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Global Solution to a Model of Tumor Invasion[1]

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Abstract. This paper deals with a mathematical model which is used to investigate the role of extracellular matrix (ECM) concentration in tumor cell invasion. The model is a system of partial differential equations governing tumor cell density, the tumor cell-derived protease concentration and the collagen gel concentration. In this system, the equation describing the evolution of the tumor cell density is a *diffusion-haptotaxis* parabolic equation. For general haptotactic coefficient, the global existence of solutions for this model is proved. The proof is based on *a priori* estimates, together with the L^p estimates and the Schauder estimates of parabolic equations.

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1. Model

Most of existing mathematical models of tumor growth and treatment in the literature (for example, see [19, 21-25, 28-29] and references cited therein) focus on avascular tumors. Since the avascular tumor is dependent on diffusion as the only means of receiving nutrients, its growth is limited. For any further development to occur the tumor must initiate angiogenesis–the formation of new blood vessels. Clearly, angiogenesis, the process which results in the tumor having a vascular network, is a key process for metastatic invasion. The tumor invades the surrounding healthy tissue, just after angiogenesis has occurred. The process of tumor cell invasion is an active, dynamic process that requires

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protein synthesis and degradation [13]. Tumor invasion is associated with the degradation of the extracellular matrix (ECM). On contact with ECM, tumor cells can produce proteolytic enzymes, such as matrix metallo-proteases (MMPs), which degrade the ECM. This degradation creates space into which the cells then migrate. The ECM degradation also creates spatial gradients which direct the migration of invasive cells either via *chemotaxis* (spatial gradients of diffusible chemicals) or *haptotaxis* (spatial gradients of non-diffusible chemicals). There are wide variations in the composition of ECM in the various tissues of the body. The ECM composition can influence the degree of tumor cell invasion (see [13]). Recently, there is an increasing biological and mathematical interest in tumor invasion and the corresponding mathematical models have been developed (for example, see [1-8, 10, 12, 14-18, 20]). As said in [15] by Marchant, Norbury and Byrne, a weakness of many invasion models is that they are not amenable to analysis and must be solved using *numerical methods*. In this paper we focus on the *analytical* study of the model developed by Perumpanani and Byrne [20], because this model is relatively simple and it captures the main characteristics of tumor cell invasion.

Perumpanani and Byrne's model was used to investigate the role of ECM *concentration* in tumor cell invasion. They also valid their model using the experimental results from the collagen gel invasion assay. The key physical variables are assumed as follows:

$$\begin{aligned} n &= \text{density of tumor cells,} \\ p &= \text{concentration of protease secreted by tumor cells,} \\ c &= \text{concentration of collagen gel.} \end{aligned}$$

The experiment was conducted within an individual well $\Omega \subset \mathbb{R}^3$. The model was derived by applying the principle of mass conservation to each of the key variables. The model developed in [20] consists of the following system of equations:

$$\frac{\partial n}{\partial t} = \underbrace{\bigtriangledown \cdot (\mu_n \bigtriangledown n)}_{\text{random motion}} - \underbrace{\bigtriangledown \cdot (\chi n \bigtriangledown c)}_{\text{haptotaxis}} + \underbrace{\lambda_0 n(1 - n - \lambda_1 c)}_{\text{modified logistic growth}}, \tag{1.1}$$

$$\frac{\partial p}{\partial t} = \underbrace{\bigtriangledown \cdot (\mu_p \bigtriangledown p)}_{\text{diffusion}} + \underbrace{\lambda_2 nc}_{\text{production}} - \underbrace{\lambda_3 p}_{\text{decay}}, \tag{1.2}$$

$$\frac{\partial c}{\partial t} = - \underbrace{\lambda_4 pc}_{\text{degradation}} . \tag{1.3}$$

In (1.1), μ_n and χ are assumed constant random motility and haptotactic, respectively, λ_0 represents the proliferation rate of tumor cells and λ_1 describes the competition for space caused by the presence of the collagen gel. The term for tumor cell taxis incorporates the sensitivity of the cells to spatial gradients of collagen. Given that the collagen gel is static, this behavior is haptotactic rather than chemotatic.

In (1.2), μ_p is the assumed constant diffusion coefficient of the protease. We assumed that protease production is proportional to the product of the tumor cell density and the collagen gel concentration. λ_2 is the rate of protease production and λ_3 denotes the rate of protease decay.

In (1.3), since the collagen gel is static, we neglected random motion of the collagen gel and focused soled on its degradation by the protease. λ_4 represents the rate at which the protease degrade the collagen gel.

Guided by the experimental protocol [20], in which invasion takes place within an isolated system, we assumed that there is no cells or protease can escape from the well Ω. As in [20], we introduce the no-flux boundary conditions

$$\mu_n \frac{\partial n}{\partial \nu} - \chi n \frac{\partial c}{\partial \nu} = 0 \quad \text{on } \Gamma \times \{0 \leq t < \infty\}, \tag{1.4}$$

$$\frac{\partial p}{\partial \nu} = 0 \quad \text{on } \Gamma \times \{0 \leq t < \infty\}, \tag{1.5}$$

where Γ is the boundary of Ω and ν is the outward normal to Γ. We prescribe the following initial conditions:

$$n(x,0) = n_0(x), \quad p(x,0) = p_0(x), \quad c(x,0) = c_0(x), \quad x \in \Omega. \tag{1.6}$$

The system (1.1)-(1.6) is *not* a standard parabolic system due to the haptotaxis term in (1.1). In [20], the authors numerically studied the evolution of the tumor cell density n, the protease concentration p, and the collagen gel concentration c of the model (1.1)-(1.6) in radially symmetrical form. In [15], dropping the random motion of tumor cells in (1.1) and neglecting the diffusion of the protease in (1.2), Marchant, Norburg and Byrne recently studied the biphasic dependence of the tumor cell invasion speed on the density of the surrounding normal tissue for the corresponding model (1.1)-(1.3) and (1.6). In [24], under the assumption that the haptotactic coefficient is *small* compared with the diffusion coefficient of the tumor cell, Tao and Yang proved the global existence of solutions for an *approximate* problem. In present paper, we will prove the global existence of solutions to the model (1.1)-(1.6) for general haptotactic coefficient $\chi > 0$. In section 2 we first transform the problem (1.1)-(1.6) to a new problem in which the equation corresponding to the density of tumor cells *does not* include the second spatial derivative of the variable c, then we introduce some notations and state a result on the local existence and uniqueness of solutions to the model (1.1)-(1.6). In section 3 we establish some *a priori* estimates. In section 4 we prove the global existence of solutions to the model (1.1)-(1.6). The proof is based on a priori estimates, together with the L^p estimates and the Schauder estimates of parabolic equations, the Young's inequality and the Gagliard-Nirenberg's inequality.

2. Local existence

For any $0 < T \le \infty$ we set

$$\Omega_T = \Omega \times \{0 \le t < T\}, \quad \Gamma_T = \Gamma \times \{0 \le t < T\}.$$

Introduce the variable transformation:

$$m = ne^{-\frac{\chi}{\mu_n}c}. \tag{2.1}$$

In terms of the variables $m,\ p,\ c$, the system (1.1)-(1.6) becomes

$$\begin{aligned} &\frac{\partial m}{\partial t} - \mu_n e^{-\frac{\chi}{\mu_n}c} \bigtriangledown \cdot (e^{\frac{\chi}{\mu_n}c} \bigtriangledown m) \\ &= \lambda_0 m(1 - e^{\frac{\chi}{\mu_n}c}m - \lambda_1 c) + \lambda_4 \frac{\chi}{\mu_n} mpc \quad \text{in } \Omega_T, \end{aligned} \tag{2.2}$$

$$\frac{\partial p}{\partial t} - \mu_p \bigtriangleup p = \lambda_2 e^{\frac{\chi}{\mu_n}c} mc - \lambda_3 p \quad \text{in } \Omega_T, \tag{2.3}$$

$$c = c_0(x) e^{-\int_0^t \lambda_4 p(x,\tau) d\tau} \quad \text{in } \Omega_T, \tag{2.4}$$

$$\frac{\partial m}{\partial \nu} = \frac{\partial p}{\partial \nu} = 0 \quad \text{on } \Gamma_T, \tag{2.5}$$

$$m(x,0) = m_0(x), \quad p(x,0) = p_0(x), \quad x \in \Omega, \tag{2.6}$$

where $m_0(x) = n_0(x) e^{-\frac{\chi}{\mu_n}c_0(x)}$.

Throughout this paper we assume that

$$\begin{aligned} &m_0(x) \ge 0,\ p_0(x) \ge 0,\ 0 \le c_0(x) \le c_0, \\ &\Gamma \in C^{2+\alpha},\ 0 < \alpha < 1, \\ &m_0(x),\ p_0(x),\ c_0(x) \in C^{2+\alpha}(\overline{\Omega}), \\ &\frac{\partial m_0(x)}{\partial \nu} = \frac{\partial p_0(x)}{\partial \nu} = 0 \quad \text{on } \Gamma. \end{aligned} \tag{2.7}$$

We denote by $C^{k+\alpha,\ \beta}_{x,\ t}(\Omega_T)$ (k integer ≥ 0, $0 < \alpha < 1$, $0 < \beta < 1$) the space of function $u(x,t)$ with finite norm

$$\| u \|_{C^{k+\alpha,\ \beta}_{x,\ t}(\Omega_T)} = \sum_{|l|=0}^{k} [\sup_{\Omega_T} |D^l_x u| + < D^l_x u >^{(\alpha)}_{x,\ \Omega_T} + < D^l_x u >^{(\beta)}_{t,\ \Omega_T}]$$

where

$$< w >^{(\alpha)}_{x,\ \Omega_T} = \sup_{(x,t),\ (y,t) \in \Omega_T} \frac{|w(x,t) - w(y,t)|}{|x-y|^\alpha},$$

$$< w >^{(\beta)}_{t,\ \Omega_T} = \sup_{(x,t),\ (x,\tau) \in \Omega_T} \frac{|w(x,t) - w(x,\tau)|}{|t-\tau|^\beta}.$$

We denote by $C^{2+\alpha,\ 1+\beta}_{x,\ t}(\Omega_T)$ the space of functions $u(x,t)$ with norm

$$\| u \|_{C^{2+\alpha,\ \beta}_{x,\ t}(\Omega_T)} + \| u_t \|_{C^{\alpha,\ \beta}_{x,\ t}(\Omega_T)} .$$

For brevity we set

$$U = (m,\ p,\ c). \tag{2.8}$$

The local existence of solutions to the system (2.2)-(2.7) has been proved by Tao and Yang [24] by a fixed point argument. For convenience of readers and our later proof of global existence, we here give the main idea of the proof of local existence:

We introduce the Banach space X of the vector-functions U with norm

$$\| U \| = \| U \|_{C^{\alpha,\ \alpha/2}_{x,\ t}(\Omega_T)} \quad (0 < T < 1)$$

and a subset

$$X_M = \{U \in X,\ \| U \| \leq M\}, \quad M > 0$$

where M is an appropriate constant. Given any $U \in X_M$, we define a corresponding function $\overline{U} \equiv FU$ by

$$\overline{U} = (\overline{m},\ \overline{p},\ \overline{c})$$

where $\overline{U}$ satisfies the equations

$$\frac{\partial \overline{p}}{\partial t} - \mu_p \triangle \overline{p} = \lambda_2 e^{\frac{\chi}{\mu_n} c} mc - \lambda_3 p \quad \text{in } \Omega_T, \tag{2.9}$$

$$\frac{\partial \overline{p}}{\partial \nu} |_{\Gamma_T} = 0, \quad \overline{p}(x,0) = p_0(x) \quad \text{for } x \in \Omega, \tag{2.10}$$

$$\overline{c} = c_0(x) e^{-\int_0^t \lambda_4 \overline{p}(x,\tau) d\tau} \quad \text{in } \Omega_T, \tag{2.11}$$

$$\begin{aligned} &\frac{\partial \overline{m}}{\partial t} - \mu_n e^{-\frac{\chi}{\mu_n} \overline{c}} \nabla \cdot (e^{\frac{\chi}{\mu_n} \overline{c}} \nabla \overline{m}) \\ &= \lambda_0 m (1 - e^{\frac{\chi}{\mu_n} c} m - \lambda_1 c) + \lambda_4 \frac{\chi}{\mu_n} mpc \quad \text{in } \Omega_T, \end{aligned} \tag{2.12}$$

$$\frac{\partial \overline{m}}{\partial \nu} |_{\Gamma_T} = 0, \quad \overline{m}(x,0) = m_0(x) \quad \text{for } x \in \Omega. \tag{2.13}$$

We then prove that F is a contraction in X_M, provided T is small (for the details of the proof, see [24]). By the contraction mapping theorem F has a unique fixed point U, which is the unique solution of (2.2)-(2.7). From the proof of Theorem 2.1 in [24], we find that the size T of the time interval $[0,T]$ for the existence of local solution depends on $\| U(\cdot,0) \|_{C^{2+\alpha}_x(\Omega)}$.

We now restate the local existence result as follows:

Theorem 2.1 (Tao and Yang [24]). *There exists a unique solution* $U \in C^{2+\alpha,\ 1+\alpha/2}_{x,\ t}(\Omega_T)$ *of the system (2.2)-(2.7) for some small* $T > 0$ *which depends on* $\| U(\cdot,0) \|_{C^{2+\alpha}_x(\Omega)}$.

3. A priori estimates

To continue the local solution established in above section to all $t > 0$, we need to establish some *a priori* estimates.

Lemma 3.1. *Assume that* $U \in C^{2,1}_{x,t}(\Omega_T)$ *(for some* $0 < T < \infty$*) is a solution of the system (2.2)-(2.7). Then, there holds*

$$m \geq 0, \quad p \geq 0, \quad 0 \leq c \leq c_0. \tag{3.1}$$

Proof. It follows from (2.4) and $c_0(x) \geq 0$ that

$$c(x,t) \geq 0. \tag{3.2}$$

Note that (2.2) can be rewritten as

$$\frac{\partial m}{\partial t} - \mu_n \triangle m - \chi \bigtriangledown c \cdot \bigtriangledown m = a(x,t)m \quad \text{in } \Omega_T \tag{3.3}$$

where $a(x,t) = \lambda_0(1 - e^{\frac{\chi}{\mu_n}c}m - \lambda_1 c) + \frac{\lambda_4 \chi}{\mu_n}pc$. Clearly, $\underline{m} \equiv 0$ is a sub-solution of (3.3) with the initial-boundary conditions $\frac{\partial m}{\partial \nu}|_{\Gamma_T} = 0,\ m(x,0) = m_0(x) \geq 0$. Therefore, it follows from the maximum principle that

$$m(x,t) \geq \underline{m} \equiv 0. \tag{3.4}$$

By (2.3), (3.2) and (3.4) we get

$$\frac{\partial p}{\partial t} - \mu_p \triangle p \geq -\lambda_3 p \quad \text{in } \Omega_T. \tag{3.5}$$

This, together with $\frac{\partial p}{\partial \nu}|_{\Gamma_T} = 0,\ p(x,0) = p_0(x) \geq 0$ and the maximum principle, yields

$$p(x,t) \geq 0. \tag{3.6}$$

Combining (2.4), (3.2) and (3.6), we get

$$0 \leq c(x,t) \leq c_0(x) \leq c_0. \tag{3.7}$$

This completes the proof of Lemma 3.1. □

Lemma 3.2. *Assume that* $U \in C^{2,1}_{x,t}(\Omega_T)$ *(for some* $0 < T < \infty$*) is a solution of the system (2.2)-(2.7). Then, there holds*

$$\| m \|_{L^1(\Omega)} \leq \max(\| n_0 \|_{L^1(\Omega)},\ |\Omega|), \tag{3.8}$$

$$\| p \|_{L^1(\Omega)} \leq \| p_0 \|_{L^1(\Omega)} + \frac{\lambda_2 c_0}{\lambda_3} \max(\| n_0 \|_{L^1(\Omega)},\ |\Omega|). \tag{3.9}$$

Proof. Integrating (1.1) in Ω and noting (1.4) and (3.1), we have

$$\begin{aligned}\frac{d}{dt}\parallel n\parallel_{L^1(\Omega)} &\leq \lambda_0\parallel n\parallel_{L^1(\Omega)}-\lambda_0\int_\Omega n^2\,dx \\ &\leq \lambda_0\parallel n\parallel_{L^1(\Omega)}-\frac{\lambda_0}{|\Omega|}\parallel n\parallel^2_{L^1(\Omega)}\end{aligned}\tag{3.10}$$

where we have used the Hölder's inequality: $(\int_\Omega n\,dx)^2\leq\int_\Omega 1^2\,dx\cdot\int_\Omega n^2\,dx$ $=|\Omega|\int_\Omega n^2\,dx$. (3.10) yields

$$\parallel n\parallel_{L^1(\Omega)}\leq\frac{1}{\frac{1}{|\Omega|}+\big(\frac{1}{\|n_0\|_{L^1(\Omega)}}-\frac{1}{|\Omega|}\big)e^{-\lambda_0 t}}\leq\max(\parallel n_0\parallel_{L^1(\Omega)},\ |\Omega|).\tag{3.11}$$

Integrating (1.2) in Ω and noting (1.5) and (3.1), we have

$$\frac{d}{dt}\parallel p\parallel_{L^1(\Omega)}\leq\lambda_2c_0\parallel n\parallel_{L^1(\Omega)}-\lambda_3\parallel p\parallel_{L^1(\Omega)},$$

which yields

$$\parallel p\parallel_{L^1(\Omega)}\leq\parallel p_0\parallel_{L^1(\Omega)}+\frac{\lambda_2c_0}{\lambda_3}\parallel n\parallel_{L^1(\Omega)}.\tag{3.12}$$

This completes the proof of Lemma 3.2. □

For convenience of notations, in the sequel we shall denote generic constants which are independent of T by A_0 and we denote various constants which depend on T by A.

To establish required *a priori* estimates, we need the following lemma about the regularity of the solution semigroup of the heat equation:

Lemma 3.3 (Taylor [26; p. 274])**.** *Let M be a bounded $N-$dimensional C^∞ manifold without boundary. Let $T_1(t)=e^{\triangle t}$ denote the solution semigroup of the heat equation on M. Assume*

$$0<t\leq 1,\quad r'\geq\rho$$

then

$$T_1(t):\ L^\rho(M)\to L^{r'}(M)\ \text{with norm}\ A_0t^{-\alpha}$$

where

$$\alpha=\frac{N}{2}\Big(\frac{1}{\rho}-\frac{1}{r'}\Big).$$

The assumptions on M are satisfied by the heat equation on a rectangular $[0,l_1]\times\cdots\times[0,l_N]$ with periodic boundary conditions. The regularity results also apply to homogeneous Neumann boundary conditions, since problems with Neumann boundary conditions can be extended to problems with periodic boundary conditions on a larger domain by gluing together copies of mirror images of the original rectangular.

Lemma 3.4. *Assume that $U \in C^{2,1}_{x,t}(\Omega_T)$ (for some $0 < T < \infty$) is a solution of the system (2.2)-(2.7), and suppose that*

$$\| m \|_{L^\rho(\Omega)} \leq A \tag{3.13}$$

for all $t \in (0, T]$ and $1 \leq \rho < \infty$. Then there holds

$$\| p \|_{L^{r'}(\Omega)} \leq A \tag{3.14}$$

for all $t \in (0, T]$ and any $r' > \rho$ satisfying $\frac{1}{r'} + \frac{2}{N} > \frac{1}{\rho}$, where $N :=$ the dimension of the spatial domain Ω.

Proof. Set $\tilde{p} = e^{\lambda_3 t} p$. Then (2.3) yields

$$\frac{\partial \tilde{p}}{\partial t} - \mu_p \triangle \tilde{p} = f \tag{3.15}$$

where $f = \lambda_2 e^{\lambda_3 t} e^{\frac{\chi}{\mu_n} c} mc$. By $0 \leq c \leq c_0$ (see (3.1)) and the assumption (3.13), we easily find that

$$\| f \|_{L^\rho(\Omega)} \leq A. \tag{3.16}$$

We write the solution of (3.15) as (without loss of generality, we here assume that $\mu_p = 1$)

$$\tilde{p}(t) = T_1(t)\tilde{p}(0) + \int_0^t T_1(t-s) f(s) \; ds. \tag{3.17}$$

Applying Lemma 3.3 with $0 < \alpha < 1$ and using (3.16), (3.17), (2.5) and (2.7), we easily find that for $0 < t \leq 1$

$$\begin{aligned} \| \tilde{p}(t) \|_{L^{r'}(\Omega)} &\leq \| p(0) \|_{L^{r'}(\Omega)} + A_0 t^{1-\alpha} \max_{0 \leq s \leq t} \| f(s) \|_{L^\rho(\Omega)} \\ &\leq A. \end{aligned} \tag{3.18}$$

Note that for $1 < t \leq 2$,

$$\begin{aligned} \tilde{p}(t) &= T_1(t)\tilde{p}(1) + \int_1^t T_1(t-s) f(s) \; ds \\ &= T_1(t)\tilde{p}(1) + \int_0^{t-1} T_1(t-1-\tilde{s}) f(\tilde{s}+1) \; d\tilde{s} \\ &= T_1(\tilde{t}+1)\tilde{p}(1) + \int_0^{\tilde{t}} T_1(\tilde{t}-\tilde{s}) f(\tilde{s}+1) \; d\tilde{s}, \end{aligned} \tag{3.19}$$

where $\tilde{t} = t - 1, \; 0 < \tilde{t} \leq 1$. Applying Lemma 3.3 with $0 < \alpha < 1$ and using (3.16), (3.18), (3.19) and (2.5), we have for $1 < t \leq 2$

$$\begin{aligned} \| \tilde{p}(t) \|_{L^{r'}(\Omega)} &\leq \| p(1) \|_{L^{r'}(\Omega)} + A_0 \tilde{t}^{1-\alpha} \max_{0 \leq \tilde{s} \leq \tilde{t}} \| f(\tilde{s}+1) \|_{L^\rho(\Omega)} \\ &\leq A + A_0 \max_{1 \leq s \leq t} \| f(s) \|_{L^\rho(\Omega)} \\ &\leq A. \end{aligned}$$

Continuing above procedure, we have for all $t \in (0, T]$

$$\| \tilde{p} \|_{L^{r'}(\Omega)} \leq A.$$

This completes the proof of Lemma 3.4. □

From (3.8) we have the L^1-estimate of m. In the following we shall use bootstrap method and Walker-Webb's idea [27] to raise the regularity of m. In fact, we have

Lemma 3.5. *Assume that $U \in C^{2,1}_{x,t}(\Omega_T)$ (for some $0 < T < \infty$) is a solution of the system (2.2)-(2.7), and suppose that*

$$\| m \|_{L^{\rho}(\Omega)} \leq A \tag{3.20}$$

for all $t \in (0, T]$ and $1 \leq \rho < \infty$. Then there holds

$$\| m \|_{L^{\frac{13}{12}\rho}(\Omega)} \leq A \tag{3.21}$$

for all $t \in (0, T]$.

Proof. Denote $s := \frac{13}{12}\rho$. If $s \geq 2$, we set $\gamma := 0$; otherwise we fix $\gamma \in (0, 1)$. Then we put $m_\gamma := m + \gamma \geq \gamma > 0$ and therefore

$$\bigtriangledown m_\gamma^{s/2} = \frac{s}{2} m_\gamma^{s/2-1} \bigtriangledown m_\gamma$$

makes sense. Thus, given any $\Lambda(z) \in C^2((0, \infty))$ and $\Lambda(z),\ \Lambda'(z) \geq 0$ for $z \in [0, \infty)$ we derive from (2.2) and (3.1)

$$\begin{aligned}
&\frac{d}{dt} \int_\Omega e^{\frac{\chi}{\mu_n} c}\ \Lambda(m_\gamma)\ dx \\
= &- \frac{\lambda_4 \chi}{\mu_n} \int_\Omega \Lambda(m_\gamma)\ p\ c\ e^{\frac{\chi}{\mu_n} c}\ dx + \mu_n \int_\Omega \Lambda'(m_\gamma)\ \bigtriangledown \cdot (e^{\frac{\chi}{\mu_n} c}\ \bigtriangledown m_\gamma)\ dx \\
&+ \lambda_0 \int_\Omega \Lambda'(m_\gamma)\ e^{\frac{\chi}{\mu_n} c}\ m_\gamma (1 + e^{\frac{\chi}{\mu_n} c}\ \gamma - e^{\frac{\chi}{\mu_n} c}\ m_\gamma - \lambda_1\ c)\ dx \\
&- \lambda_0\ \gamma \int_\Omega \Lambda'(m_\gamma)\ e^{\frac{\chi}{\mu_n} c}\ (1 + e^{\frac{\chi}{\mu_n} c}\ \gamma - e^{\frac{\chi}{\mu_n} c}\ m_\gamma - \lambda_1\ c)\ dx \\
&+ \frac{\lambda_4 \chi}{\mu_n} \int_\Omega \Lambda'(m_\gamma)\ e^{\frac{\chi}{\mu_n} c}\ m_\gamma\ p\ c\ dx - \frac{\lambda_4 \chi \gamma}{\mu_n} \int_\Omega \Lambda'(m_\gamma)\ e^{\frac{\chi}{\mu_n} c}\ p\ c\ dx \\
\leq\ &\mu_n \int_\Omega \Lambda'(m_\gamma)\ \bigtriangledown \cdot (e^{\frac{\chi}{\mu_n} c}\ \bigtriangledown m_\gamma)\ dx \\
&+ A_0 \int_\Omega \Lambda'(m_\gamma)\ dx\ +\ A_0 \int_\Omega \Lambda'(m_\gamma)\ m_\gamma\ dx\ +\ A_0 \int_\Omega \Lambda'(m_\gamma)\ m_\gamma\ p\ dx \\
= &- \mu_n\ \int_\Omega \Lambda''(m_\gamma)\ e^{\frac{\chi}{\mu_n} c}\ |\bigtriangledown m_\gamma|^2\ dx \\
&+ A_0 \int_\Omega \Lambda'(m_\gamma)\ dx\ +\ A_0 \int_\Omega \Lambda'(m_\gamma)\ m_\gamma\ dx\ +\ A_0 \int_\Omega \Lambda'(m_\gamma)\ m_\gamma\ p\ dx.
\end{aligned}$$

In particular, taking $\Lambda(z) = z^s$ we have

$$\begin{aligned}
(3.22)\qquad & \frac{d}{dt}\int_\Omega e^{\frac{\chi}{\mu_n}c}\, m_\gamma^s\, dx \\
\le\ & -4\mu_n\, \frac{s-1}{s} \int_\Omega e^{\frac{\chi}{\mu_n}c}\, |\bigtriangledown m_\gamma^{s/2}|^2\, dx \\
& +A_0 \int_\Omega m_\gamma^{s-1}\, dx \ +\ A_0 \int_\Omega m_\gamma^s\, dx +\ A_0 \int_\Omega p\, m_\gamma^s\, dx \\
\le\ & -4\mu_n\, \frac{s-1}{s} \int_\Omega e^{\frac{\chi}{\mu_n}c}\, |\bigtriangledown m_\gamma^{s/2}|^2\, dx \\
& +A_0\ +\ A_0 \int_\Omega m_\gamma^s\, dx +\ A_0 \int_\Omega p\, m_\gamma^s\, dx
\end{aligned}$$

where we have used the Young's inequality: $m_\gamma^{s-1} \le \frac{s-1}{s} m_\gamma^s + \frac{1}{s}$. We easily check that for $\rho \ge 1$ and $s = \frac{13}{12}\rho$, $(\rho,\ s)$ satisfies the following inequality:

$$(3.23)\qquad \frac{Ns}{Ns+2\rho}\ <\ 1\ +\ \frac{2}{N}\ -\ \frac{1}{\rho}\quad \Big(\Leftrightarrow \frac{13}{21}\ <\ \frac{14}{21}\ +\ 1-\ \frac{1}{\rho}\,\Big)$$

where $N := 3$ is the dimension of the domain Ω. (3.23) allows us to fix $r > 1$ such that

$$(3.24)\qquad \frac{Ns}{Ns+2\rho}\ <\ \frac{1}{r}\ < 1\ +\ \frac{2}{N}\ -\ \frac{1}{\rho}.$$

The first inequality of (3.24) warrants the following version of the Gagliard-Nirenberg's inequality (see [9; p.37])

$$(3.25)\qquad \|\cdot\|_{L^{2r}}^{2r} \le A_0\, \|\cdot\|_{L^{2\rho/s}}^{2(r-1)} \|\cdot\|_{W_2^1}^2\ ,$$

and the second inequality of (3.24) allows us to take r' in (3.14) to be the dual exponent of r. Applying Young's inequality, and using the given L^ρ-bound on m (see (3.20)) and the inequality (3.25), it follows for $\varepsilon > 0$ that

$$\begin{aligned}
(3.26)\qquad \int_\Omega p\, m_\gamma^s\, dx \ \le\ & A_0(\varepsilon) \int_\Omega p^{r'}\, dx\ +\ \varepsilon \int_\Omega m_\gamma^{sr}\, dx \\
\le\ & A(\varepsilon,T) +\ \|\, m_\gamma^{s/2}\, \|_{L^{2r}}^{2r} \\
\le\ & A(\varepsilon,T)\ +\ \varepsilon\, C_0\ \|\, m_\gamma\, \|_{L^\rho}^{s(r-1)} \|\, m_\gamma^{s/2}\, \|_{W_2^1}^2 \\
\le\ & A(\varepsilon,T)\ +\ A(\varepsilon,T) \int_\Omega m_\gamma^s\, dx \\
& +\ \varepsilon\, A(T) \int_\Omega |\nabla m_\gamma^{s/2}|^2\, dx.
\end{aligned}$$

Inserting (3.26) into (3.22), noting $0 \le c \le c_0$ (and therefore $1 \le e^{\frac{\chi}{\mu_n}c} \le e^{\frac{\chi}{\mu_n}c_0}$) and taking ε small that $\varepsilon A(T) - 4\mu_n(s-1)/s < 0$, we then have

$$(3.27)\qquad \frac{d}{dt}\int_\Omega e^{\frac{\chi}{\mu_n}c}\, m_\gamma^s\, dx \le A\ +\ A \int_\Omega e^{\frac{\chi}{\mu_n}c}\, m_\gamma^s\, dx.$$

This further yields

$$\int_\Omega e^{\frac{\chi}{\mu_n}c}\ m_\gamma^s\ dx \leq A. \tag{3.28}$$

We finally let $\gamma \to 0^+$ and use Lebesgue's theorem to obtain

$$\int_\Omega m^s\ dx \leq A. \tag{3.29}$$

This completes the proof of Lemma 3.5. □

We introduce Sobolev space

$$W_k^{2,1}(\Omega_T) = \{u|\ u, D_x u, D_x^2 u, D_t u \in L^k(\Omega_T)\}$$

with norm

$$\| u \|_{W_k^{2,1}(\Omega_T)} = \| u \|_{L^k(\Omega_T)} + \| D_x u \|_{L^k(\Omega_T)} + \| D_x^2 u \|_{L^k(\Omega_T)} + \| D_t u \|_{L^k(\Omega_T)}$$

in which $k \geq 1$ are integers, $T > 0$ and the derivatives are in the weak sense.

Lemma 3.6. *Assume that $U \in C_{x,t}^{2,1}(\Omega_T)$ (for some $0 < T < \infty$) is a solution of the system (2.2)-(2.7). Then, there exists a constant A, depending on T, such that*

$$\| U \|_{C_{x,\ t}^{2+\alpha,\ 1+\alpha/2}(\Omega_T)} \leq A. \tag{3.30}$$

Proof. Using Lemma 3.2 and repeatedly applying Lemmas 3.4 and 3.5 (i.e. using bootstrap technique) , we can get, for any inter $k \geq 1$

$$\| m \|_{L^k(\Omega)}\ , \quad \| p \|_{L^k(\Omega)} \leq A. \tag{3.31}$$

Equation (2.3) can be rewritten as

$$\frac{\partial p}{\partial t} - \mu_p \triangle p = f_1(m, p, c),$$

where by (3.1) and (3.31) we have, for any integer $k \geq 1$

$$\| f_1 \|_{L^k(\Omega_T)} \leq A.$$

By the parabolic L^p estimates ([11]) we have

$$\| p \|_{W_k^{2,1}(\Omega_T)} \leq A. \tag{3.32}$$

where A is some constant depending on T. By (2.4), (2.7) and (3.32) we get

$$\| c \|_{W_k^{2,1}(\Omega_T)} \leq A. \tag{3.33}$$

By the Sobolev imbedding Theorem (see [11; Lemma 3.3, p. 80]), if we take k sufficiently large, then (3.33) yields

$$\| \nabla c \|_{C_{x,\ t}^{\alpha,\ \alpha/2}(\Omega_T)} \leq A, \tag{3.34}$$

and therefore

$$\| \bigtriangledown c \|_{L^\infty(\Omega_T)} \le A. \tag{3.35}$$

Now, (2.2) can be rewritten as

$$\frac{\partial m}{\partial t} - \mu_n \triangle m - \chi \bigtriangledown c \cdot \bigtriangledown m = f_2(m,p,c) \tag{3.36}$$

where the haptactic term $\chi \bigtriangledown c$ is a bounded function by (3.35) and the right-hand term f_2 satisfying

$$\| f_2 \|_{L^k(\Omega_T)} \le A \quad \text{for any integer } k \ge 1$$

by (3.1) and (3.31). By the parabolic L^p estimates we then have

$$\| m \|_{W_k^{2,1}(\Omega_T)} \le A. \tag{3.37}$$

By (3.37) and the Sobolev imbedding Theorem (taking k large),

$$\| m \|_{C_{x,\ t}^{\alpha,\ \alpha/2}(\Omega_T)} \le A. \tag{3.38}$$

Also, (3.32), (3.33) and the Sobolev imbedding Theorem (taking k large) yield

$$\| p \|_{C_{x,\ t}^{\alpha,\ \alpha/2}(\Omega_T)} \le A, \quad \| c \|_{C_{x,\ t}^{\alpha,\ \alpha/2}(\Omega_T)} \le A. \tag{3.39}$$

Now, from (2.3), (2.7), (3.38), (3.39) and the parabolic Schauder estimates we have

$$\| p \|_{C_{x,\ t}^{2+\alpha,\ 1+\alpha/2}(\Omega_T)} \le A, \tag{3.40}$$

and therefore

$$\| c \|_{C_{x,\ t}^{2+\alpha,\ 1+\alpha/2}(\Omega_T)} \le A. \tag{3.41}$$

Finally, we conclude from (3.36), (3.34), (3.38), (3.39), (2.7) and the parabolic Schauder estimates that

$$\| m \|_{C_{x,\ t}^{2+\alpha,\ 1+\alpha/2}(\Omega_T)} \le A. \tag{3.42}$$

This completes the proof of Lemma 3.6. □

4. Global existence

We now state the main result of this paper as follows:

Theorem 4.1. *There exists a unique global solution* $U \in C_{x,\ t}^{2+\alpha,\ 1+\alpha/2}(\Omega_\infty)$ *of the system (2.2)-(2.7).*

Proof. Suppose to the contrary that $[0, T)$ (where $0 < T < \infty$) is the maximum time interval for the existence of the solution. We take $U(x, T-\varepsilon)$ (where $0 < \varepsilon < T$ is arbitrary) as *new initial value*, then we can extend the solution to $Q_{(T-\varepsilon)+\delta}$ for small $\delta > 0$ by Theorem 2.1. Furthermore, Theorem 2.1 tells us that δ depends only on an upper bound on $\| U(x, T-\varepsilon) \|_{C^{2+\alpha}(\Omega)}$. By *a priori* estimate (3.30) we find that δ depends on $A(T)$ (but δ is independent of ε), i.e., $\delta = \delta(T)$. If we take $\varepsilon < \delta(T)$, then we get

$$(T-\varepsilon) + \delta > T,$$

which contradicts the assumption that $[0, T)$ is the maximum time interval for the existence of the solution. Therefore, the maximum time interval for the existence of the solution is $[0, \infty)$.

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