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GLOBAL EXISTENCE OF CLASSICAL SOLUTIONS FOR A HAPTOTAXIS MODEL*

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Abstract. A system of nonlinear partial differential equations modeling haptotaxis is investigated. The model arises in cell migration processes involved in tumor invasion. The existence of unique global classical solutions is proved.

Key words. haptotaxis, diffusion, global existence, uniqueness, classical solutions

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1. Introduction.

Models of complex dynamic biological processes frequently involve systems of nonlinear partial differential equations for production, growth, decay, interaction, and spatial movement. For models that include spatial movement the equations typically contain both diffusion and taxis terms. Our goal in this paper is to examine the issues of global existence and uniqueness for a model involving spatial movement and haptotaxis. The term *haptotaxis* originated with S. B. Carter in 1965: "...the movement of a cell is controlled by the relative strengths of its peripheral adhesions, and that movements directed in this way, together with the influence of patterns of adhesion on cell shape are responsible for the arrangement of cells into complex and ordered tissues" [8]. Cell movement in morphogenesis, inflammation, wound healing, tumor invasion, and other migrations are the result of haptotactic responses of cells to differential adhesion strengths [8, 9].

The haptotaxis model we investigate here is a simplified version of a model proposed by Anderson [5] in 2005 to describe tumor invasion into surrounding tissue (see also [6]). The model involves four key components of the process: tumor cells, surrounding tissue macromolecules, degradative enzymes, and oxygen. The model in [5] hybridizes continuum partial differential equations and cellular automata formulations to incorporate cell cycle elements, and a similar model in [7] uses continuum cell age structure for the same purpose. Both of these investigations model other features of tumor invasion, including the role of quiescent cells and the evolution of mutated cell lines of increasingly invasive aggressiveness. Our objective is to investigate the simplified system of four nonlinear partial differential equations which underlie the models in [5] and [7]. The mathematical formulation of haptotaxis is similar to that of more familiar chemotaxis processes for which we refer to the survey article [16] and the extensive list of references therein. Haptotaxis in tumor growth, however, possesses unique features in that the movement of tumor cells is directed to the bound (i.e., nondiffusible) extracellular environment, which supplies essential oxygen and available space, as it is degraded by the tumor-produced degradative enzyme. The mathematical difficulty in treating haptotaxis in this context is that the

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haptotaxis term is nonlinearly dependent on the tumor cells through the diffusion of the degradative enzyme produced by these cells.

We make the following assumptions: The tumor is contained in a region of tissue Ω. The dependent variables of the model are as follows: $p(x,t)$ is the density of tumor cells at $x \in \Omega$ at time t, $m(x,t)$ is the concentration of matrix degradative enzyme (MDE) at $x \in \Omega$ at time t, $f(x,t)$ is the density of extracellular matrix macromolecules at $x \in \Omega$ at time t, and $w(x,t)$ is the concentration of oxygen at $x \in \Omega$ at time t. The equations of the model are as follows:

$$(H_1) \qquad \partial_t f \;=\; -\underbrace{a(x)\,m\,f}_{\text{degradation}}\,,$$

$$(H_2) \qquad \partial_t m \;=\; \underbrace{\alpha\,\Delta m}_{\text{diffusion}} \;+\; \underbrace{d(x)\,p}_{\text{production}} \;-\; \underbrace{b(x)\,m}_{\text{decay}}\,,$$

$$(H_3) \qquad \partial_t p \;=\; \underbrace{\beta\,\Delta p}_{\text{cell motility}} \;-\; \underbrace{\nabla\cdot(p\,\chi(f)\,\nabla f)}_{\text{haptotaxis}} - \underbrace{\theta(x,w)\,p}_{\text{cell death}} + \underbrace{\varrho(x,w)\,p}_{\text{cell division}}\,,$$

$$(H_4) \qquad \partial_t w \;=\; \underbrace{\gamma\,\Delta w}_{\text{diffusion}} \;+\; \underbrace{g(x)\,f}_{\text{production}} \;-\; \underbrace{\omega(x,p)\,w}_{\text{uptake}} \;-\; \underbrace{e(x)\,w}_{\text{decay}}$$

for $(t,x) \in (0,\infty)\times\Omega$ supplemented with Neumann boundary conditions

$$(H_5) \qquad \partial_\nu m \;=\; \partial_\nu p \;-\; p\chi(f)\partial_\nu f \;=\; \partial_\nu w \;=\; 0 \quad \text{on } \partial\Omega$$

and initial conditions

$$(H_6) \qquad f(0) \;=\; f^0\,, \quad m(0) \;=\; m^0\,, \quad p(0) \;=\; p^0\,, \quad w(0) \;=\; w^0\,.$$

It seems that (H_1)–(H_6) have not been considered analytically thus far, but rather related equations of the form

$$\partial_t f \;=\; h(p,f), \tag{1}$$

$$\partial_t p \;=\; \beta\,\Delta p \;-\; \nabla\cdot\big(p\,\chi(f)\,\nabla f\big) \tag{2}$$

have attracted attention, in particular the case

$$h(p,f) \;=\; \sigma\,p\,f^r \quad \text{with} \quad \sigma = \pm 1 \quad \text{and} \quad r > 0\,. \tag{3}$$

We refer to [13] for the case of general functions h satisfying suitable hypotheses. As for (1), (2) with h of the form (3), we refer to [10, 11, 12, 17, 19, 20, 21, 23], where existence of solutions and phenomena such as blowup or stability of steady states are investigated depending on the sign of σ, on r, and on the sensitivity χ.

We point out that our model differs from (1), (2), (3) with $\sigma = -1$, in that the ordinary differential equation in (H_1) is coupled to (H_3) via the "intermediate" equation (H_2).

Solving (H_3) or (2) classically requires that f have second order derivatives (with respect to x) in some L_q-space. In our model the regularity of f is determined by m for which one has a smoothing effect due to (H_2). This induces the regularity that allows us to derive an L_q-bound on p, which is sufficient to deduce global existence for $n \le 3$ and without smallness assumptions on the initial data. As for (1)–(3), the regularity of f is determined by p. Thus, the second order derivatives of p should also be in L_q. Local existence and uniqueness of "smooth" solutions for (1)–(3) can be obtained using maximal regularity for the p-equation (2). However, global existence then requires estimates on p that are stronger than L_q-estimates and which are far from obvious.

In order to state our main result regarding the solvability of (H_1)–(H_6) we assume that Ω is a bounded and smooth domain in $\mathbb{R}^n$, $n \leq 3$, and that the diffusion coefficients α, β, and γ are positive constants. Concerning the data in (H_1)–(H_4) we assume throughout that there exists some $s > 0$ such that

$$\begin{cases} a \in W^2_\infty(\Omega) \ , \quad \partial_\nu a = 0 \text{ on } \partial\Omega \ , \\ b \, , \, d \in C^s(\bar{\Omega}) \ , \quad g \, , \, e \in L_\infty(\Omega) \ , \end{cases} \tag{4}$$

and that all functions are nonnegative. We also assume that

$$\chi \in C^1(\mathbb{R}^+) \ , \qquad \chi \geq 0 \ , \qquad \chi \text{ and } \chi' \text{ are globally Lipschitz continuous.} \tag{5}$$

Furthermore, regarding ϱ, θ, $\omega \in C(\bar{\Omega} \times \mathbb{R}, \mathbb{R}^+)$ we suppose that, for some $c_0 > 0$,

$$|\phi(x,\eta) - \phi(x,\bar{\eta})| \leq c_0 \, |\eta - \bar{\eta}| \ , \quad x \in \Omega \ , \quad \eta \, , \, \bar{\eta} \in \mathbb{R} \ , \quad \phi \in \{\varrho, \theta, \omega\} \ . \tag{6}$$

Note that this implies, for some $c > 0$,

$$|\phi(x,\eta)| \leq c \, (1 + |\eta|) \ , \quad x \in \Omega \ , \quad \eta \in \mathbb{R} \ , \quad \phi \in \{\varrho, \theta, \omega\} \ . \tag{7}$$

To simplify the notation we put $\vartheta := \varrho - \theta$.

For brevity of notation we set $L_q := L_q(\Omega)$ and $W^\tau_q := W^\tau_q(\Omega)$ for $1 \leq q \leq \infty$ and $\tau \geq 0$. Moreover, we denote by $W^\tau_{q,\mathcal{B}} := W^\tau_{q,\mathcal{B}}(\Omega)$ the Sobolev–Slobodeckii spaces including the Neumann boundary conditions, that is,

$$W^\tau_{q,\mathcal{B}} := \begin{cases} \{ u \in W^\tau_q \, ; \, \partial_\nu u = 0 \} \ , & \tau > 1 + 1/q \ , \\ W^\tau_q \ , & 0 \leq \tau < 1 + 1/q \ . \end{cases}$$

If $J \subset \mathbb{R}^+$ is an interval containing 0, we set $\dot{J} := J \setminus \{0\}$.

We shall prove then the following result.

THEOREM 1.1. *Let assumptions* (4)–(6) *be satisfied, and let* $(1 \vee n/2) < q < \infty$ *and* $2\delta \in (0,2) \setminus \{1 + 1/q\}$. *Given any nonnegative initial value*

$$(f^0, m^0, p^0, w^0) \in W^2_{q,\mathcal{B}} \times W^{2\delta}_{q,\mathcal{B}} \times L_q \times L_q$$

there exists a global nonnegative solution (f, m, p, w) *to* (H_1)–(H_6) *such that*

$$\begin{aligned} & f \in C(\mathbb{R}^+, W^2_{q,\mathcal{B}}) \cap C^1(\dot{\mathbb{R}}^+, W^2_{q,\mathcal{B}}) \ , \\ & m \in C(\mathbb{R}^+, W^{2\delta}_{q,\mathcal{B}}) \cap C(\dot{\mathbb{R}}^+, W^2_{q,\mathcal{B}}) \cap C^1(\dot{\mathbb{R}}^+, L_q) \ , \\ & p \in C(\mathbb{R}^+, L_q) \cap C(\dot{\mathbb{R}}^+, W^2_{q,\mathcal{B}}) \cap C^1(\dot{\mathbb{R}}^+, L_q) \ , \\ & w \in C(\mathbb{R}^+, L_q) \cap C(\dot{\mathbb{R}}^+, W^2_{q,\mathcal{B}}) \cap C^1(\dot{\mathbb{R}}^+, L_q) \ . \end{aligned}$$

This solution satisfies

$$t^\eta \, \|p(t)\|_{W^{2\eta}_q} \to 0 \quad \textit{and} \quad t^\lambda \, \|m(t)\|_{W^2_q} \to 0 \quad \textit{as} \quad t \to 0^+ \tag{8}$$

for all (η, λ) *such that*

$$n/q < 2\eta < 2 \ , \quad 2\eta \geq 1 \ , \quad (1-\delta) \vee \eta \leq \lambda < 1 \ , \tag{9}$$

and it is the only solution satisfying (8) *for some* (η, λ) *as in* (9).

Remarks 1.2. (a) Except for (H_1), which lacks a smoothing effect due to diffusion, the regularity assumptions on the initial values and the restriction on the integrability index q seem to be fairly weak. In particular, we do not impose bounded initial values or assume that $q > n$, and also the Sobolev regularity on m^0 can be arbitrary low.

(b) The no-flux boundary condition on p in (H_5) is correct from a modeling point of view, since neither diffusion nor haptotaxis should change the tumor mass. Notice that it reduces to a Neumann boundary condition $\partial_\nu p(t) = 0$ provided that $\partial_\nu f(t) = 0$. The latter is guaranteed due to the imposed Neumann boundary conditions on f^0 and a. Thus, these assumptions decouple p and f on the boundary.

(c) The solution depends continuously on the initial value in the sense stated in Proposition 3.1.

(d) The local existence and uniqueness statement of the theorem above is also true for space dimensions $n > 3$ as it follows from the proof given below.

We state the following simplified version of the above theorem for the particular case $q > n$.

COROLLARY 1.3. *Let* a, b, d, e, g *be nonnegative constants and suppose* (5), (6). *If* $q > n$, *then problem* (H_1)–(H_6) *has, for any nonnegative initial value*

$$(f^0, m^0, p^0, w^0) \in X := W_q^2 \times W_q^1 \times W_q^1 \times L_q$$

such that $\partial_\nu f^0 = 0$, *a unique global nonnegative classical solution* (f, m, p, w) *in the space* $C(\mathbb{R}^+, X)$.

A proof of Corollary 1.3 could be obtained by applying the general semigroup theory for semilinear parabolic problems. However, we shall point out that Theorem 1.1 actually ensures existence and uniqueness of classical solutions under considerably weaker assumptions on the integrability index q but also on the regularity of the initial values p^0 and m^0. Also note that any classical solution belonging to $C(\mathbb{R}^+, X)$ satisfies (8) for some (η, λ) as in (9). In this sense, the uniqueness (and existence) result stated in Theorem 1.1 is more general than in Corollary 1.3.

The outline of this paper is as follows: In section 2 we collect some auxiliary results which are used in the proof of local existence and uniqueness of solutions in section 3. Section 4 is devoted to positivity of solutions, and in section 5 we prove global existence. In section 6 some numerical examples are given in order to illustrate the role of haptotaxis in spatial movement. In section 7 we summarize our results.

2. Preliminaries.

In what follows, we denote for $1 < q < \infty$ by $\Delta := \Delta_q$ the Laplace operator defined on $W^2_{q,\mathcal{B}}$ and observe that it generates a positive, strongly continuous analytic semigroup $\{e^{t\Delta}\,;\, t \geq 0\}$ of contractions on L_q [1, 22]. Moreover, we will use the inequality

$$\|e^{t\Delta}\|_{\mathcal{L}(W^{2\sigma}_{q,\mathcal{B}}, W^{2\tau}_{q,\mathcal{B}})} \leq c(T)\, t^{\sigma-\tau} \ , \quad 0 < t \leq T \ , \tag{10}$$

which is true provided that $0 \leq 2\sigma \leq 2\tau \leq 2$ with $2\sigma, 2\tau \neq 1 + 1/q$, where $c(T)$ depends on the involved parameters. We also use the inequality

$$\|e^{t\Delta}\|_{\mathcal{L}(L_q, L_p)} \leq c(T)\, t^{-(1/q-1/p)n/2} \ , \quad t \in (0, T] \ , \tag{11}$$

for $1 < q \le p \le \infty$. Given $\xi > 0$ we then put $U_\xi(t) := e^{t\xi\Delta}$. Furthermore, for any measurable function $u : \dot{J} \to L_q$ we set

$$U_\xi \star u(t) := \int_0^t U_\xi(t-s)\, u(s)\, \mathrm{d}s\ , \quad t \in \dot{J}\ ,$$

whenever these integrals exist. If E is a Banach space and $\mu \in \mathbb{R}$, we denote by $BC_\mu(\dot{J}, E)$ the Banach space of all functions $u : \dot{J} \to E$ such that $\big(t \mapsto t^\mu u(t)\big)$ is bounded and continuous from $\dot{J}$ into E, equipped with the norm

$$u \mapsto \|u\|_{C_\mu(\dot{J},E)} := \sup_{t\in\dot{J}} t^\mu\, \|u(t)\|_E\ .$$

We write $C_\mu(\dot{J}, E)$ for the closed linear subspace consisting of all u satisfying $t^\mu u(t) \to 0$ in E as $t \to 0^+$. Note that $C_\nu((0,T], E) \hookrightarrow C_\mu((0,T], E)$ for $\nu \le \mu$ and $T > 0$.

For later use we state the following auxiliary result on pointwise multiplication.

LEMMA 2.1. *Suppose that* $n/q < 2\eta$ *with* $2\eta \ge 1$ *and let* $0 < 2r < (s \wedge 2\eta)$. *Then pointwise multiplication is a continuous mapping*

(i) $W_q^{2\eta} \times L_q \to L_q$,

(ii) $W_q^{2\eta-1} \times W_q^1 \to L_q$,

(iii) $C^s(\bar{\Omega}) \times W_q^{2\eta} \to W_q^{2r}$.

Proof. (i) follows from the embedding $W_q^{2\eta} \hookrightarrow L_\infty$, while statements (ii) and (iii) are easy consequences of [2, Thm. 4.1]. ∎

Evidently, given suitable functions $f^0 = f^0(x)$ and $m = m(x,t)$, the solution to (H_1) is

$$F_1(m) := F_1[f^0](m) := \left[t \mapsto \exp\left(-\int_0^t am(s)\mathrm{d}s\right) f^0\right]\ .$$

Note then that the gradient and the Laplacian take the form

$$\nabla F_1(m)(t) = \exp\left(-\int_0^t am(s)\mathrm{d}s\right)\left[\nabla f^0 - \int_0^t \nabla(am)(s)\mathrm{d}s\, f^0\right] \tag{12}$$

and

$$\begin{aligned}\Delta F_1(m)(t) &= \exp\left(-\int_0^t am(s)\mathrm{d}s\right)\left[\Delta f^0 - \int_0^t \Delta(am)(s)\mathrm{d}s\, f^0\right.\\ &\qquad\left. + \left|\int_0^t \nabla(am)(s)\mathrm{d}s\right|^2 f^0 - 2\int_0^t \nabla(am)(s)\mathrm{d}s\cdot\nabla f^0\right]\ .\end{aligned} \tag{13}$$

In particular, (12) warrants that $\partial_\nu F_1(m)(t) = 0$ provided $\partial_\nu f^0 = \partial_\nu m(t) = 0$ for all t since $a \in W^2_{\infty,\mathcal{B}}$. Furthermore, F_1 has the following properties.

LEMMA 2.2. *For* $0 < T \le T_0$ *put* $I := [0,T]$. *If* $(1 \vee n/2) < q < \infty$ *and* $f^0 \in W^2_{q,\mathcal{B}}$, *there holds*

(i) $F_1(m) \in C^1(I, W^2_{q,\mathcal{B}})$ *for* $m \in C(I, W^2_{q,\mathcal{B}})$;

(ii) $F_1(m) \in C(I, W^2_{q,\mathcal{B}})$ *for* $m \in C_\mu(\dot{I}, W^2_{q,\mathcal{B}})$ *and* $\mu < 1$, *and for* $R_0 > 0$ *there exists a constant* $k := k(T_0, R_0) > 0$ *such that*

$$\|F_1(m) - F_1(\bar{m})\|_{C(I,W^2_{q,\mathcal{B}})} \le k\, \|f^0\|_{W^2_q}\, T^{1-\mu}\, \|m - \bar{m}\|_{C_\mu(\dot{I},W^2_{q,\mathcal{B}})}$$

provided $\|m\|_{C_\mu(\dot{I},W^2_{q,\mathcal{B}})}\, ,\ \|\bar{m}\|_{C_\mu(\dot{I},W^2_{q,\mathcal{B}})} \le R_0$.

Proof. (i) Fix $m \in C(I, W^2_{q,\mathcal{B}}) \hookrightarrow C(I, L_\infty)$ and temporarily set $F_1 := F_1(m)$. Owing to Lemma 2.1, (4), and (13) we deduce $(1+\Delta)F_1 \in C(I, L_q)$, from which it follows that $F_1 \in C(I, W^2_{q,\mathcal{B}})$ since $\partial_\nu F_1 = 0$. Clearly, this implies $F_1 \in C^1(I, W^2_{q,\mathcal{B}})$ owing to $\partial_t F_1 = -amF_1$ and the fact that pointwise multiplication is a continuous mapping from $W^2_{q,\mathcal{B}} \times W^2_{q,\mathcal{B}}$ into $W^2_{q,\mathcal{B}}$.

(ii) Given $m, \bar{m} \in C_\mu(\dot{I}, W^2_{q,\mathcal{B}})$ with norm less than $R_0 > 0$, we have

$$\int_0^t \|m(s)\|_\infty \, \mathrm{d}s \,\le\, c \int_0^t \|m(s)\|_{W^2_q} \, \mathrm{d}s \,\le\, c(R_0)\, t^{1-\mu} \ , \quad t \in I \ .$$

This yields for $0 \le t \le T$

$$\begin{aligned} \|F_1(m)(t) - F_1(\bar{m})(t)\|_{L_q} \,&\le\, c(T_0, R_0) \int_0^t \|m(s) - \bar{m}(s)\|_\infty \, \mathrm{d}s \, \|f^0\|_{L_q} \\ &\le\, c(T_0, R_0)\, \|f^0\|_{L_q}\, T^{1-\mu}\, \|m - \bar{m}\|_{C_\mu(\dot{I}, W^2_{q,\mathcal{B}})} \ . \end{aligned}$$

Similarly, Lemma 2.1 and (13) entail

$$\|\Delta F_1(m)(t) - \Delta F_1(\bar{m})(t)\|_{L_q} \,\le c(T_0, R_0)\, \|f^0\|_{W^2_q}\, T^{1-\mu}\, \|m - \bar{m}\|_{C_\mu(\dot{I}, W^2_{q,\mathcal{B}})}$$

for $0 \le t \le T$, and the assertion follows. ∎

LEMMA 2.3. *Let $1 < q < \infty$, $2\sigma \in (0,2) \setminus \{1 + 1/q\}$ and $T, \xi > 0$. Then*

(i) *$U_\xi u := [t \mapsto U_\xi(t)u] \in C_\sigma\big((0,T], W^{2\sigma}_{q,\mathcal{B}}\big)$ for $u \in L_q$;*

(ii) *$U_\xi u = [t \mapsto U_\xi(t)u] \in C_{1-\sigma}\big((0,T], W^2_{q,\mathcal{B}}\big)$ for $u \in W^{2\sigma}_{q,\mathcal{B}}$.*

Proof. The proof of [4, Prop. 6] is easily adapted to the case (i). In much the same way one shows (ii). ∎

3. Local existence and uniqueness.

In the following we use the abbreviations

$$\begin{aligned} S(m,p) \,&:=\, d\,p \,-\, b\,m \ , \\ Q(f,p,w) \,&:=\, -\nabla \cdot \big(p\,\chi(f)\,\nabla f\big) \,+\, \vartheta(w)\,p \ , \\ R(f,p,w) \,&:=\, -\,e\,w \,-\, \omega(p)\,w \,+\, g\,f \ . \end{aligned}$$

Here and below we denote by $\vartheta(w)$ and $\omega(p)$ the Nemitskii operators of $\vartheta(\cdot, w)$ and $\omega(\cdot, p)$, respectively; that is, we set $\phi(u) := [x \mapsto \phi(x, u(x))]$ for $\phi \in \{\vartheta, \omega\}$ and $u : \Omega \to \mathbb{R}$.

The proof of the existence and uniqueness statement of Theorem 1.1 is based on the next result.

PROPOSITION 3.1. *Let $1 < q < \infty$ and $n/q < 2\eta \le 2\xi \le 2\mu < 2$ with $2\eta \ge 1$. Given $B \ge 1$ there exists $T := T(B) > 0$ such that, for any*

$$u^0 := \big(f^0, m^0, p^0, w^0\big) \in E := W^2_{q,\mathcal{B}} \times W^{2(1-\mu)}_{q,\mathcal{B}} \times L_q \times L_q$$

with $\|u^0\|_E \le B$, the problem

$$\text{(M)} \qquad \begin{cases} f(t) = \exp\big(-\int_0^t am(s)\mathrm{d}s\big) f^0 \ , & t \in I \ , \\ m(t) = U_\alpha(t)\, m^0 \,+\, U_\alpha \star S(m,p)(t) \ , & t \in I \ , \\ p(t) = U_\beta(t)\, p^0 \,+\, U_\beta \star Q(f,p,w)(t) \ , & t \in I \ , \\ w(t) = U_\gamma(t)\, w^0 \,+\, U_\gamma \star R(f,p,w)(t) \ , & t \in I \ , \end{cases}$$

has a unique solution

$$u := (f, m, p, w) \in \mathcal{V}_T := C(I, W^2_{q,\mathcal{B}}) \times C_\mu(\dot{I}, W^2_{q,\mathcal{B}}) \times C_\xi(\dot{I}, W^{2\eta}_{q,\mathcal{B}}) \times C(I, L_q) ,$$

where $I := [0,T]$. *Moreover, the solution depends continuously on the initial value in the sense that if* $\bar{u} \in \mathcal{V}_T$ *denotes the solution corresponding to* $\bar{u}^0 \in E$ *with* $\|\bar{u}^0\|_E \le B$, *then* $\bar{u} \to u$ *in* $\mathcal{V}_T$ *as* $\bar{u}^0 \to u^0$ *in* E.

Proof. Given $T \in (0,1]$ we put

$$W_T := C\big([0,T], W^2_{q,\mathcal{B}}\big) , \quad X_T := C_\mu\big((0,T], W^2_{q,\mathcal{B}}\big) ,$$
$$Y_T := C_\xi\big((0,T], W^{2\eta}_{q,\mathcal{B}}\big) , \quad Z_T := C\big([0,T], L_q\big) ,$$

so that $\mathcal{V}_T = W_T \times X_T \times Y_T \times Z_T$. For $u^0 = \big(f^0, m^0, p^0, w^0\big) \in E$ it then follows from Lemma 2.3 that

$$V^0 := \big(f^0, U_\alpha m^0, U_\beta p^0, U_\gamma w^0\big) \in \mathcal{V}_T .$$

Defining

$$F_2(m,p) := U_\alpha m^0 + U_\alpha \star S(m,p) ,$$
$$F_3(f,p,w) := U_\beta p^0 + U_\beta \star Q(f,p,w) ,$$
$$F_4(f,p,w) := U_\gamma w^0 + U_\gamma \star R(f,p,w) ,$$

and

$$F(u) := F(f,m,p,w) := \big(F_1(m), F_2(m,p), F_3(f,p,w), F_4(f,p,w)\big) ,$$

problem (M) can be recast as a fixed point problem of the form $F(u) = u \in \mathcal{V}_T$. In order to solve this problem, we first recall that Lemma 2.2(ii) implies that there exists for any given $R_0 > 0$ a constant $c(R_0) > 0$ with

$$\|F_1(m) - F_1(\bar{m})\|_{W_T} \le c(R_0)\, T^{1-\mu}\, \|m - \bar{m}\|_{X_T} \tag{14}$$

provided $m, \bar{m} \in X_T$ with $\|m\|_{X_T}, \|\bar{m}\|_{X_T} \le R_0$ and $\|f^0\|_{W^2_{q,\mathcal{B}}} \le R_0$. We fix r such that $0 < 2r < (s \wedge 2\eta \wedge (1 + 1/q))$, where $s > 0$ is given in (4). For $m \in X_T$ and $p \in Y_T$ we derive from Lemma 2.1(iii), (10), and (4)

(15)
$$\begin{aligned}\|U_\alpha \star S(m,p)(t)\|_{W^2_q} &\le c \int_0^t \|U_\alpha(t-s)\|_{\mathcal{L}(W^{2r}_{q,\mathcal{B}}, W^2_{q,\mathcal{B}})} \big(\|p(s)\|_{W^{2\eta}_q} + \|m(s)\|_{W^2_q}\big)\, \mathrm{d}s \\ &\le c\, t^{r-\xi}\, \mathsf{B}(r, 1-\xi)\, \|p\|_{Y_T} + c\, t^{r-\mu}\, \mathsf{B}(r, 1-\mu)\, \|m\|_{X_T} ,\end{aligned}$$

where B denotes the beta function. Therefore,

$$\|F_2(m,p) - F_2(\bar{m},\bar{p})\|_{X_T} \le c\, T^r \left(\|p - \bar{p}\|_{Y_T} + \|m - \bar{m}\|_{X_T}\right) \tag{16}$$

for $m, \bar{m} \in X_T$ and $p, \bar{p} \in Y_T$. Next observe that

$$\nabla \cdot \big(p\, \chi(f)\, \nabla f\big) = p\, \chi(f)\, \Delta f + \chi(f)\, \nabla p \cdot \nabla f + p\, \chi'(f)\, |\nabla f|^2;$$

hence

$$\|\nabla\cdot\big(p\,\chi(f)\,\nabla f\big)\|_{L_q}\;\le\;c\,\|p\|_{W_q^{2\eta}}\,(1+\|f\|^3_{W_q^2})\ ,\quad p\in W^{2\eta}_{q,\mathcal{B}}\ ,\quad f\in W^2_{q,\mathcal{B}}\ ,$$

by Lemma 2.1 and (5). Given $f\in W_T$, $p\in Y_T$, and $w\in Z_T$ we thus compute, using (10) and (7),

(17)

$$\begin{aligned}\|U_\beta\star Q(f,p,w)(t)\|_{W_q^{2\eta}}\le c\int_0^t\|U_\beta(t-s)\|_{\mathcal{L}(L_q,W^{2\eta}_{q,\mathcal{B}})}\Big\{&\|p(s)\|_{W_q^{2\eta}}\,\big(1+\|f(s)\|^3_{W_q^2}\big)\\&+\,\big(1+\|w(s)\|_{L_q}\big)\,\|p(s)\|_{W_q^{2\eta}}\Big\}\,\mathrm{d}s\\ \le\;c\,t^{1-\eta-\xi}\,\mathsf{B}(1-\eta,1-\xi)\,\|p\|_{Y_T}&\big(1+\|f\|^3_{W_T}+\|w\|_{Z_T}\big)\ .\end{aligned}$$

Similarly, for $f,\bar f\in W_T$, $p,\bar p\in Y_T$, and $w,\bar w\in Z_T$ we obtain

(18)

$$\begin{aligned}\|F_3(f,p,w)\,-\,F_3(\bar f,\bar p,\bar w)\|_{Y_T}\;\le&\,c\,T^{1-\eta}\,\|p\|_{Y_T}\,\big(1+\|f\|_{W_T}+\|\bar f\|_{W_T}\big)^2\,\|f-\bar f\|_{W_T}\\&+c\,T^{1-\eta}\,\big(1+\|\bar f\|^3_{W_T}+\|w\|_{Z_T}\big)\,\|p-\bar p\|_{Y_T}\\&+c\,T^{1-\eta}\,\|p\|_{Y_T}\,\|w-\bar w\|_{Z_T}\ .\end{aligned}$$

Given $f,\bar f\in W_T$, $p,\bar p\in Y_T$, and $w,\bar w\in Z_T$ analogous computations show that

$$\begin{aligned}\|F_4(f,p,w)-F_4(\bar f,\bar p,\bar w)\|_{Z_T}\;\le&\,c\,T^{1-\xi}\,\big(1+\|\bar p\|_{Y_T}\big)\,\|w-\bar w\|_{Z_T}\\&+\;c\,T^{1-\xi}\,\|w\|_{Z_T}\,\|p-\bar p\|_{Y_T}\\&+\;c\,T\,\|f-\bar f\|_{W_T}\ .\end{aligned}\tag{19}$$

Combining (14), (16), (18), (19), and defining $\lambda:=(1-\mu)\wedge r\wedge(1-\xi)>0$ we find a constant $\kappa(R_0)>0$ such that

$$\|F(u)-F(\bar u)\|_{\mathcal{V}_T}\;\le\;\kappa(R_0)\,T^\lambda\,\big(1+\|u\|_{\mathcal{V}_T}+\|\bar u\|_{\mathcal{V}_T}\big)\,\|u-\bar u\|_{\mathcal{V}_T}\ ,\tag{20a}$$

$$\|F(u)-V^0\|_{\mathcal{V}_T}\;\le\;\kappa(R_0)\,T^\lambda\,\big(1+\|u\|_{\mathcal{V}_T}\big)\,\|u\|_{\mathcal{V}_T}\ ,\tag{20b}$$

provided $u=(f,m,p,w)\,,\,\bar u=(\bar f,\bar m,\bar p,\bar w)\in\mathcal{V}_T$ are such that $\|m\|_{X_T},\|\bar m\|_{X_T}\le R_0$ and $\|f^0\|_{W_q^2}\le R_0$, where $R_0>0$ and $T\in(0,1]$ are arbitrary. Put

$$\mathcal{K}:=1+\sup_{0<t\le 1}\big(t^\mu\,\|U_\alpha(t)\|_{\mathcal{L}(W^{2(1-\mu)}_{q,\mathcal{B}},W^2_{q,\mathcal{B}})}\,+\,t^\xi\,\|U_\beta(t)\|_{\mathcal{L}(L_q,W^{2\eta}_{q,\mathcal{B}})}\big),$$

which is a finite constant according to (10), and let $R_0:=(1+\mathcal{K})B$ for $B\ge1$ given. Choose then $T:=T(B)\in(0,1]$ such that

$$\kappa(R_0)\,(1+R_0)\,R_0\,T^\lambda\;\le\;\frac12\quad\text{and}\quad k(1,R_0)\,B\,T^{1-\mu}\;\le\;\frac14\ ,\tag{21}$$

the constant $k(1,R_0)>0$ stemming from Lemma 2.2(ii). Notice that, in particular, for $u^0=\big(f^0,m^0,p^0,w^0\big)\in E$ with $\|u^0\|_E\le B$, there holds

$$\|V^0\|_{\mathcal{V}_T}\le\mathcal{K}\,B\ ,\quad V^0=\big(f^0,U_\alpha m^0,U_\beta p^0,U_\gamma w^0\big)\ .$$

Denoting by $\mathcal{B}_T$ the closed ball in $\mathcal{V}_T$ with center V^0 and radius B, we hence have

$$\|u\|_{\mathcal{V}_T} \le (1+\mathcal{K})\, B = R_0 , \quad u \in \mathcal{B}_T .$$

Therefore, in view of (20a), (20b), and (21), the mapping $F : \mathcal{B}_T \to \mathcal{B}_T$ is a contraction (with contraction constant less than 1/2), which implies the existence of a unique solution to problem (M) for any $u^0 = \big(f^0, m^0, p^0, w^0\big) \in E$ with $\|u^0\|_E \le B$. If $\bar u^0 = \big(\bar f^0, \bar m^0, \bar p^0, \bar w^0\big) \in E$ with $\|\bar u^0\|_E \le B$ is another initial value, there exists a corresponding unique solution $\bar u = \big(\bar f, \bar m, \bar p, \bar w\big) \in \mathcal{V}_T$ satisfying $\|\bar u\|_{\mathcal{V}_T} \le R_0$. Defining

$$\tilde F := (F_2, F_3, F_4) \quad \text{and} \quad \bar V^0 := \big(\bar f^0, U_\alpha \bar m^0, U_\beta \bar p^0, U_\gamma \bar w^0\big)$$

we derive from (20a), (20b), and Lemma 2.2(ii) that

$$\begin{aligned}
\|u-\bar u\|_{\mathcal{V}_T} \le\ & \|F_1[f^0](m) - F_1[\bar f^0](\bar m)\|_{W_T} + \|\tilde F(u) - \tilde F(\bar u)\|_{X_T\times Y_T\times Z_T} \\
& + \|U_\alpha(m^0-\bar m^0)\|_{X_T} + \|U_\beta(p^0-\bar p^0)\|_{Y_T} + \|U_\gamma(w^0-\bar w^0)\|_{Z_T} \\
\le\ & k(1,R_0)\|f^0\|_{W^2_{q,\mathcal{B}}}\, T^{1-\mu}\, \|m-\bar m\|_{X_T} + k(1,R_0)\, \|\bar m\|_{X_T}\, \|f^0 - \bar f^0\|_{W^2_{q,\mathcal{B}}} \\
& + \frac12 \|u-\bar u\|_{\mathcal{V}_T} + \|V^0 - \bar V^0\|_{\mathcal{V}_T} .
\end{aligned}$$

But then, due to (21),

$$\|u-\bar u\|_{\mathcal{V}_T} \le c(R_0)\, \|V^0-\bar V^0\|_{\mathcal{V}_T} \le c(R_0)\, \mathcal{K}\, \|u^0 - \bar u^0\|_E ,$$

whence $\bar u \to u$ in $\mathcal{V}_T$ as $\bar u^0 \to u^0$ in E. This proves the proposition. ∎

We now focus on the existence of a unique maximal solution to (H_1)–(H_6) enjoying the regularity properties stated in Theorem 1.1.

Let $(1\vee n/2) < q < \infty$ and $2\delta \in (0,2)\setminus\{1+1/q\}$ be given. Fix η and λ such that $n/q < 2\eta < 2$ with $2\eta \ge 1$ and $(1-\delta)\vee\eta \le \lambda < 1$ and put $(\xi,\mu) := (\eta,\lambda)$. Then, for $\big(f^0, m^0, p^0, w^0\big) \in W^2_{q,\mathcal{B}} \times W^{2\delta}_{q,\mathcal{B}} \times L_q \times L_q$, Proposition 3.1 ensures the existence of $T>0$ and a unique solution

$$u = (f,m,p,w) \in C([0,T], W^2_{q,\mathcal{B}}) \times C_\mu((0,T], W^2_{q,\mathcal{B}}) \times C_\xi((0,T], W^{2\eta}_{q,\mathcal{B}}) \times C([0,T], L_q)$$

to problem (M). As in (17),

$$\|U_\beta \star Q(f,p,w)(t)\|_{L_q} \le c(T)\, t^{1-\xi} \to 0 \quad \text{as} \quad t \to 0^+ ,$$

and therefore

$$p = U_\beta\, p^0 + U_\beta \star Q(f,p,w) \in C([0,T], L_q)$$

is a mild L_q-solution to (H_3). From this and the identity

$$m = U_\alpha\, m^0 + U_\alpha \star S(m,p)$$

we obtain that $m \in C([0,T], W^{2\delta}_{q,\mathcal{B}})$ is a mild L_q-solution to (H_2). Clearly, $w \in C([0,T], L_q)$ is a mild L_q-solution to (H_4).

Next we show that these mild solutions are actually classical solutions. First, we fix $\varepsilon \in (0,T]$ and set $I := [0, T-\varepsilon]$. Then

$$f_\varepsilon := f(\cdot+\varepsilon) \in C(I, W^2_{q,\mathcal{B}}) , \qquad m_\varepsilon := m(\cdot+\varepsilon) \in C(I, W^2_{q,\mathcal{B}}) ,$$

$$p_\varepsilon := p(\cdot+\varepsilon) \in C(I, W^{2\eta}_{q,\mathcal{B}}) , \qquad w_\varepsilon := w(\cdot+\varepsilon) \in C(I, L_q) .$$

Furthermore, Lemma 2.2(i) warrants $f_\varepsilon \in C^1(I, W^2_{q,\mathcal{B}})$ and thus, letting $\varepsilon \to 0^+$, we obtain $f \in C^1((0,T], W^2_{q,\mathcal{B}})$. Next, $h_\varepsilon := S(m_\varepsilon, p_\varepsilon) \in C(I, W^{2r}_{q,\mathcal{B}})$ with $r > 0$ sufficiently small by Lemma 2.1(iii). Therefore, observing that $W^{2r}_{q,\mathcal{B}}$ is a (real) interpolation space between L_q and $W^2_{q,\mathcal{B}}$ (cf. [24]) and taking into account that m_ε is a mild L_q-solution to the linear problem

$$\dot{M} - \alpha\Delta M = h_\varepsilon(t) \ , \quad t \in \dot{I} \ , \qquad M(0) = m_\varepsilon(0) \in W^2_{q,\mathcal{B}} \ ,$$

we conclude that $m_\varepsilon \in C^1(\dot{I}, L_q) \cap C(I, W^2_{q,\mathcal{B}})$ since mild solutions to linear problems are unique; see [3, II.Thm. 1.2.2]. Letting $\varepsilon \to 0^+$ we deduce that m is a classical solution to (H_2) possessing the same regularity properties as m_ε on $(0,T]$. Next, define $j_\varepsilon := Q(f_\varepsilon, p_\varepsilon, w_\varepsilon) \in C(I, L_q)$ and notice that p_ε is a mild L_q-solution to the linear problem

$$\dot{P} - \beta\Delta P = j_\varepsilon(t) \ , \quad t \in \dot{I} \ , \qquad P(0) = p_\varepsilon(0) \in W^{2\eta}_{q,\mathcal{B}} \ . \tag{22}$$

Thus, $p_\varepsilon \in C^\varrho(I, W^{2\sigma}_{q,\mathcal{B}})$ with $2\eta > 2\sigma > n/q$ and $2\sigma \geq 1$, where $\varrho := \eta - \sigma > 0$ owing to [3, II.Thm. 5.3.1]. Clearly, due to $k_\varepsilon := R(f_\varepsilon, p_\varepsilon, w_\varepsilon) \in C(I, L_q)$ and (10) we have

$$w_\varepsilon \ = \ U_\gamma \, w_\varepsilon(0) \ + \ U_\gamma \star k_\varepsilon \in C(I, W^{2\nu}_{q,\mathcal{B}}) \ , \quad \nu < 1 \ .$$

Applying again [3, II.Thm. 5.3.1] we obtain $w_\varepsilon \in C^\varrho(I, L_q)$. From (6) and the fact that $f_\varepsilon \in C^1(I, W^2_{q,\mathcal{B}})$ and $p_\varepsilon \in C^\varrho(I, W^{2\sigma}_{q,\mathcal{B}})$ it follows that $k_\varepsilon \in C^\varrho(I, L_q)$; hence, as above, $w_\varepsilon \in C^1(\dot{I}, L_q) \cap C(\dot{I}, W^2_{q,\mathcal{B}})$ by [3, II.Thm. 1.2.2], which ensures that w is a classical solution to (H_4) with the corresponding regularity properties. Moreover, recalling that $2\sigma > n/q$ with $2\sigma \geq 1$ and invoking Lemma 2.1, we deduce $j_\varepsilon \in C^\varrho(I, L_q)$ thanks to (5). Due to [3, II.Thm. 1.2.2] and (22) this implies that p_ε belongs to $C^1(\dot{I}, L_q) \cap C(\dot{I}, W^2_{q,\mathcal{B}})$, whence $p \in C^1((0,T], L_q) \cap C((0,T], W^2_{q,\mathcal{B}})$ is a classical solution to (H_3).

Let us now prove that this solution is unique in the sense stated in Theorem 1.1. Suppose therefore that there exist two solutions $(\tilde{f}, \tilde{m}, \tilde{p}, \tilde{w})$ and $(\bar{f}, \bar{m}, \bar{p}, \bar{w})$ to (H_1)–(H_6) on some interval $[0,T]$ satisfying

$$\begin{aligned} &\tilde{f}\,,\, \bar{f} \in C\big([0,T], W^2_{q,\mathcal{B}}\big) \ , && \tilde{w}\,,\, \bar{w} \in C\big([0,T], L_q\big) \ , \\ &\tilde{m} \in C_{\tilde{\lambda}}\big((0,T], W^2_{q,\mathcal{B}}\big) \ , && \bar{m} \in C_{\bar{\lambda}}\big((0,T], W^2_{q,\mathcal{B}}\big) \ , \\ &\tilde{p} \in C_{\tilde{\eta}}\big((0,T], W^{2\tilde{\eta}}_{q,\mathcal{B}}\big) \ , && \bar{p} \in C_{\bar{\eta}}\big((0,T], W^{2\bar{\eta}}_{q,\mathcal{B}}\big) \end{aligned}$$

for some $n/q < 2\tilde{\eta}\,,\, 2\bar{\eta} < 2$ with $2\tilde{\eta}\,,\, 2\bar{\eta} \geq 1$ and $\tilde{\lambda}\,,\, \bar{\lambda} < 1$. Defining

$$\eta := \tilde{\eta} \wedge \bar{\eta} \ , \qquad \xi := \tilde{\eta} \vee \bar{\eta} \ , \qquad \mu := \tilde{\lambda} \vee \bar{\lambda} \vee \xi \vee (1 - \delta)$$

we obtain two solutions to (M) such that both $\tilde{m}, \bar{m}$ belong to $C_\mu((0,T], W^2_{q,\mathcal{B}})$ and both $\tilde{p}, \bar{p}$ belong to $C_\xi((0,T], W^{2\eta}_{q,\mathcal{B}})$, where $n/q < 2\eta \leq 2\xi \leq 2\mu < 2$ with $2\eta \geq 1$. Making T smaller if necessary, Proposition 3.1 guarantees that $(\tilde{f}, \tilde{m}, \tilde{p}, \tilde{w})$ coincides with $(\bar{f}, \bar{m}, \bar{p}, \bar{w})$ on $[0,T]$.

Evidently, local uniqueness warrants that we may extend the solution (f, m, p, w) constructed above to a maximal solution on an interval $J := [0, t^+)$. Since, according to Proposition 3.1, the local existence time $T > 0$ can be chosen uniformly with respect to initial values that are bounded in $W^2_{q,\mathcal{B}} \times W^{2\delta}_{q,\mathcal{B}} \times L_q \times L_q$, we surely have

$$\limsup_{t\nearrow t^+} \big\| \big(f(t), m(t), p(t), w(t)\big) \big\|_{W_q^2 \times W_q^{2\delta} \times L_q \times L_q} = \infty \tag{23}$$

in the case that $t^+ < \infty$.

Summing up, we have shown thus far that problem (H_1)–(H_6) admits a maximal solution being unique and possessing the regularity properties in the sense stated in Theorem 1.1. Moreover, this solution satisfies (8) and, if $t^+ < \infty$, then (23) also holds.

Remark 3.2. Given $p^0 \in W^{2\eta}_{q,\mathcal{B}}$ with $n/q < 2\eta < 2$ and $2\eta \geq 1$ there holds $p \in C(J, W^{2\eta}_{q,\mathcal{B}})$. In particular, one may choose $2\eta = 1$ if $q > n$; see Corollary 1.3. This readily follows by taking $C([0,T], W^{2\eta}_{q,\mathcal{B}})$ as state space for p instead of the weighted space $C_\xi((0,T], W^{2\eta}_{q,\mathcal{B}})$ in the above proof.

4. Positivity. Using ideas as in [18] we now show positivity of the solution corresponding to positive initial values. Given

$$\big(f^0, m^0, p^0, w^0\big) \in W^2_{q,\mathcal{B}} \times W^{2\delta}_{q,\mathcal{B}} \times L_q \times L_q$$

such that $f^0 \geq 0$, $m^0 \geq 0$, $p^0 \geq 0$, and $w^0 \geq 0$ (a.e. on Ω) let (f, m, p, w) denote the maximal solution on J constructed in the previous section. Then obviously $f(t) \geq 0$ on Ω for $t \in J$.

First suppose that $q > (n \vee 2)$ and $p^0, w^0 \in W^2_{q,\mathcal{B}}$. Fix $T \in \dot{J}$ and $n/q < 2\sigma < 1$. Then choose $\eta \in \big(1/2, 1 - \sigma\big)$ and observe that $p \in C_\eta(\dot{J}, W^{2\eta}_{q,\mathcal{B}})$ in view of (8). Analogously to (17) it follows from Lemma 2.1 that

$$\|U_\beta \star Q(f, p, w)(t)\|_{W_q^{2\sigma}} \leq c(T)\, t^{1-\sigma-\eta} \longrightarrow 0 \quad \text{as} \quad t \to 0^+ ,$$

and consequently

$$p = U_\beta\, p^0 + U_\beta \star Q(f, p, w) \in C([0,T], W^{2\sigma}_{q,\mathcal{B}}) \hookrightarrow C([0,T] \times \bar{\Omega}) .$$

Similarly, there holds

$$w = U_\gamma\, w^0 + U_\gamma \star R(f, p, w) \in C([0,T], W^{2\sigma}_{q,\mathcal{B}}) \hookrightarrow C([0,T] \times \bar{\Omega}) ,$$

and thus, in particular,

$$\vartheta(w) \in C([0,T] \times \bar{\Omega}) . \tag{24}$$

According to [18, p. 451] there exist a function $H \in C^2(\mathbb{R})$ and a constant $c_0 > 0$ such that $H(z) = 0$ for $z \geq 0$ and $H(z) > 0$ for $z < 0$ and such that

$$0 \leq H''(z)\, z^2 \leq c_0\, H(z) , \quad z \in \mathbb{R} ,$$

and

$$0 \leq H'(z)\, z \leq c_0\, H(z) , \quad z \in \mathbb{R} .$$

Define $M \in C^1((0,T]) \cap C([0,T])$ as

$$M(t) := \int_\Omega H\big(p(t,x)\big)\ \mathrm{d}x\ , \quad t \in [0,T]\ .$$

Owing to $\partial_\nu p(t) = \partial_\nu f(t) = 0$ we deduce from (H_3) that

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t} M(t) &= \int_\Omega H'(p)\left(\beta\Delta p - \nabla\cdot\big(p\,\chi(f)\,\nabla f\big) + \vartheta(w)\,p\right)\,\mathrm{d}x \\ &= -\beta\int_\Omega H''(p)\,|\nabla p|^2\ \mathrm{d}x + \int_\Omega H''(p)\,p\,\chi(f)\,\nabla p\cdot\nabla f\ \mathrm{d}x \\ &\quad + \int_\Omega H'(p)\,\vartheta(w)\,p\ \mathrm{d}x. \end{aligned}$$

Therefore, since

$$|p\,\chi(f)\,\nabla p\cdot\nabla f| \le \frac{\beta}{2}\,|\nabla p|^2 + \frac{1}{2\beta}\,p^2\,\chi(f)^2\,|\nabla f|^2$$

we infer from (7) and the fact that both f and ∇f belong to $C([0,T]\times\bar\Omega)$, from (24), and the properties of the function H that

$$\frac{\mathrm{d}}{\mathrm{d}t} M(t) \le c(T) M(t)\ , \quad t \in (0,T]\ .$$

Thus $M(0) = 0$ ensures $M(t) = 0$ for $t \in [0,T]$, that is, $p(t) \ge 0$ on Ω for $t \in [0,T]$. It is then straightforward to prove that $m(t) \ge 0$ and $w(t) \ge 0$ on Ω for $t \in [0,T]$. But $T > 0$ was arbitrary, so the desired positivity follows.

Finally, to show positivity in the general case $q > (1 \vee n/2)$ we approximate $p^0, w^0 \in L_q$ by nonnegative smooth functions and use the continuous dependence of the solution on the initial value provided by Proposition 3.1.

5. Global existence. It remains only to prove global existence. We denote by (f,m,p,w) the maximal nonnegative solution on $J = [0,t^+)$ corresponding to the nonnegative initial value

$$\big(f^0, m^0, p^0, w^0\big) \in W^2_{q,\mathcal{B}} \times W^{2\delta}_{q,\mathcal{B}} \times L_q \times L_q\ .$$

We first claim that it suffices to prove

$$\sup_{t\in J\cap[0,T]} \|p(t)\|_{L_q} < \infty\ , \quad T > 0\ , \tag{25}$$

in order to conclude that $t^+ = \infty$. Indeed, suppose that (25) holds for any $T > 0$ and set $J_T := J \cap [0,T]$. Replacing the solution by the shifted solution $(f_\varepsilon, m_\varepsilon, p_\varepsilon, w_\varepsilon)$ introduced in the existence proof in section 3, we may assume without loss of generality that all m, p, w belong to $C(J, W^2_{q,\mathcal{B}}) \cap C^1(J, L_q)$, in particular that $m^0 \in W^2_{q,\mathcal{B}}$. Observe then that $w \in L_\infty(J_T, L_\infty)$ as it follows from (H_4) since $w(t) \ge 0$ and $\|f(t)\|_\infty \le \|f^0\|_\infty$. Next, since $b \in L_\infty$, we may choose $\lambda > 0$ sufficiently large such that $-(\lambda + b - \alpha\Delta)$ has bounded imaginary powers with angle strictly less than $\pi/2$ (for instance, see [3, III.Ex. 4.7.3(d), III.Thm. 4.8.7]). Therefore, defining $n(t) := e^{-\lambda t} m(t)$ and noticing that

$$\dot n + (\lambda + b - \alpha\Delta)\,n = d\,e^{-\lambda t}\,p(t) =: z(t)\ , \quad n(0) = m^0 \in W^2_{q,\mathcal{B}}\ ,$$

it follows from [3, III.Thm. 4.10.7] that $n \in L_q(J_T, W^2_{q,\mathcal{B}})$ since $z \in L_\infty(J_T, L_q)$ by (25) and $n(0) \in W^2_{q,\mathcal{B}}$. But then

$$\int_0^t \|m(s)\|_{W^2_q} \,\mathrm{d}s \,\le\, c(T) \ , \quad t \in J_T \ ,$$

and we deduce from (13) that $f \in L_\infty(J_T, W^2_{q,\mathcal{B}})$. Finally, owing to $p \in L_\infty(J_T, L_q)$, (10), and Gronwall's inequality we conclude from (H_2) that $m \in L_\infty(J_T, W^{2\delta}_{q,\mathcal{B}})$. Consequently, combining all the estimates on f, m, p, and w we see that the blowup criterion (23) implies $t^+ = \infty$ since $T > 0$ was arbitrary. Therefore, (25) is indeed sufficient to conclude global existence.

To derive the desired L_q-bound on p we employ a change of variable of the form $p \mapsto \frac{p}{\phi(f)}$, where ϕ solves

$$\phi'(z) \,=\, \frac{\chi(z)}{\beta}\,\phi(z) \ , \quad z > 0 \ , \qquad \phi(0) = 1 \ .$$

This device has been used in [11, 12, 14] for equations of the form (1), (2), (3) and leads in our case to the equation in divergence form

$$\text{(26)} \qquad \frac{\mathrm{d}}{\mathrm{d}t}\frac{p}{\phi(f)} \,=\, \frac{\beta}{\phi(f)}\,\nabla\cdot\left(\phi(f)\,\nabla\frac{p}{\phi(f)}\right) \,+\, \vartheta(w)\,\frac{p}{\phi(f)} \,+\, \frac{a}{\beta}\,\chi(f)\,f\,m\,\frac{p}{\phi(f)} \ .$$

Global existence is then an easy consequence of the following proposition, where the basic idea of its proof is adapted from [11]. We point out here again that in our case, the coupling of (H_1) and (H_3) via (H_2) allows us to derive the a priori estimate for p (which does not seem to be possible without a smallness condition on the initial value in the case of (1), (2), (3) with $\sigma = -1$; see [11]).

PROPOSITION 5.1. *Suppose that $\|p(t)\|_{L_\rho} \le c(T)$, $t \in J_T := J \cap [0,T]$, for some $\rho \in [1,q)$ and suppose there exists $\varrho \in (\rho, 2\rho \wedge q]$ such that*

$$\text{(27)} \qquad \varrho\left(\frac{n}{\rho} - 2\right) \,<\, 2\left(\rho - 1 + \frac{2\rho}{n}\right) \ .$$

Then $\|p(t)\|_{L_\varrho} \le c(T)$ for $t \in J_T$.

Proof. We first observe that (27) allows to fix $r > 1$ such that

$$\text{(28)} \qquad \frac{n\varrho}{n\varrho + 2\rho} \,<\, \frac{1}{r} \,<\, 1 + \frac{2}{n} - \frac{1}{\rho} \ .$$

If $\varrho \ge 2$, we set $\mu := 0$; otherwise we fix $\mu \in (0,1)$. Then we put $p_\mu := p + \mu \ge \mu$ and note that

$$\nabla\left(\frac{p_\mu}{\phi(f)}\right)^{\varrho/2} \,=\, \frac{\varrho}{2}\,\left(\frac{p_\mu}{\phi(f)}\right)^{\varrho/2-1}\,\nabla\frac{p_\mu}{\phi(f)}$$

by the chain rule. Hence $\big(\frac{p_\mu}{\phi(f)}\big)^{\varrho/2} \in W^1_2$ since $W^1_q \hookrightarrow L_2$ due to $q > n/2$. Moreover, $\partial_\nu \frac{p_\mu}{\phi(f)} = 0$ owing to $\partial_\nu p = \partial_\nu f = 0$. Thus, given any $\Lambda \in C^2\big((0,\infty)\big)$ we derive from (26)

$$
\begin{aligned}
&\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \phi(f)\,\Lambda\left(\frac{p_\mu}{\phi(f)}\right)\,\mathrm{d}x \\
&\quad = \beta\int_\Omega \Lambda'\left(\frac{p_\mu}{\phi(f)}\right)\nabla\cdot\left(\phi(f)\,\nabla\frac{p_\mu}{\phi(f)}\right)\,\mathrm{d}x + \int_\Omega \Lambda'\left(\frac{p_\mu}{\phi(f)}\right)\vartheta(w)\,p\,\mathrm{d}x \\
&\qquad + \frac{1}{\beta}\int_\Omega \Lambda'\left(\frac{p_\mu}{\phi(f)}\right)a\,m\,\chi(f)\,f\,p\,\mathrm{d}x - \frac{1}{\beta}\int_\Omega \Lambda\left(\frac{p_\mu}{\phi(f)}\right)a\,m\,\chi(f)\,f\,\phi(f)\,\mathrm{d}x \\
&\qquad + \mu\int_\Omega \Lambda'\left(\frac{p_\mu}{\phi(f)}\right)\nabla\cdot\big(\chi(f)\nabla f\big)\,\mathrm{d}x + \frac{\mu}{\beta}\int_\Omega \Lambda'\left(\frac{p_\mu}{\phi(f)}\right)a\,m\,\chi(f)\,f\,\mathrm{d}x \\
&\quad = -\beta\int_\Omega \Lambda''\left(\frac{p_\mu}{\phi(f)}\right)\phi(f)\left|\nabla\frac{p_\mu}{\phi(f)}\right|^2\,\mathrm{d}x \\
&\qquad + \frac{1}{\beta}\int_\Omega a\,m\,\chi(f)\,f\left[p\,\Lambda'\left(\frac{p_\mu}{\phi(f)}\right) - \phi(f)\,\Lambda\left(\frac{p_\mu}{\phi(f)}\right)\right]\,\mathrm{d}x \\
&\qquad + \int_\Omega \Lambda'\left(\frac{p_\mu}{\phi(f)}\right)\vartheta(w)\,p\,\mathrm{d}x - \mu\int_\Omega \Lambda''\left(\frac{p_\mu}{\phi(f)}\right)\chi(f)\,\nabla\frac{p_\mu}{\phi(f)}\cdot\nabla f\,\mathrm{d}x \\
&\qquad + \frac{\mu}{\beta}\int_\Omega \Lambda'\left(\frac{p_\mu}{\phi(f)}\right)a\,m\,\chi(f)\,f\,\mathrm{d}x
\end{aligned}
$$

for $t \in J$. In particular, taking $\Lambda(z) = z^\varrho$ we have

(29)

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \phi(f)\left(\frac{p_\mu}{\phi(f)}\right)^\varrho\,\mathrm{d}x \le{}& -4\beta\,\frac{\varrho-1}{\varrho}\int_\Omega \phi(f)\left|\nabla\left(\frac{p_\mu}{\phi(f)}\right)^{\varrho/2}\right|^2\,\mathrm{d}x \\
&+ S_0\int_\Omega m\left(\frac{p_\mu}{\phi(f)}\right)^\varrho\,\mathrm{d}x \\
&+ \varrho\,\|\vartheta(w)\|_\infty\int_\Omega \phi(f)\left(\frac{p_\mu}{\phi(f)}\right)^\varrho\,\mathrm{d}x \\
&+ \mu\,\varrho\,(\varrho-1)\|\chi(f)\|_\infty\int_\Omega\left(\frac{p_\mu}{\phi(f)}\right)^{\varrho-2}\left|\nabla\frac{p_\mu}{\phi(f)}\cdot\nabla f\right|\mathrm{d}x \\
&+ \mu\,S_0\int_\Omega m\left(\frac{p_\mu}{\phi(f)}\right)^{\varrho-1}\,\mathrm{d}x
\end{aligned}
$$

for $t \in J$, where

$$
S_0 := \frac{\varrho-1}{\beta}\,\|a\|_\infty \sup_{0<z<\|f^0\|_\infty}\big(z\,\chi(z)\,\phi(z)\big) < \infty
$$

since $\|f(t)\|_\infty \le \|f^0\|_\infty$ and $\|\vartheta(w)\|_\infty < \infty$ on J_T due to $w \in L_\infty(J_T, L_\infty)$. Next, we use the second inequality of (28), (11), the given L_ρ-bound on p, and Gronwall's inequality to derive from (H_2) that

$$
\|m(t)\|_{L_{r'}} \le c(T)\,, \quad t \in J_T\,,
$$

where r' denotes the dual exponent of r. Hence, taking into account that the first inequality of (28) warrants the following version of the Gagliardo–Nirenberg inequality (see [15, p. 37])

$$\|\cdot\|_{L_{2r}}^{2r} \leq c_0 \,\|\cdot\|_{L_{2\rho/\varrho}}^{2(r-1)} \,\|\cdot\|_{W_2^1}^2 \ ,$$

applying Young's inequality, and using once again the given L_ρ-bound on p, it follows for $\varepsilon > 0$ that

$$\begin{aligned} S_0 \int_\Omega m \left(\frac{p_\mu}{\phi(f)}\right)^{\varrho} \mathrm{d}x &\leq c(\varepsilon)\int_\Omega m^{r'}\,\mathrm{d}x + \varepsilon \int_\Omega \left(\frac{p_\mu}{\phi(f)}\right)^{\varrho r} \mathrm{d}x \\ &\leq c(T,\varepsilon) + \varepsilon \left\| \left(\frac{p_\mu}{\phi(f)}\right)^{\varrho/2} \right\|_{L_{2r}}^{2r} \\ &\leq c(T,\varepsilon) + \varepsilon\, c_0 \left\| \frac{p_\mu}{\phi(f)} \right\|_{L_\rho}^{\varrho(r-1)} \left\| \left(\frac{p_\mu}{\phi(f)}\right)^{\varrho/2} \right\|_{W_2^1}^2 \\ &\leq c(T,\varepsilon) + c(T,\varepsilon)\int_\Omega \left(\frac{p_\mu}{\phi(f)}\right)^{\varrho} \mathrm{d}x \\ &\qquad + \varepsilon\, c(T) \int_\Omega \left| \nabla \left(\frac{p_\mu}{\phi(f)}\right)^{\varrho/2} \right|^2 \mathrm{d}x \ . \end{aligned}$$

We can estimate the last term in (29) similarly, since

$$\begin{aligned} \mu\, S_0 \int_\Omega m \left(\frac{p_\mu}{\phi(f)}\right)^{\varrho-1} \mathrm{d}x &\leq \mu\, c(T,\varepsilon) + \mu\, c(T,\varepsilon) \int_\Omega \left(\frac{p_\mu}{\phi(f)}\right)^{\varrho} \mathrm{d}x \\ &\qquad + \mu\,\varepsilon\, c(T) \int_\Omega \left| \nabla \left(\frac{p_\mu}{\phi(f)}\right)^{\varrho/2} \right|^2 \mathrm{d}x \ . \end{aligned}$$

In the case that $\varrho < 2$ we have by Young's inequality for $\delta > 0$

$$\begin{aligned} &\mu\, \varrho\, (\varrho-1) \|\chi(f)\|_\infty \int_\Omega \left(\frac{p_\mu}{\phi(f)}\right)^{\varrho-2} \left| \nabla \frac{p_\mu}{\phi(f)} \cdot \nabla f \right| \mathrm{d}x \\ &\qquad \leq \delta\, \mu\, \frac{\varrho^2}{4} \int_\Omega \left(\frac{p_\mu}{\phi(f)}\right)^{\varrho-2} \left| \nabla \frac{p_\mu}{\phi(f)} \right|^2 \mathrm{d}x \\ &\qquad\quad + \mu\, c(\delta) \int_\Omega \left(\frac{p_\mu}{\phi(f)}\right)^{\varrho-2} |\nabla f|^2 \,\mathrm{d}x \\ &\qquad \leq \mu\, \delta \int_\Omega \left| \nabla \left(\frac{p_\mu}{\phi(f)}\right)^{\varrho/2} \right|^2 \mathrm{d}x + \mu^{\varrho-1}\, c(\delta) \int_\Omega \phi(f)^{\varrho-2} |\nabla f|^2 \,\mathrm{d}x \ . \end{aligned}$$

Therefore, due to $\phi(f) \geq 1$ and $\mu < 1$, we infer from (29) by combining the above estimates that for all $t \in J_T$

(30)
$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \phi(f)\left(\frac{p_\mu}{\phi(f)}\right)^\varrho \mathrm{d}x &\le c(T,\varepsilon) + c(T,\varepsilon)\int_\Omega \phi(f)\left(\frac{p_\mu}{\phi(f)}\right)^\varrho \mathrm{d}x \\ &+ \left(\varepsilon\, c(T) + \delta - 4\beta\,\frac{\varrho-1}{\varrho}\right)\int_\Omega \left|\nabla\left(\frac{p_\mu}{\phi(f)}\right)^{\varrho/2}\right|^2 \mathrm{d}x \\ &+ \mu^{\varrho-1}\, c(\delta)\int_\Omega \phi(f)^{2-\varrho}\,|\nabla f|^2\, \mathrm{d}x\ .\end{aligned}$$

We then choose $\varepsilon > 0$ and $\delta > 0$ sufficiently small so that the term involving the gradient of $\frac{p_\mu}{\phi(f)}$ becomes negative. Recalling that $\|\phi(f)\|_\infty \le c\big(\|f^0\|_\infty\big)$ on J_T, that $\nabla f(t) \in L_2$, and that $p \in C^1(J, L_q)$ we may then let $\mu \to 0^+$ and use Lebesgue's theorem to obtain

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \phi(f)\left(\frac{p}{\phi(f)}\right)^\varrho \mathrm{d}x \le c(T) + c(T)\int_\Omega \phi(f)\left(\frac{p}{\phi(f)}\right)^\varrho \mathrm{d}x$$

for all $t \in J_T$ since $1 < \varrho \le q$. Thus, we conclude $\|p(t)\|_{L_\varrho} \le c(T)$ for $t \in J_T$. ∎

We are now in a position to prove that indeed $J = \mathbb{R}^+$. Since p is nonnegative, $\|\vartheta(w(t))\|_\infty \le c(T)$, and $\partial_\nu p(t) = \partial_\nu f(t) = 0$ for $t \in J_T$ it follows that $\|p(t)\|_{L_1} \le c(T)$, $t \in J_T$, by integrating (H_3). Therefore, we may apply Proposition 5.1 successively to derive $\|p(t)\|_{L_q} \le c(T)$ for $t \in J_T$; hence $J = \mathbb{R}^+$ according to (25). Consequently, the proof of Theorem 1.1 is complete.

6. Numerical examples. We illustrate the theoretical results above with numerical examples (a numerical treatment of a more general model is given in [7]). The parameters for the example are chosen for illustrative purposes.

The region Ω is $[0,6]\times[0,6] \subset \mathbb{R}^2$, the parameters are $a(x) \equiv 5.0$, $\alpha = .01$, $d(x) \equiv 1.0$, $b(x) \equiv 1.0$, $\beta = .01$, $\chi(f) \equiv 0.0$, or $\chi(f) \equiv 0.4$, $\theta(x,w) \equiv 0.1$, $\varrho(x,w) = 2.0\,w/(1.0+w)$, $\gamma = 0.1$, $e(x) \equiv 1.0$, $\omega(x,p) = 2.0\,p/(1.0+p)$, $g(x) \equiv 5.0$, and the initial conditions are

$$\begin{aligned}f^0(x) &= 0.05\cos\big((10.0\,\pi/36.0)\,x_1^2\big)\sin\big((13.0\,\pi/72.0)\,x_2^2\big) + 0.3\ , \\ p^0(x) &= 5.0\max\big\{0.3 - (x_1-3.0)^2 - (x_2-3.0)^2\,,\,0.0\big\}\,,\end{aligned}$$

$m^0(x) = p^0(x)$, and $w^0(x) = 4.0\,f^0(x)$, where $x = (x_1, x_2)$. The normalized tumor density is initially distributed symmetrically in a circle. The normalized extracellular matrix density is immobile and heterogeneous above a uniform background value. The haptotactic parameter χ is an indicator of the relative strength of cell-matrix adhesion, and the value of χ increases through successive mutations of the tumor cell lines, as tumor cells gain greater capacity to invade the surrounding bound substrate [5]. We provide two choices for the haptotaxis parameter χ to demonstrate this increase in χ. In Figures 1, 2, 3 the value of χ is 0.0, so that all movement of cells is due only to cell motility. In Figures 4, 5, 6 the value of χ is 0.4, so that movement of cells is due to both cell motility and haptotactic directed attraction. The simulations demonstrate that haptotaxis produces a profound distinction in the spatial behavior in the two cases. Without haptotaxis the tumor expands slowly and symmetrically (Figures 1 and 2) as the total population declines (Figure 3). With haptotaxis the

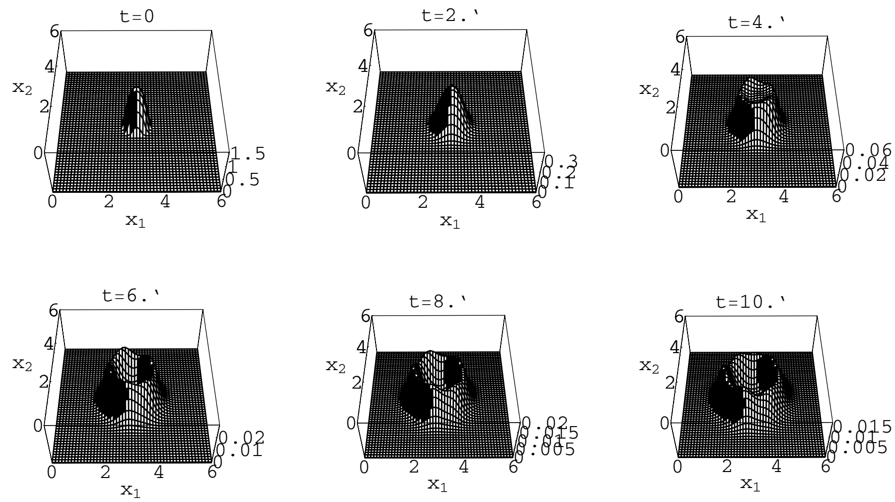

Fig. 1. *The normalized tumor cell density for various times in the case without haptotaxis* ($\chi = 0.0$)*. The tumor slowly expands nearly symmetrically as it decreases in total mass. The interior of the tumor becomes necrotic as tumor cells consume and exhaust the supply of oxygen furnished by the extracellular matrix.*

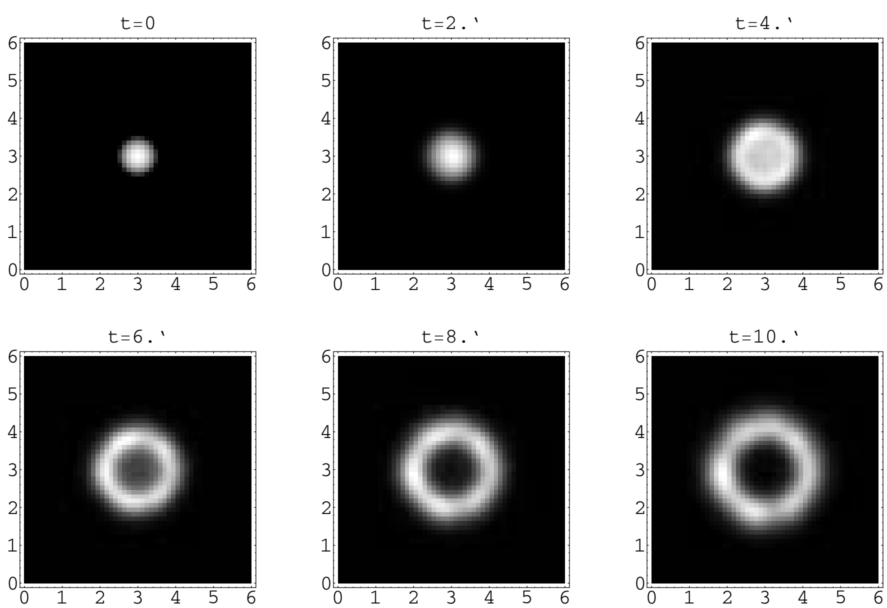

Fig. 2. *The density plots in the* (x_1, x_2)*-coordinate system of the tumor cell distributions in Figure* 1 ($\chi = 0.0$)*.*

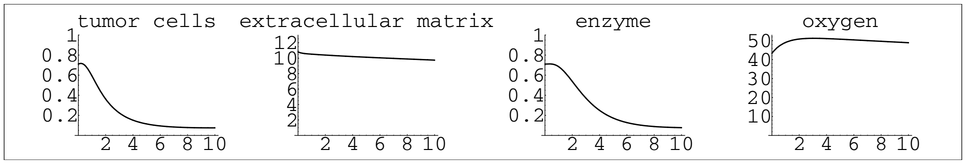

FIG. 3. *The total populations in the case without haptotaxis* ($\chi = 0.0$)*:* $\int_\Omega p(x,t)\mathrm{d}x$, $\int_\Omega f(x,t)\mathrm{d}x$, $\int_\Omega m(x,t)\mathrm{d}x$, $\int_\Omega w(x,t)\mathrm{d}x$ *as functions of time. The total tumor mass eventually shrinks to a very low value.*

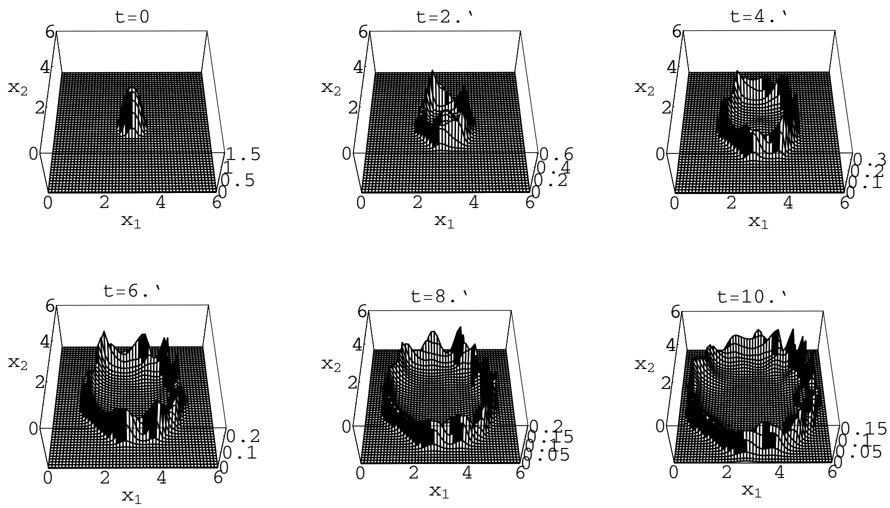

FIG. 4. *The normalized tumor cell density for various times in the case with haptotaxis* ($\chi = 0.4$)*. The tumor expands more rapidly and asymmetrically as it increases in total mass.*

tumor spreads much more rapidly and asymmetrically (Figures 4 and 5) as the total tumor cell population increases (Figure 6) for a time. The distinction of the two cases demonstrates the importance of haptotaxis in the ability of tumors to invade surrounding tissue.

7. Summary. In Theorem 1.1 we have proven the existence of unique classical global solutions to the model of tumor growth (H_1)–(H_6). The model describes the spatial invasion of a tumor mass into its surrounding extracellular matrix. A key feature of the model is that the migration of tumor cells is due primarily to haptotaxis-directed movement. The interpretation of haptotaxis in tumor growth is that cell movement is controlled by the differential strengths of cell-cell adhesion gradients. Haptotaxis differs from chemotaxis in that the directed migration of the tumor cells toward concentrations of the extracellular macromolecules is mediated by a diffusive enzyme produced by the tumor cells. This enzyme degrades the matrix macromolecules, which produce the oxygen essential for tumor growth, and thus alters patterns of tumor movement and proliferation. The haptotaxis process in the model produces technical complications, but also yields the regularity of solutions essential in the analysis. We have demonstrated the role of haptotaxis in two numerical examples. In the first example, without haptotaxis, the only spatial movement of tumor

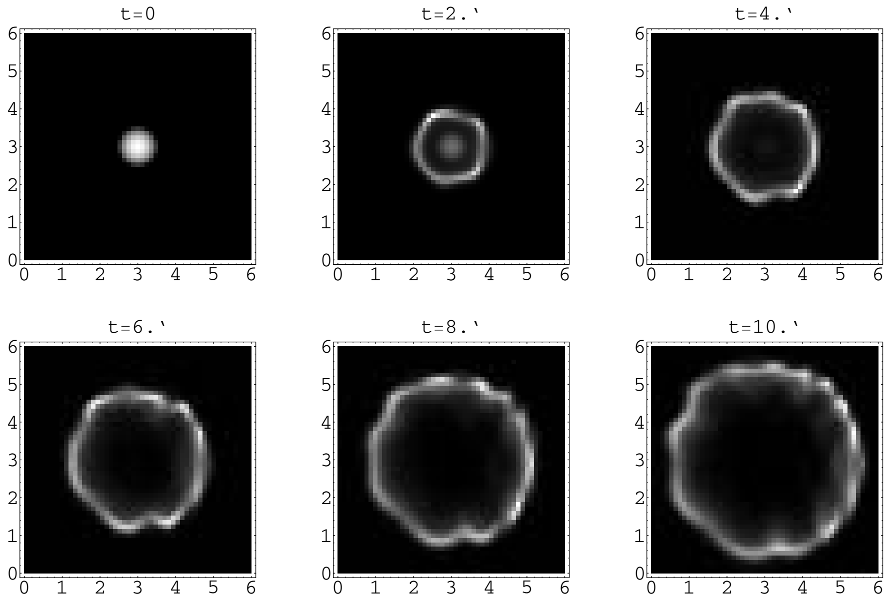

FIG. 5. *The density plots in the* (x_1, x_2)*-coordinate system of the tumor cell distributions in Figure* 4 $(\chi = 0.4)$*.*

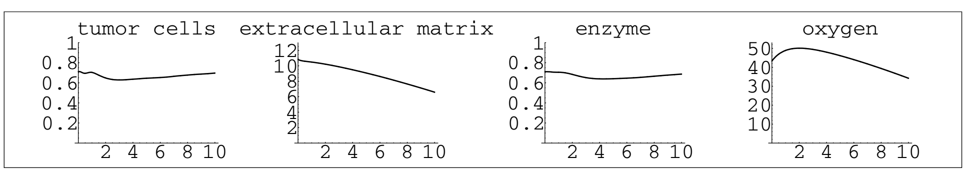

FIG. 6. *The total populations in the case with haptotaxis* $(\chi = 0.4)$*:* $\int_\Omega p(x,t)\mathrm{d}x$*,* $\int_\Omega f(x,t)\mathrm{d}x$*,* $\int_\Omega m(x,t)\mathrm{d}x$*,* $\int_\Omega w(x,t)\mathrm{d}x$ *as functions of time. The total tumor mass grows for an interval of time.*

cells is due to cell motility modeled by diffusion. In this example the tumor invades slowly and decreases in total tumor mass. In the second example, with all parameters the same as in the first example, but with the addition of haptotaxis, the tumor invades more rapidly and with increasing total tumor mass. Both examples show the characteristic interior necrosis of tumor cells due to exhaustion of the oxygen supply, but the effect is much more pronounced with haptotaxis. The utilization of oxygen by the tumor cell population is critical in understanding the distinction of the two examples. If the oxygen concentration is constant in time, then the evolution of the total tumor mass is independent of haptotaxis. If the oxygen concentration evolves in time due to tumor consumption and degradation of its source, then haptotaxis-directed spatial migration enables a more efficient utilization of the environmental resources and results in a more aggressive invasion of the tumor into the surrounding tissue.

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