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GLOBAL EXISTENCE AND ASYMPTOTIC BEHAVIOR OF A TUMOR ANGIOGENESIS MODEL WITH CHEMOTAXIS AND HAPTOTAXIS

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We consider a system of differential equations modeling tumor angiogenesis. The system consists of three equations: two parabolic equations with chemotactic terms to model endothelial cells and tumor angiogenesis factors coupled to an ordinary differential equation which describes the evolution of the fibronectin concentration. We study global existence of solutions and, under extra assumption on the initial data of the fibronectin concentration we obtain that the homogeneous steady state is asymptotically stable.

Keywords: Angiogenesis; chemotaxis; haptotaxis.

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1. Introduction

Nowadays, many different issues related to the mathematical approach to the modeling of cancer phenomena are proposed (see, for instance, Ref. 4). In this paper we will focus on the analysis of a macroscopic model arising in tumor angiogenesis. Angiogenesis is the physiological process that involves the formation of new blood vessels from a pre-existing vascular network. Angiogenesis plays an important role in the development of embryo, wound healing or tumor growth. During the tumor growth angiogenesis provide extra nutrients to the tumor which allows the transition from a dormant tumor to a malignant one. Tumor induced angiogenesis starts when cancer cells secrete a chemical signal known as *tumor angiogenesis factors* (TAFs). TAFs diffuse in the extracellular matrix and arrive to the endothelial cells which form the linings of the blood vessels. Then, TAFs bind to specific receptors of the endothelial cells and activate them. Activated endothelial cells release enzymes that degrade the basal membrane of the blood vessels to allow the migration of endothelial cells following the gradients of TAF (chemotaxis). The endothelial cells then proliferate into the surrounding matrix, interact with the components of the matrix, in particular fibronectin and form solid sprouts connecting neighboring vessels. Once the new capillary network penetrates the tumor more nutrients are supplied to the tumor which grows further. See for instance the Ref. 16 for details.

The mathematical model we will consider is a small variation of the model proposed in Ref. 3. As in Ref. 3 we will focus on three variable involved in tumor angiogenesis, endothelial cells, TAF and fibronectin, a component of the extracellular matrix that enhance cell adhesion to the matrix. Therefore we will take into account the interactions between the endothelial cells, TAF and the extracellular matrix. We denote by p the density of the endothelial cell, by c the density of TAF and by w the density of fibronectin.

Endothelial cells. We assume that the motion of the endothelial cells is induced mainly by the TAF and fibronectin. More precisely, endothelial cells move towards the TAF gradients (chemotaxis) and towards the fibronectin gradients (haptotaxis). In addition we assume that the endothelial cells diffuse into the extracellular matrix and we will also consider the endothelial cells proliferation that it is described by a logistic source. As a consequence the equation for the endothelial cell density is given by

$$\frac{\partial p}{\partial t} = \operatorname{div}\left(d_p \nabla p - p\left(\frac{\alpha}{1+c}\nabla c + \rho \nabla w \right)\right) + \lambda p(N_S - p),$$

where d_p is the diffusion coefficient that we assume to be constant, α and ρ are the chemotaxis and haptotaxis coefficients respectively, λ is the proliferation rate and N_S is the saturation parameter.

Tumor angiogenic factors. The TAF diffuses into the surrounding tissue and decays. Moreover there is a loss of TAF after binding to the endothelial cells. Therefore we assume that the TAF concentration c satisfies the following equation:

$$\frac{\partial c}{\partial t} = d_c \Delta c - \eta c - \mu p c,$$

where d_c stands for the TAF diffusion coefficient, η is the decay rate and μ is a positive constant.

Fibronectin. We assume that the fibronectin is produced by the endothelial cells and there is also some uptake and binding of fibronectin to the endothelial cells.

Therefore we derive the following equation:

$$\frac{\partial w}{\partial t} = \theta p - \gamma p w,$$

where γ and θ are positive constants.

In order to reduce number of parameters, we introduce the rescaled variables

$$t^* = \eta t, \quad x^* = \frac{x}{(d_c/\eta)^{\frac{1}{2}}}, \quad p^* = \frac{p}{N_S}, \quad c^* = c, \quad w^* = \frac{\gamma}{\theta} w.$$

We define the following variables:

$$D = \frac{d_p}{d_c}, \quad \alpha^* = \frac{\alpha}{d_c}, \quad \rho^* = \frac{\rho\theta}{\gamma d_c},$$

$$\lambda^* = \frac{\lambda N_s}{\eta}, \quad \mu^* = \frac{\mu N_S}{\eta}, \quad \gamma^* = \frac{\gamma N_S}{\eta}.$$

Dropping the asterisks we obtain the following system of partial differential equations:

$$\frac{\partial p}{\partial t} = \operatorname{div}\left(D\nabla p - p\left(\frac{\alpha}{1+c}\nabla c + \rho\nabla w\right)\right) + \lambda p(1-p), \tag{1.1}$$

$$\frac{\partial c}{\partial t} = \Delta c - c - \mu p c, \tag{1.2}$$

$$\frac{\partial w}{\partial t} = \gamma p(1-w). \tag{1.3}$$

We consider a bounded domain $\Omega \subset \mathbb{R}^N$ with regular boundary $\partial\Omega$ and the following boundary conditions:

$$D\frac{\partial p}{\partial n} - p\left(\frac{\alpha}{1+c}\frac{\partial c}{\partial n} + \rho\frac{\partial w}{\partial n}\right) = 0, \tag{1.4}$$

$$\frac{\partial c}{\partial n} = 0, \tag{1.5}$$

where n stands for the outward normal vector field to Ω. The initial data

$$p(x,0) = p_0(x), \quad w(x,0) = w_0(x), \quad c(x,0) = c_0(x). \tag{1.6}$$

In the following sections we assume

$$0 \le p_0(x) \le \bar{p}_0, \tag{1.7}$$

$$0 \le c_0(x) \le \bar{c}_0, \tag{1.8}$$

$$0 \le w_0(x) \le \bar{w}_0, \tag{1.9}$$

$$p_0(x) \neq 0, \tag{1.10}$$

$$(p_0, w_0, c_0) \in (W^{1,s}(\Omega))^3 \quad \text{for } s \in (\max\{2, N\}, +\infty). \tag{1.11}$$

In Secs. 3 and 4 we also consider classical solutions and the following assumption in the initial data is required

$$(p_0, w_0, c_0) \in (C^{2,\alpha}(\bar{\Omega}))^3 \quad \text{for some } \alpha \in (0, 1). \tag{1.12}$$

Modeling angiogenesis in cancer has been treated by several authors in the last two decades. Some mathematical models of angiogenesis existing in the scientific literature consider systems of partial differential equations to model the process (see Refs. 7 and 17 for details). The mathematical models of PDEs consider chemotactic terms in one- or two-dimensional domains. Levine and Sleeman,[13] Levine, Sleeman and Nilsen-Hamilton[14] and Othmer and Stevens[20] consider a system of PDEs using a probabilistic framework of reinforced random walks to obtain deterministic models.

Anderson and Chaplain[3] (see also Ref. 7) proposed a model of tumor induced angiogenesis consisting of three equations: a parabolic equation to describe the behavior of the endothelial cells with chemotaxis and haptotaxis term, and two nonlinear ODEs to model the concentration of fibronectin denoted by w and TAFs by c. Recently, systems of three PDEs modeling cancer invasion has been analyzed by several authors. Tao and Wang in Ref. 24 have proved global existence for a parabolic–elliptic–ode system with chemotaxis and haptotaxis terms and logistic growth (see also Ref. 25 for the case of nonlinear diffusion). Tao and Cui[23] also show global existence for a parabolic–parabolic–ode system with logistic source. More recently, in Ref. 9 Hillen, Painter and Winkler have proved the convergence of a cancer invasion model to a chemotaxis model in one-dimensional domains.

The structure of the paper is as follows. In Sec. 2 we study the local existence of solutions, under assumptions (1.7)–(1.12). After that we obtain appropriate estimates of the solution that provide global existence for $N = 1, 2$ (see Theorem 3.1). The most technical part of the proof is the L^∞ estimate and it is based on an iterative method. The steady states of the system are studied in Sec. 4. Section 5 is devoted to the asymptotic behavior of the solutions. The results are presented in Theorem 5.1, where under extra assumptions on the initial data we prove that the homogeneous state is asymptotically stable. In Sec. 6 we present some numerical experiments. Finally, the last section is devoted to a brief discussion of the results.

2. Local Existence

During the manuscript, for the sake of clarity, proofs are done for (1.1)–(1.6) with $D = 1$. We left to the reader the trivial changes that are needed for $D > 0$.

Theorem 2.1. *Let the initial data be positive and* $(p_0, c_0, w_0) \in (W^{1,s}(\Omega))^3$ *with* $s \in (\max\{2, N\}, \infty)$. *Then, there exists a unique maximal positive solution to*

(1.1)–(1.6) *satisfying*

$$(p, c, w) \in C([0, T_{\max}), (W^{1,s}(\Omega))^3) \cap C^1((0, T_{\max}), ((W^{1,s}(\Omega))')^2 \times W^{1,s}(\Omega)).$$

Moreover, if there exists a constant θ *such that*

$$\|(p(t), c(t), w(t))\|_{(W^{1,s}(\Omega))^3} \leq \theta(T), \quad 0 \leq t \leq T < \infty, \ \ t < T_{\max},$$

then $T_{\max} = +\infty$.

Proof. Let us consider the open set $G \subset \mathbb{R}^2 \times \mathbb{R}$, defined by

$$G := (-\delta, +\infty)^3.$$

We denote by $a^1 = a^1(p, c, w) \in C^\infty(G, \mathcal{M}_{2\times 2}(\mathbb{R}))$ the matrix

$$a^1 = \begin{pmatrix} 1 & -\frac{\alpha p}{1+c} \\ 0 & 1 \end{pmatrix}$$

and by $a^2 \in C^\infty(G, \mathbb{R}^2)$ the vector

$$a^2 = (0, \rho p).$$

Let $u = (p, c)$. We define the following differential operators

$$\mathcal{A}_1(u, w) = -\frac{\partial}{\partial x}\left(a^1 \frac{\partial}{\partial x} u\right), \quad \mathcal{A}_2(u, w) = -\frac{\partial}{\partial x}\left(a^2 \frac{\partial}{\partial x} w\right),$$

and

$$\mathcal{B}_1(u, w)u = a^1 \frac{\partial u}{\partial n}, \quad \mathcal{B}_2(u, w)w = a^2 \frac{\partial w}{\partial n}.$$

Let $f_1 = (\lambda p(1-p), -c-\mu pc)$ and $f_2 = \gamma p(1-w)$; then (1.1)–(1.5) can be written as

$$\begin{cases} u_t + \mathcal{A}_1(u, w)u + \mathcal{A}_2(u, w)w = f_1(u, w) & \text{in } \Omega \times (0, +\infty), \\ w_t = f_2(u, w) & \text{in } \Omega \times (0, +\infty), \\ \mathcal{B}_1(u, w)u + \mathcal{B}_2(u, w)w = 0 & \text{on } \partial\Omega \times (0, +\infty). \end{cases}$$

Since the principal part of $\mathcal{A}_1$ with the boundary condition satisfies condition (iii) of Remark 4.1(a) of Ref. 1, we can apply Theorem 6.4 of Ref. 1 to get the existence of a maximal weak solution. Next the positivity of c and w is a consequence of a standard maximum principle for parabolic equations. However, the positivity of p demands an additional work, to this aim we introduce the functions

$$H_\epsilon(s) := \begin{cases} 0 & \text{if } s \geq 0, \\ \dfrac{s}{\epsilon} & \text{if } -\epsilon < s \leq 0, \\ -1 & \text{if } s \leq -\epsilon, \end{cases} \quad \phi_\epsilon(s) := \begin{cases} 0 & \text{if } s \geq 0, \\ \dfrac{s^2}{2\epsilon} & \text{if } -\epsilon < s \leq 0, \\ -s - \dfrac{\epsilon}{2} & \text{if } s \leq -\epsilon. \end{cases}$$

Notice that $\phi_\epsilon' = H_\epsilon$, $sH_\epsilon(s) \le 2\phi_\epsilon$ and

$$H_\epsilon'(s) := \begin{cases} 0 & \text{if } s \ge 0, \\ \dfrac{1}{\epsilon} & \text{if } -\epsilon < s \le 0, \\ 0 & \text{if } s \le -\epsilon. \end{cases}$$

We multiply (1.1) by $H_\epsilon(p)$ and after integration over Ω we obtain

$$\begin{aligned} &\int_\Omega p_t H_\epsilon(p) + \int_\Omega H_\epsilon'(p)|\nabla p|^2 \\ &\quad = \int_\Omega H_\epsilon'(p)p\left(\frac{\alpha}{1+c}\nabla c + \rho\nabla w\right)\cdot\nabla p + \int_\Omega H_\epsilon(p)\lambda p(1-p). \end{aligned}$$

Since

$$\int_\Omega p_t H_\epsilon(p) = \frac{d}{dt}\int_\Omega \phi_\epsilon(p),$$

$$\int_\Omega H_\epsilon'(p)p\frac{\alpha}{1+c}\nabla p\cdot\nabla c \le \frac{1}{4}\int_\Omega H_\epsilon'(p)|\nabla p|^2 + \int_\Omega H_\epsilon'(p)p^2\frac{\alpha^2}{(1+c)^2}|\nabla c|^2,$$

$$\int_\Omega H_\epsilon'(p)\rho p\nabla p\cdot\nabla w \le \frac{1}{4}\int_\Omega H_\epsilon'(p)|\nabla p|^2 + \int_\Omega H_\epsilon'(p)p^2\rho^2|\nabla w|^2,$$

$$H_\epsilon(p)\lambda p(1-p) \le 2\lambda(1+\delta)\phi_\epsilon(p) = k_0\phi_\epsilon(p),$$

for some $\delta > 0$. Therefore we have

$$\begin{aligned} &\frac{d}{dt}\int_\Omega \phi_\epsilon(p) + \frac{1}{2}\int_\Omega H_\epsilon'(p)|\nabla p|^2 \\ &\quad \le \int_\Omega H_\epsilon'(p)p^2\frac{\alpha^2|\nabla c|^2}{(1+c)^2} + \int_\Omega H_\epsilon'(p)p^2\rho^2|\nabla w|^2 + k_0\int_\Omega \phi_\epsilon(p). \end{aligned}$$

Since

$$0 \le H_\epsilon'(p)p^2 \le \epsilon$$

and $c \ge 0$ we have

$$\frac{d}{dt}\int_\Omega \phi_\epsilon(p) \le \epsilon k_1\left[\int_\Omega |\nabla c|^2 + \int_\Omega |\nabla w|^2\right] + k_0\int_\Omega \phi_\epsilon(p).$$

After integration over $(0,t)$ for $t < T_{\max}$, we obtain

$$\int_\Omega \phi_\epsilon(p) \le \epsilon k_1 e^{k_0 t}\int_0^t e^{-k_0\tau}\int_\Omega(|\nabla c|^2 + |\nabla w|^2).$$

By definition of weak solution we know that $c, w \in L^2(0,t,W^{1,2})$ therefore

$$\epsilon k_1 e^{k_0 t}\int_0^t e^{-k_0\tau}\int_\Omega(|\nabla c|^2 + |\nabla w|^2) \le \epsilon k_2 \quad \text{for any } t \in [0, T_{\max}),$$

which implies

$$\int_\Omega \phi_\epsilon(p) \leq \epsilon k_2.$$

Taking limits as ϵ goes to 0 we have $\int_\Omega \phi_0(p) = 0$ which concludes the theorem. □

Remark 2.1. Since $p \in C((0,T_{\max}), W^{1,s}(\Omega)) \cap C^1((0,T_{\max}), (W^{1,s}(\Omega))')$ we have that $p \in C((0,T_{\max}), L^\infty(\Omega))$.

Remark 2.2. In the case $N = 1$ we can pick $s = 2$ because it satisfies $W^{1,2}(\Omega) \hookrightarrow L^\infty(\Omega)$ a condition that it is required to apply Theorem 6.4 of Ref. 1. We have not included this case in the previous theorem in order to simplify the notation.

In order to conclude this section we show that if the initial data is sufficiently regular and satisfies a compatibility condition then the weak solution is a classical solution.

Theorem 2.2. *Let $s > N+2$, $\alpha = 1 - (N+2)/s > 0$ and assume that*

$$(p,c,w) \in C([0,T_{\max}), (W^{1,s}(\Omega))^3) \cap C^1((0,T_{\max}), ((W^{1,s}(\Omega))')^2 \times W^{1,s}(\Omega))$$

is a weak solution to (1.1)–(1.6). *Then if* $(p_0, w_0, c_0) \in (C^{2+\alpha}(\bar{\Omega}))^3$ *and*

$$\frac{\partial p_0}{\partial n} - p_0\left(\frac{\alpha}{1+c_0}\frac{\partial c_0}{\partial n} + \rho\frac{\partial w_0}{\partial n}\right) = 0, \qquad \frac{\partial c_0}{\partial n} = 0 \tag{2.1}$$

on $\partial\Omega \times \{0\}$ then

$$(p,c,w) \in (C^{2+\alpha,1+\alpha/2}(\bar{\Omega} \times [0,T]))^3$$

for any $T < T_{\max}$ where $T_{\max}$ is the maximal existence time for the weak solution.

Proof. The new variable $z = e^{-\rho w}p$ satisfies

$$\begin{aligned} z_t = \Delta z + \rho\nabla w \cdot \nabla z - \frac{\alpha z}{1+c}\Delta c - \frac{\alpha}{1+c}\nabla z \cdot \nabla c \\ + \frac{\alpha z}{(1+c)^2}|\nabla c|^2 - \frac{\rho z}{1+c}\nabla w \cdot \nabla c + h(z,w), \end{aligned}$$

where $h(z,w) := \lambda z(1 - ze^{\rho w}) - \rho\gamma e^{\rho w} z^2(1-w)$. By Theorem 9.1, Chap. IV of Ref. 12 for $q = s$ we know that

$$z \in W_s^{2,1}(\Omega \times (0,T)).$$

Therefore, the embedding

$$W_s^{2,1}(\Omega \times (0,T)) \hookrightarrow C^{1+\alpha,(1+\alpha)/2}(\bar{\Omega} \times [0,T])$$

entails that $z(t) \in C^{1+\alpha}(\bar\Omega)$ for each $T < T_{\max}$. Since, $w_t = \gamma z e^{-\rho w}(1-w)$ then

$$\begin{aligned}\|w(t)\|_{C^{1+\alpha}(\bar\Omega)} &\le \|w_0\|_{C^{1+\alpha}(\bar\Omega)} + \gamma \int_0^t \|z e^{-\rho w}(1-w)\|_{C^{1+\alpha}(\bar\Omega)} \\ &\le \|w_0\|_{C^{1+\alpha}(\bar\Omega)} + C\gamma \int_0^t \|e^{-\rho w}(1-w)\|_{C^{1+\alpha}(\bar\Omega)} \|z\|_{C^{1+\alpha}(\bar\Omega)} \\ &\le \|w_0\|_{C^{1+\alpha}(\bar\Omega)} + C\gamma \int_0^t \|w\|_{C^{1+\alpha}(\bar\Omega)} \|z\|_{C^{1+\alpha}(\bar\Omega)} \\ &\le \|w_0\|_{C^{1+\alpha}(\bar\Omega)} + C(t)\gamma \int_0^t \|w\|_{C^{1+\alpha}(\bar\Omega)}.\end{aligned}$$

By the Gronwall lemma we obtain $w \in C([0,T]; C^{1+\alpha}(\bar\Omega))$. Moreover,

$$w_t = \gamma z e^{-\rho w}(1-w) \in C^{1+\alpha}(\bar\Omega).$$

Hence

$$w \in C^1([0,T]; C^{1+\alpha}(\bar\Omega)). \tag{2.2}$$

On the other hand, $z e^{\rho w} \in C^{\alpha,\alpha/2}(\bar\Omega \times [0,T])$ and applying Theorem 5.4, Chap. IV of Ref. 12 we infer that $c \in C^{2+\alpha,1+\alpha/2}(\bar\Omega \times [0,T])$. In particular

$$\Delta c \in C^{\alpha,\alpha/2}(\bar\Omega \times [0,T]). \tag{2.3}$$

Thanks to (2.3) and (2.2) we can deduce by Theorem 5.4, Chap. IV of Ref. 12 that

$$z \in C^{2+\alpha,1+\alpha/2}(\bar\Omega \times [0,T]).$$

Again, by the Gronwall lemma we get that $w \in C^1([0,T]; C^{2+\alpha}(\bar\Omega))$. Finally, since w_t is a product of $C^1([0,T]; C^{2+\alpha}(\bar\Omega))$ functions then $w \in C^2([0,T]; C^{2+\alpha}(\bar\Omega))$. In particular, $w \in C^{2+\alpha,1+\alpha/2}(\bar\Omega \times [0,T])$. Since, p is a product of $C^{2+\alpha,1+\alpha/2}(\bar\Omega \times [0,T])$ functions then $p \in C^{2+\alpha,1+\alpha/2}(\bar\Omega \times [0,T])$. This concludes the theorem. □

3. Global Existence

In this section we study the global existence of solutions. As we have seen in the previous section we just need to find bounds of the solution in the Sobolev space $W^{1,s}(\Omega)$. The main difficulty we encounter here is the way of coupling between p and w. In fact the lack of regularization effect in the space variable in the w-equation and the presence of p there demands tedious estimates of the solution. During the following lemmas we will obtain proper bounds of the solutions from the L^1-norm till the $W^{1,s}$-norm by a bootstrap argument.

From now on (p, c, w) is the unique maximal weak solution provided by Theorem 2.1 and $T < T_{\max}$. In order to avoid regularity problems we assume in the rest of the paper that the initial data satisfies (1.12) and (2.1).

Lemma 3.1. *We have*

$$0 \le \int_\Omega p \le c_1 := \max\left\{\int_\Omega p_0, |\Omega|\right\} \quad \textit{for any } t \le T.$$

Proof. We integrate (1.1) in the spatial variable to obtain

$$\frac{d}{dt}\int_\Omega p = \lambda \int_\Omega p - \lambda \int_\Omega p^2, \tag{3.1}$$

and Hölder's inequality yields

$$0 \leq \int_\Omega p \leq |\Omega|^{\frac{1}{2}} \left(\int_\Omega p^2 \right)^{\frac{1}{2}}.$$

Therefore

$$\frac{d}{dt}\int_\Omega p \leq \lambda \int_\Omega p - \frac{\lambda}{|\Omega|}\left(\int_\Omega p \right)^2.$$

After solving the differential equation the proof ends. □

Lemma 3.2. *For any $t \leq T$ we have*

$$\int_0^t \int_\Omega p^2 \leq c_2(t) := c_1(1/\lambda + t).$$

Proof. Integrating (3.1) on the interval $(0,t)$ and thanks to Lemma 3.1 it results

$$\int_0^t \int_\Omega p^2 = \frac{1}{\lambda}\left(\int_\Omega p - \int_\Omega p_0 \right) + \int_0^t \int_\Omega p \leq c_1(1/\lambda + t),$$

which ends the proof. □

Lemma 3.3. *For any $t \leq T$ we have*

$$\int_0^t e^{-2s} \int_\Omega p^2 ds \leq \|p_0\|_{L^1(\Omega)} + c_3|\lambda - 2|,$$

where c_3 is a constant which does not depend on t.

Proof. On multiplying (3.1) by e^{-2t} and subtracting the term $-2e^{-2t}\int_\Omega p$ we obtain

$$\frac{d}{dt}\left(e^{-2t} \int_\Omega p \right) = (\lambda - 2)e^{-2t} \int_\Omega p - e^{-2t} \int_\Omega p^2.$$

Upon integration on the time interval $(0,t)$ we get

$$\int_0^t e^{-2s} \int_\Omega p^2 ds = -e^{-2t} \int_\Omega p + \int_\Omega p_0 + (\lambda - 2) \int_0^t e^{-2s} \int_\Omega p.$$

Applying Lemma 3.1 in the above equality the lemma follows. □

Lemma 3.4. *For any $t \leq T$ we have*

$$\left| \int_0^t \int_\Omega p(1-p) \right| \leq c_1/\lambda.$$

Proof. We integrate (1.1) over $(0,t)\times\Omega$ to obtain

$$\lambda\int_0^t\int_\Omega p(1-p)=\int_\Omega p(t)-\int_\Omega p_0.$$

Finally taking the absolute value of both sides of the above equality and by Lemma 3.1 we conclude the proof. □

Lemma 3.5. *For any $t\le T$ the component c decays exponentially to zero. More precisely we have*

$$0\le c\le \|c_0\|_{L^\infty(\Omega)}e^{-t}. \tag{3.2}$$

Proof. We know that $p\ge 0$ and by regularity $p\in L^\infty(0,t;L^\infty(\Omega))$. Hence, the standard sub–supersolutions method is available. Let us observe that $\underline{c}=0$ and $\bar{c}=\|c_0\|_{L^\infty(\Omega)}e^{-t}$, and are sub and supersolutions respectively to the problem

$$c_t-\Delta c+c-\mu pc=0,$$
$$\frac{\partial c}{\partial n}=0,$$
$$c(x,0)=c_0(x).$$

As a consequence, we have that $c\in(\underline{c},\bar{c})$ which ends the proof. □

Lemma 3.6. *Let $T>0$. Then the following inequality holds*:

$$\int_0^T\int_\Omega |c_t|^2+\int_\Omega|\nabla c|^2\le \mu^2c_4\|c_0\|^2_{L^\infty(\Omega)}+\|c_0\|^2_{H^1(\Omega)},$$

where c_4 is a positive constant independently of T.

Proof. We take c_t as test function in (1.2) to obtain

$$\int_\Omega|c_t|^2+\frac12\frac{d}{dt}\left(\int_\Omega|\nabla c|^2+c^2\right)=-\mu\int_\Omega pcc_t.$$

By Lemma 3.5 the last term in the above equation is bounded in the following way

$$\left|-\mu\int_\Omega pcc_t\right|\le\frac{\mu^2}{2}\int_\Omega p^2c^2+\frac12\int_\Omega c_t^2\le\frac{\mu^2}{2}\|c_0\|^2_{L^\infty(\Omega)}e^{-2t}\int_\Omega p^2+\frac12\int_\Omega c_t^2.$$

Therefore

$$\frac12\int_\Omega|c_t|^2+\frac12\frac{d}{dt}\left(\int_\Omega|\nabla c|^2+c^2\right)\le\frac{\mu^2}{2}\|c_0\|^2_{L^\infty(\Omega)}e^{-2t}\int_\Omega p^2.$$

We integrate on the time interval $(0,t)$ to get

$$\int_0^t\int_\Omega|c_s|^2+\|c\|^2_{H^1(\Omega)}\le\mu^2\|c_0\|^2_{L^\infty(\Omega)}\int_0^t e^{-2s}\int_\Omega p^2+\|c_0\|^2_{H^1(\Omega)}.$$

By Lemma 3.3 the lemma is proved. □

Lemma 3.7. *For any $t \leq T$ we have*

$$\int_\Omega |\nabla c(t)|^2 + \int_0^t \int_\Omega |\nabla c|^2 + \frac{1}{2}\int_0^t \int_\Omega |\Delta c|^2 \leq c_5,$$

where c_5 does not depend on t.

Proof. We multiply Eq. (1.2) by $-\Delta c$ and integrate over Ω to obtain

$$\frac{1}{2}\frac{d}{dt}\int_\Omega |\nabla c|^2 + \int_\Omega |\Delta c|^2 + \int_\Omega |\nabla c|^2 = \mu \int_\Omega pc\Delta c.$$

Since

$$\left|\mu \int_\Omega pc\Delta c\right| \leq \frac{\mu^2}{2}\int_\Omega p^2c^2 + \frac{1}{2}\int_\Omega |\Delta c|^2 \leq \frac{\mu^2}{2}e^{-2t}\|c_0\|^2_{L^\infty(\Omega)}\int_\Omega p^2 + \frac{1}{2}\int_\Omega |\Delta c|^2$$

we have

$$\frac{d}{dt}\int_\Omega |\nabla c|^2 + \int_\Omega |\Delta c|^2 + 2\int_\Omega |\nabla c|^2 \leq \mu^2 e^{-2t}\|c_0\|^2_{L^\infty(\Omega)}\int_\Omega p^2.$$

We integrate on the time interval $(0, t)$ to get

$$\int_\Omega |\nabla c(t)|^2 + \int_0^t \int_\Omega (|\Delta c|^2 + 2|\nabla c|^2) \leq \mu^2 \|c_0\|^2_{L^\infty(\Omega)}\int_0^T e^{-2s}\int_\Omega p^2 + \|\nabla c_0\|^2_{L^2(\Omega)}.$$

By Lemma 3.3 the proof ends. □

Lemma 3.8. *For any $t \leq T$*

$$\int_\Omega |\nabla c(t)|^2 \leq e^{-2t}\left(\int_\Omega |\nabla c_0|^2 + c_2(t)\mu^2\|c_0\|^2_{L^\infty(\Omega)}\right),$$

where $c_2(t)$ is a linear function of t (see Lemma 3.2).

Proof. As in the previous lemma we multiply Eq. (1.2) by $-\Delta c$ to obtain

$$\frac{d}{dt}\int_\Omega |\nabla c|^2 + 2\int_\Omega |\nabla c|^2 \leq \mu^2\|c_0\|^2_{L^\infty(\Omega)}e^{-2t}\int_\Omega p^2.$$

Solving the previous differential inequality we infer

$$\int_\Omega |\nabla c(t)|^2 \leq e^{-2t}\left(\int_\Omega |\nabla c_0|^2 + \mu^2\|c_0\|^2_{L^\infty(\Omega)}\int_0^t \int_\Omega p^2\right).$$

Finally, we apply Lemma 3.2 to conclude. □

Lemma 3.9. *For any $t \leq T$ we have*

$$w(t) \leq \max\{\|w_0\|_{L^\infty(\Omega)}, 1\}.$$

Proof. We solve the differential equation (1.3) to get

$$w(x,t) = e^{-\gamma \int_0^t p}(w_0 - 1) + 1 \tag{3.3}$$

by the positivity of p and we have the result. □

Lemma 3.10. *For any $t \leq T$ and $n \in (1, +\infty)$ there exists $k(n, \|p_0\|_{L^n(\Omega)}, T) < \infty$ such that*

$$\|p\|_{L^n(\Omega)} \leq k.$$

Proof. We introduce the new unknown q defined by

$$q = p(c+1)^{-\alpha} e^{-\rho w}, \quad \text{i.e. } p = q(c+1)^{\alpha} e^{\rho w}, \tag{3.4}$$

which satisfies

$$\begin{aligned} q_t(c+1)^{\alpha} e^{\rho w} &= \operatorname{div}((c+1)^{\alpha} e^{\rho w} \nabla q) + \lambda (c+1)^{\alpha} e^{\rho w} q(1 - (c+1)^{\alpha} e^{\rho w} q) \\ &\quad - \rho \gamma q^2 (1+c)^{2\alpha} e^{2\rho w}(1-w) - \alpha q (c+1)^{\alpha - 1} \\ &\quad \cdot e^{\rho w}(\Delta c - c - \mu c q (c+1)^{\alpha} e^{\rho w}). \end{aligned} \tag{3.5}$$

Having in mind previous equality we compute

$$\begin{aligned} \frac{1}{n}\frac{d}{dt}(q^n (c+1)^{\alpha} e^{\rho w}) &= q^{n-1} \operatorname{div}((c+1)^{\alpha} e^{\rho w} \nabla q) \\ &\quad + \lambda (c+1)^{\alpha} e^{\rho w} q^n (1 - (c+1)^{\alpha} e^{\rho w} q) \\ &\quad + \frac{1-n}{n}(\gamma \rho q^{n+1} (c+1)^{2\alpha} e^{2\rho w}(1-w) \\ &\quad + \alpha q^n (c+1)^{\alpha-1} e^{\rho w}(\Delta c - c - \mu c q (c+1)^{\alpha} e^{\rho w})). \end{aligned}$$

After integration in the spatial variable we have

$$\begin{aligned} \frac{1}{n}\frac{d}{dt}\int_\Omega q^n (c+1)^{\alpha} e^{\rho w} &= -\frac{4(n-1)}{n^2}\int_\Omega (c+1)^{\alpha} e^{\rho w} |\nabla q^{\frac{n}{2}}|^2 \\ &\quad + \lambda \int_\Omega (c+1)^{\alpha} e^{\rho w} q^n (1 - (c+1)^{\alpha} e^{\rho w} q) \\ &\quad + \left(\frac{1}{n} - 1\right)\gamma\rho \int_\Omega q^{n+1}(1+c)^{2\alpha} e^{2\rho w}(1-w) + \left(\frac{1}{n} - 1\right)\alpha \\ &\quad \cdot \int_\Omega q^n (c+1)^{\alpha-1} e^{\rho w}(\Delta c - c - \mu c q (c+1)^{\alpha} e^{\rho w}). \end{aligned}$$

Since $4\frac{n-1}{n} \geq 2$ (for $n \geq 2$) we have that

$$\frac{d}{dt}\int_\Omega q^n (c+1)^{\alpha} e^{\rho w} + 2\int_\Omega |\nabla q^{\frac{n}{2}}|^2 \leq n k_0 \int_\Omega q^n (1 + |\Delta c|) + n(k_1 - \lambda)\int_\Omega q^{n+1},$$

where

$$k_0 = k_0(\lambda, \alpha, \|c_0\|_{L^\infty(\Omega)}, \|w_0\|_{L^\infty(\Omega)}), \quad k_1 = k_1(\alpha, \mu, \rho, \|c_0\|_{L^\infty(\Omega)}, \|w_0\|_{L^\infty(\Omega)}).$$

We introduce the change of variable $z := q^{\frac{n}{2}}$ to get

$$\frac{d}{dt}\int_\Omega z^2(c+1)^\alpha e^{\rho w} + 2\int_\Omega |\nabla z|^2 \le nk_0\int_\Omega z^2(1+|\Delta c|) + n(k_1-\lambda)\int_\Omega z^{2+\frac{2}{n}}. \tag{3.6}$$

We estimate the first term in the right-hand side of the above equation using the Gagliardo–Nirenberg inequality in dimension 2 (that it is also true in dimension 1)

$$\int_\Omega z^2|\Delta c| \le \left(\int_\Omega z^4\right)^{\frac{1}{2}}\left(\int_\Omega |\Delta c|^2\right)^{\frac{1}{2}} \le C(\Omega)\|z\|_{H^1(\Omega)}\|z\|_{L^2(\Omega)}\|\Delta c\|_{L^2(\Omega)}$$

and Young inequality yields

$$\int_\Omega z^2|\Delta c| \le \epsilon\int_\Omega(|\nabla z|^2 + z^2) + \frac{C(\Omega)^2}{4\epsilon}\|z\|^2_{L^2(\Omega)}\int_\Omega |\Delta c|^2.$$

We replace the above estimate into (3.6) to obtain

$$\frac{d}{dt}\int_\Omega z^2(c+1)^\alpha e^{\rho w} + (2-nk_0\epsilon)\int_\Omega |\nabla z|^2 \le nk_0\left(1+\epsilon+\frac{C(\Omega)^2}{4\epsilon}\int_\Omega |\Delta c|^2\right)\int_\Omega z^2 + n(k_1-\lambda)\int_\Omega z^{2+\frac{2}{n}}. \tag{3.7}$$

In order to estimate $\int_\Omega z^{2+\frac{2}{n}}$ we apply the Gagliardo–Nirenberg inequality

$$\begin{aligned}\int_\Omega z^{2+\frac{2}{n}} &\le C(\Omega)\|z\|_{H^1(\Omega)}\|z\|^{1+\frac{2}{n}}_{L^{1+\frac{2}{n}}(\Omega)}\\ &\le C(\Omega)\|z\|_{H^1(\Omega)}\|z\|^{1+\frac{2}{n}}_{L^2(\Omega)}\\ &\le \epsilon\|z\|^2_{H^1(\Omega)} + \frac{c_2}{\epsilon}\|z\|^4_{L^2(\Omega)} + 1,\end{aligned}$$

and then

$$\begin{aligned}&\frac{d}{dt}\int_\Omega z^2(c+1)^\alpha e^{\rho w} + (2-n(k_0+k_1-\lambda)\epsilon)\int_\Omega |\nabla z|^2\\ &\quad\le \frac{nk_0C(\Omega)^2}{4\epsilon}\|z\|^2_{L^2}\int_\Omega |\Delta c|^2 + ((1+\epsilon)nk_0 + n(k_1-\lambda)\epsilon)\|z\|^2_{L^2(\Omega)}\\ &\qquad + n(k_1-\lambda)\frac{c_2}{\epsilon}\|z\|^4_{L^2(\Omega)} + c_3.\end{aligned}$$

We take ϵ (that depends on n) small enough to get

$$\frac{d}{dt}\int_\Omega z^2(c+1)^\alpha e^{\rho w} + \int_\Omega |\nabla z|^2 \le c_{10}\|z\|^2_{L^2(\Omega)}\int_\Omega |\Delta c|^2 + c_{11}\|z\|^2_{L^2(\Omega)} + c_{12}\|z\|^4_{L^2(\Omega)} + c_3. \tag{3.8}$$

We define

$$y_m := \int_\Omega q^{2^m}(c+1)^\alpha e^{\rho w}$$

and

$$z_m := q^{2^m}$$

then, by the boundedness from below of the weight $(c+1)^\alpha e^{\rho w}$ we have

$$\frac{d}{dt}y_m + \int_\Omega |\nabla z_{m-1}|^2 \le a(t)y_m + c_3, \tag{3.9}$$

where

$$a(t) := c_{10}\int_\Omega |\Delta c|^2 + c_{11} + c_{12}\int_\Omega z_m.$$

For $m = 1$ we know that $z_1 \in L^1(0,T;L^1(\Omega))$, therefore $a(t) \in L^1(0,T)$ and solving (3.9) we get

$$y_1 \le C\int_\Omega z_1 \le C(T), \quad \int_0^T\int_\Omega |\nabla z_0|^2 \le C(T).$$

Now, we use induction to prove that $y_m \in L^\infty(0,T)$ with $m \ge 2$. For this purpose it is enough to prove that $\int_\Omega z_m \in L^1(0,T)$. We notice that

$$\begin{aligned}\int_\Omega z_m &= \int_\Omega z_{m-2}^4 \le C\|z_{m-2}\|^2_{H^1(\Omega)}\|z_{m-2}\|^2_{L^2(\Omega)} \\ &= C\left(\int_\Omega |\nabla z_{m-2}|^2 + \int_\Omega z_{m-1}\right)\int_\Omega z_{m-1},\end{aligned}$$

and by induction we get the result. □

Remark 3.1. Let us observe that during the proof of the previous theorem we have to prove that for $n \ge 2$

$$\int_0^T\int_\Omega |\nabla q^{\frac{n}{2}}|^2 \le C(T).$$

Remark 3.2. At this point we should point out that by contrast with previous lemmas the L^n-bound depends on the time variable. Actually in Sec. 5 we will be able to remove the time dependence under some additional conditions.

Lemma 3.11. *For every $t \le T$ and any $k > 1$ we denote by $\Omega_k(t)$ the set*

$$\Omega_k(t) := \{x \in \Omega : q(x,t) > k\}$$

and $|\Omega_k(t)|$ stands for the Lebesgue measure of $\Omega_k(t)$. We have

$$(k+1)^4|\Omega_k(t)|^{1/4} \le C(T),$$

where C is a constant that does not depend on k.

Proof. By the representation of the L^q-norm of q with the level sets we obtain

$$(k-1)^q|\Omega_k(t)| < \int_{k-1}^{k} s^q|\Omega_s(t)|ds < \int_0^\infty s^q|\Omega_s(t)|ds = \frac{1}{q+1}\|q(t)\|_{L^q(\Omega)}.$$

Next we pick $q = 16$ and we apply the previous lemma to get the result. □

Lemma 3.12. *For any $s < \infty$ we have*

$$\int_0^T \int_\Omega |c_t|^s + |\Delta c|^s \le C(T). \tag{3.10}$$

Proof. Let $f := -pc$; then c solves the linear problem

$$c_t - \Delta c + c = f$$

with Neumann boundary conditions. Next we apply Remark 48.3 on p. 439 of Ref. 21 to get

$$\|c\|_{L^s(0,T;W^{2,s}(\Omega))} \le C\|f\|_{L^s(0,T;L^s(\Omega))}.$$

Finally, the lemma follows by Lemmas 3.10 and 3.5. □

Lemma 3.13.

$$\sup_{t\in[0,T]} \|p\|_{L^\infty(\Omega)} \le C(T).$$

Proof. Let $q_k = (q-k)_+$ where $(\,\cdot\,)_+$ denotes the positive part function and q is as defined in (3.4). On multiplying (3.5) by q_k and following the estimates of Lemma 3.10 we obtain

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\int_\Omega q_k^2(c+1)^\alpha e^{\rho w} \le &-\int_\Omega (c+1)^\alpha e^{\rho w}|\nabla q_k|^2 \\ &+ C\left(\int_\Omega q_k^3 + k\int_\Omega q_k^2 + \int_\Omega q_k + \int_\Omega (q_k^2 + kq_k)|\Delta c|\right).\end{aligned}$$

We add the term $\int_\Omega q_k^2$ to both sides of the previous inequality, we multiply by 2 and by the bound $1 \le (c+1)^\alpha e^{\rho w}$ we get

$$\begin{aligned}\frac{d}{dt}\int_\Omega q_k^2(c+1)^\alpha e^{\rho w} + 2\int_\Omega q_k^2 \le &-2\int_\Omega |\nabla q_k|^2 + C\int_\Omega q_k^3 + C(k+1)\int_\Omega q_k^2 \\ &+ k^2\int_\Omega q_k + C\int_\Omega (q_k^2 + kq_k)|\Delta c|.\end{aligned} \tag{3.11}$$

In what follow we estimate the positive terms in the right-hand side. By the boundedness of q in L^n for any $n \in (1,\infty)$, the Gagliardo–Nirenberg inequality (in dimension 2) and the Young inequality we obtain

$$\begin{aligned}C\|q_k\|_{L^3(\Omega)}^3 &\le C\|q_k\|_{L^3(\Omega)}^2 \le \|q_k\|_{H^1(\Omega)}^{4/3}\|q_k\|_{L^1(\Omega)}^{2/3} \le \epsilon\|q_k\|_{H^1(\Omega)}^2 + C(\epsilon)\|q_k\|_{L^1(\Omega)}^2 \\ &\le \epsilon\|q_k\|_{H^1(\Omega)}^2 + C(\epsilon)\|q_k\|_{L^1(\Omega)}.\end{aligned}$$

In the same manner we have

$$C(k+1)\int_\Omega q_k^2 \le C(k+1)\|q_k\|_{L^1(\Omega)}\|q_k\|_{H^1(\Omega)}$$
$$\le \epsilon\|q_k\|^2_{H^1(\Omega)} + C(k+1)^2\|q_k\|_{L^1(\Omega)}.$$

Next, by the Hölder inequality, the Gagliardo–Nirenberg inequality and the Young inequality we infer

$$C\int_\Omega q_k^2|\Delta c| \le \|q_k\|^2_{L^4(\Omega)}\|\Delta c\|_{L^2(\Omega)} \le \|q_k\|_{L^2(\Omega)}\|q_k\|_{H^1(\Omega)}\|\Delta c\|_{L^2(\Omega)}$$
$$\le \epsilon\|q_k\|^2_{H^1(\Omega)} + C(\epsilon)\|q_k\|^2_{L^2(\Omega)}\|\Delta c\|^2_{L^2(\Omega)}.$$

Finally, we estimate the last term in the right-hand side by the Sobolev embedding to get

$$Ck^2\int_\Omega q_k|\Delta c| \le Ck^2\|1_{|\Omega_k}\|_{L^{4/3}(\Omega)}\|q_k\|_{L^8(\Omega)}\|\Delta c\|_{L^8(\Omega)}$$
$$= Ck^2|\Omega_k|^{3/4}\|q_k\|_{H^1(\Omega)}\|\Delta c\|_{L^8(\Omega)}$$
$$\le \epsilon\|q_k\|^2_{H^1(\Omega)} + k^4C(\epsilon)(1+\|\Delta c\|^8_{L^8(\Omega)})|\Omega_k|^{3/2}.$$

Putting the previous estimates into (3.11) we obtain

$$\frac{d}{dt}\int_\Omega q_k^2(c+1)^\alpha e^{\rho w} + (2-\epsilon)\int_\Omega q_k^2$$
$$\le (\epsilon-2)\int_\Omega |\nabla q_k|^2 + k^4C(\epsilon)(1+\|\Delta c\|^8_{L^8(\Omega)})|\Omega_k|^{3/2}$$
$$+ C(\epsilon)\|q_k\|^2_{L^2(\Omega)}\|\Delta c\|^2_{L^2(\Omega)} + C(k+1)^2\|q_k\|_{L^1(\Omega)}.$$

Next, we handle with the L^1-norm of q_k in the following way

$$C(k+1)^2\|q_k\|_{L^1(\Omega)} \le C(k+1)^2\|1_{|\Omega_k}\|_{L^{4/3}(\Omega)}\|q_k\|_{L^4(\Omega)}$$
$$\le \epsilon\|q_k\|^2_{H^1(\Omega)} + C(\epsilon)(k+1)^4|\Omega_k|^{3/2}.$$

Therefore, we have

$$\frac{d}{dt}\int_\Omega q_k^2(c+1)^\alpha e^{\rho w} + (2-\epsilon)\int_\Omega q_k^2$$
$$\le (\epsilon-2)\int_\Omega |\nabla q_k|^2 + (k+1)^4C(\epsilon)(1+\|\Delta c\|^8_{L^8(\Omega)})|\Omega_k|^{3/2}$$
$$+ C(\epsilon)\|q_k\|^2_{L^2(\Omega)}\|\Delta c\|^2_{L^2(\Omega)}.$$

Let us denote by

$$y(t) = \int_\Omega q_k^2(c+1)^\alpha e^{\rho w}.$$

Now, we pick ϵ sufficiently small to get $\epsilon - 2 < 0$ and we apply Lemma 3.11 to remove the polynomial growth of the constant with respect to k. Since the weight

$(c+1)^\alpha e^{\rho w}$ is bounded from up and below by positive constants we obtain the following differential inequality

$$y'(t) + \sigma y(t) \le C(\epsilon)\|\Delta c\|^2_{L^2(\Omega)} y(t) + C(\epsilon)(1 + \|\Delta c\|^8_{L^8(\Omega)})|\Omega_k|^{5/4},$$

where $\sigma < 2$ is a positive constant. Hence, if $a(t) = \sigma - C\|\Delta c\|^2_{L^2(\Omega)}$ and we solve the differential inequality we get

$$y(t) \le e^{-\int_0^t a(s)ds} \int_0^t C(1 + \|\Delta c\|^8_{L^8(\Omega)}) e^{\int_0^s a(\sigma)d\sigma} |\Omega_k(s)|^{5/4} ds.$$

Let us observe that by Lemma 3.7

$$e^{-\int_0^t a(s)ds} = e^{-\sigma t} e^{C\int_0^t \|\Delta c\|^2_{L^2(\Omega)} ds} \le C_0 e^{-\sigma t} \quad \text{and} \quad e^{\int_0^t a(s)ds} \le e^{\sigma t}.$$

As a consequence, applying Lemma 3.12 we have

$$\begin{aligned} y(t) &\le e^{-\sigma t} C_0 \int_0^t C(1 + \|\Delta c(s)\|^8_{L^8(\Omega)}) e^{\sigma s} ds \sup_{t\in[0,T]} |\Omega_k(t)|^{5/4} \\ &\le C(T) \sup_{t\in[0,T]} |\Omega_k(t)|^{5/4}. \end{aligned}$$

From the previous estimate we infer

$$\|q_k\|^2_{L^2(\Omega)} \le Cy(t) \le C(T) \left(\sup_{t\in[0,T]} |\Omega_k(t)| \right)^{5/4}.$$

On the other hand, since $\Omega_j \subset \Omega_k$ for $j > k > 1$ then

$$\|q_k(t)\|^2_{L^2(\Omega)} \ge \int_{\Omega_j(t)} q_k^2 \ge (j-k)^2 |\Omega_j(t)|.$$

Therefore, we have

$$(j-k)^2 \sup_{t\in[0,T]} |\Omega_j(t)| \le C(T) \left(\sup_{t\in[0,T]} |\Omega_k(t)| \right)^{5/4}.$$

Let $\varphi(s) = \sup_{t\in[0,T]} |\Omega_s(t)|$, so we may rewrite the above inequality as follows:

$$\varphi(j) \le C(j-k)^{-2} (\varphi(k))^{5/4}.$$

Since φ is a non-negative and non-increasing function by Lemma B.1, Appendix B on p. 63 of Ref. 11 there exists $k_0 < \infty$ such that $\varphi(k_0) = 0$. Therefore $q_{k_0} \equiv 0$ which ends the proof. □

Lemma 3.14. *For any $t \le T$ we have*

$$\int_\Omega |\nabla w|^2 \le C(T).$$

Proof. We know that

$$w_t = \gamma q(c+1)^{\alpha} e^{\rho w}(1-w).$$

From the above equality we easily obtain

$$\begin{aligned}\frac{d}{2dt}\int_\Omega |\nabla w|^2 &= \gamma \int_\Omega (c+1)^{\alpha} e^{\rho w}(1-w)\nabla q\cdot\nabla w \\ &\quad + \alpha\gamma\int_\Omega (c+1)^{\alpha-1} e^{\rho w}(1-w)\nabla c\cdot\nabla w \\ &\quad + \gamma\int_\Omega q(c+1)^{\alpha} e^{\rho w}(\rho-\rho w-1)|\nabla w|^2.\end{aligned}$$

Hence, previous lemma entails

$$\frac{d}{2dt}\int_\Omega |\nabla w|^2 \le C(T)\left(\int_\Omega |\nabla q|^2 + \int_\Omega |\nabla c|^2 + \int_\Omega |\nabla w|^2\right). \tag{3.12}$$

By Remark 3.1 and Lemma 3.7 we know

$$\int_0^T \left(\int_\Omega |\nabla q|^2 + |\nabla c|^2\right) \le C(T).$$

Therefore, solving the differential inequality (3.12) we conclude the proof. □

Lemma 3.15. *For any $t \le T$ we have*

$$\|c(t)\|_{W^{1,\infty}(\Omega)} \le C(T).$$

Proof. Let us note that c solves the linear equation

$$c_t - \Delta c + c = f$$

under Neumann boundary condition with $f := pc$. Since

$$\|f\|_{L^\infty(0,T;L^n(\Omega))} \le C(T)$$

for $n > 2$ we can use linear semigroup theory to conclude the lemma (see, for instance, p. 430 in Ref. 19 or Lemma 4.1 in Ref. 10). □

Lemma 3.16. *For any $t \le T$ there exists $C(T)$ such that*

$$\int_\Omega |\nabla p|^2 \le C(T), \quad \int_\Omega |\nabla z|^2 \le C(T), \quad \int_0^T\int_\Omega z_t^2 \le C(T),$$

where $z = e^{-\rho w} p$.

Proof. Let us note that z satisfies

$$\begin{aligned}z_t &= e^{-\rho w}\nabla\cdot(e^{\rho w}\nabla z) - e^{-\rho w}\nabla\cdot\left(\frac{\alpha z e^{\rho w}}{1+c}\nabla c\right) \\ &\quad + \lambda z(1 - z e^{\rho w}) - \rho\gamma e^{\rho w} z^2(1-w).\end{aligned}$$

Taking $z_t e^{\rho w}$ as test function in the above equation and integrating in the spatial variable we deduce

$$\begin{aligned}
&\int_\Omega e^{\rho w} z_t^2 + \int_\Omega e^{\rho w} \nabla z \cdot \nabla z_t \\
&\quad = -\int_\Omega z_t e^{\rho w}\left(\frac{\alpha}{1+c}\nabla z \cdot \nabla c + \frac{\alpha\rho z}{1+c}\nabla w \cdot \nabla c - \frac{\alpha z}{(1+c)^2}|\nabla c|^2 + \frac{\alpha z}{1+c}\Delta c\right) \\
&\qquad + \int_\Omega z_t e^{\rho w}(\lambda z(1 - z e^{\rho w}) - \rho\gamma e^{\rho w} z^2(1-w)).
\end{aligned} \tag{3.13}$$

Notice that

$$\begin{aligned}
&\int_\Omega e^{\rho w}\nabla z \cdot \nabla z_t = \frac{d}{2dt}\int_\Omega e^{\rho w}|\nabla z|^2 - \frac{\gamma\rho}{2}\int_\Omega e^{2\rho w} z(1-w)|\nabla z|^2, \\
&-\int_\Omega z_t \frac{\alpha e^{\rho w}}{1+c}\nabla z \cdot \nabla c \le \epsilon \int_\Omega z_t^2 e^{\rho w} + C(\epsilon)\|\nabla c\|^2_{L^\infty(\Omega)}\int_\Omega e^{\rho w}|\nabla z|^2, \\
&-\int_\Omega z_t \frac{\alpha z e^{\rho w}}{1+c}\nabla w \cdot \nabla c \le \epsilon \int_\Omega z_t^2 e^{\rho w} + C(\epsilon)\|\nabla c\|^2_{L^\infty(\Omega)}\|z\|^2_{L^\infty(\Omega)}\int_\Omega |\nabla w|^2, \\
&\int_\Omega z_t \frac{\alpha z e^{\rho w}}{(1+c)^2}|\nabla c|^2 \le \epsilon \int_\Omega z_t^2 e^{\rho w} + C(\epsilon)\|\nabla c\|^4_{L^\infty(\Omega)}\|z\|^2_{L^\infty(\Omega)}, \\
&-\int_\Omega z_t \frac{\alpha z e^{\rho w}}{1+c}\Delta c \le \epsilon \int_\Omega z_t^2 e^{\rho w} + C(\epsilon)\|z\|^2_{L^\infty(\Omega)}\int_\Omega |\Delta c|^2, \\
&\int_\Omega z_t e^{\rho w}(\lambda z(1 - z e^{\rho w}) - \rho\gamma e^{\rho w} z^2(1-w)) \le \epsilon \int_\Omega z_t^2 e^{\rho w} + C(\epsilon, T).
\end{aligned} \tag{3.14}$$

We pick $\epsilon \le 1/5$ to obtain

$$\frac{d}{dt}\int_\Omega e^{\rho w}|\nabla z|^2 \le C(T)\left(\int_\Omega |\nabla z|^2 + \int_\Omega |\nabla w|^2 + \int_\Omega |\Delta c|^2 + 1\right).$$

Solving the above differential inequality we get the bound for $\nabla z(t)$ in $H^1(\Omega)$. At this point we easily get the bounds for z_t. □

Lemma 3.17. *We have*

$$\int_0^T \|\Delta z\|^2_{L^2(\Omega)} \le C(T).$$

Proof. We know that

$$\begin{aligned}
z_t = \Delta z + \rho\nabla w \cdot \nabla z - \frac{\alpha z}{1+c}\Delta c - \frac{\alpha}{1+c}\nabla z \cdot \nabla c \\
+ \frac{\alpha z}{(1+c)^2}|\nabla c|^2 - \frac{\rho z}{1+c}\nabla w \cdot \nabla c + h(z,w),
\end{aligned}$$

where $h(z,w) := \lambda z(1 - ze^{\rho w}) - \rho\gamma e^{\rho w} z^2(1-w)$. Hence,

$$\int_0^T \|\Delta z\|^2_{L^2(\Omega)} \le C(T) \int_0^T (\|z_t\|^2_{L^2(\Omega)} + \|\nabla w \cdot \nabla z\|^2_{L^2(\Omega)} + \|\nabla z \cdot \nabla c\|^2_{L^2(\Omega)} + \||\nabla c|^2\|^2_{L^2(\Omega)} + \|\nabla w \cdot \nabla c\|^2_{L^2(\Omega)} + \|h(z,w)\|^2_{L^2(\Omega)}). \tag{3.15}$$

In order to see an upper bound of the right-hand side term of the (3.15) we just need to find a bound for the term $\int_0^T \|\nabla w \cdot \nabla z\|^2_{L^2(\Omega)}$. By the Hölder inequality we have

$$\int_0^T \|\nabla w \cdot \nabla z\|^2_{L^2(\Omega)} \le \int_0^T \|\nabla w\|^2_{L^4(\Omega)} \|\nabla z\|^2_{L^4(\Omega)}. \tag{3.16}$$

Next lines are devoted to find a bound for $\|\nabla w\|^2_{L^4(\Omega)}$, to this end we take gradient in the equation for w to get

$$\nabla w_t = \gamma(e^{\rho w}(1-w)\nabla z + \rho z e^{\rho w}(1-w)\nabla w - ze^{\rho w}\nabla w).$$

We multiply the above equality by $\nabla w |\nabla w|^2$ to deduce by the Young inequality that

$$\frac{d}{dt}\|\nabla w\|^4_{L^4(\Omega)} \le C(\|\nabla z\|^4_{L^4(\Omega)} + \|z\|_{L^\infty(\Omega)}\|\nabla w\|^4_{L^4(\Omega)}).$$

Solving the differential inequality and thanks to Lemma 3.15 we get

$$\|\nabla w\|^4_{L^4(\Omega)} \le C_1(T)\left(1 + \int_0^t \|\nabla z\|^4_{L^4(\Omega)} ds\right),$$

where $C_1(T) := e^{C\int_0^T \|z\|_{L^\infty(\Omega)}} \max\{\|\nabla w_0\|^4_{L^4(\Omega)}, C\}$. Therefore, by the inequality $|x^2+y^2|^{\frac{1}{2}} \le |x| + |y|$ we deduce

$$\|\nabla w\|^2_{L^4(\Omega)} \le C_1(T)^{\frac{1}{2}}\left(1 + \left(\int_0^t \|\nabla z\|^4_{L^4(\Omega)} ds\right)^{\frac{1}{2}}\right).$$

Coming back to (3.16) we have

$$\int_0^T \|\nabla w \cdot \nabla z\|^2_{L^2(\Omega)} \le C_1^{\frac{1}{2}}(T)\int_0^T \left(\|\nabla z\|^2_{L^4(\Omega)} + \left(\int_0^t \|\nabla z\|^4_{L^4(\Omega)} ds\right)^{\frac{1}{2}} \|\nabla z\|^2_{L^4(\Omega)}\right)$$
$$= C_1^{\frac{1}{2}}(T)\int_0^T \left(\|\nabla z\|^2_{L^4(\Omega)} + \left(\|\nabla z\|^4_{L^4(\Omega)} \int_0^t \|\nabla z\|^4_{L^4(\Omega)} ds\right)^{\frac{1}{2}}\right).$$

We notice that

$$\int_0^t \|\nabla z(\sigma)\|^4_{L^4(\Omega)} d\sigma \|\nabla z(s)\|^4_{L^4(\Omega)} = \frac{1}{2}\frac{d}{dt}\left(\int_0^t \|\nabla z(\sigma)\|^4_{L^4(\Omega)} d\sigma\right)^2,$$

and by the Hölder inequality in the time variable

$$\int_0^T \left(\|\nabla z\|^4_{L^4(\Omega)} \int_0^t \|\nabla z\|^4_{L^4(\Omega)} ds \right)^{\frac{1}{2}}$$

$$= \int_0^T \left[\frac{1}{2} \frac{d}{dt} \left(\int_0^t \|\nabla z(\sigma)\|^4_{L^4(\Omega)} d\sigma \right)^2 \right]^{\frac{1}{2}}$$

$$\leq \frac{T^{\frac{1}{2}}}{2} \left[\int_0^T \frac{d}{dt} \left(\int_0^t \|\nabla z(\sigma)\|^4_{L^4(\Omega)} d\sigma \right)^2 \right]^{\frac{1}{2}}$$

$$\leq \frac{T^{\frac{1}{2}}}{2} \left[\int_0^T \|\nabla z(\sigma)\|^4_{L^4(\Omega)} \right]^{\frac{1}{2}},$$

we infer

$$\int_0^T \|\nabla w \cdot \nabla z\|^2_{L^2(\Omega)} \leq C_1^{\frac{1}{2}}(T) \int_0^T \|\nabla z(s)\|^2_{L^4(\Omega)} ds + \frac{T^{1/2}}{2} \left[\int_0^T \|\nabla z(s)\|^4_{L^4(\Omega)} d\sigma \right]^{\frac{1}{2}}.$$

Now, we apply the Gagliardo–Nirenberg inequality

$$\|\nabla z\|^2_{L^4(\Omega)} \leq C(\Omega) \|\Delta z\|_{L^2(\Omega)} \|\nabla z\|_{L^2(\Omega)}$$

to get

$$\int_0^T \|\nabla w \cdot \nabla z\|^2_{L^2(\Omega)} \leq \epsilon \int_0^T \|\Delta z(s)\|^2_{L^2(\Omega)} ds + C(\epsilon) \int_0^T \|\nabla z\|^2_{L^2(\Omega)} + C(T) \left[\int_0^T \|\Delta z\|^2_{L^2(\Omega)} \|\nabla z\|^2_{L^2(\Omega)} \right]^{\frac{1}{2}}.$$

By Lemma 3.16 we have

$$\int_0^T \|\nabla w \cdot \nabla z\|^2_{L^2(\Omega)} \leq \epsilon \int_0^T \|\Delta z\|^2_{L^2(\Omega)} ds + C(T, \epsilon) + C(T) \left[\int_0^T \|\Delta z\|^2_{L^2(\Omega)} \right]^{\frac{1}{2}}.$$

Next, we pick ϵ small enough and thanks to (3.15) we have

$$\int_0^T \|\Delta z\|^2_{L^2(\Omega)} ds \leq \frac{C(T)}{1 - \epsilon C(T)} \left(1 + \left[\int_0^T \|\Delta z\|^2_{L^2(\Omega)} \right]^{\frac{1}{2}} \right). \tag{3.17}$$

In order to conclude the proof we notice that the inequality $x \leq A + Bx^{\frac{1}{2}}$ implies the boundedness of x. □

Lemma 3.18. *We have that*

$$\|z\|_{L^2(0,T;H^2(\Omega))} \leq C(T).$$

Proof. Let us define the set

$$K := \left\{ \varphi \in H^2(\Omega) : \frac{\partial \varphi}{\partial n} = 0, \int_\Omega \varphi = 0 \right\}.$$

It is known that $-\Delta$ is an isomorphism from K to $L^2(\Omega)$. Since $z - \bar{z} \in K$ where $\bar{z} = \frac{1}{|\Omega|}\int_\Omega z$ then

$$\begin{aligned} \|z\|_{H^2(\Omega)} &\leq \|z - \bar{z}\|_{H^2(\Omega)} + \|\bar{z}\|_{H^2(\Omega)} \leq \|\Delta(z - \bar{z})\|_{L^2(\Omega)} + \|\bar{z}\|_{H^2(\Omega)} \\ &= \|\Delta z\|_{L^2(\Omega)} + C, \end{aligned}$$

which ends the proof. □

Remark 3.3. Thanks to the previous lemma and the Sobolev embedding we may assert that $\nabla z \in (L^2(0,T;L^n(\Omega)))^N$ for any $n \geq 2$.

Lemma 3.19. *For any $t \leq T$ and $n \geq 2$ we have*

$$\|w(t)\|_{W^{1,n}(\Omega)} \leq C(T).$$

Proof. We take the equation that satisfies ∇w_t we multiply it by $|\nabla w|^{n-2}\nabla w$ and we integrate in the space variable to get

$$\begin{aligned} \frac{d}{ndt}\int_\Omega |\nabla w|^n &\leq C(T)\int_\Omega |\nabla w|^n + C(T)\|\nabla z\|_{L^n(\Omega)}\|\nabla w\|_{L^n(\Omega)} \\ &\leq C(T)\int_\Omega |\nabla w|^n + C(T)(1 + \|\nabla z\|^2_{L^n(\Omega)})(1 + \|\nabla w\|^n_{L^n(\Omega)}). \end{aligned}$$

Let us observe that the above inequality can be rewritten in the form

$$y'(t) \leq a(t)y(t) + b(t),$$

where $y(t) = \int_\Omega |\nabla w|^n$ and $a(t), b(t) \in L^1(0,T)$. Therefore, solving the differential equation we get the result. □

Lemma 3.20. *For any $t \leq T$ and $n \geq 2$ we have*

$$\|p(t)\|_{W^{1,n}(\Omega)} \leq C(T).$$

Proof. Let us note that the equation for z can be rewritten in the form

$$z_t = \Delta z + b(x,t) \cdot \nabla z + a(x,t)z,$$

where

$$\|b\|_{(L^5(0,T;L^5(\Omega)))^N} \leq C(T), \quad \|a\|_{L^5(0,T;L^5(\Omega))} \leq C(T)$$

and

$$\lim_{\tau \to 0} \|b\|_{(L^5(t,t+\tau;L^5(\Omega)))^N} = \lim_{\tau \to 0} \|a\|_{L^5(t,t+\tau;L^5(\Omega))} = 0.$$

Therefore, by Theorem 9.1, Chap. IV of Ref. 12 ($q = 5$) we have

$$\|z\|_{W_5^{2,1}(\Omega\times(0,T))} \leq C(T).$$

Since $q > N + 2$ the corollary after Theorem 9.1, Chap. IV of Ref. 12 asserts, in particular, that

$$\|z(t)\|_{W^{1,n}(\Omega)} \leq C(T).$$

From here we easily get the result. □

Theorem 3.1. *Under the assumptions* (1.7)–(1.12) *and* (2.1) *there exists a unique global classical solution to* (1.1)–(1.6) *satisfying*

$$(p, c, w) \in C^{2+\alpha,1+\alpha/2}(\bar{\Omega} \times [0, T])$$

for any $T < +\infty$*.*

Proof. The result is a consequence of the local existence result given in Theorem 2.1, the bounds of the unknowns in $L^\infty(0, T; W^{1,s}(\Omega))$ and Theorem 2.2. □

4. Steady States

We study in this section the positive steady states of (1.1)–(1.5) defined by

$$\begin{aligned}
&\operatorname{div}\left(\nabla p - p\left(\frac{\alpha}{1+c}\nabla c + \rho\nabla w\right)\right) + \lambda p(1-p) = 0, && x \in \Omega,\\
&p(1-w) = 0, && x \in \Omega,\\
&-\Delta c + (1+\mu p)c = 0, && x \in \Omega,
\end{aligned}$$

and the boundary conditions (1.6)–(1.7) for each $x \in \partial\Omega$.

Lemma 4.1. *The positive steady states of* (1.1)–(1.5) *are defined by*

$$(p, c, w) = (1, 0, 1), \quad (p, c, w) = (0, 0, \tilde{w}),$$

where $\tilde{w}$ *is any function in* $W^{2,s}(\Omega)$*.*

Proof. We multiply the c-equation by c to obtain

$$\int_\Omega |\nabla c|^2 + (1+\mu p)c^2 = 0.$$

Hence, we have $c = 0$.

Case 1. $w \equiv 1$ then $p \geq 0$ is a solution to

$$-\Delta p = \lambda p(1-p), \quad \frac{\partial p}{\partial n} = 0.$$

Clearly $p = 0$ and $p = 1$ are solutions to the above problem. Moreover, by Lemma 1 of Ref. 6, $p \equiv 1$ is the only positive solution.

Case 2. $w \not\equiv 1$ then either $p \equiv 0$ or $p \not\equiv 0$. If $p \not\equiv 0$ then $z \geq 0$, $z \not\equiv 0$ satisfies

$$-\Delta z + \rho \nabla w \cdot \nabla z + \lambda z^2 e^{\rho w} = \lambda z, \quad \frac{\partial z}{\partial n} = 0.$$

Thus, z is a strict super solution of

$$\left(-\Delta \varphi + \rho \nabla w \cdot \nabla \varphi + \lambda \varphi z e^{\rho w}, \frac{\partial \varphi}{\partial n}\right).$$

Therefore, by the strong maximum principle (see Theorem 2.4 of Ref. 2) we have $z(x) > 0$ for each $x \in \bar{\Omega}$ and, as a consequence, $p(x) > 0$ for each $x \in \bar{\Omega}$ that contradicts $p(1-w) = 0$ and ends the proof. □

5. Asymptotic Behavior

In this section we study the long-time behavior for (1.1)–(1.5). We restrict our study to domains up to dimension 2. Basically, we will have two kind of restrictions ensuring the convergence to the homogeneous steady-states. Both conditions involve only to the initial data w_0.

Lemma 5.1. *Under conditions of Theorem* 3.1 *we have*

$$\int_0^{+\infty} \int_\Omega p|w-1| \leq \|w_0 - 1\|_{L^1(\Omega)}.$$

Proof. We multiply the w-equation by $H(w-1)$ (the Heaviside function) to get

$$\frac{d}{dt} \int_\Omega |w-1| = -\int_\Omega p|w-1|. \tag{5.1}$$

Therefore, integrating the above equation on the time variable the lemma is concluded. □

Lemma 5.2. *Under conditions of Theorem* 3.1 *we have*

$$\int_0^{+\infty} \int_\Omega p|\nabla c|^2 \leq C$$

for some positive constant C*.*

Proof. By the Hölder inequality and the Gagliardo–Nirenberg inequality we deduce

$$\begin{aligned}
\int_0^{+\infty} \int_\Omega p|\nabla c|^2 &\leq \int_0^{+\infty} \|p\|_{L^2(\Omega)} \|\nabla c\|^2_{L^4(\Omega)} \\
&\leq \int_0^{+\infty} \|p\|_{L^2(\Omega)} \|\Delta c\|_{L^2(\Omega)} \|\nabla c\|_{L^2(\Omega)} \\
&\leq \frac{1}{2} \int_0^{+\infty} \|p\|^2_{L^2(\Omega)} \|\nabla c\|^2_{L^2(\Omega)} + \frac{1}{2} \int_0^{+\infty} \|\Delta c\|^2_{L^2(\Omega)}.
\end{aligned}$$

By Lemmas 3.7 and 3.8 we infer

$$\int_0^{+\infty}\int_\Omega p|\nabla c|^2 \le \frac{1}{2}\int_0^{+\infty}\|p\|^2_{L^2(\Omega)}e^{-2s}(C+Cs)+C.$$

Next, we apply Lemma 3.3 and the bound $se^{-\epsilon s} \le C(\epsilon)$ for any $s>0$ to get

$$\int_0^{+\infty}\int_\Omega p|\nabla c|^2 \le C + C\int_0^{+\infty} e^{\epsilon-2}\|p\|^2_{L^2(\Omega)}.$$

Finally, we pick $\epsilon < 2$ and we argue as in Lemma 3.3 to conclude the proof. □

Let us denote by $\bar{p}$ the mean value of p i.e.

$$\bar{p} := \frac{1}{|\Omega|}\int_\Omega p.$$

Lemma 5.3. *Under conditions of Theorem* 3.1 *we have*

$$\int_\Omega (p-\bar{p})^2 \le C\int_\Omega \frac{|\nabla p|^2}{p}$$

for some positive constant C.

Proof. Notice that the Poincare–Wintinger inequality and the Hölder inequality assert

$$\int_\Omega (p-\bar{p})^2 \le C\left(\int_\Omega |\nabla p|\right)^2 \le C\int_\Omega p\int_\Omega \frac{|\nabla p|^2}{p}.$$

Thus, by Lemma 3.1 the lemma follows. □

Lemma 5.4. *For every* $t \ge 0$ *and* $\kappa > 0$ *the following equality holds*:

$$\frac{d}{dt}F(p(t),w(t)) = G(p(t),w(t),c(t)),$$

where

$$F(p,w) = \kappa\int_\Omega |\nabla w|^2 + \int_\Omega p(\ln p - 1) + \rho\int_\Omega p(w-1) - \gamma\kappa\int_\Omega p(w-1)^2,$$

$$\begin{aligned}G(p,w,c) = &-\int_\Omega \frac{|\nabla p|^2}{p} + \int_\Omega \frac{\alpha}{1+c}\nabla p\cdot\nabla c + \int_\Omega (2\alpha\gamma\kappa(1-w)+\alpha\rho)\frac{p}{1+c}\nabla c\cdot\nabla w\\ &+\int_\Omega(\rho^2 - 2\gamma\kappa + 2\rho\gamma\kappa(1-w))p|\nabla w|^2 + \lambda\int_\Omega p(1-p)\ln p\\ &+\lambda\rho\int_\Omega p(1-p)(w-1) + \gamma\rho\int_\Omega p^2(1-w)\\ &+2\gamma^2\kappa\int_\Omega p^2(w-1)^2 - \lambda\gamma\kappa\int_\Omega p(1-p)(w-1)^2.\end{aligned}$$

Proof. From the w-equation we have

$$\kappa \frac{d}{dt}\int_\Omega |\nabla w|^2 = 2\gamma\kappa \int_\Omega (1-w)\nabla p\cdot\nabla w - 2\gamma\kappa\int_\Omega p|\nabla w|^2. \tag{5.2}$$

Next, we multiply the p-equation by $\ln p$ and we integrate in the space variable to get

$$\frac{d}{dt}\int_\Omega p(\ln p - 1) = -\int_\Omega \frac{|\nabla p|^2}{p} + \int_\Omega \frac{\alpha}{1+c}\nabla p\cdot\nabla c + \rho\int_\Omega \nabla p\cdot\nabla w \\ + \lambda\int_\Omega p(1-p)\ln p. \tag{5.3}$$

Moreover, we know that

$$\rho\frac{d}{dt}\int_\Omega p(w-1) = -\rho\int_\Omega \nabla p\cdot\nabla w + \alpha\rho\int_\Omega \frac{p}{1+c}\nabla c\cdot\nabla w + \rho^2\int_\Omega p|\nabla w|^2 \\ + \lambda\rho\int_\Omega p(1-p)(w-1) + \gamma\rho\int_\Omega p^2(1-w), \tag{5.4}$$

and

$$\gamma\kappa\frac{d}{dt}\int_\Omega p(w-1)^2 = -2\gamma\kappa\int_\Omega (w-1)\nabla p\cdot\nabla w + 2\alpha\gamma\kappa\int_\Omega \frac{p(w-1)}{1+c}\nabla c\cdot\nabla w \\ + 2\rho\gamma\kappa\int_\Omega (w-1)p|\nabla w|^2 - 2\gamma^2\kappa\int_\Omega p^2(w-1)^2 \\ + \lambda\gamma\kappa\int_\Omega p(1-p)(w-1)^2.$$

Hence, adding (5.2)–(5.4) and subtracting the above equality we deduce the result. □

The following lemma will provide us a some crucial estimates that will allow us to remove the time dependence of p in the L^∞-norm. Let us denote by **(H1)**, **(H2)** the following hypotheses:

$$(\mathbf{H1})\quad \|w_0 - 1\|_{L^\infty(\Omega)} < \delta,$$

$$(\mathbf{H2})\quad w_0 > 1.$$

Lemma 5.5. *There exist* $\delta, \kappa > 0$ *such that if* $(\mathbf{H1})$ *is satisfied then*

$$G(p,w,c) \le -\epsilon\int_\Omega \frac{|\nabla p|^2}{p} + C(\epsilon)\int_\Omega p|w-1| + C(\epsilon)\int_\Omega p|\nabla c|^2 - \epsilon\int_\Omega p|\nabla w|^2$$

for some $\epsilon > 0$.

Proof. By the Hölder and Young inequalities we have

$$\int_\Omega \frac{\alpha}{1+c}\nabla p\cdot\nabla c \le \epsilon\int_\Omega \frac{|\nabla p|^2}{p} + C(\epsilon)\int_\Omega p|\nabla c|^2,$$

$$\int_\Omega (2\alpha\gamma\kappa(1-w)+\alpha\rho)\frac{p}{1+c}\nabla c\cdot\nabla w \le \epsilon'\int_\Omega p|\nabla w|^2 + C(\epsilon')\int_\Omega p|\nabla c|^2,$$

for any $\epsilon, \epsilon' > 0$. Let us denote by $\theta(p,w)$ to the lower-order terms of $G(p,w,c)$

$$\theta(p,w) := \lambda\int_\Omega p(1-p)\ln p + \lambda\rho\int_\Omega p(1-p)(w-1) + \gamma\rho\int_\Omega p^2(1-w)$$
$$+ 2\gamma^2\kappa\int_\Omega p^2(w-1)^2 - \lambda\gamma\kappa\int_\Omega p(1-p)(w-1)^2.$$

Since $s(1-s)\ln s \le 0$ for $s \ge 0$ it results

$$\theta(p,w) \le \rho(\lambda+\gamma)\int_\Omega p^2|w-1| + \lambda\rho\int_\Omega p|w-1| + \gamma\kappa(\lambda+2\gamma)\int_\Omega p^2(w-1)^2$$
$$\le (\rho(\lambda+\gamma)+\gamma\kappa(\lambda+2\gamma)\|w-1\|_{L^\infty(\Omega)})\int_\Omega p^2|w-1| + \lambda\rho\int_\Omega p|w-1|.$$

Next, we apply Lemma 5.3 to get

$$\int_\Omega p^2|w-1| \le \int_\Omega (p-\bar{p})^2|w-1| + 2\bar{p}\int_\Omega p|w-1|$$
$$\le \|w-1\|_{L^\infty(\Omega)}\int_\Omega (p-\bar{p})^2 + 2C\int_\Omega p|w-1|$$
$$\le \|w-1\|_{L^\infty(\Omega)}C\int_\Omega \frac{|\nabla p|^2}{p} + 2C\int_\Omega p|w-1|.$$

On the other hand, from the w-equation (see (3.3)) we have

$$\|w(t)-1\|_{L^\infty(\Omega)} \le \|w_0-1\|_{L^\infty(\Omega)}, \quad \forall\, t\ge 0.$$

Hence, previous estimates assert

$$G(p,w,c) \le k_1(w_0,\epsilon,\kappa)\int_\Omega \frac{|\nabla p|^2}{p} + k_2(w_0,\epsilon,\kappa)\int_\Omega p|\nabla w|^2$$
$$+ C(\epsilon,\epsilon')\int_\Omega p|\nabla c|^2 + C\int_\Omega p|w-1|,$$

where

$$k_1(w_0,\epsilon,\kappa) := \epsilon + (\rho(\lambda+\gamma)+\gamma\kappa(\lambda+2\gamma)\|w_0-1\|_{L^\infty(\Omega)})C\|w_0-1\|_{L^\infty(\Omega)} - 1,$$
$$k_2(w_0,\epsilon,\kappa) := \epsilon' + \rho^2 + 2\rho\gamma\kappa\|w_0-1\|_{L^\infty(\Omega)} - 2\gamma\kappa.$$

In particular, we pick $\kappa > 0$ such that $\rho^2 - 2\gamma\kappa < 0$. Then for $\epsilon, \epsilon' > 0$ sufficiently small there exists $\delta > 0$ such that

$$k_1(\|w_0 - 1\|_{L^\infty(\Omega)}) \leq k_1 < 0, \quad k_2(\|w_0 - 1\|_{L^\infty(\Omega)}) \leq k_2 < 0$$

whenever $\|w_0 - 1\|_{L^\infty(\Omega)} < \delta$. □

Lemma 5.6. *There exists $\delta > 0$ such that whenever* (**H1**) *holds then*

$$\int_\Omega |p(t) \ln p(t)| \leq C, \quad \forall\, t \geq 0,$$

and

$$\int_0^{+\infty} \int_\Omega \frac{|\nabla p|^2}{p} + \int_0^{+\infty} \int_\Omega p|\nabla w|^2 \leq C.$$

for some constant $C > 0$.

Proof. Combining Lemma 5.4 and Lemma 5.5 we infer

$$\frac{d}{dt} F(p, w) \leq -\epsilon \int_\Omega \frac{|\nabla p|^2}{p} + C(\epsilon) \int_\Omega p|w - 1| + C(\epsilon) \int_\Omega p|\nabla c|^2 - \epsilon \int_\Omega p|\nabla w|^2.$$

Therefore, by integration on the time variable the above inequality and applying Lemmas 5.1 and 5.2 we conclude the proof. □

Remark 5.1. The estimates provided by the previous lemma will allow us to remove the time dependence for the L^∞-norm of p. Such an estimate it is crucial in our proof of the convergence to the steady-state.

In what follows we will show that the estimates of Lemma 5.6 also holds when $w_0 > 1$.

Lemma 5.7. *Under the assumption* (**H2**) *there exists a constant $C > 0$ such that*

$$\sup_{t \geq 0} \int_\Omega |p(t) \ln p(t)| < C, \quad \int_0^{+\infty} \int_\Omega \frac{|\nabla p|^2}{p} < C, \quad \int_0^{+\infty} \int_\Omega p|\nabla w|^2 < C.$$

Proof. We consider the unknown $v = w - 1$. Since $w_0 > 1$ then, solving the w-equation we have that $v(x, t) > 0$ for all $(x, t) \in \Omega \times (0, +\infty)$. Thus, $\sqrt{v}$ is well defined for each $(x, t) \in \Omega \times (0, +\infty)$. We know that

$$\begin{aligned} \frac{2\rho}{\gamma} \frac{d}{dt} \int_\Omega |\nabla \sqrt{v}|^2 &= \frac{4\rho}{\gamma} \int_\Omega \nabla \sqrt{v} \cdot \nabla \left(\frac{1}{2\sqrt{v}} (-\gamma p v) \right) \\ &= -2\rho \int_\Omega p|\nabla \sqrt{v}|^2 - \rho \int_\Omega \nabla p \cdot \nabla v. \end{aligned}$$

Moreover, we have (see (5.3))

$$\frac{d}{dt}\int_\Omega p(\ln p - 1) + \int_\Omega \frac{|\nabla p|^2}{p} = \int_\Omega \frac{\alpha}{1+c}\nabla p \cdot \nabla c + \rho \int_\Omega \nabla p \cdot \nabla w + \lambda \int_\Omega p(1-p)\ln p.$$

Adding previous inequalities we obtain

$$\begin{aligned}
&\frac{d}{dt}\int_\Omega p(\ln p - 1) + \frac{2\rho}{\gamma}\frac{d}{dt}\int_\Omega |\nabla\sqrt{v}|^2 \\
&\quad = -\int_\Omega \frac{|\nabla p|^2}{p} + \int_\Omega \frac{\alpha}{1+c}\nabla p\cdot\nabla c + \lambda\int_\Omega p(1-p)\ln p - 2\rho\int_\Omega p|\nabla\sqrt{v}|^2 \\
&\quad \le (\epsilon - 1)\int_\Omega \frac{|\nabla p|^2}{p} + C(\epsilon)\int_\Omega p|\nabla c|^2 - 2\rho\int_\Omega p|\nabla\sqrt{v}|^2,
\end{aligned}$$

for any $\epsilon > 0$. Thus, we pick $\epsilon > 0$ small enough and integrate in the time variable to apply Lemma 5.2 which ends the proof. □

Lemma 5.8. *If w_0 satisfies either* (**H1**) *or* (**H2**) *then there exists $C > 0$ such that*

$$\sup_{t\ge 0}\|p(t)\|_{L^\infty(\Omega)} \le C.$$

Proof. We have that (see (3.7))

$$\begin{aligned}
&\frac{d}{dt}\int_\Omega z^2(c+1)^\alpha e^{\rho w} + (2 - nk_0\epsilon)\int_\Omega |\nabla z|^2 \\
&\qquad \le nk_0\left(1 + \epsilon + \frac{C(\Omega)^2}{4\epsilon}\int_\Omega |\Delta c|^2\right)\int_\Omega z^2 + n(k_1 - \lambda)\int_\Omega z^{2+\frac{2}{n}}.
\end{aligned}$$

At this point, we estimate $\int_\Omega z^{2+2/n}$. We distinguish between the cases $n = 2$ or $n > 2$. If $n = 2$ then $z := q$. By **(H1)** or **(H2)** we have

$$\sup_{t\ge 0}\|p(t)\ln p(t)\|_{L^1(\Omega)} \le C.$$

Hence,

$$\sup_{t\ge 0}\|z(t)\ln z(t)\|_{L^1(\Omega)} \le C.$$

Next, we apply (22) of Ref. 5 to obtain

$$\int_\Omega z^3 \le \epsilon\|z\|_{H^1(\Omega)}\|z\ln z\|_{L^1(\Omega)} + C(\epsilon)\|z\|_{L^1(\Omega)} \le \epsilon\|z\|_{H^1(\Omega)}C + C(\epsilon)\|z\|_{L^1(\Omega)}.$$

If $n > 2$ then by the Gagliardo–Nirenberg inequality there exists $k_1(n) < 2$ such that

$$\int_\Omega z^{2+2/n} \le C\|z\|_{H^1(\Omega)}^{k_1(n)}\|z\|_{L^1(\Omega)} \le \epsilon\|z\|_{H^1(\Omega)}^2 + C(\epsilon)\|z\|_{L^1(\Omega)}^{k_2(n)}.$$

Moreover, the Gagliardo–Nirenberg inequality also entails

$$\|z\|_{L^2(\Omega)} \leq \epsilon \|z\|_{H^1(\Omega)} + C(\epsilon)\|z\|_{L^1(\Omega)}.$$

We pick $\epsilon > 0$ sufficiently small in the previous inequalities and we substitute them into (3.7) to get

$$\frac{d}{dt}\int_\Omega z^2(c+1)^\alpha e^{\rho w} + \int_\Omega z^2(c+1)^\alpha e^{\rho w}$$
$$\leq C\int_\Omega |\Delta c|^2 \int_\Omega z^2 + C\left(\left(\int_\Omega z\right)^2 + \left(\int_\Omega z\right)^{k_2(n)}\right).$$

Let us note that if we define

$$y_m := \int_\Omega q^{2^m}(c+1)^\alpha e^{\rho w}$$

then from the previous inequality we obtain

$$\frac{d}{dt}y_m + y_m \leq c\int_\Omega |\Delta c|^2 y_m + C(y_{m-1}^2 + y_{m-1}^{k_2(m)}).$$

It is known that $\sup_{t\geq 0} y_0(t) < C$. As a consequence, if we pick $m = 1$ in the above inequality and we solve the differential inequality we get $\sup_{t\geq 0} y_1(t) < C$. Therefore, by a recursive argument we get that for any $m \in \mathbb{N}$ we have $\sup_{t\geq 0} y_m(t) < C$. As a consequence

$$\sup_{t\geq 0} \|p(t)\|_{L^n(\Omega)} \leq C$$

for any $n \in \mathbb{N}$. From here, we just need to argue as in Lemma 3.13 to conclude the lemma. □

Lemma 5.9. *If either* (**H1**) *or* (**H2**) *holds then*

$$\lim_{t\to+\infty} \|p - \bar{p}\|_{L^2(\Omega)} = 0.$$

Proof. We consider the function $k(t) \geq 0$ defined by

$$k(t) := \int_\Omega |p - \bar{p}|^2.$$

By Lemma 6.3 of Ref. 15 it is enough to prove that

$$\int_0^{+\infty} k(s)ds < +\infty, \quad \int_0^{+\infty} |k'(s)|ds < +\infty.$$

In order to estimate $\int_0^{+\infty} k(s)ds$ we just need to apply Lemmas 5.3, 5.6 and 5.7. In fact,

$$\int_0^{+\infty} k(t)dt \leq C\int_0^{+\infty}\int_\Omega \frac{|\nabla p|^2}{p} \leq C.$$

An estimate for $\int_0^{+\infty} |k'(s)|ds$ will demand an estimate of $\int_0^{+\infty}\int_\Omega p(p-1)^2$. To this end we argue as follows:

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\int_\Omega (p-1)^2 &= -\int_\Omega |\nabla p|^2 + \int_\Omega p\nabla w\cdot\nabla p + \int_\Omega \frac{p}{1+c}\nabla c\cdot\nabla p - \lambda\int_\Omega p(p-1)^2\\ &\le (\epsilon-1)\int_\Omega |\nabla p|^2 + C(\epsilon)\int_\Omega (p^2|\nabla w|^2 + p^2|\nabla c|^2) - \lambda\int_\Omega p(p-1)^2.\end{aligned}$$

From the above inequality and Lemma 5.8 we easily infer

$$\int_0^{+\infty}\int_\Omega p(p-1)^2 \le C.$$

On multiplying the p-equation by $(p-\bar{p})$ we obtain

$$\begin{aligned}\frac{1}{2}|k'(t)| &\le \int_\Omega |\nabla p|^2 + C\left(\int_\Omega p|\nabla w|^2 + \int_\Omega p|\nabla c|^2\right) + \lambda\int_\Omega p|p-1||p-\bar{p}|\\ &\le \int_\Omega |\nabla p|^2 + C\left(\int_\Omega p|\nabla w|^2 + \int_\Omega p|\nabla c|^2\right)\\ &\quad + \lambda\left(\int_\Omega p(p-1)^2 + C\int_\Omega (p-\bar{p})^2\right).\end{aligned}$$

Hence, if we integrate the above inequality on the time variable we get

$$\int_0^{+\infty} |k'(s)|ds < C$$

and the lemma follows. □

Lemma 5.10. *If either* (**H1**) *or* (**H2**) *holds then*

$$\lim_{t\to+\infty} \bar{p}(t)(\bar{p}(t)-1)^2 = 0.$$

Proof. We integrate the p-equation on the spatial variable Ω to obtain

$$\bar{p}_t = \lambda\left(\bar{p} - \frac{1}{|\Omega|}\int_\Omega p^2\right) = \lambda\left(\bar{p} - \frac{1}{|\Omega|}\int_\Omega (p-\bar{p})^2 - \bar{p}^2\right).$$

As in previous lemma we introduce $k(t)$ defined by

$$k(t) := \frac{1}{|\Omega|}\int_\Omega (p-\bar{p})^2$$

therefore,

$$\bar{p}_t = \lambda(\bar{p} - \bar{p}^2 - k(t)).$$

We multiply the above equation by $\bar{p}-1$ to get

$$\frac{d}{dt}(\bar{p}-1)^2 + \lambda\bar{p}(\bar{p}-1)^2 = -k(t)(\bar{p}-1).$$

Next, we integrate over $(0, \infty)$ the above equality to deduce

$$\lambda \int_0^\infty \bar{p}(\bar{p}-1)^2 \le (\bar{p}(0)-1)^2 + \sup_{t\ge 0} |\bar{p}-1| \int_0^\infty k(t)dt.$$

Hence, we obtain

$$\int_0^\infty \bar{p}(\bar{p}-1)^2 \le C. \tag{5.5}$$

On the other hand, we have

$$\frac{d}{dt}\bar{p}(\bar{p}-1)^2 = \bar{p}_t((\bar{p}-1)^2 + 2\bar{p}(\bar{p}-1)).$$

Since $0 \le \bar{p} \le C$ and $|\bar{p}_t| \le \lambda(|\bar{p}| + |\Omega|^{-1}\|p(t)\|_{L^2(\Omega)}) < C$ we deduce

$$\left|\frac{d}{dt}\bar{p}(\bar{p}-1)^2\right| < C. \tag{5.6}$$

By (5.5) and (5.6) we conclude that $\lim_{t\to+\infty} \bar{p}(t)(\bar{p}(t)-1)^2 = 0$ (see Lemma 5.1 in Ref. 8). □

Lemma 5.11. *If either* (**H1**) *or* (**H2**) *holds then*

$$\lim_{t\to\infty} |\bar{p}-1| = 0.$$

Proof. By Lemma 5.10 we have that either $\bar{p} \to 0$ or $\bar{p} \to 1$. We know that

$$\bar{p}_t = \lambda\left(\bar{p} - \bar{p}^2 - \frac{1}{|\Omega|}\int_\Omega (p-\bar{p})^2\right).$$

Moreover, Lemma 5.3 entails

$$\int_\Omega (p(t)-\bar{p})^2 \le C\bar{p}\int_\Omega \frac{|\nabla p|^2}{p}.$$

As a consequence, if we denote by

$$b(t) =: \frac{C}{|\Omega|}\int_\Omega \frac{|\nabla p|^2}{p},$$

we obtain

$$-\frac{1}{|\Omega|}\int_\Omega (p-\bar{p})^2 \ge -b(t)\bar{p}.$$

By the above estimate we have that

$$\bar{p}_t \ge \lambda(1-\bar{p}-b(t))\bar{p}.$$

Notice that, by Lemmas 5.6 and 5.7 we know that $\int_0^{+\infty} b(t) \le k_{11} < +\infty$. As a consequence, we obtain

$$\bar{p} \ge \bar{p}_0 e^{\lambda t - \lambda\int_0^t \bar{p}(s) - \lambda\int_0^t b(s)ds} \ge \bar{p}_0 e^{\lambda t - \lambda\int_0^t \bar{p}(s)} e^{-\lambda\int_0^\infty b(s)ds},$$

$$\bar{p}_0 e^{\lambda t - \lambda\int_0^t \bar{p}(s) - \lambda\int_0^\infty b(s)ds} \ge k_0 e^{\lambda t - \lambda\int_0^t \bar{p}(s)}.$$

In order to finish the proof we assume $\lim_{t\to+\infty} \bar{p}(t) = 0$ and we will arrive to a contradiction. Since $\lim_{t\to+\infty} \bar{p}(t) = 0$ then there exists $T_0 \ge 0$ such that $\bar{p} < \frac{\lambda}{2}$ for

$t > T_0$. Hence,

$$\int_0^t \bar{p} \leq \frac{\lambda}{2}(t - T_0) + k_1.$$

From the above inequality we deduce that

$$\bar{p} \geq k_0 e^{(\lambda/2)T_0 - k_1} e^{\frac{\lambda}{2}t}, \tag{5.7}$$

which contradicts the assumption for sufficiently large t and ends the proof. □

Theorem 5.1. *If either* (**H1**) *or* (**H2**) *holds, then*

$$\lim_{t\to\infty} \|w - 1\|_{L^\infty(\Omega)} = 0.$$

Proof. The proof is a consequence of previous lemmas. □

6. Numerical Simulations

In this section we perform some numerical experiments in order to illustrate the results of previous sections as well as exploring the behavior of the system for some small perturbations of the original model. In particular we will focus on the role of different boundary conditions for the TAF at the boundary of the tumor. It seems reasonable to think that TAF is continuously secreted at the boundary of the tumor. The simulations are done in a one-dimensional domain applying an explicit first-order finite difference scheme in time and a second-order finite difference scheme in the spatial variable on an uniform mesh. Since the motion of endothelial cells is driven mainly by chemotaxis and haptotaxis we assume

$$D \ll \rho, \quad D \ll \chi.$$

Moreover the diffusion coefficient for the endothelial cells is much smaller than the diffusion coefficient of the TAF. More precisely in Ref. 3 it is claimed that $D \sim 10^{-3}$. In all the simulations we consider the following parameters:

$$\Delta x = \frac{1}{70}, \quad \Delta t = 10^{-4}, \quad \alpha = 0.03, \quad \rho = 0.03, \quad \gamma = 1, \quad \mu = 1, \quad D = 0.001.$$

Here Δx represents the distance between two points of the spatial mesh and Δt is the time step. The initial conditions for the endothelial cells, TAF and fibronectin are

$$p_0(x) = e^{-100x^2}, \quad c_0(x) = 0.6e^{-100(x-1)^2}, \quad w_0(x) = 1 + 0.2\cos(\pi x).$$

In all the figures we plot the evolution of the system at different times $t = 1$, $t = 5$, $t = 10$ and $t = 40$.

In Fig. 1 simulations indicate that the endothelial cells expand throughout the domain, the TAF is decreasing to zero very fast and the fibronectin reach very slowly the value 1.

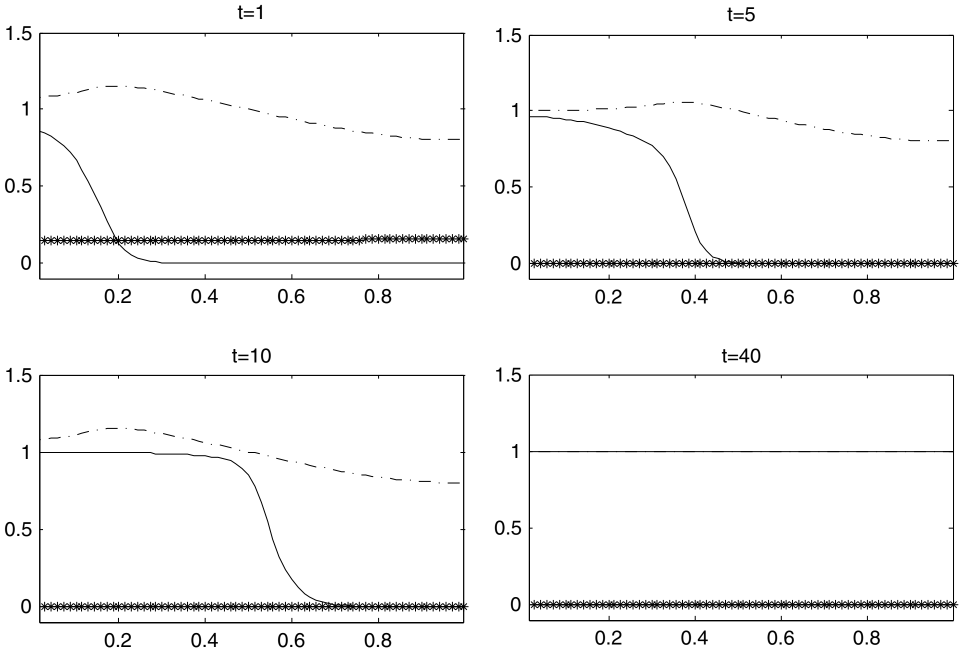

Fig. 1. Neumann boundary condition.

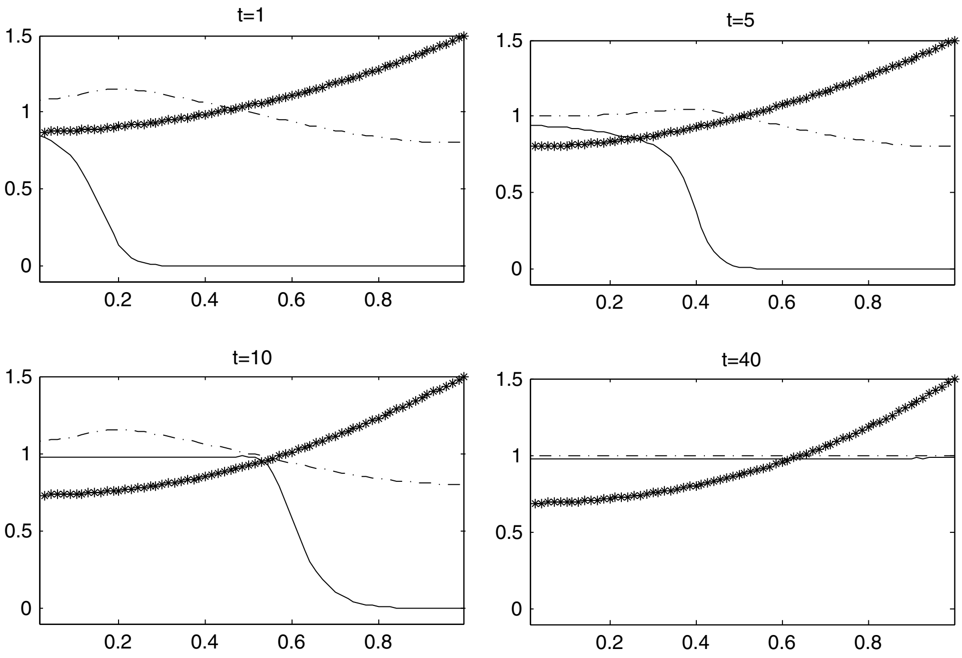

Fig. 2. Dirichlet boundary condition.

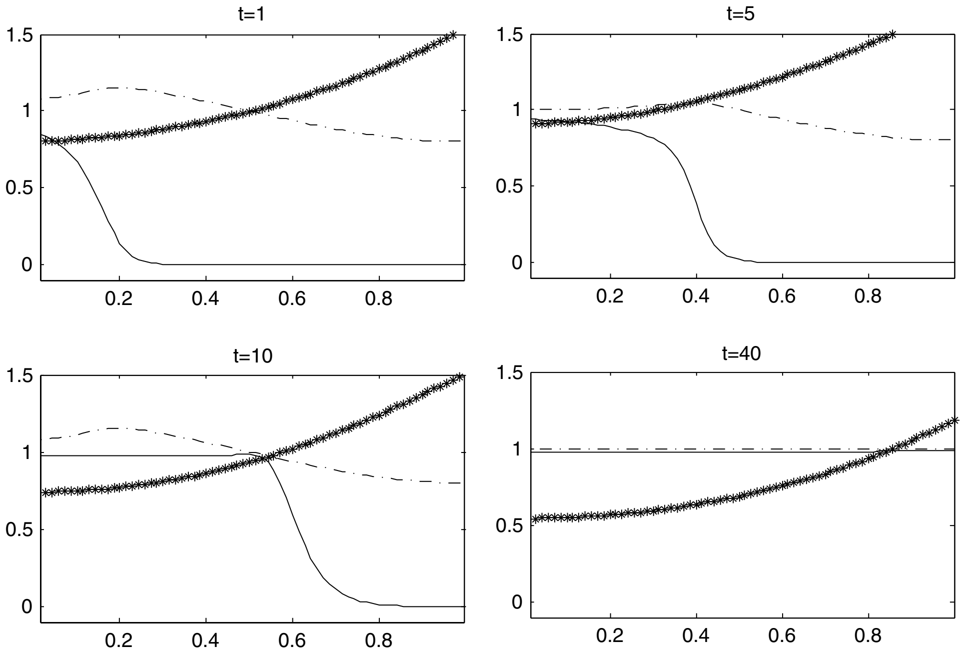

Fig. 3. Non-homogeneous Neumann boundary condition.

In Fig. 2 we have changed the boundary condition for c at the tumor boundary $x = 1$ and instead of Neumann we consider the Dirichlet boundary condition $c(1) = 1.5$. Here we observe that the motion of the endothelial cells is faster because a higher gradient of TAF produced by the boundary conditions. Moreover, simulations show that the TAF is monotone increasing as the distance to the tumor decreases. The behavior of the fibronectin in that case is similar to the case with Neumann boundary condition. It should be noted that endothelial cells remains non-homogeneous and they do not reach the value 1 but remains close to. In fact, the minimum is attained at $x = 0$ and the maximum at $x = 1$. It seems that there is a loss of endothelial cells because the flux at $x = 1$ caused by the gradient of TAF.

In Fig. 3 we consider the non-homogeneous boundary condition $\frac{\partial c}{\partial n}(1) = 1.5$. The behavior of the system is similar to the case of Dirichlet boundary condition.

7. Discussion

In this paper we have presented a mathematical model of angiogenesis that is a small variation of the continuous model proposed in Ref. 3. More precisely we have considered the random motility, the decay of the TAF and the birth and death terms associated with the endothelial cells. The problem is a system of three equations: two parabolic equations with chemotactic terms to model endothelial cells and tumor angiogenesis factors coupled to an ordinary differential equation which describes the evolution of the fibronectin concentration. The original problem has a large number of parameters that have been reduced after renormalization. Additionally in order to simplify the analysis we have assumed, for the analytical part of the paper, that the diffusion coefficient in (1.1) is given by $D = 1$, the computations and results can easily be adapted for the general case $D > 0$. The choice of $D = 1$ was done exclusively for the sake of clarity.

In Sec. 3 we have proved that the solutions of the problem are global and regular in dimension 2 independently of the value of the parameters. Moreover, under additional hypothesis on the initial fibronectin concentration (**H1**) or (**H2**), we prove that the endothelial cells expand throughout the domain and distributes in an homogeneous way on the spatial domain. Additionally we have proved that the TAF goes to zero and the fibronectin goes to the constant value 1 when the time is large.

In Sec. 6 we have performed a series of numerical investigations in a one-dimensional domain with the purpose of validate the analytical results of previous sections as well as explore numerically the behavior of the system for different boundary conditions of the TAF at the tumor boundary. Numerical simulations suggest that the results in Sec. 5 remain valid even when assumptions (**H1**) and (**H2**) are not satisfied. We explore different boundary conditions for the TAF based on the idea that TAF is continuously secreted at the boundary of the tumor. We propose, as it is suggested in Ref. 18, that the boundary condition at the tumor boundary for the TAF depends on the nutrients concentration at the tumor boundary. More precisely, low nutrients imply high rate of production of TAF and the other way round. Therefore, if we denote by r the amount of nutrients at $x = 1$ we should have

$$\frac{\partial c}{\partial n}(1) = \gamma(r),$$

where γ is a decreasing function on r which is zero for $r \geq r^* > 0$. Since the nutrients are provided mainly by the blood vessels we could argue that an efficient vasculature it is asymptotically equivalent to the Neumann boundary because the nutrients available at the boundary will be over the threshold value r^* whereas if the blood vessels are not efficient we should have TAF produced continuously at the tumor boundary. Therefore we may argue that non-homogeneous Neumann boundary condition or Dirichlet boundary condition refers to the case of poor vasculature and the Neumann boundary refers to the case of efficient vasculature. However, as it is pointed out in Ref. 22 in tumor angiogenesis the pattern of blood vessels are abnormal and there are deficiencies in oxygenation. As a consequence, it seems that non-homogeneous Neumann boundary conditions or Dirichlet boundary conditions at the tumor boundary are more realistic for the tumor angiogenesis. Nevertheless we have explored the Neumann boundary condition for a deeper understanding of the model proposed in Ref. 3.

Numerical simulations show that in the case of non-homogeneous boundary condition as well as Dirichlet boundary condition at the tumor boundary the motion of the endothelial cells is faster than in the case of Neumann boundary condition. Moreover, after some time the endothelial cells reach a non-homogeneous steady state, i.e. the endothelial cells distribute in a non-homogeneous way in the domain.

Our estimates work only for one- and two-dimensional domains and clearly the Sobolev embeddings used in Secs. 3 and 4 do not allow us to extend the results to the three-dimensional case. We believe that the results should be also true for three-dimensional domains (without any restriction on the parameters or the size for the initial data) however the analytical proof will demand new ideas.

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