Mathematical Models and Methods in Applied Sciences
© World Scientific Publishing Company

ANALYSIS OF A MATHEMATICAL MODEL OF TUMOR LYMPHANGIOGENESIS

AVNER FRIEDMAN *

Mathematical Biosciences Institute, Ohio State University
Department of Mathematics, 231 West 18th Avenue
Columbus, 43210-1174
United States
afriedman@mbi.osu.edu

GEORGIOS LOLAS

Mathematical Biosciences Institute, Ohio State University
Department of Mathematics, 231 West 18th Avenue
Columbus, Ohio 43210-1174
United States
georgioslolas@hotmail.com

Received (27 May 2004)
Revised (Day Month Year)
Communicated by (xxxxxxxxxx)

Tumor survival, growth and dissemination are associated with the formation of both new blood vessels (angiogenesis) and new lymph vessels (lymphangiogenesis). A mathematical model of tumor lymphangiogenesis was recently developed by the authors, based on experimental results established in the last five years. The model consists of a coupled system of eight parabolic equations. In this paper we prove existence and uniqueness of a solution for this system, for all $t > 0$.

Keywords: Lymphangiogenesis, tumor invasion, parabolic equations.

AMS Subject Classification: 22E46, 53C35, 57S20

1. The model

Tumor growth and dissemination are associated with the formation of new blood vessels, a process called angiogenesis, and new lymph vessels, a process called lymphangiogenesis. The lymphatic system provides a much more favorable environment for tumor invasion and metastasis than does the blood vasculature. Although intensive research in tumor angiogenesis has been going on for the past four decades, experimental results in lymphangiogenesis began to appear only in the last five

*Mathematical Biosciences Institute, Ohio State University, Department of Mathematics, 231 West 18th Avenue, Columbus, 43210-1174, United States

years. A major obstacle to research in lymphangiogenesis has been the lack of specific markers that could accurately differentiate between the two systems of vasculatures. There are quite elaborate mathematical models of tumor angiogenesis; see for instance, [3], [4] and the references therein. Recently the authors developed in [5] a mathematical model of lymphangiogenesis for tumors, and obtained some numerical results. The walls of lymph vessels are made up of loosely connected endothelial cells, and, in this mathematical model, the presence of lymph vessels is equated with the presence of "high" density of endotheliall cells. The model consists of eight semilinear parabolic PDEs. The purpose of the present paper is to prove that this parabolic system has a unique solution for all $t > 0$.

The eight relevant dependent variables are defined as follows:

$$\begin{aligned}
e &= \text{density lymphatic endothelial cells (LEC)},\\
c &= \text{density of cancer cells},\\
m &= \text{concentration of the extracellular matrix (ECM)},\\
f &= \text{concentration of vascular endothelial growth factor} - \text{C (VEGF} - \text{C)},\\
u_e &= \text{concentration of urokinase secreted by LEC},\\
p_e &= \text{concentration of plasmin activated by LEC},\\
u_c &= \text{concentration of urokinase secreted by cancer cells},\\
p_c &= \text{concentration of plasmin activated by cancer cells}\ .
\end{aligned}$$

Urokinase is also called urokinase plasminogen activator (uPA), and by binding to its cell-surface receptor (uPAR) it activates plasminogen. Plasminogen then activates and enhances plasmin formation. Plasmin is a protease which can degrade the ECM. The model developed in [5] consists of the following system of equations:

$$\begin{aligned}
\frac{\partial e}{\partial t} = {} & \underbrace{\nabla\cdot(D_e\nabla e)}_{\text{dispersion}} - \underbrace{\nabla\cdot\Big(\lambda_{11}\frac{e\cdot\nabla f}{\sqrt{1+|\nabla f|^2}} + \lambda_{12}\frac{e\cdot\nabla u_e}{\sqrt{1+|\nabla u_e|^2}} + \lambda_{13}\frac{e\cdot\nabla p_e}{\sqrt{1+|\nabla p_e|^2}}\Big)}_{chemotaxis} \\
& - \Big(\nabla\cdot\underbrace{\lambda_{14}\frac{e\cdot\nabla m}{\sqrt{1+|\nabla m|^2}}}_{haptotaxis}\Big) + \underbrace{\mu_{11}\ e\ (1-e) + \mu_{12}ef + \mu_{13}p_c ef}_{proliferation}\ ,
\end{aligned} \tag{1.1}$$

$$\begin{aligned}
\frac{\partial c}{\partial t} = {} & \underbrace{\nabla\cdot(D_c\nabla c)}_{\text{dispersion}} - \underbrace{\nabla\cdot\Big(\lambda_{21}\frac{c\cdot\nabla p_c}{\sqrt{1+|\nabla p_c|^2}} + \lambda_{22}\frac{c\cdot\nabla u_c}{\sqrt{1+|\nabla u_c|^2}}\Big)}_{chemotaxis} - \underbrace{\nabla\cdot\Big(\lambda_{23}\frac{c\cdot\nabla m}{\sqrt{1+|\nabla m|^2}}\Big)}_{haptotaxis} \\
& + \underbrace{\mu_{21}\ c\ (1-c)}_{proliferation}\ ,
\end{aligned} \tag{1.2}$$

$$\frac{\partial m}{\partial t} = \underbrace{\nabla \cdot (D_m \nabla m)}_{\text{dispersion}} - \underbrace{(\delta_{31}\, p_e\, m \,+\, \delta_{32}\, p_c\, m)}_{proteolysis} + \underbrace{\mu_{31}\, m\,(1 - m)}_{re-establishment}\ , \tag{1.3}$$

$$\begin{aligned}\frac{\partial f}{\partial t} = {} & \underbrace{D_f\, \nabla^2 f}_{diffusion} + \underbrace{\underbrace{\alpha_{41}\, c}_{secreted} + \underbrace{\alpha_{42}\, p_c\, \frac{f}{1+f} + \alpha_{43}\, p_c\, m\, \frac{f}{1+f}}_{mature\ form}}_{production} - \\ & - \underbrace{\beta_{41}\, f}_{natural\ decay} - \underbrace{(\beta_{42}\, e\, f \,+\, \beta_{43}\, p_c\, e\, \frac{f}{1+f})}_{neutrilization}\ ,\end{aligned} \tag{1.4}$$

$$\begin{aligned}\frac{\partial u_e}{\partial t} = {} & \underbrace{D_{u_e}\, \nabla^2 u_e}_{dispersion} + \underbrace{\alpha_{51}\, e \,+\, \alpha_{52}\, e\, f + \alpha_{53}\, p_c\, e\, \frac{f}{1+f}}_{production} \\ & - \underbrace{\beta_{51}\, u_e}_{natural\ decay} - \underbrace{\beta_{52}\, p_e\, m}_{inhibition} - \underbrace{\beta_{53}\, e\, u_e}_{neutrilization}\ ,\end{aligned} \tag{1.5}$$

$$\frac{\partial p_e}{\partial t} = \underbrace{D_{p_e}\, \nabla^2 p_e}_{diffusion} + \underbrace{\alpha_{61}\, e\, u_e}_{production} - \underbrace{\beta_{61}\, p_e}_{natural\ decay} - \underbrace{\beta_{62}\, p_e\, m}_{inhibition}\ , \tag{1.6}$$

$$\frac{\partial u_c}{\partial t} = \underbrace{D_{u_c}\, \nabla^2 u_c}_{dispersion} + \underbrace{\alpha_{71}\, c}_{production} - \underbrace{\beta_{71}\, u_c}_{natural\ decay} - \underbrace{\beta_{72}\, p_c\, m}_{inhibition} - \underbrace{\beta_{73}\, c\, u_c}_{neutralization}\ , \tag{1.7}$$

$$\frac{\partial p_c}{\partial t} = \underbrace{D_{p_c}\, \nabla^2 p_c}_{diffusion} + \underbrace{\alpha_{81}\, c\, u_c}_{production} - \underbrace{\beta_{81}\, p_c}_{natural\ decay} - \underbrace{\beta_{82}\, p_c\, m}_{inhibition}\ . \tag{1.8}$$

The experimental support of the above system is documented in [5]. Here we shall just explain the meaning of the main terms.

On the right-hand side of (1.1), the first term represents random dispersion (or diffusion); the next three terms account for chemotaxis (migration of cells in the direction of a gradient of a soluble attractant), the fifth term represents haptotaxis (cell motility toward high concentration of ECM substratum-bound insolubilized components), the sixth term accounts for proliferation of LEC, using logistic growth, the seventh term is the result of VEGF-C stimualting lymphatic endothelial cells mitosis before their cleavage by plasmin, and the last term represents the same effect of VEGF-C after its cleavage by plasmin.

The specific form of the chemotactic factor in (1.1),

$$\lambda_{11} \frac{\nabla f}{\sqrt{1 + |\nabla f|^2}}\ ,$$

could be replaced by any other function of ∇f which behaves like

$$\alpha \text{ if } |\nabla f| \text{ is small, and}$$

$$\beta \text{ if } \frac{\nabla f}{|\nabla f|} \text{ is large (saturation)}$$

where α, β are positive constants; our mathematical results easily extend to this more general case. In [5] we have actually taken this chemotactic term to be simply $\lambda_{11}\nabla f$, which is a good approximation to the present choice if $|\nabla f|$ is small. In the lack of experimental results, either choice may be acceptable. The same comment applies to all the other chemotactic and haptotactic terms.

The explanation for equation (1.2) is similar to that of (1.1). On the right-hand side of (1.3) the negative terms account for proteolysis: plasmin p_e, and p_c are proteases that break down the ECM. The last term in (1.3) represents re-establishment of the ECM, using again logistic growth.

VEGF-C is secreted by the cancer cells and is also greatly enhanced by cancer cells activated plasmin p_c. Indeed, plasmin p_c cleaves VEGF-C thereby greatly increasing its binding effectiveness to the lymphatic endothelial cell-surface receptors. The third and fourth terms on the right-hand side of (1.4) represents the effects of p_c in cleavage of both secreted VEGF-C and bound VEGF-C to the ECM. The last two terms in (1.4) represents neutrilization of free and mature f due to its binding to LEC receptors.

In (1.5) the uPA, u_e, is secreted by LEC while its production is greatly enhanced by the binding of cleaved and uncleaved VEGF-C to LE cell-surface receptors. In addition, u_e decays either naturally or by binding to its lymphatic endothelial cell-surface receptor uPAR. The uPA/uPAR binding activates plasminogen which then enhances the rate of plasmin formation, as seen in (1.6). Plasmin degrades the ECM and, in this process, plasmin is inhibited in proportion to $p_e m$.

Equations (1.7), (1.8) are analogous to equations (1.5), (1.6). The only differences between the pairs (p_c, u_c) and (p_e, u_e) is in the special role of p_c in enhancing (by cleavage) the binding effectiveness of VEGF-C in (1.4) and the lack of VEGF-C receptors in the cancer cells surface.

The rate $\dfrac{f}{1+f}$ in equations (1.4), (1.5) can be made more general, requiring only that this function of f it behaves like

$$\alpha_1 f \text{ if } f \text{ is small, and}$$

$$\alpha_2 \text{ if } f \text{ is large (saturation) ;}$$

this will not change the mathematical results. In [5] we have actually taken, for simplicity, f instead of $\dfrac{f}{1+f}$.

As we said above, the model equations (1.1)-(1.8) are based on experimental results described in [5], where most of the rate coefficients are also known; the mathematical analysis of the present paper does not depend, however, on the particular choice of these coefficients.

We shall consider the system (1.1)-(1.8) in a fixed bounded domain Ω in $\mathbb{R}^n$

$(n \geq 1)$ and denote the boundary of Ω by Γ. For any $0 < T \leq \infty$ we set

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

As in [5], we introduce the no-flux boundary conditions

$$-D_e \frac{\partial e}{\partial n} + \lambda_{11} \frac{e \cdot \frac{\partial e}{\partial n} f}{\sqrt{1 + |\frac{\partial e}{\partial n} f|^2}} + \lambda_{12} \frac{e \cdot \frac{\partial u_e}{\partial n}}{\sqrt{1 + |\frac{\partial u_e}{\partial n}|^2}} + \lambda_{13} \frac{e \cdot \frac{\partial p_e}{\partial n}}{\sqrt{1 + |\frac{\partial p_e}{\partial n}|^2}} + \lambda_{14} \frac{e \cdot \frac{\partial m}{\partial n}}{\sqrt{1 + |\frac{\partial m}{\partial n}|^2}} = 0 \text{ on } \Gamma_\infty\ , \tag{1.9}$$

$$-D_c \frac{\partial c}{\partial n} + \lambda_{21} \frac{c \cdot \frac{\partial u_c}{\partial n}}{\sqrt{1 + |\frac{\partial u_c}{\partial n}|^2}} + \lambda_{22} \frac{c \cdot \nabla p_c}{\sqrt{1 + |\frac{\partial p_c}{\partial n}|^2}} + \lambda_{14} \frac{c \cdot \frac{\partial m}{\partial n}}{\sqrt{1 + |\frac{\partial m}{\partial n}|^2}} = 0 \text{ on } \Gamma_\infty\ , \tag{1.10}$$

$$\begin{aligned} &\frac{\partial m}{\partial n} = 0,\ \frac{\partial f}{\partial n} = 0,\ \frac{\partial u_e}{\partial n} = 0,\ \frac{\partial f}{\partial n} = 0,\ \frac{\partial u_e}{\partial n} = 0,\ \frac{\partial p_e}{\partial n} = 0, \\ &\frac{\partial u_c}{\partial n} = 0,\ \frac{\partial p_c}{\partial n} = 0 \text{ on } \Gamma_\infty\ , \end{aligned} \tag{1.11}$$

and prescribe initial conditions

$$\begin{aligned} &e|_{t=0} = e_0(x),\ c|_{t=0} = c_0(x),\ m|_{t=0} = m_0(x),\ f|_{t=0} = f_0(x), \\ &u_e|_{t=0} = u_{e_0}(x),\ p_e|_{t=0} = p_{e_0}(x),\ u_c|_{t=0} = u_{c_0}(x),\ p_c|_{t=0} = p_{c_0}(x) \ \text{ in } \Omega\ , \end{aligned} \tag{1.12}$$

In dealing with tumor growth it is natural to expect the tumor region $\Omega(t)$ to vary with time. The PDE models of angiogenesis do not include this (free boundary) feature, and neither does our model. For the angiogenesis models this is more serious limitation, since the formation of new blood vessels induced by the cancer cells provide new nutrients to the tumor which enable it to grow at a much faster rate. There are instances where lymphangiogenesis precedes angiogenesis (see [5]) and in such cases the assumption that Ω does not change with time is not a serious limitation of our model.

In this paper we prove that the system of equations (1.1) - (1.12) has a unique solution in Ω_∞. The proof is given in section 3. It is based on a priori estimates which are derived in section 2.

The system (1.1) - (1.8) is not a standard parabolic system. Nonetheless it does exhibit the features of a parabolic system. Indeed, given (e, f), if we solve (1.3)-(1.8) with the boundary and initial conditions of ((1.9) - (1.11)), (1.12), we get

the smoothing effect of standard parabolic equations. Hence, if we substitute this solution (as function of (e, f)) into (1.1), (1.2), we obtain a parabolic system for (e, f) with terms that are nonlinear and nonlocal functions of e, f, but nevertheless possess sufficient regularity for proving existence and uniqueness, at least locally in time.

2. A priori estimates

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

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

where

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

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

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

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

Throughout the rest of this paper we assume that:

$$\begin{aligned} &\Gamma \text{ is in } C^{2+\alpha}, 0 < \alpha < 1, \text{ the functions } e_0,\ c_0,\ m_0,\ f_0,\ u_{e_0}, p_{e_0},\ u_{c_0},\ p_{c_0}, \text{ are} \\ &\text{nonnegative they belong to } C^{2+\alpha}(\bar{\Omega}), \text{ and their normal derivatives on } \Gamma \\ &\text{are, equal to zero.} \end{aligned} \tag{2.1}$$

For brevity we set

$$W = (e, c, m, f, u_e, p_e, u_c, p_c) \tag{2.2}$$

Throughout this section we assume that

$$\begin{aligned} &W \text{ is a solution of } (1.1) - (1.12), \\ &W \text{ belongs to } C^{2+\alpha,1+\alpha/2}_{x,t}(\Omega(x,T)) \text{ for some } 0 < T < \infty \ . \end{aligned} \tag{2.3}$$

Theorem 2.1. *Under the assumptions (2.1) - (2.3) there exists a constant A, depending on T, such that*

$$\|W\|_{C^{2+\alpha,1+\alpha/2}_{x,t}(\Omega_T)} \leq A \tag{2.4}$$

In the sequel we shall denote various constants which depend on T by A, and constants which are independent of T by A_o or α_o. The proof of Theorem 2.1 depends on several lemmas.

Lemma 2.1. *There holds:*

$$e \geq 0, c \geq 0, m \geq 0, f \geq 0, u_e \geq 0, p_e \geq 0, u_c \geq 0, p_c \geq 0 \ . \tag{2.5}$$

Proof. The inequalities $e \geq 0$, $c \geq 0$, $m \geq 0$, $f \geq 0$ follow from the maximum principle. Later on we shall prove that there exists a unique solution for a small time interval, and that it depends continuously on the initial data. Hence in order to prove that, for this small time interval,

$$u_e, p_e, u_c, p_c \ .$$

are ≥ 0 we may assume that these functions are initially strictly positive. Then, if the assertion is not true, there is a smallest time t_0, $t_0 > 0$, such that at this time, at least one of the above variables vanishes at some point (x_0, t_0), $x_0 \in \bar{\Omega}$. But this contradicts the strong maximum principle, as is easily seen from the parabolic equations for this variable. The above argument can now be extended as long as the solution exists. □

Lemma 2.2. *For any $1 < q < \infty$ there exists a constant A_q, depending on T, such that*

$$\|W\|_{L^q(\Omega_T)} \leq A_q \tag{2.6}$$

Proof. Multiplying (1.1) by e^κ (κ integer > 0) and integrating over Ω_T, we get

$$\begin{aligned}
&\frac{1}{1+\kappa}\int_\Omega e^{\kappa+1}(x,T)dxdt - \frac{1}{1+\kappa}\int_\Omega e_0^{\kappa+1}(x)dxdt + \kappa D_e \int_0^T\int_\Omega e^{\kappa-1}|\nabla e|^2 dxdt \\
&+ \mu_{11}\int_0^T\int_\Omega e^{\kappa+2}dxdt \leq \mu_{11}\int_0^T\int_\Omega e^{\kappa+1}dxdt + \int_0^T\int_\Omega \kappa e^\kappa[\lambda_{11}\frac{\nabla e\cdot\nabla f}{\sqrt{1+|\nabla f|^2}} \\
&+ \lambda_{12}\frac{\nabla e\cdot\nabla m}{\sqrt{1+|\nabla m|^2}} + \lambda_{13}\frac{\nabla e\cdot\nabla u_e}{\sqrt{1+|\nabla u_e|^2}} + \lambda_{14}\frac{\nabla e\cdot\nabla p_e}{\sqrt{1+|\nabla p_e|^2}}]dxdt.
\end{aligned}$$

Since the last integral is bounded by

$$\alpha_0\kappa\int_0^T\int_\Omega e^\kappa|\nabla e|dxdt \leq \frac{1}{2}\kappa D_e\int_0^T\int_\Omega e^{k-1}|\nabla e|^2 dxdt + A_0\kappa\int_0^T\int_\Omega e^{\kappa+1}dxdt,$$

it follows that

$$\begin{aligned}
\mu_{11}\int_0^T\int_\Omega e^{\kappa+2}dxdt &\leq A_0\kappa\int_0^T\int_\Omega e^{\kappa+1} + A_0 \\
&\leq A_0\kappa(\int_0^T\int_\Omega e^{\kappa+2}dxdt)^{\frac{\kappa+1}{\kappa+2}}\, T^{\frac{1}{\kappa+2}} + A_0,
\end{aligned}$$

by Hölder's inequality. Hence

$$\|e\|_{L^{\kappa+2}(\Omega_T)} \leq A_0 \kappa T^{\frac{1}{\kappa+2}} + A_0 \ . \tag{2.7}$$

$$\tag{2.8}$$

In the same way one can prove that

$$\|c\|_{L^{\kappa+2}(\Omega_T)} \leq A_0\, \kappa\, T^{\frac{1}{\kappa+2}} + A_0, \tag{2.9}$$

$$\|m\|_{L^{\kappa+2}(\Omega_T)} \leq A_0\, T^{\frac{1}{\kappa+2}} + A_0. \tag{2.10}$$

We next turn to (1.5) multiply it by u_e^κ and integrate over Ω_t. We get

$$\frac{1}{\kappa+1}\frac{d}{dt}\int_{\Omega_t} u_c^{\kappa+1} + \kappa D_{u_c}\int_{\Omega_t} u_e^{\kappa-1}|\nabla u_c|^2 \leq \alpha_{71}\int_{\Omega_t} u_c^\kappa c$$
$$\leq \alpha_{71}(\int_{\Omega_t} u_c^{\kappa+1})^{\frac{\kappa}{\kappa+1}}\,(\int_{\Omega_t} c^{\kappa+1})^{\frac{1}{\kappa+1}}.$$

Using (2.9) we see that the function

$$\phi(t) = \int_{\Omega_t} u_c^{\kappa+1}$$

satisfies:

$$\frac{d\phi}{dt} \leq A\kappa^2\phi^{\frac{\kappa}{\kappa+1}} \leq A\kappa^2(\phi+1),$$

from which it follows that $\phi(t) \leq A$, *i.e.*

$$\|u_c\|_{L^{\kappa+1}(\Omega_t)} \leq A.$$

Then also $\|cu_c\|_{L^q(\Omega_T)} \leq A_q$ for any $q > 1$, and from (1.8) we deduce, by the same argument as before, that

$$\|p_c\|_{L^{\kappa+1}(\Omega_T)} \leq A$$

for any $\kappa > 0$. The same procedure applies to f:

$$\frac{1}{\kappa+1}\frac{d}{dt}\int_{\Omega_t} f^{\kappa+1} \leq A\int_{\Omega_t} f^\kappa(c + p_c + p_c m)$$

and, since

$$(\int_{\Omega_t} |c + p_c + p_c m|^{\kappa+1})^{\frac{1}{\kappa+1}} \leq A,$$

we get

$$\|f\|_{L^{\kappa+1}(\Omega_T)} \leq A.$$

By the same argument we can then proceed to estimate the $L^{\kappa+1}(\Omega_T)$-norm of u_e, and then also the of $L^{\kappa+1}_{(\Omega_T)}$-norm of p_e. □

Lemma 2.3. *For any $p > 1$ there exists a constant $\tilde{A}_p$, depending on T, such that*

$$\|D_x W\|_{L^p(\Omega_T)} + \|D_x^2 W\|_{L^p(\Omega_T)} + \|D_t W\|_{L^p(\Omega_T)} \leq \tilde{A}_p \ . \tag{2.11}$$

Proof. Set

$$w = (m, f, u_e, p_e, u_c, p_c) \tag{2.12}$$

Then each component u of w satisfies a parabolic equation of the form

$$u_t = D_u \nabla^2 u + h \tag{2.13}$$

where $h \in L^p(\Omega_T)$, by Lemma 2.2. By parabolic L^p estimates [2] we then conclude that

$$\|D_x w\|_{L^p(\Omega_T)} + \|D_x^2 w\|_{L^p(\Omega_T)} + \|D_t w\|_{L^p(\Omega_T)} \leq \tilde{A}_p \|h\|_{L^p(\Omega_T)} \leq A \ . \tag{2.14}$$

We now turn to e and begin by examining the chemotactic term due to f,

$$-\lambda_{11} \frac{\nabla f \cdot \nabla e}{\sqrt{1 + |\nabla f|^2}} - \lambda_{11} e \nabla \cdot \frac{\nabla f}{\sqrt{1 + |\nabla f|^2}} \equiv \alpha(x,t) \cdot \nabla e + \beta(x,t) e \ . \tag{2.15}$$

Clearly $\alpha(x,t)$ is a bounded function and, by (2.14) $\beta \in L^p(\Omega_T)$ for any $p > 1$. The other chemotactic and haptotactic terms have a similar structure, so that we can write

$$\frac{\partial e}{\partial t} = D_e \nabla^2 e + \tilde{\alpha}(x,t) \cdot \nabla e + h \tag{2.16}$$

where $\tilde{\alpha}(x,t)$ is a bounded function and $h \in L^p(\Omega_{\mathrm{T}})$ for any $p > 1$. By the parabolic L^p estimates [2] we then conclude that (2.14) holds also for e and, similarly, it holds also for c. □

Proof. of Theorem 2.1 From lemma 2.3 and Sobolev's inequalities [1] it follows that

$$\|W\|_{C^{\gamma,\gamma}_{x,t}(\Omega_{\mathrm{T}})} \leq A \text{ for any } 0 < \gamma < 1.$$

We can then apply the parabolic Schauder estimates [2] to (2.13) where u is any component of w and $h \in C^{\alpha,\alpha/2}_{x,t}$. We conclude that

$$\|w\|_{C^{2+\alpha,1+\alpha/2}_{x,t}(\Omega_T)} \leq A. \tag{2.17}$$

We next turn to e and again consider first the chemotactic term (2.15). By (2.17) both $\alpha(x,t)$ and $\beta(x,t)$ are Hölder continuous with bounded $C^{\alpha,\alpha/2}_{x,t}(\Omega_T)$ - norm. The other chemotactic and haptotactic terms have the same structure. Hence we can again apply the Schauder estimates to conclude that (2.17) holds also for e, and similarly it holds also for c. □

3. Existence and uniqueness

We first prove local existence by a fixed point argument. We introduce the Banach space X of the vector-functions W (defined in (2.2)) with norm

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

and a subset

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

where M will be chosen later on. Given any $W \in X_M$, we define a corresponding function $\overline{W} \equiv SW$ by

$$\overline{W} = (\bar{e}, \bar{c}, \bar{m}, \bar{f}, \bar{u}_e, \bar{p}_e, \bar{u}_c, \bar{p}_c)$$

where $\overline{W}$ satisfies the equations

$$\frac{\partial \bar{m}}{\partial t} - \underbrace{\nabla \cdot (D_m \nabla \bar{m})}_{\text{dispersion}} = \underbrace{(\delta_{31}\, p_e\, m\, + \delta_{32}\, p_c\, m)}_{proteolysis} + \underbrace{\mu_{31}\, m\, (1 - \frac{m}{m_o})}_{re-establishment}\,, \tag{3.1}$$

$$\begin{aligned} \frac{\partial \bar{f}}{\partial t} - \underbrace{D_f\, \nabla^2 \bar{f}}_{diffusion} = \underbrace{\underbrace{\alpha_{41}\, c}_{secreted} + \underbrace{\alpha_{42}\, p_c\, f}_{mature\, form}}_{production} - \underbrace{\beta_{41}\, f}_{natural\, decay} \\ - \underbrace{\beta_{42}\, e\, f\, - \beta_{43}\, p_c\, e\, f}_{neutrilization}\,, \end{aligned} \tag{3.2}$$

$$\begin{aligned} \frac{\partial \bar{u}_e}{\partial t} - \underbrace{D_{u_e}\, \nabla^2 \bar{u}_e}_{dispersion} = \underbrace{\alpha_{51}\, e\, + \alpha_{52}\, e\, f + \alpha_{53}\, p_c\, f\, e}_{production} - \underbrace{\beta_{51}\, u_e}_{natural\, decay} \\ - \underbrace{\beta_{52}\, p_e\, m}_{inhibition} - \underbrace{\beta_{53}\, e\, u_e}_{neutrilization}\,, \end{aligned} \tag{3.3}$$

$$\frac{\partial \bar{p}_e}{\partial t} - \underbrace{D_{p_e}\, \nabla^2 \bar{p}_e}_{diffusion} = \underbrace{\alpha_{61}\, e\, u_e}_{production} - \underbrace{\beta_{61}\, p_e}_{natural\, decay} - \underbrace{\beta_{62}\, p_e\, m}_{inhibition}\,, \tag{3.4}$$

$$\frac{\partial \bar{u}_c}{\partial t} - \underbrace{D_{u_c}\, \nabla^2 \bar{u}_c}_{dispersion} = \underbrace{\alpha_{71}\, c}_{production} - \underbrace{\beta_{71}\, u_c}_{natural\, decay} - \underbrace{\beta_{72}\, p_c\, m}_{inhibition} - \underbrace{\beta_{73}\, c\, u_c}_{neutralization} \tag{3.5}$$

$$\frac{\partial \bar{p}_c}{\partial t} - \underbrace{D_{p_c}\, \nabla^2 \bar{p}_c}_{diffusion} = \underbrace{\alpha_{81}\, c\, u_c}_{production} - \underbrace{\beta_{81}\, p_c}_{natural\, decay} - \underbrace{\beta_{82}\, p_c\, m}_{inhibition}\,, \tag{3.6}$$

$$\begin{aligned} \frac{\partial \bar{e}}{\partial t} - \underbrace{\nabla \cdot (D_e \nabla \bar{e})}_{\text{dispersion}} + \underbrace{\nabla \cdot (\lambda_{11} \frac{\bar{e} \cdot \nabla \bar{f}}{\sqrt{1 + |\nabla \bar{f}|^2}} + \lambda_{12} \frac{\bar{e} \cdot \nabla \bar{u}_e}{\sqrt{1 + |\nabla \bar{u}_e|^2}} + \lambda_{13} \frac{\bar{e} \cdot \nabla \bar{p}_e}{\sqrt{1 + |\nabla \bar{p}_e|^2}})}_{chemotaxis} \\ + \underbrace{\nabla \cdot (\lambda_{14} \frac{\bar{e} \cdot \nabla \bar{m}}{\sqrt{1 + |\nabla \bar{m}|^2}})}_{haptotaxis} = \underbrace{\mu_{11}\, e\, (1 - e) + \mu_{12}\, e\, f + \mu_{13}\, p_c\, e\, f}_{proliferation}\,, \end{aligned} \tag{3.7}$$

$$\frac{\partial \bar{c}}{\partial t} - \underbrace{\nabla \cdot (D_c \nabla \bar{c})}_{\text{dispersion}} + \underbrace{\nabla \cdot (\lambda_{21} \frac{\bar{c} \cdot \nabla \bar{p}_c}{\sqrt{1+|\nabla p_c|^2}} + \lambda_{22} \frac{\bar{c} \cdot \nabla \bar{u}_c}{\sqrt{1+|\nabla \bar{u}_c|^2}})}_{chemotaxis} + \underbrace{\lambda_{23} \frac{\bar{c} \cdot \nabla \bar{m}}{\sqrt{1+|\nabla \bar{m}|^2}}}_{haptotaxis} = \underbrace{\mu_{21}\ c\ (1-c)}_{proliferation}, \tag{3.8}$$

the boundary conditions ((1.9) - (1.11)), and the initial conditions (1.12). We wish to prove that S has a unique fixed point.

Setting

$$\bar{w} = (\bar{m}, \bar{f}, \bar{u}_e, \bar{p}_e, \bar{u}_c, \bar{p}_c), \tag{3.9}$$

we see that each component $\bar{u}$ of $\bar{w}$ satisfies a linear parabolic equation of the form (2.13) with

$$\|h\|_{C^{\alpha,\alpha/2}_{x,t}(\Omega_T)} \leq B_1(M)$$

where $B_1(M)$ is a constant depending only on M. By the parabolic Schauder theory [2] there exists a unique solution $\bar{u}$ to any such component of $\bar{w}$, and

$$\|\bar{w}\|_{C^{2+\alpha,1+\alpha/2}_{x,t}(\Omega_T)} \leq B_o + B_2(M), \tag{3.10}$$

where

$$B_o = \|w|_{t=0}\|_{C^{2+\alpha}_x(\Omega)}$$

and B_2 depends only on M.

We now turn to equation (3.7), and begin by examining the chemotactic term for $\bar{f}$ (cf. (2.15))

$$-\lambda_{11} \frac{\nabla \bar{f} \cdot \nabla \bar{e}}{\sqrt{1+|\nabla \bar{f}|^2}} - \lambda_{11} \bar{e}\, \nabla \cdot \frac{\nabla \bar{f}}{\sqrt{1+|\nabla \bar{f}|^2}} \equiv \bar{\alpha}(x,t) \nabla \bar{e} + \bar{\beta}(x,t) \bar{e}\ . \tag{3.11}$$

In view of (3.10)

$$\|\bar{\alpha}\|_{C^{\alpha,\alpha/2}_{x,t}} + \|\bar{\beta}\|_{C^{\alpha,\alpha/2}_{x,t}} \leq B_3(B_o + B_2(M))$$

where B_3 is a constant independent of M.

The other chemotactic and haptotactic terms have the same structure. Hence (3.7) is a linear parabolic equation with $C^{\alpha,\alpha/2}_{x,t}(\Omega_T)$ coefficients and, by the Schauder theory, it has a unique solution $\bar{e}$ satisfying

$$\|\bar{e}\|_{C^{2+\alpha,1+\alpha/2}_{x,t}(\Omega_T)} \leq \|e|_{t=0}\|_{C^{2+\alpha}_x(\bar{\Omega})} + B_4(B_o, M)$$

where B_4 is a constant depending only on B_o and M. The same analysis applies to equation (3.8). We conclude that

$$\|\overline{W}\|_{C^{2+\alpha,1+\alpha/2}_{x,t}(\Omega_T)} \leq \tilde{B}_o + B_5(\tilde{B}_o, M), \tag{3.12}$$

where

$$\tilde{B}_o = \|W(\cdot,0)\|_{C_x^{2+\alpha}(\Omega)}$$

and B_5 depends only on $\tilde{B}_o$ and M.

We now note that for any function $\overline{W}(x,t)$,

$$\|\overline{W}(x,t) - \overline{W}(x,0)\|_{C_{x,t}^{\alpha,\alpha/2}(\Omega_T)} \leq \eta(T)\|\overline{W}\|_{C_{x,t}^{2+\alpha,1+\alpha/2}(\Omega_T)}$$

where $\eta(T) \to 0$ if $T \to 0$ (Actually $\eta(T) \sim T^{1/2+\alpha/2}$). Substituting $\overline{W}$ from (3.12) into this inequality we conclude that if $M = \tilde{B}_o + 1$ and T is sufficiently small then $\overline{W} \in X_M$, *i.e.*, S maps X_M into itself.

We next show that S is a contraction. Take W_1, W_2 in X_M and set $\overline{W}_1 = SW_1$, $\overline{W}_2 = SW_2$. We also introduce the vector functions $\overline{w}_1$, and $\overline{w}_2$ analogously to (3.9). Setting

$$\delta = \|W_1 - W_2\| \ ,$$

it is easily seen that the difference between each pair of right-hand sides in (3.1)-(3.6) for w_1 and w_2 is bounded in the $C_{x,t}^{\alpha,\alpha/2}(\Omega_T)$ norm by $A_0\delta$. Hence, since $\bar{w}_1 - \bar{w}_2 = 0$ at $t = 0$,

$$\|\bar{w}_1 - \bar{w}_2\|_{C_{x,t}^{2+\alpha,1+\alpha/2}(\Omega_T)} \leq A_0\delta \ . \tag{3.13}$$

We now turn to the equation for $\bar{e}_1 - \bar{e}_2$ and consider first the difference for the chemotactic terms corresponding to f (cf. (3.11)):

$$\lambda_{11}\frac{\nabla\bar{f}_1}{\sqrt{1+|\nabla\bar{f}_1|^2}} \cdot \nabla(\bar{e}_1 - \bar{e}_2) - \lambda_{11}\nabla\bar{e}_2 \cdot \left(\frac{\nabla\bar{f}_1}{\sqrt{1+|\nabla\bar{f}_1|^2}} - \frac{\nabla\bar{f}_2}{\sqrt{1+|\nabla\bar{f}_2|^2}}\right)$$
$$\lambda_{11}(\bar{e}_1 - \bar{e}_2)\nabla \cdot \frac{\nabla\bar{f}_1}{\sqrt{1+|\nabla\bar{f}_1|^2}} - \lambda_{11}\bar{e}_2\nabla \cdot \left(\frac{\nabla\bar{f}_1}{\sqrt{1+|\nabla\bar{f}_1|^2}} - \frac{\nabla\bar{f}_2}{\sqrt{1+|\nabla\bar{f}_2|^2}}\right).$$

The first and third terms combined have the form

$$\bar{\alpha}_1\nabla \cdot (\bar{e}_1 - \bar{e}_2) + \bar{\beta}_1(\bar{e}_1 - \bar{e}_2)$$

where $\bar{\alpha}_1$, $\bar{\beta}_1$ belong to $C_{x,t}^{\alpha,\alpha/2}(\Omega_T)$ (here we use (3.12)), and the second and fourth terms are each bounded in the $C_{x,t}^{\alpha,\alpha/2}(\Omega_T)$ norm by $A_0\delta$ (by (3.13)) with another constant A_0. The same analysis can be applied to the other chemotactic and haptotactic terms in the equation for $\bar{e}_1 - \bar{e}_2$. Hence we deduce that

$$\|\bar{e}_1 - \bar{e}_2\|_{C_{x,t}^{2+\alpha,1+\alpha/2}(\Omega_T)} \leq A_0\delta$$

with another constant A_0. The same estimate holds also for $\bar{c}_1 - \bar{c}_2$, and, combining this with (3.13), we get

$$\|\overline{W}_1 - \overline{W}_2\|_{C_{x,t}^{2+\alpha,1+\alpha/2}(\Omega_T)} \leq A_0\delta.$$

Then, as before,

$$\|\overline{W}_1 - \overline{W}_2\|_{C_{x,t}^{\alpha,\alpha/2}(\Omega_T)} \leq \eta(T)A_0\delta, \ \eta(T) \to 0 \text{ if } T \to 0.$$

Taking T such $\eta(T)A_0 < \frac{1}{2}$ we conclude that S is a contraction in X_M with norm $< \frac{1}{2}$. By the contraction mapping theorem S has a unique fixed point W, which is the unique solution of (1.1)-(1.12) in Ω_T.

We have thus established the existence of a unique solution in Ω_T for small $T > 0$, and, as the proof shows, T depends only on an upper bound on the size of the $C^{2+\alpha}$ norm of $W(x, 0)$. Since we have already established, for any $T > 0$, the a priori estimate (2.4), we can extend the solution to all of Ω_∞. We have thus proved the following theorem:

Theorem 3.1. *Under the assumption (2.1) there exists a unique solution of the system (1.1)-(1.12) in* Ω_∞

From Lemma 2.2 we also know that each component of the solution is nonnegative.

Acknowledgment

The first author is partially supported by National Science Foundation Grant DMS-0098520. This work is also supported by the National Science Foundation upon aggrement No. 0112050. The second author wishes to acknowledge the hospitality of the Mathematical Biosciences Institute.

References

1. A. Friedman, *Partial Differential Equations*, Holt, Reinhart and Winston, New York, 1969; reprinted by Krieger, New York, 1976.
2. O.A. Ladyzhenskaya, V.A. Solonnikov, and N.N. Uraltseva, *Linear and Quasilinear Equations of Parabolic Type*, American Mathematical Society, Providence, 1969.
3. H.A. Levine, B.D. Sleeman, and M. Nislen-Hamilton, Mathematical modeling of the onset of capillary formation initiating angiogenesis, *Jour. Math. Bio.* **42** (2001) 195–238.
4. H.A. Levine, S. Pamuk, B.D. Sleeman, and M. Nislen-Hamilton, Mathematical modeling of capillary formation and development in tumor angiogenesis: penetration into the stroma, *Bull. Math. Bio.* **63** (2001) 801–863.
5. G. Lolas, and A. Friedman, Lymphangiogenesis in tumors: a mathematical model, to appear.