bounded for non-negative initial conditions. Boundedness of solutions has been shown using the framework of bounded invariant rectangles applied to the transformed system in the form of reaction-diffusion equations with a convection term. Since the change of variables leads to a model with modified zeroth-order term in the first equation, the bound on the solutions can be different from the bound given by a zeroth-order term of logistic type. It is observed in the numerical simulations, see Fig. 1 and the simulations presented in Ref. 32, that sum of concentrations $u + v$ might be larger than the threshold given in the logistic growth function (the carrying capacity). The analysis performed here explains this observation. The zeroth-order term in the reformulated parabolic system includes an additional non-negative term, which depends on the rate of ECM degradation by the MDE, and also on the ratio of the sensitivity function to the diffusion coefficient. Therefore, the sum of the solutions $u + v$ may exceed the bound given in the logistic growth term. Moreover, we see that if the sensitivity function is large in comparison to the diffusion rate, i.e. haptotaxis is

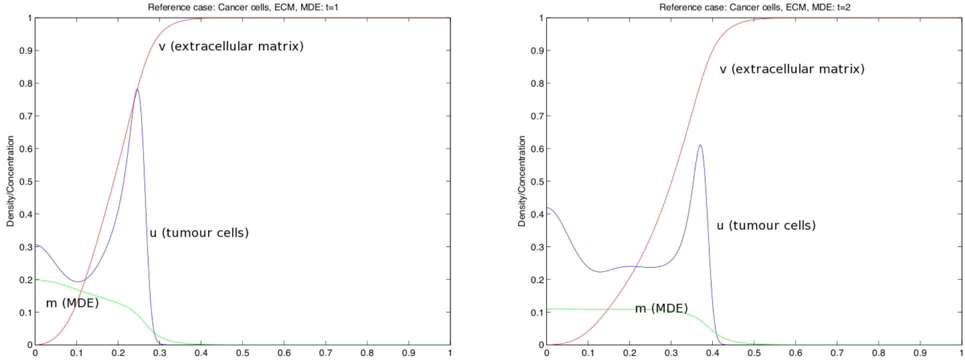

Fig. 1. Numerical simulations of the model (2.1)−(2.3) showing the evolution of the density of cancer cells (u) and the concentrations of ECM (v) and MDEs (m) in different time points. The figures show that in some spatial points x the sum of concentrations $u + v$ exceeds the carrying capacity 1. Simulations were performed for the set of parameters $D_u = 0.00035$, $D_m = 0.00491$, $\chi_u = 0.0285$, $\mu_u = 1$, $\mu_m = 0.5$, $\alpha = 8.15$, $\delta_m = 0.5$.

relatively strong, the solution u describing cancer cell concentration may itself grow above the logistic bound.

The logistic zeroth-order term in the first equation corresponds to the assumption that the proliferation of cells ceases when space is exhausted. If $u + v = 1$, there is no more proliferation, and if $u + v > 1$, the "proliferation term" becomes negative. It could be interpreted as cell death occurring if the cell concentration is too high. In this sense, there is competition between the cells and the ECM. However, cells may still migrate to the area of high density of cells and ECM. To prevent this, it is possible to consider a model with a nonlinear haptotaxis term and a sensitivity function χ vanishing when $u + v \geq 1$, similarly as it was done by Hillen and Painter.[11] This corresponds to the assumption that haptotaxis is switched off at high cell densities by a population-sensing mechanism. The analysis performed in this paper indicates that modeling of cell proliferation is a more delicate issue than frequently believed. Specifically, assuming the logistic growth term in the model with haptotaxis has different implications than in the models of reaction-diffusion equations.

Appendix A. Regularization of the System

In order to prove *a priori* estimates and to use the maximum principle and the framework of invariant rectangles we have to regularize the system. The equation for v can be regularized by the convolution as follows:

$$\partial_t v^\varepsilon = -\alpha v^\varepsilon (m^\varepsilon * \rho^\varepsilon)$$

for some regularizing kernel $\rho^\varepsilon = \frac{1}{\varepsilon^N}\rho(\frac{x}{\varepsilon})$ with $\rho \in D^+(\mathcal{R}^N)$, $\int_{\mathcal{R}^N} \rho\, dx = 1$. Since the Neumann boundary conditions are assumed, m can be extended into a domain $\tilde{\Omega}$, $\Omega \subset\subset \tilde{\Omega}$, with zero at $\partial\tilde{\Omega}$ using reflection and truncation. This implies that the convolution $m^\varepsilon * \rho^\varepsilon$ is defined in the whole Ω. Here ρ^ε can be chosen as an approximation of the Dirac distribution. The initial conditions are approximated by smooth functions. Then, the system of parabolic equations admits a unique smooth solution.

Since *a priori* estimates for the approximation $(u^\varepsilon, v^\varepsilon, m^\varepsilon)$ hold uniformly in ε, we can pass to the limit in the approximate equations and obtain the solution (u, v, m) of the original system that remains non-negative and bounded.

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