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MATHEMATICAL ANALYSIS AND NUMERICAL SIMULATIONS FOR THE CANCER TISSUE INVASION MODEL

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Abstract. Cancer cell invasion is one of the most important stages of metastasis. In this paper, the local existence and uniqueness of the cancer cell invasion model is proved using an iterative procedure. Moreover the numerical simulations are performed using a combination of a nonstandard finite difference scheme and backward and forward Euler methods. It is seen that the results agree well with the expected behaviour of the invasion.

1. Introduction

Cancer is a multi-step disease which starts with the abnormal proliferation of a single cell due to a DNA mutation. The successive rounds of mutation of these abnormal cells result with a mass which is called a tumor. The tumors are categorized in two categories: benign and malignant. Both types grow in an uncontrolled way. But unlike the benign tumors, the malignant tumors invade the surrounding tissue and reach to the other parts of the body by blood or lymph system and form a secondary tumor there. This process is called metastasis. The reason of cancer deaths is often the metastasis.

The cancer cells have two kinds of directed movements: chemotaxis and haptotaxis. Chemotaxis is the movement of the cells from the direction of the higher concentration of a substance (chemoattractant) to the direction where the concentration is lower. On the other hand, the cells have to adhere to extracellular matrix (ECM) fibres in order to move and their migration is directed from the regions having higher concentration of an existing adhesive molecule on the ECM to the regions with lower concentration. This type of movement is called haptotaxis. Moreover, the contact with the surrounding tissue stimulates the production of the proteolytic matrix degrading enzymes(MDEs) for the degradation of the tissue fibres.

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The mathematical modelling of cancer invasion, their analysis and simulations provide an understanding on the behavior of the modelling systems and the studies in this area gain importance in recent years. The models can be grouped as the ordinary differential equation (ODE) models, partial differential equation (PDE) models and stochastic models. The ODE models are usually used for the cell migration controlling models starting at the cell level [1, 2] and for the therapy approach models [3, 4]. The disadvantage of the ODE models is that they consider only the temporal change and do not give information about the spatial effects. Since cancer invasion and metastasis have spatial dependence, the models considering the variations in space are more realistic for this phenomena and are described by using the PDEs. In these PDE models the different factors on cancer invasion are analyzed. For instance, the effect of environmental pH has been analyzed initially by Gatenby et. al. [5] and the well posedness of an extended model, which has been developed to include the crowding effects in the growth of normal cells, has been shown in [6]. Then the model has been extended to include the intracellular dynamics and it has been shown that the new multiscale model has a global unique solution [7]. Another approach analyzing the effect of chemotaxis and haptotaxis has been made in [8]. On the other hand, in some cases models may contain stochastic effects like the ones in the studies [9, 10, 11] considering the stochasticity in pH dynamics.

In this study we consider the haptotaxis-chemotaxis model [8]. Because of the highly nonlinear character of the model system, the analysis of the system, finding the analytical solution or the numerical solution are not easy tasks. In this paper, using an iterative procedure [6] the local existence of a unique weak solution is shown. Moreover, the numerical simulations are performed using a finite difference scheme which includes a nonstandard FDM and backward and forward Euler methods. The results of the simulations show the expected behavior of the model system.

2. Mathematical Model

In this section, the mathematical model given in [8] is considered. The model describes the interaction between the cancer cells (c), the normal cells(n) and the MDE (m) and is given by

$$\begin{aligned}
\frac{\partial c}{\partial t} &= \underbrace{D_c \nabla^2 c}_{\text{dispersion}} - \underbrace{\nabla \cdot (\chi_c c \nabla m)}_{\text{chemotaxis}} - \underbrace{\nabla \cdot (\xi_c c \nabla n)}_{\text{haptotaxis}} + \underbrace{\mu_1 c \left(1 - \frac{c}{K_c} - \frac{n}{K_n}\right)}_{\text{proliferation}}, \\
\frac{\partial n}{\partial t} &= \underbrace{-\delta m n}_{\text{degredation}} + \underbrace{\mu_2 n \left(1 - \frac{c}{K_c} - \frac{n}{K_n}\right)}_{\text{re-establishment}}, \qquad (2.1) \\
\frac{\partial m}{\partial t} &= \underbrace{D_m \nabla^2 m}_{\text{dispersion}} + \underbrace{\alpha c}_{\text{production}} - \underbrace{\beta m}_{\text{decay}}
\end{aligned}$$

with the parameters and their explanations given in Table 1.

Parameter	Explanation	Parameter	Explanation
D_c	Diffusion coefficient for cancer cells	K_c	Carrying capacity for cancer cells
D_m	Diffusion coefficient for MDE	K_n	Carrying capacity for normal cells
χ_c	Chemotaxis coefficient	δ	Degradation rate for normal cells
ξ_c	Haptotaxis coefficient	α	Production rate for MDE
μ_1	Proliferation rate for cancer cells	β	Decay rate for MDE
μ_2	Re-establisment rate for normal cells		

TABLE 1. Problem Parameters

2.1. **Boundary and Initial Conditions.** According to the in vitro experimental protocol the invasion takes place in an isolated system and this gives the no flux boundary conditions for the cancer cells and MDEs across the boundary of the domain $\Omega \subseteq \mathbb{R}^d, (d = 1, 2, 3)$ and thus the boundary conditions (BCs) are given by

$$\frac{\partial m}{\partial \upsilon} = \frac{\partial c}{\partial \upsilon} = 0, \quad on \quad \partial\Omega \tag{2.2}$$

where υ denotes the outward unit normal to the boundary $\partial\Omega$ of the smooth enough domain Ω. The initial conditions (ICs) are given by

$$\begin{array}{rcl} c(0,x) & = & c_0(x), \\ n(0,x) & = & n_0(x), \qquad x \in \Omega \\ m(0,x) & = & m_0(x), \end{array} \tag{2.3}$$

where c_0, n_0 and m_0 are nonnegative functions and c_0 and m_0 satisfy the boundary conditions(2.2).

3. MATHEMATICAL ANALYSIS OF THE MODEL

In this section the proof for the existence and uniqueness of the solutions for the system (2.1) with the boundary and initial conditions (2.2) and (2.3) is given. To this end, an iterative technique [6] is used for the proof. To this end, the function spaces

$$X := L^\infty\left(0, T; H^1(\Omega)\right), \tag{3.1}$$

$$Y := \left\{m \in L^2\left(0, T; H^2(\Omega)\right), m_t \in L^2\left(0, T; H^2(\Omega)\right)\right\}, \tag{3.2}$$

$$Z := L^\infty(0, T; L^2(\Omega)), \tag{3.3}$$

are considered. Here $\Omega \subseteq \mathbb{R}^d, (d = 1, 2, 3)$ is an open bounded domain.

Definition 1. *The weak solution of the initial and boundary value problem* (2.1)-(2.3) *is defined as the triple* $(m, n, c) \in X \times Y \times Z$ *satisfying the following three equations:*

$$\int_\Omega \mu_1 c \left(1 - \frac{c}{K_c} - \frac{n}{K_n}\right) \phi dx = \int_\Omega \frac{\partial c}{\partial t} \phi dx + \int_\Omega D_c \nabla c \nabla \phi dx - \chi_c \int_\Omega \nabla m \nabla \phi c dx - \xi_c \int_\Omega \nabla n \nabla \phi c dx, \tag{3.4}$$

$$\int_\Omega \mu_2 n \left(1 - \frac{c}{K_c} - \frac{n}{K_n}\right) \phi dx = \int_\Omega \frac{\partial n}{\partial t} \phi dx + \int_\Omega \delta m n \phi dx, \tag{3.5}$$

$$\int_\Omega \alpha c \phi dx = \int_\Omega \frac{\partial m}{\partial t} \phi dx + \int_\Omega D_m \nabla m \nabla \phi dx + \int_\Omega \beta m \phi dx, \tag{3.6}$$

for every $\phi \in H^1(\Omega)$.

Definition 2. *For* $k \in \mathbb{N}$ *and* $(m^k, c^k) \in (X \times X) \cap (Y \times Y)$ *and* $n^k \in Z$, *the sequence* (m^k, c^k, n^k) *is defined as follows:*

For $k = 0$, $(m^0, c^0) \in (X \times X) \cap (Y \times Y)$ *and* $n^0 \in Z$ *is defined as the weak solution of the homogeneous system*

$$\frac{\partial m^0}{\partial t} - D_m \nabla^2 m^0 + \beta m^0 = 0, \tag{3.7}$$

$$\frac{\partial n^0}{\partial t} + \delta m^0 n^0 = 0, \tag{3.8}$$

$$\frac{\partial c^0}{\partial t} - D_c \nabla^2 c^0 + \nabla \cdot (\chi_c c^0 \nabla m^0) + \nabla \cdot (\xi_c c^0 \nabla n^0) = 0, \tag{3.9}$$

and for $k > 0$, $(m^k, c^k) \in (X \times X) \cap (Y \times Y)$ *and* $n^k \in Z$ *is defined as the weak solution of*

$$\frac{\partial m^{k+1}}{\partial t} - D_m \nabla^2 m^{k+1} + \beta m^{k+1} = \alpha c^k, \tag{3.10}$$

$$\frac{\partial n^{k+1}}{\partial t} + \delta m^{k+1} n^{k+1} = \mu_2 n^k \left(1 - \frac{c^k}{K_c} - \frac{n^k}{K_n}\right), \tag{3.11}$$

$$\frac{\partial c^{k+1}}{\partial t} - D_c \nabla^2 c^{k+1} + \nabla \cdot (\chi_c c^{k+1} \nabla m^{k+1}) + \nabla \cdot (\xi_c c^{k+1} \nabla n^{k+1}) = \mu_1 n^k \left(1 - \frac{c^k}{K_c} - \frac{n^k}{K_n}\right). \tag{3.12}$$

Lemma 1. *Assume that*

$$m_0 \in H^1(\Omega) \cap C(\Omega),\ n_0 \in L^\infty(\Omega) \cap H^1(\Omega),\ c_0 \in H^1(\Omega) \tag{3.13}$$

$$m_0 \geq C_H > 0,\ 0 < n_0 < \frac{K_n}{2},\ 0 < c_0 < K_c \tag{3.14}$$

for $T > 0$. Then

(i) the systems (3.7)-(3.9) *and* (3.10)-(3.12) *with the BCs* (2.2) *and ICs* (2.3) *have a unique weak solution with*

$$n^k, \frac{\partial n^k}{\partial t} \in L^\infty((0,T] \times \Omega) \tag{3.15}$$

$$m^k, c^k \in L^2(0,T;H^2(\Omega)) \cap L^\infty(0,T;H^1(\Omega)) \tag{3.16}$$

$$\frac{\partial m^k}{\partial t}, \frac{\partial c^k}{\partial t} \in L^2(0,T;L^2(\Omega)) \tag{3.17}$$

(ii)The functions m^k, c^k, n^k are positive and they satisfy

$$m^k(t,x) \geq C_H e^{-\beta t}, n^k(t,x) \leq \frac{K_v}{2} \text{ and } c^k(t,x) \leq K_c \tag{3.18}$$

for a.e. $x \in \Omega$ and $t \in [0,T]$

(iii) The functions m^k, c^k, n^k satisfy

$$\left\|m^k\right\|_X + \left\|m^k\right\|_{L^2(0,T;H^2(\Omega))} \leq C(\Omega,t)(\|c_0\|_{H^1(\Omega)} + \|m_0\|_{H^1(\Omega)}) \tag{3.19}$$

$$\left\|n^k\right\|_X^2 \leq C(\Omega,t)\,\|n_0\|_{H^1(\Omega)}^2 \tag{3.20}$$

$$\left\|c^k\right\|_X + \left\|c^k\right\|_{L^2(0,T;H^2(\Omega))} \leq 2C(\Omega,t)\,\|c_0\|_{H^1(\Omega)} \tag{3.21}$$

with the appropriate embedding constants $C(\Omega,T)$.

Remark 1. *i) One can conclude from* (3.15) *that*

$$n^k \in L^\infty((0,T];L^2(\Omega)) \tag{3.22}$$

ii) T is going to be defined as

$$T := \prod_{i=1}^{6} T_i \tag{3.23}$$

in the proof.

Proof. The proof will be done by using induction.

Basis Step (k=0): The proof is done for each of the equations (3.7)-(3.12) separately.

a) The substitution $m^0 = \tilde{m}e^{-\beta t}$ transforms equation (3.7) to the heat equation:

$$\frac{\partial \tilde{m}}{\partial t} - D_m \nabla^2 \tilde{m} = 0 \tag{3.24}$$

and by the linear PDE theory [12] with the hypothesis $m_0 \in H^1(\Omega)$ we conclude that equation (3.7) has a unique solution such that

$$\begin{aligned} m^0 &\in L^2(0,T;H^2(\Omega)) \cap L^\infty(0,T;H^1(\Omega)) \\ m_t^0 &\in L^2(0,T;L^2(\Omega)) \end{aligned}$$

satisfying

$$\left\|m^0\right\|_X + \left\|m^0\right\|_{L^2(0,T;H^2(\Omega))} \leq C(\Omega,T)\left\|m^0\right\|_{H^1(\Omega)}$$

b) Equation (3.8) is a linear ODE and has a positive solution depending on $m^0(t,x)$ which is given by

$$n^0(t,x) = n_0 e^{-\int_0^t \delta m^0(s,x)ds} > 0 \tag{3.25}$$

and since

$$\left\|n^0\right\|^2_{L^\infty(0,T;H^1(\Omega))} = \left\|n_0 e^{-\int_0^t \delta m^0(s,x)ds}\right\|^2_{L^\infty(0,T;H^1(\Omega))} \leq \|n_0\|^2_{H^1(\Omega)} \tag{3.26}$$

the inequality (3.20) is satisfied for $n=0$. Moreover, for $t \geq \eta > 0$

$$\left\|n^0\right\|_{L^\infty((0,T]\times\Omega)} \overset{(3.25)}{=} \left\|n_0 e^{-\int_0^t \delta m^0(s,x)ds}\right\|_{L^\infty((0,T]\times\Omega)} \leq \|n_0\|_{L^\infty(\Omega)} < \infty \tag{3.27}$$

is obtained. It is known that as $t \to 0$ solution of equation (3.24) satisfies [12]

$$\lim_{(t,x)\to(0,x^0)} \tilde{m}^0(t,x)\, e^{D_m t} = m_0\left(x^0\right) \tag{3.28}$$

and this gives

$$\lim_{(t,x)\to(0,x^0)} m^0(t,x) = \lim_{(t,x)\to(0,x^0)} \tilde{m}^0(t,x)\, e^{D_m t} = m_0\left(x^0\right) \tag{3.29}$$

which shows the inequalities in (3.14) are satisfied.

c) To complete the proofs for (3.16), (3.17) and (3.21) one starts with equation (3.9) and the proof procedure depends on Theorem 7.1.5 in [12]. To apply the Galerkin Method, the function

$$c_n(t) := \sum_{i=1}^{n} d_n^i(t) w_i(x) \tag{3.30}$$

and the symmetric bilinear form

$$A[c_n,c_n] = \int_\Omega D_c(\nabla c_n)^2 dx \tag{3.31}$$

are defined with $\{w_i(x)\}_{i=1}^\infty$ being the orthogonal bases for $H^1(\Omega)$ and orthonormal bases for $L^2(\Omega)$. If the ideas in [12] are used with $a(t,x) = D_c$ then one has

$$\left\|\frac{\partial c_n^0}{\partial t}\right\|^2_{L^2(\Omega)} + \frac{d}{dt}\left(\frac{1}{2}A[c_n^0,c_n^0]\right) \leq \frac{C}{4\epsilon}\left\|c_n^0\right\|^2_{H_0^1(\Omega)} + \epsilon\left\|\frac{\partial c_n^0}{\partial t}\right\|^2_{L^2(\Omega)}$$

Therefore with $c_0 \in H^1(\Omega)$ the unique weak solution of (3.9) is obtained and it satisfies the following properties:

$$\begin{aligned} c^0 \in L^2(0,T;H^2(\Omega)) &\cap& L^\infty(0,T;H^1(\Omega)), \\ \frac{\partial c^0}{\partial t} &\in& L^2\left(0,T;L^2\left(\Omega\right)\right) \\ \left\|c^0\right\|_X + \left\|c^0\right\|_{L^2(0,T;H^2(\Omega))} &\leq& C(\Omega,T)\left\|c_0\right\|_{H^1(\Omega)} \end{aligned} \tag{3.32}$$

Moreover, since $c_0 > 0$ the weak maximum principle leads to $c^0(t,x) > 0$, i.e., the positivity of $c^0(t,x)$.

Induction Hypothesis Assume that for an arbitrary $k \in \mathbb{N}$ the claims in Lemma 1 are satisfied.

Induction Step In this step, the proof is done separately for each of the three equations given in (3.10-3.12) For the appropriate embedding constant $c_1 := c_1(\Omega,T)$ [13] together with the induction hypothesis it is found that

$$\int_0^T \left\|c^k\right\|^2_{L^2(\Omega)} dt \leq c_1 \int_0^T \left\|c^k\right\|^2_{H^1(\Omega)} dt \tag{3.33}$$

$$\leq 4c_1 C^2(\Omega,T)T\left\|c_0\right\|^2_{H^1(\Omega)} < \infty \tag{3.34}$$

and thus it is found that $c^k \in L^2(0,T;L^2(\Omega))$. Together with the linear parabolic differential equation theory this leads to the existence of the unique weak solution of the initial and boundary value problem (2.2),(2.3) and (3.10) and this solution satisfies

$$m^{k+1} \in L^2(0,T;H^2(\Omega)) \cap L^\infty(0,T;H^1(\Omega)) \tag{3.35}$$

$$\frac{\partial m^{k+1}}{\partial t} \in L^2(0,T;L^2(\Omega))$$

and

$$\begin{aligned} \left\|m^{k+1}\right\|_X + \left\|m^{k+1}\right\|_{L^2(0,T;H^2(\Omega))} &\leq C_1(\Omega,T)\Big(2\alpha C(\Omega,T)\sqrt{c_1 T}\left\|c_0\right\|_{H^1(\Omega)} \\ &\quad + \left\|m_0\right\|_{H^1(\Omega)}\Big) \\ &\leq C(\Omega,T)\Big(\left\|c_0\right\|_{H^1(\Omega)} + \left\|m_0\right\|_{H^1(\Omega)}\Big) \end{aligned} \tag{3.36}$$

for $C(\Omega,T) = \max\left\{C_1(\Omega,T), C_1(\Omega,T)2\alpha C(\Omega,T)\sqrt{c_1 T}\right\}$.

In order to determine the lower bound for m^{k+1} an auxiliary function

$$\varphi^{k+1}(t,x) := m^{k+1}(t,x) - C_H e^{-\beta t} \tag{3.37}$$

is defined and by using (3.10) it can be easily seen that

$$\left\langle \varphi_t^{k+1}(t), \phi \right\rangle + D_m \int_\Omega \nabla\varphi^{k+1}\nabla\phi dx + \beta\int_\Omega \varphi^{k+1}\phi dx = \left\langle \alpha c^k, \phi \right\rangle \tag{3.38}$$

is satisfied. In equation (3.38) $\langle , \rangle$ denotes the L_2 inner product. For all nonnegative $\phi \in H^1(\Omega)$ the right hand side of (3.37) is positive. On the other hand, by definition $\phi^{k+1}(0,x) \geq 0$. Therefore by the weak maximum principle, it is found that $\phi(0,x) \geq 0$ and this results with $m^{k+1}(t,x) \geq C_H e^{-\beta t}$.

Solution of the nonhomogeneous linear differential equation (3.11) is given by

$$n^{k+1}(t,x) = e^{-\gamma_1 t}\left(n_0(x) + \int_0^t \gamma_2(s,x)e^{\gamma_1(s,x)}ds\right) \tag{3.39}$$

where

$$\gamma_1(t,x) = \int_0^t \delta m^{n+1}(v,x)dv$$

and

$$\gamma_2(s,x) = \mu_2 n^k(s,x)\left(1 - \frac{n^k(s,x)}{K_n} - \frac{c^k(s,x)}{K_c}\right)$$

The first claim in (3.15) is trivial by the induction hypothesis. To prove the second claim on the time derivative, Equation (3.11) is made use of which gives the inequality

$$\begin{aligned}\left\|\frac{\partial n^{k+1}}{\partial t}\right\|_{L^\infty((0,T]\times\Omega)} \leq\ & \mu_2\left\|n^k\right\|_{L^\infty((0,T]\times\Omega)}\left\|1 - \frac{n^k}{K_n} - \frac{c^n}{K_c}\right\|_{L^\infty((0,T]\times\Omega)} \\ & +\delta\left\|n^{k+1}\right\|_{L^\infty((0,T]\times\Omega)}\left\|m^{k+1}\right\|_{L^\infty((0,T]\times\Omega)}.\end{aligned} \tag{3.40}$$

The induction hypothesis, the smoothness of the initial data and the properties of the heat equation lead to the result that the right hand side of the equation (3.40) is finite.

In order to show that n^{k+1} is bounded by the half of the carrying capacity, the induction hypothesis and the inequality $m^{k+1}(t,x) \geq C_H$ for $x \in \Omega$, $t \in [0,T]$ with C_H positive are used:

$$\begin{aligned} n^{k+1}(t,x) &\leq \frac{K_n}{2}e^{-\gamma_1(t,x)} + \int_0^t \gamma_2(s,x)e^{-(\gamma_1(t,x)-\gamma_1(s,x))}ds \\ &\leq \frac{K_n}{2}e^{-\gamma_1(t,x)} + \mu_2\frac{K_n}{2}\int_0^t e^{-(\gamma_1(t,x)-\gamma_1(s,x))}ds \\ &\leq \frac{K_n}{2}e^{-\delta\tilde{C}_H t} + \mu_2\frac{K_n}{2}\frac{1}{\delta\tilde{C}_H}\left(1 - e^{-\delta\tilde{C}_H t}\right) \\ &\leq \frac{v_c}{2}\left(\left(1 - \frac{\mu_2}{\delta\tilde{C}_H}\right)e^{-\delta\tilde{C}_H t} + \frac{\mu_2}{\delta\tilde{C}_H}\right) \leq \frac{K_n}{2}\end{aligned}$$

and this gives the positivity of n^{k+1} together with (3.39).

Next, inequality (3.20) is obtained by using equation (3.39) and the induction hypothesis:

$$
\begin{aligned}
\left\|n^{k+1}(t)\right\|^2_{H^1(\Omega)} &= \left\| e^{-\gamma_1(t)} n_0 + e^{-\gamma_1(t)} \int_0^t \gamma_2 e^{\alpha(s)} ds \right\|^2_{H^1(\Omega)} \\
&\leq \left\| n_0 + \int_0^t \left(\mu_2 n^k(s) - \mu_2 \frac{(n^k(s))^2}{K_n} - \mu_2 \frac{n^k(s) - c^k(s)}{K_c} \right) \right\|^2_{H^1(\Omega)} \\
&\leq 2\left\|n_0\right\|^2_{H^1(\Omega)} + 2\mu_2^2 \left\| \int_0^t n^k(s) \left(1 - \frac{n^k(s)}{K_n} - \frac{c^k(s)}{K_c}\right) ds \right\|^2_{H^1(\Omega)} \\
&\leq 2\left\|n_0\right\|^2_{H^1(\Omega)} + 2\mu_2^2 \left\| \int_0^t n^k(s) \left(1 - \frac{n^k(s)}{K_n}\right) ds \right\|^2_{H^1(\Omega)} \\
&\leq 2\left\|n_0\right\|^2_{H^1(\Omega)} + 4\mu_2^2 \left(\left\| \int_0^t n^k(s) ds \right\|^2_{H^1(\Omega)} + \frac{1}{K_n^2} \left\| \int_0^t (n^k(s))^2 ds \right\|^2_{H^1(\Omega)} \right) \\
&\leq 2\left\|n_0\right\|^2_{H^1(\Omega)} \left[2 + 4\mu_2^2 C(\Omega, T) T^2\right] \leq \Theta(\Omega, T) \left\|n_0\right\|^2_{H^1(\Omega)}
\end{aligned}
$$

In order to complete the proof for (3.15) and (3.17) the term on the right hand side of Equation (3.12) is considered. By using the induction hypothesis and the property of the initial condition $c_0(x) \in H^1(\Omega)$ it can be bounded as

$$
\begin{aligned}
\int_0^T \left\| c^k \left(1 - \frac{c^k}{K_c} - \frac{n^k}{K_n}\right) \right\|^2_{L^2(\Omega)} dt &\leq \int_0^T \left\| c^k \left(1 - \frac{c^k}{K_c}\right) \right\|^2_{L^2(\Omega)} dt \\
&\leq 2 \int_0^T \left\|c^k\right\|^2_{L^2(\Omega)} dt + 2 \int_0^T \left\| \frac{\left(c^k\right)^2}{K_c} \right\|^2_{L^2(\Omega)} dt \\
&\leq 2c_1^2 \int_0^T \left\|c^k\right\|^2_{H^1(\Omega)} dt + 2\frac{c_2^4}{K_c^2} \int_0^T \left\|c^k\right\|^4_{H^1(\Omega)} dt \\
&\leq 8c_1^2 C^2(\Omega, T) \left\|c_0\right\|^2_{H^1(\Omega)} T_1 T_2 \\
&\qquad + 32 \frac{c_2^4}{K_c^2} C^4(\Omega, T) \left\|c_0\right\|^4_{H^1(\Omega)} T_1 T_2 < \infty
\end{aligned}
$$

with an appropriate embedding constant $c_2 := c_2(\Omega, T)$. Therefore $c\left(1 - \frac{c^k}{K_c} - -\frac{n^k}{K_n}\right) \in L^2(0,T;L^2(\Omega))$ and thus by Theorem 7.1.5 in [12] one obtains the unique weak solution with the properties

$$\begin{aligned} c^{k+1} &\in L^2(0,T;H^2(\Omega)) \cap L^\infty(0,T;H^1(\Omega)) \\ \frac{\partial c^{k+1}}{\partial t} &\in L^2(0,T;L^2(\Omega)). \end{aligned}$$

Choosing $\max\left\{T_1 C^2(\Omega,T), T_1 C^4(\Omega,T)\right\} \leq 1$ and

$$T_2 := \min\left\{\frac{1}{2}, \frac{1}{16\mu_2^2 c_1^2 \|k_0\|}, \frac{1}{64\mu_2^2 c_1^4 \|c_0\|^2}\right\}$$

gives

$$\int_0^T \left\|\mu_2 c^k \left(1 - \frac{c^k}{K_c} - \frac{n^k}{K_n}\right)\right\|_{L^2(\Omega)}^2 dt \leq \|c_0\|_{H^1(\Omega)}$$

thus one has

$$\left\|c^k\right\|_X + \left\|c^k\right\|_{L^2(0,T;H^2(\Omega))} \leq 2C(\Omega,T)\left(\|c_0\|_{H^1(\Omega)}\right).$$

In order to prove that c^{k+1} is bounded above by the half of the carrying capacity the auxiliary function

$$\sigma^k := \frac{\eta t + K_c}{2} - c^k(t,x) \tag{3.41}$$

is defined and induction is used. The proof for the basis step; i.e. for $k = 0$; is identical with the proof in the induction step.

Induction Hypothesis: Assume that c^k is bounded above by the half of the carrying capacity for an arbitrary $k \in \mathbb{N}$.

Induction Step: If one uses the auxiliary function given in (3.41) with the equation (3.12) then

$$\begin{aligned} \frac{\partial \sigma^{k+1}}{\partial t} - D_c \nabla^2 \sigma^{k+1} - \nabla\left(\chi_c c^k \nabla m^{k+1}\right) - \nabla\left(\xi_c c^k \nabla n^{k+1}\right) \\ = \frac{\eta}{2} - \mu_1 c^k \left(1 - \frac{c^k}{K_c} - \frac{n^k}{K_n}\right) \end{aligned} \tag{3.42}$$

is obtained. By using the induction hypothesis one has

$$c^k\left(1 - \frac{c^k}{K_c} - \frac{n^k}{K_n}\right) \leq \frac{K_c}{2}$$

and thus the inequality

$$\frac{\eta}{2} - \mu_1 c^k\left(1 - \frac{c^k}{K_c} - \frac{n^k}{K_n}\right) \geq \mu_1\left(\frac{K_c}{2} - \left(1 - \frac{c^k}{K_c} - \frac{n^k}{K_n}\right)\right) \geq 0$$

is obtained for the right hand side of the inequality in (3.42) where

$$\eta = \frac{K_c}{T_3} \qquad \text{and} \qquad T_3 \leq \frac{1}{\mu_1}.$$

Since $c^k < K_c$ and $\sigma^{n+1}(0,x) \geq 0$ by its definition, the weak maximum principle for $T \leq \dfrac{1}{\mu_1}$ leads to

$$\sigma^k := \frac{\eta t + K_c}{2} - c^k(t,x) = \sigma^{k+1} \geq 0$$

which gives the positivity of c^{k+1} with the positivity of the initial condition. □

Theorem 1. *(The Local Existence of the Solution) There exists a unique weak solution* $(m,c) \in (X \times X) \cap (Y \times Y)$ *and* $n \in Z$ *of the boundary and initial value problem (IBVP)* (2.1)-(2.3) *for* $T > 0$ *satisfying the conditions* (3.13) *and* (3.14)*.*

Proof. To prove the existence of the unique weak solution of the IBVP (2.1) - (2.3), the sequence $(n^k, c^k, m^k)_{k\in\mathbb{Z}^+}$ is going to be shown to be a Cauchy sequence, which leads to the convergence to the limit function (n,c,m) with the completeness of the function spaces we work on. Throughout the proof, the results obtained in Lemma 1 are going to be used.

For the ease of notation, we define the differences

$$\begin{array}{rcl c rcl} m^{k+1} - m^k &=& M_1 & \qquad & m^k - m^{k-1} &=& M_2 \\ c^{k+1} - c^k &=& C_1 & & c^k - c^{k-1} &=& C_2 \\ n^{k+1} - n^k &=& N_1 & & n^k - n^{k-1} &=& N_2 \end{array} \tag{3.43}$$

Let $k \in \mathbb{Z}^+$ be arbitrary. Since m^k, $m^{k+1} \in H^1(\Omega)$ and $c^k, c^{k+1} \in L^2\left(0,T;L^2(\Omega)\right)$

$$m^{k+1} - m^k \in H^1(\Omega)$$

and

$$c^{k+1} - c^k \in L^2(0,T;L^2(\Omega))$$

are obtained. In the next step, one can write [12]

$$\left\|m^{k+1} - m^k\right\|_X^2 \leq C\left(\Omega,T\right) \int_0^T \left\|\alpha c^k - \alpha c^{k-1}\right\|_{L^2(\Omega)}^2 dt.$$

and

$$\begin{aligned} \left\|m^{k+1} - m^k\right\|_X^2 &\leq C\left(\Omega,T\right)\alpha^2 c_3^2 \int_0^T \left\|c^k - c^{k-1}\right\|_{H^1(\Omega)}^2 dt \\ &\leq C\left(\Omega,T\right)\alpha^2 c_3^2 T_4 \left\|c^k - c^{k-1}\right\|_X^2 \\ &\leq \frac{1}{4}\left\|c^k - c^{k-1}\right\|_X^2 \end{aligned} \tag{3.44}$$

for the embedding constant $c_3 := c_3(\Omega,T)$ and $T_4 = \min\left\{\dfrac{1}{4}, \dfrac{1}{4C\left(\Omega,T\right)\alpha^2 c_3^2}\right\}$

For the sequence $(c^k)_{k\in\mathbb{N}}$, if one substitutes n^k and n^{k+1} in equation (3.11)

$$\frac{\partial\left(n^{k+1}-n^k\right)}{\partial t}+\delta\left(m^{k+1}n^{k+1}-m^kn^k\right)$$
$$=\mu_2\left(n^k\left(1-\frac{c^k}{K_c}-\frac{n^k}{K_n}\right)-n^{k-1}\left(1-\frac{c^{k-1}}{K_c}-\frac{n^{k-1}}{K_n}\right)\right). \tag{3.45}$$

When both sides of Equation (3.45) is multiplied by $N_1=n^{k+1}-n^k$ and is integrated over Ω

$$\frac{1}{2}\int_\Omega\frac{\partial}{\partial t}\left(N_1\right)^2dx+\delta\int_\Omega\left(N_1\right)^2m^{k+1}dx=\int_\Omega\left[h\left(n^k,n^{k-1}\right)-\delta n^k\left(M_1\right)\right]\left(N_1\right)dx$$

where

$$h\left(n^k,n^{k-1}\right):=\mu_2\left(n^k\left(1-\frac{c^k}{K_c}-\frac{n^k}{K_n}\right)-n^{k-1}\left(1-\frac{c^{k-1}}{K_c}-\frac{n^{k-1}}{K_n}\right)\right)$$

which leads to

$$\begin{aligned}\frac{d}{dt}\left\|N_1\right\|^2_{L^2(\Omega)} &\leq 2\mu_2\int_\Omega|\left(n^k\left(1-\frac{c^k}{K_c}-\frac{n^k}{K_n}\right)\right.\\ &\quad\left.-n^{k-1}\left(1-\frac{c^{k-1}}{K_c}-\frac{n^{k-1}}{K_n}\right)\right)\left(N_1\right)|dx\\ &\quad+2\delta\int_\Omega\left|n^k\left(M_1\right)\left(N_1\right)\right|dx\\ &\leq 2\mu_2\left\|n^k\left(1-\frac{c^k}{K_c}-\frac{n^k}{K_n}\right)\right.\\ &\quad\left.-n^{k-1}\left(1-\frac{c^{k-1}}{K_c}-\frac{n^{k-1}}{K_n}\right)\right\|_{L^2(\Omega)}\\ &\quad+2\delta\left\|n^k(M_1)\right\|_{L^2(\Omega)}\left\|N_1\right\|_{L^2(\Omega)}\end{aligned} \tag{3.46}$$

and

$$\left\|2\mu_2n^k-n^{k-1}-\frac{\left(n^k\right)^2}{K_n}+\frac{\left(n^k-1\right)^2}{K_n}-\frac{n^kc^k}{K_c}+\frac{n^{k-1}c^{k-1}}{K_c}\right\|$$
$$\leq 2\mu_2\left\|N_2\right\|_{L^2(\Omega)}+\frac{4\mu_2M_{\max}}{K_n}\left\|N_2\right\|_{L^2(\Omega)}+2\frac{\mu_2K_n}{K_c}\left\|C_2\right\|_{L^2(\Omega)}+2\mu_2\left\|N_2\right\|_{L^2(\Omega)}$$
$$\leq C_{\tilde{n}}\left\|N_2\right\|_{L^2(\Omega)}+C_{\tilde{c}}\left\|C_2\right\|_{L^2(\Omega)}$$

with the embedding constant $c_4 := c_4(\Omega, T)$ and

$$M_{\max} := \left\{ M_{m^k} := \left\| n^k \right\|_{L^\infty((0,T]\times\Omega)}, \quad N_{n^{k-1}} := \left\| n^{k-1} \right\|_{L^\infty((0,T]\times\Omega)} \right\}$$

$$C_{\tilde{n}} := 4\mu_2 \left(1 + \frac{M_{\max}}{v_c} \right) and C_{\tilde{c}} := \frac{2\mu_2 v_c}{k_c}$$

For the second term on the right hand side of the inequality (3.46) one has

$$2\delta \left\| n^k (M_1) \right\|_{L^2(\Omega)} \leq C_{\tilde{m}} \left\| M_1 \right\|_{H^1(\Omega)}$$

where $C_{\tilde{m}} := \delta K_n C_4$. Therefore for the inequality (3.46)

$$\begin{aligned} \frac{d}{dt} \left\| N_1 \right\|^2_{L^2(\Omega)} &\leq C^2_{\tilde{n}} \left\| N_2 \right\|^2_{L^2(\Omega)} + C^2_{\tilde{c}} \left\| C_2 \right\|^2_{L^2(\Omega)} \\ &\quad + C^2_{\tilde{m}} \left\| M_1 \right\|^2_{H^1(\Omega)} + \frac{1}{2} \left\| N_1 \right\|^2_{L^2(\Omega)} \end{aligned}$$

is obtained. This inequality can be written as

$$\left\| N_1 \right\|^2_{L^2(\Omega)} \leq e^{t/2} \int_0^t \left(C^2_{\tilde{n}} \left\| N_2 \right\|^2_{L^2(\Omega)} + C^2_{\tilde{c}} \left\| C_2 \right\|^2_{L^2(\Omega)} + C^2_{\tilde{m}} \left\| M_1 \right\|^2_{H^1(\Omega)} \right) ds$$

by using Gronwall's inequality which leads to

$$\begin{aligned} \left\| N_1 \right\|^2_{L^\infty(0,T;L^2(\Omega))} &\leq D(\Omega, T) \left(\left\| N_2 \right\|^2_{L^\infty(0,T;L^2(\Omega))} \right. \\ &\quad \left. + \left\| C_2 \right\|^2_{L^\infty(0,T;L^2(\Omega))} + \left\| M_1 \right\|^2_X \right) T_5 \\ &\leq \frac{1}{4} \left(\left\| N_2 \right\|^2_{L^\infty(0,T;L^2(\Omega))} \right. \\ &\quad \left. + \left\| C_2 \right\|^2_{L^\infty(0,T;L^2(\Omega))} + \left\| M_1 \right\|^2_X \right) \\ &\leq \frac{1}{4} \left(\left\| N_2 \right\|^2_{L^\infty(0,T;L^2(\Omega))} + \frac{5}{4} \left\| C_2 \right\|^2_X \right) \end{aligned} \tag{3.47}$$

where $D(\Omega, T) = e^{t/2} \max \left\{ C^2_{\tilde{v}}, C^2_{\tilde{k}}, C^2_{\tilde{u}} \right\} T_5,\ D(\Omega, T) T_5 \leq \dfrac{1}{4}$.

On the other hand, since

$$c^k, c^{k+1} \in H^1(\Omega) and c^k (1 - \frac{c^k}{K_c} - \frac{n^k}{K_n}), c^{k+1} (1 - \frac{c^{k+1}}{K_c} - \frac{n^{k+1}}{K_n}) \in L^2(0,T; L^2(\Omega))$$

one obtains

$$c^{k+1} - c^k \in H^1(\Omega)$$

and

$$\left[\mu_1 c^{k+1} \left(1 - \frac{c^{k+1}}{K_c} - \frac{n^{k+1}}{K_n} \right) - \mu_1 c^k \left(1 - \frac{c^k}{K_c} - \frac{n^k}{K_n} \right) \right] \in L^2 \left(0, T; L^2 (\Omega) \right)$$

If one once more applies Theorem 7.1.5 in [12] to the difference $c^{k+1}-c^k$, the two inequalities

$$\begin{aligned}\|C_1\|_X^2 \quad &\le \quad C(\Omega,T)\int_0^T \left\|\mu_1 n^k\left(1-\frac{c^k}{K_c}-\frac{n^k}{K_n}\right)\right. \\ &\qquad \left.-\mu_1 n^{k-1}\left(1-\frac{c^{k-1}}{K_c}-\frac{n^{k-1}}{K_n}\right)\right\| dt \end{aligned} \tag{3.48}$$

$$\begin{aligned}\mu_1 &\left\| c^k - c^{k-1} - \frac{\left(c^k\right)^2}{K_c} \right. \\ &\left. + \frac{\left(c^{k-1}\right)^2}{K_c} - \frac{c^k n^k}{K_n} + \frac{c^{k-1}n^{k-1}}{K_n}\right\|_{L^2(\Omega)} \quad \le \quad \mu_1\|C_2\|_{L^2(\Omega)} \\ &\qquad + \frac{2\mu_1 K_{\max}}{K_c}\|C_2\|_{L^2(\Omega)} \\ &\qquad + \frac{\mu_1 K_c}{K_n}\|N_2\|_{L^2(\Omega)}\end{aligned} \tag{3.49}$$

are obtained with

$$K_{\max} := \max\left\{C_{c^k} := \left\|c^k\right\|_{L^2(\Omega)}, N_{c^{k-1}} := \left\|c^{k-1}\right\|_{L^2(\Omega)}\right\}.$$

The inequality (3.49) leads to

$$\mu_1\|C_2\|_{L^2(\Omega)} + \frac{2\mu_1 K_{\max}}{K_c}\|C_2\|_{L^2(\Omega)} + \frac{\mu_1 K_c}{K_n}\|N_2\|_{L^2(\Omega)} = c_{\tilde{c}}\|C_2\|_{L^2(\Omega)} + c_{\tilde{n}}\|N_2\|_{L^2(\Omega)}$$

and

$$\begin{aligned}\|C_1\|_X^2 \quad &\le \quad C(\Omega,T)\int_0^T \left(c_{\tilde{c}}\|C_2\|_{L^2(\Omega)} + c_{\tilde{n}}\|N_2\|_{L^2(\Omega)}\right)^2 dt \\ &\le \quad C(\Omega,T)\left[c_{\tilde{c}}^2\int_0^T \|C_2\|_{L^2(\Omega)}^2 dt + c_{\tilde{n}}^2\int_0^T \|N_2\|_{L^2(\Omega)}^2 dt\right] \\ &\le \quad C(\Omega,T)\left[c_{\tilde{c}}^2 c_6^2\int_0^T \|C_2\|_{H^1(\Omega)}^2 dt + c_{\tilde{n}}^2 c_7^2\int_0^T \|N_2\|_{H^1(\Omega)}^2 dt\right] \\ &\le \quad C(\Omega,T)\,c_{\tilde{c}}^2 c_6^2 T_6\|C_2\|_X^2 + C(\Omega,T)\,c_{\tilde{n}}^2 c_7^2 T_7\|N_2\|_X^2 \\ &\le \quad \frac{1}{4}\|C_2\|_X^2 + \frac{1}{4}\|N_2\|_X^2 \end{aligned} \tag{3.50}$$

where

$$T_6 = \min\left\{\frac{1}{4}, \frac{1}{4C(\Omega,T)\,c_{\tilde{c}}^2 c_6^2}\right\}, T_7 = \min\left\{\frac{1}{4}, \frac{1}{4C(\Omega,T)\,c_{\tilde{n}}^2 c_7^2}\right\}$$

and

$$c_{\tilde{c}} := \mu_1\left(1+\frac{2K_{\max}}{K_c}\right),\ c_{\tilde{n}} := \frac{\mu_1 K_c}{K_v}.$$

The inequalities (3.45), (3.47) and (3.50) results with

$$\begin{aligned}
\|C_1\|_X^2 + \|N_1\|_Z^2 & \\
+\|M_1\|_X^2 &\leq \frac{1}{4}\|C_2\|_X^2 + \frac{1}{4}\|N_2\|_X^2 \\
&\quad + \frac{1}{4}\left(\|N_2\|_{L^\infty(0,T;L^2(\Omega))}^2 + \frac{5}{4}\|C_2\|_X^2\right) \\
&\quad + \frac{1}{4}\|C_2\|_X^2 \\
&\leq \frac{1}{16}\left[13\|C_2\|_X^2 + 8\|N_2\|_{L^\infty(0,T;L^2(\Omega))}^2\right] \qquad (3.51)
\end{aligned}$$

Therefore (m^k, n^k, c^k) is a Cauchy sequence in $X \times Z \times X$ which gives the existence of the weak solution.

For uniqueness one may assume that (c_1, n_1, m_1) and (c_2, n_2, m_2) are two solutions for the model problem. Then using previous estimates one may obtain

$$\begin{aligned}
\|c_1 - c_2\|_X^2 &\leq \frac{1}{4}\|c_1 - c_2\|_X^2 + \frac{1}{4}\|n_1 - n_2\|_X^2 \\
\|m_1 - m_2\|_X^2 &\leq \frac{1}{4}\|c_1 - c_2\|_X^2 \\
\|n_1 - n_2\|_X^2 &\leq \frac{1}{4}\|c_1 - c_2\|_X^2 + \frac{1}{4}\|n_1 - n_2\|_X^2
\end{aligned}$$

which gives $c_1 = c_2$, $n_1 = n_2$, $m_1 = m_2$ and completes the proof for uniqueness. □

4. Numerical Simulations

In this section, the behavior of the solution for the model system is analyzed. To this end, the nondimensionalized form of the (2.1) [8] is considered

$$\begin{aligned}
\frac{\partial c}{\partial t} &= \underbrace{\nabla \cdot (D_c \nabla c)}_{\text{dispersion}} - \underbrace{\nabla \cdot (\chi_c c \nabla m)}_{\text{chemotaxis}} - \underbrace{\nabla \cdot (\xi_c c \nabla n)}_{\text{haptotaxis}} + \underbrace{\mu_1 c (1 - c - n)}_{\text{proliferation}}, \\
\frac{\partial n}{\partial t} &= \underbrace{-\delta m n}_{\text{degredation}} + \underbrace{\mu_2 n (1 - c - n)}_{\text{re-establishment}}, \qquad (4.1) \\
\frac{\partial m}{\partial t} &= \underbrace{D_m \nabla^2 m}_{\text{dispersion}} + \underbrace{\alpha c}_{\text{production}} - \underbrace{\beta m}_{\text{decay}}
\end{aligned}$$

with the boundary conditions (2.2).

Initially we assume that cancer cells penetrated a short distance and the rest of the space is occupied by the normal cells. Moreover the MDEs are secreted by the cancer cells and thus the initial level for the MDE concentration is proportional to the initial cancer cell density. By using these assumptions the initial data is chosen as

$$
\begin{aligned}
c(x,0) &= \exp\left(\frac{-x^2}{\epsilon}\right), \quad x\in[0,1] \text{ and } \epsilon>0 \\
n(x,0) &= 1-\frac{1}{2}\exp\left(\frac{-x^2}{\epsilon}\right), \quad x\in[0,1] \text{ and } \epsilon>0 \\
m(x,0) &= \frac{1}{2}\exp\left(\frac{-x^2}{\epsilon}\right), \quad x\in[0,1] \text{ and } \epsilon>0
\end{aligned} \tag{4.2}
$$

In order to discretize the model the finite difference method is made use of. The domain $[0,1]$ is divided into l equal width subinterval with $l+1$ nodes.

For the discretization of the space derivatives seen on the right hand side of the equation describing the time evolution of the MDE concentration the central difference is used. For the time discretization a combination of the forward and backward Euler methods is used which discretizes the decay term implicitly and the production term explicitly giving the final discretized form

$$\frac{m_i^{k+1}-m_i^k}{\Delta t}=D_m\left(\frac{m_{i-1}^{k+1}-2m_i^{k+1}+m_{i+1}^{k+1}}{\Delta x^2}\right)-\alpha c_i^{k+1}-\beta m_i^{k+1} \tag{4.3}$$

with $i=1,2,\cdots,l$. In equation (4.3), k denotes the time level and Δt, Δx denote the time and space increments, respectively. The discretized equations seen in Equation (4.3) can be written in matrix-vector form as

$$\mathbf{A}_m\mathbf{m}^{k+1}=\mathbf{m}^k+\alpha\Delta t\mathbf{c}^k \tag{4.4}$$

where $\mathbf{A}_m$ is the $(l+1)\times(l+1)$ tridiagonal matrix coming from finite difference discretization, $\mathbf{c}$ and $\mathbf{m}$ are the vectors of dimension $l+1$ containing the values of c and m at the discretization points. In order to solve the corresponding equations for 1 and l the boundary conditions are made use of.

For the discretization of the equation for the normal cell density in (4.1), the forward Euler method is used with the updated m values at the discretization points and the final discretized form is obtained as

$$n_i^{k+1}=\frac{n_i^k\left(1+\left(\mu_2\Delta t-\mu_2\Delta tc_i^k-\mu_2\Delta tn_i^k\right)\right)}{1+\delta\Delta tm_i^{k+1}} \tag{4.5}$$

Because of the nonlinearity in the chemotaxis and haptotaxis terms on the right hand side of the equation for the cancer cell density in the model (4.1), the discretization has some difficulties and in order to overcome these difficulties, a non-standard finite difference technique [14] is used for these terms giving

$$\nabla\left(\chi_c c\nabla m\right)\big|_{x_i}=\frac{1}{2\Delta x^2}\sum_{j\in N_i}\left(m_j^{k+1}c_j^k+m_i^{k+1}c_i^k\right)\left(m_j^{k+1}-m_i^{k+1}\right) \tag{4.6}$$

$$\nabla\left(\xi_c c\nabla n\right)\big|_{x_i}=\frac{1}{2\Delta x^2}\sum_{j\in N_i}\left(n_j^{k+1}c_j^k+n_i^{k+1}c_i^k\right)\left(n_j^{k+1}-n_i^{k+1}\right) \tag{4.7}$$

where the index set of neighbor nodes of the node x_i is $N_i = \{i-1, i+1\}$ and $i = 1, 2, \cdots, l$. Then the discretized matrix-vector equations are obtained after using central difference for the Laplacian term and a combination of forward and backward Euler methods:

$$\mathbf{A}_c\mathbf{c}^{k+1} = \mathbf{c}^k + \mathbf{c}_c^{\tilde{k}} \tag{4.8}$$

In equation (4.8), $\mathbf{A}_c$ is the $(l+1)\times(l+1)$ tridiagonal matrix containing the information coming from chemotaxis, haptotaxis and diffusion terms, $\mathbf{c}^k$ and $\mathbf{c}^{\tilde{k}}$ are the vectors of dimension $l+1$ containing the values of c and $\mu_1(1-c^k-n^{k+1})$ at the discretization points, respectively.

For the numerical simulations the ranges for the parameter values [8] are given in Table 2

Parameter	**Value Range**
D_c	$10^{-3} - 10^{-5}$
D_m	$0.001 - 1$
χ_c	$0.001 - 1$
ξ_c	$0.001 - 1$
μ_1	$0.05 - 2$
α	$0.05 - 1$
β	$0.13 - 0.95$
$\hat{a}---$ ﬃδ	$1 - 20$
$\hat{a}---$ ﬃμ_2	$0.15 - 2.5$

Table 2. Value Range of Parameters

Throughout our simulations we fix the following parameters $D_c = 10^{-4}$, $D_m = 10^{-2}$, $\delta = 10$, $\alpha = 0.05$, $\beta = 0.3$ and $\delta = 10$.

First, we neglect the effect coming from chemotaxis and take $\chi_c = 0$. In Figure 1, the time evolution of cancer and normal cell densities and MDE concentration are shown in the absence of proliferation i.e. $\mu_1 = \mu_2 = 0$. At small times (e.g. $t = 1$), it is seen that the cancer cells penetrate into a small region whereas at larger times (e.g., $t = 20$) the cells migrate throughout the region. One also observes a cluster of cells at the leading edge of the tumor which is the result of haptotactic migration.

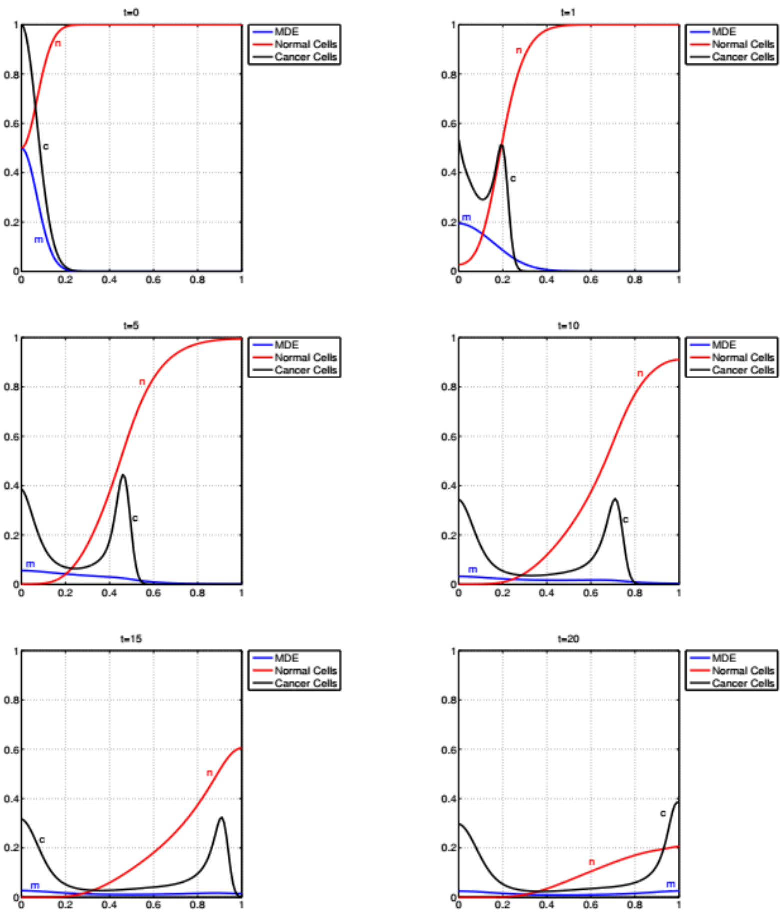

FIGURE 1. Behavior of the model system in the obsence of chemotaxis with $\xi_c = 0.02$

In the next set of figures (Figure 2) the effect of chemotaxis on the model system is analyzed. To this end, the chemotaxis coefficient χ_c is taken as 0.02 and the rest of the parameters remain to be the same. It can be observed that the cancer cells migrate slower which is the result of haptotactic migration which is the result of the fact that gradients of chemotactic and haptotactic responses have opposite directions. Moreover by the effect of chemotaxis another cluster of cancer cells is seen near the left hand boundary due to chemotaxis mediated by MDE.

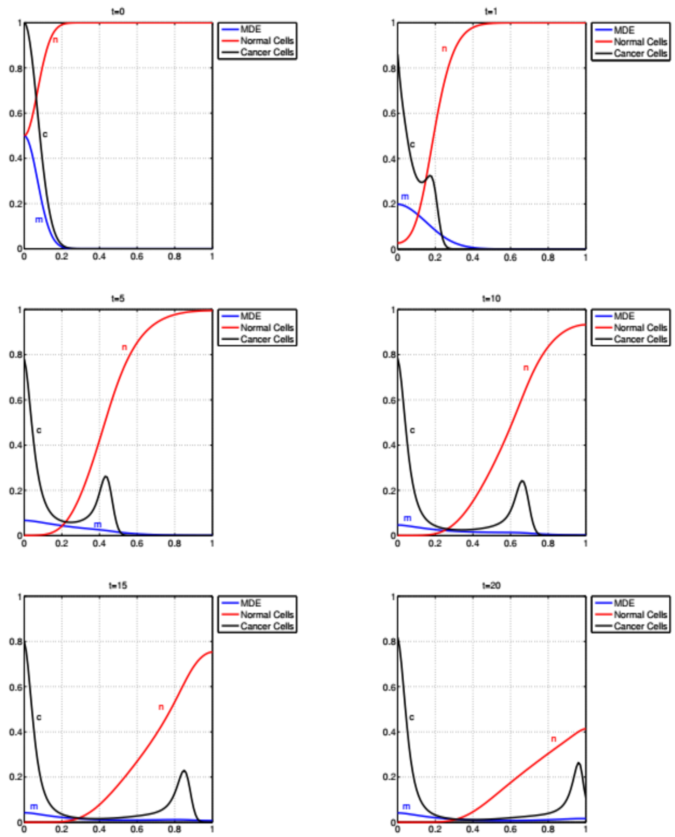

FIGURE 2. Effect of chemotaxis

Finally, in the last set of figures (Figure 3), effect of proliferation is examined. The proliferation parameters are taken as $\mu_1 = 0.5$ and $\mu_2 = 1.25$ and the rest of the parameters are taken same as the ones in Figure 1. By the effect of proliferation a larger cluster of cancer cells is formed at the leading edge of the tumor. As the time evolves (by $t = 20$) the cells migrate throughout the domain and degradation of ECM is much more visible.

5. CONCLUSION

In this study, the tissue invasion model given in [8] is considered. The local existence, uniqueness and positivity of solutions are proved for the corresponding model by using an iterative technique. Moreover, the numerical simulations are performed by using a combination of nonstandard FDM, forward and backward

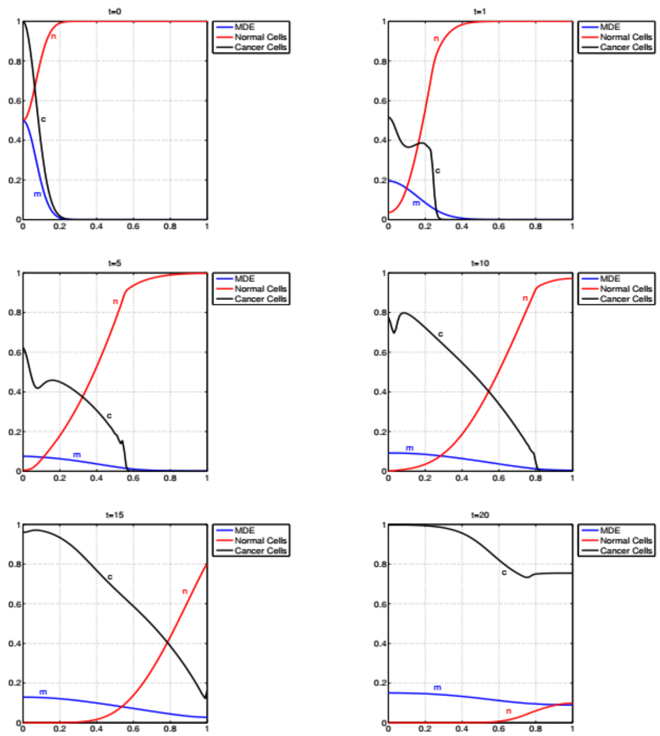

FIGURE 3. Effect of proliferation

Euler methods. Effect of haptotaxis, chemotaxis and proliferation is analyzed by the numerical simulations and the results validate the model behavior.

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