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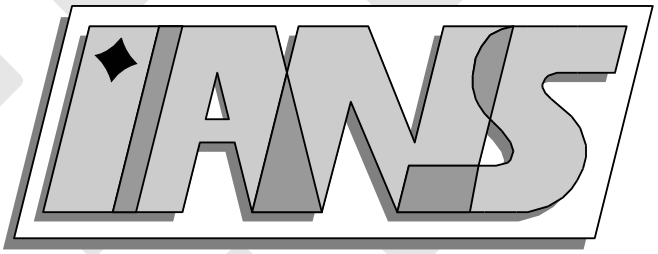

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MATHEMATICAL ANALYSIS AND NUMERICAL SIMULATIONS FOR A SYSTEM MODELING ACID-MEDIATED TUMOR CELL INVASION

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ABSTRACT. This paper is concerned with the mathematical analysis of a model proposed by Gatenby and Gawlinski (1996) in order to support the hypothesis that tumor-induced alteration of microenvironmental pH may provide a simple but comprehensive mechanism to explain cancer invasion. Numerical simulations are also performed, which endorse the predictions of the model when compared with experimentally observed qualitative facts.

1. INTRODUCTION

Despite major progress in medicine and science there still are incurable diseases which can threaten human lifes. Cancer is among the most severe ones and it manifests itself as an uncontrolled growth of cells which are produced by the body subsequently to mutations. Cancer cells migrate through the surrounding tissue and degrade it on their way towards blood vessels and distal organs where they build further tumors, a process known as metastasis.

In the last decades there have been proposed various classes of models aiming to provide a quantitative description of tumor growth. They range from the microscopic level of intracellular signaling pathways conditioning the growth of neoplastic tissue by stimulation or inhibition of apoptosis (e.g. by the influence of tumor necrosis factors, [2]) or tumor cell motility e.g. by restructuring the cytoskeleton or by producing matrix degrading enzymes [21], through the level of cell-cell or cell-tissue interactions and up to the macroscopic level characterizing the behavior of the entire cell population. Multiscale settings like the one in [15] involve several of these scales and offer a systemic approach to the modeling process.

If we ignore the settings relying on mechanical force balance and/or on the theory of mixtures, then in the study of tumor invasion and metastasis one can distinguish between the so-called kinetic approach and the direct modeling at the macroscopic level. In the former a mesoscopic model is considered, consisting

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of an integro-partial differential equation for the evolution of the cell density, possibly coupled with integro-differential and/or reaction diffusion equations for the fibre density of the extracellular matrix (ECM) and the chemotactic signal (see e.g. [10] and the references therein, [14]). Then with an appropriate scaling the macroscopic limit is deduced, usually leading to a Keller-Segel type model or some hyperbolic systems, see e.g. [4]. The latter approach involves the largest class of existing models and directly accounts for processes at the macroscopic level, leading to systems of reaction-diffusion (transport) equations like e.g. in [1], [8].

Nowadays manifold methods have been made available for cancer therapy, however none of them is exhaustive and many are accompanied by severe side effects rendering the treatment of numerous patients problematic. This motivates the quest for alternative approaches to the most frequently used chemo- and radiation therapy. One such approach was recently proposed by R. A. Gatenby [7]. He suggested to control the tumor instead of annihilating it: after reducing it to a bearable level by the usual excision and the subsequent chemotherapy, targeted treatment should confine the tumor growth and maintain it on a harmless level. This should enable the patient to leave with the cancer and not against it, an approach which seems particularly attractive when rather less aggressive cancer cells develop resistance against common therapies or for cancers which cannot be handled with other methods.

One of these controlling therapy ideas relies on the role of tumor microenvironment in determining cancer malignancy. Gatenby and Gillies [6] suggested that environmental conditions may drive the selection of the cancerous phenotype. For instance hypoxia and acidity are factors that can trigger the progression from benign to malignant growth. In order to survive in the unfavourable environment created by them, cancer cells upregulate certain proton extrusion mechanisms [11], the consequence of which is that the extracellular tumor environment has an acidic pH, which boosts apoptosis of normal cells and thus allows the neoplastic tissue to extend in the space becoming available. Tumor acidification has been recognized to be an intrinsic property of both poor vasculature and altered cancer cell metabolism.

These facts led Gatenby and Gawlinski [8], [9] to propose a model for the acid-mediated tumor invasion, which describes the interaction between the density of normal cells, tumor cells, and the concentration of H^+ ions produced by the latter via reaction-diffusion equations. Starting from this model, travelling waves have been used to explain the aggresive action of cancer cells on their surroundings. Further settings issued out of Gatenby and Gawlinski's model involve nutrient dynamics influenced by both vascular and avascular growth of multicellular tumor

spheroids [20], [3] assuming rotational symmetry and investigating existence and qualitative properties of the solutions.

In this paper we reconsider the model of Gatenby and Gawlinski [8], for which we perform mathematical analysis and numerical simulations which endorse the predictions of the model when compared with experimentally observed qualitative facts. In order to prove the existence of a unique (weak) solution we propose a very natural method relying on an iterative procedure which has been also applied in [12], [13] in a different context and allows to avoid the use of operator semigroups.

2. Problem Setting

The model of Gatenby and Gawlinski [8] describes the evolution of normal, respectively tumor cell density in a domain where these cell types interact on the basis of pH value modifications. The mathematical description of these processes is ensured by the following system of reaction-diffusion equations for the normal cell density $N(t,\boldsymbol{x})$, the tumor cell density $K(t,\boldsymbol{x})$ (both in $cells/cm^3$) and the concentration of excessive $H^+(t,\boldsymbol{x})$ ion concentration (in Mol):

$$\frac{\partial N}{\partial t} = w_N N\left(1-\frac{N}{K_N}\right) - d_N H N \quad \text{in } (0,T)\times\Omega \tag{1}$$

$$\frac{\partial K}{\partial t} = w_K K\left(1-\frac{K}{K_K}\right) + \nabla\cdot\left(D_K\left(1-\frac{N}{K_N}\right)\nabla K\right) \quad \text{in } (0,T)\times\Omega \tag{2}$$

$$\frac{\partial H}{\partial t} = w_H K - d_H H + D_H \triangle H \quad \text{in } (0,T)\times\Omega. \tag{3}$$

Thereby, $\Omega\subset\mathbb{R}^n\,(n\in\{1,2\})$ is a regular enough and bounded domain and only microscopically small processes are considered at the interface between tumor and healthy tissue. Observe that the diffusion coefficient of the cancer cells depends on the normal cells density: when the healthy tissue is at its carrying capacity the neoplastic tissue cannot diffuse, thus the tumor is confined. It can only spread if the surrounding normal tissue is diminished from its carrying capacity and this is assumed to happen due to lowering the pH level upon secretion of H^+ ions by cancer cells.

The constants w_N and w_K are given in $1/s$ and represent the growth rates, the constants K_N and K_K are expressed in $cells/cm^3$ and provide the carrying capacities of the normal, respectively the tumor cells.The death rate d_N of the normal cells is measured in $1/(Mol\cdot s)$, and the diffusion coefficient of tumor cells in absence of normal cells is given in cm^2/s. The production rate w_H of H^+ ions is expressed in $Mol\cdot cm^3/(cells\cdot s)$, the reabsorption rate d_H in $1/s$, and their diffusion coefficient of D_H in cm^2/s.

We also assume that there is no exchange of cells and H^+ ions through the boundary of the considered domain, thus

$$\frac{\partial K}{\partial \boldsymbol{n}} = \frac{\partial H}{\partial \boldsymbol{n}} = 0 \qquad \text{in } (0,T)\times\partial\Omega, \tag{4}$$

where $\boldsymbol{n}$ denotes the outer unit normal vector to $\partial\Omega$.

The initial conditions are given by

$$K(0,\boldsymbol{x}) = K_0(\boldsymbol{x}), \quad N(0,\boldsymbol{x}) = N_0(\boldsymbol{x}), \quad H(0,\boldsymbol{x}) = H_0(\boldsymbol{x}) \quad \text{in } \Omega. \tag{5}$$

Thereby $K_0(\boldsymbol{x})$, $N_0(\boldsymbol{x})$, $H_0(\boldsymbol{x})$ are strictly positive functions, which satisfy the condition

$$\frac{\partial K_0}{\partial \boldsymbol{n}} = \frac{\partial H_0}{\partial \boldsymbol{n}} = 0 \qquad \text{auf } \partial\Omega.$$

In order to render the system (1)-(3) dimensionless we use the following transformations:

$$\tilde{N} = \frac{N}{K_N}, \qquad \tilde{K} = \frac{K}{K_K}, \qquad \tilde{H} = H\cdot\frac{d_H}{w_H K_K},$$
$$\tilde{t} = w_N\cdot t, \qquad \tilde{\boldsymbol{x}} = \sqrt{\frac{w_N}{D_H}}\cdot\boldsymbol{x}$$

along with the notations

$$\delta_N = \frac{d_N w_H K_K}{d_H w_N}, \qquad \rho_K = \frac{w_K}{w_N}, \qquad \Delta_K = \frac{D_K}{D_H}, \qquad \delta_H = \frac{d_H}{w_N}.$$

We obtain the system

$$\frac{\partial N}{\partial t} = N(1-N) - \delta_N HN \tag{6}$$

$$\frac{\partial K}{\partial t} = \rho_K K(1-K) + \bigtriangledown\cdot(\Delta_K(1-N)\bigtriangledown K) \tag{7}$$

$$\frac{\partial H}{\partial t} = \delta_H K - \delta_H H + \triangle H, \tag{8}$$

where for simplicity the tilde notations have been ignored. The stability analysis of this system has been performed in [8], leading to biologically significant predictions.

3. Existence of solutions locally in time

In this section we provide a natural proof for the existence and uniqueness of a weak solution to the system (1), (2), (3) with initial data (5) and boundary conditions (4). We make use of an iterative procedure instead of the classical approach via semigroup theory; this allows for a separate treatment of the three equations in each step.

Consider the function spaces

$$X := L^\infty(0,T;H^1(\Omega)), \tag{9}$$

$$Y := \{u \in L^2(0,T;H^2(\Omega)) : u_t \in L^2(0,T;L^2(\Omega))\}, \tag{10}$$

$$Z := L^\infty(0,T;L^2(\Omega)). \tag{11}$$

Definition 3.1. *A weak solution of* (1), (2), (3) *with boundary conditions* (4) *and initial data* (5) *is a triple* (H,N,K) *of functions in* $X \times Y \times Z$, *such that for all* $\phi \in H^1(\Omega)$ a.e. in $[0,T]$ *the following three equations are satisfied:*

$$\int_\Omega w_H K\phi d\boldsymbol{x} = \int_\Omega H_t\phi d\boldsymbol{x} + \int_\Omega D_H\nabla H\nabla\phi d\boldsymbol{x} + \int_\Omega d_H H\phi d\boldsymbol{x} \tag{12}$$

$$\int_\Omega w_N N(1-\frac{N}{K_N})\phi d\boldsymbol{x} = \int_\Omega N_t\phi d\boldsymbol{x} + \int_\Omega N d_N H\phi d\boldsymbol{x} \tag{13}$$

$$\int_\Omega w_K K(1-\frac{K}{K_K})\phi d\boldsymbol{x} = \int_\Omega K_t\phi d\boldsymbol{x} + \int_\Omega D_K(1-\frac{N}{K_N})\nabla K\nabla\phi d\boldsymbol{x}\,. \tag{14}$$

Theorem 3.1. *There exists* $T > 0$, *such that the system* (1), (2), (3) *with initial data* (5) *and boundary conditions* (4) *satisfying*

$$H_0 \in L^\infty(\Omega)\cap H^1(\Omega)\cap C(\Omega)\,, \quad N_0 \in L^\infty(\Omega)\cap H^1(\Omega)\,, \quad K_0 \in H^1(\Omega) \tag{15}$$

and

$$K_0 \le \frac{K_K}{2} \tag{16}$$

has a unique solution $(H,K) \in (X\times X)\cap(Y\times Y)$ *and* $N \in Z$.

We set

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

with $T_i \le 1$ to be defined below.

In order to prove Theorem 3.1 we construct a sequence

$$(H^m,K^m)_{m\in\mathbb{N}_0} \in (X\times X)\cap(Y\times Y) \quad \text{and} \quad (N^m)_{m\in\mathbb{N}_0} \in Z$$

and prove its convergence towards the weak solution of the system.

Let $(H^0, K^0) \in (X \times X) \cap (Y \times Y)$ and $N^0 \in Z$ be the weak solution to the homogeneous system

$$\frac{\partial H^0}{\partial t} - D_H \triangle H^0 + d_H H^0 = 0 \tag{17}$$

$$\frac{\partial N^0}{\partial t} + d_N H^0 N^0 = 0 \tag{18}$$

$$\frac{\partial K^0}{\partial t} - \nabla \cdot (D_K(1 - \frac{N^0}{K_N})\nabla K^0) = 0\,, \tag{19}$$

while $(H^m, K^m)_{m\in\mathbb{N}_0} \in (X \times X) \cap (Y \times Y)$ and $(N^m)_{m\in\mathbb{N}_0} \in Z$ is the weak solution to

$$\frac{\partial H^{m+1}}{\partial t} - D_H \triangle H^{m+1} + d_H H^{m+1} = w_H K^m \tag{20}$$

$$\frac{\partial N^{m+1}}{\partial t} + d_N H^{m+1} N^{m+1} = w_N N^m (1 - \frac{N^m}{K_N}) \tag{21}$$

$$\frac{\partial K^{m+1}}{\partial t} - \nabla \cdot (D_K(1 - \frac{N^{m+1}}{K_N})\nabla K^{m+1}) = w_K K^m (1 - \frac{K^m}{K_K}) \tag{22}$$

with the respective conditions (4) and (5).

The existence and uniqueness of the functions $(H^m, K^m, N^m)_{m\in\mathbb{N}_0}$ in the above sequence are ensured by the following

Lemma 3.1. *(Properties of the iteration sequence)*
Under assumptions (15) *and* (16) *there exists $T > 0$ such that:*

(i) there exists a unique weak solution to the systems (17) - (19) *and* (20) - (22) *with conditions* (5) *and* (4)*, and for every $m \in \mathbb{N}_0$ it holds that*

$$N^m, N^m_t \in L^\infty((0,T] \times \Omega) \tag{23}$$

$$H^m, K^m \in L^2(0,T; H^2(\Omega)) \cap L^\infty(0,T; H^1(\Omega)) \tag{24}$$

$$H^m_t, K^m_t \in L^2(0,T; L^2(\Omega))\,; \tag{25}$$

(ii) the functions H^m, N^m, K^m are positive for all $m \in \mathbb{N}_0$;

(iii) the functions H^m, N^m, K^m satisfy for adequate constants $C(\Omega, T)$ and for all $m \in \mathbb{N}_0$ the estimates

$$\|H^m\|_X + \|H^m\|_{L^2(0,T;H^2(\Omega))} \leq C(\Omega,T)(\|K_0\|_{H^1(\Omega)} + \|H_0\|_{H^1(\Omega)}) \tag{26}$$

$$\|N^m\|^2_X \leq C(\Omega,T)\,\|N_0\|^2_{H^1(\Omega)} \tag{27}$$

$$\|K^m\|_X + \|K^m\|_{L^2(0,T;H^2(\Omega))} \leq 2C(\Omega,T)\,\|K_0\|_{H^1(\Omega)}\,. \tag{28}$$

Remark 3.1. *From* (23) *it follows that*

$$N^m \in L^\infty(0,T; L^2(\Omega)) \tag{29}$$

for all $m \in \mathbb{N}_0$.

Proof. (of Lemma 3.1) The proof is to be done via mathematical induction with respect to m.

Induction start:

The proof of the claims in Lemma 3.1 for $m = 0$ is done separately for each of the equations (17) - (19).

(a) With the substitution

$$\tilde{H}^0(t, \boldsymbol{x}) = H^0(t, \boldsymbol{x}) e^{-d_H t},$$

(17) becomes the heat equation

$$\tilde{H}^0_t - D_H \Delta \tilde{H}^0 = 0, \tag{30}$$

thus by the theory of linear parabolic differential equations (see e.g. [5]) and with the assumption $H_0 \in H^1(\Omega)$ it follows that there exists a unique solution H^0 of (17) such that

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

This weak solution also satisfies

$$\left\|H^0\right\|_X + \left\|H^0\right\|_{L^2(0,T;H^2(\Omega))} \leq C(\Omega, T) \left\|H_0\right\|_{H^1(\Omega)}.$$

Further it is known (se e.g., [19]) that (17) has the explicit solution

$$H^0(t, \boldsymbol{x}) = \frac{1}{2\sqrt{\pi D_H t}} e^{-\frac{\boldsymbol{x}^2}{4D_H t} - d_H t} > 0 \qquad (\boldsymbol{x} \in \Omega,\ t > 0) \tag{31}$$

and is therefore positive.

(b) Equation (18) is linear and has a positive solution

$$N^0(t, \boldsymbol{x}) = N_0 e^{-\int_0^t d_N H^0(s, \boldsymbol{x}) ds} > 0 \tag{32}$$

which depends on $H^0(t, \boldsymbol{x})$. With (31) and (32) it follows that

$$\begin{aligned} \left\|N^0\right\|^2_{L^\infty(0,T;H^1(\Omega))} &= \left\| N_0 e^{-\int_0^t d_N H^0 dt} \right\|^2_{L^\infty(0,T;H^1(\Omega))} \\ &\leq \left\|N_0\right\|^2_{H^1(\Omega)}, \end{aligned}$$

and thus the estimation (27) for $m = 0$.

The corresponding statement (23) for N^0 is to be proved below.

(c) In order to prove the claims of Lemma 3.1 for K^0 we show first that

$$N^0 \in L^\infty((0,T] \times \Omega) \tag{33}$$

and

$$N^0_t \in L^\infty((0,T] \times \Omega). \tag{34}$$

The former follows from

$$\left\|N^0\right\|_{L^\infty((0,T]\times\Omega)} \overset{(32)}{=} \left\|N_0 e^{-\int_0^t d_N H^0 dt}\right\|_{L^\infty((0,T]\times\Omega)} \leq \|N_0\|_{L^\infty(\Omega)} < \infty.$$

For $t \geq \delta > 0$ it is

$$\begin{aligned}
\left\|N_t^0\right\|_{L^\infty((0,T]\times\Omega)} &\overset{(32)}{=} \left\|N_0 \cdot e^{-\int_0^t d_N H^0 dt} \cdot H^0 d_N\right\|_{L^\infty((0,T]\times\Omega)} \\
&\leq d_N \left\|N_0 \cdot H^0\right\|_{L^\infty((0,T]\times\Omega)} \\
&\overset{(31)}{=} d_N \left\|N_0 \frac{1}{2\sqrt{\pi D_H t}} e^{-\frac{\boldsymbol{x}^2}{4D_H t} - d_H t}\right\|_{L^\infty((0,T]\times\Omega)} \\
&\leq d_N \left\|N_0 \frac{1}{2\sqrt{\pi D_H t}}\right\|_{L^\infty((0,T]\times\Omega)} < \infty.
\end{aligned}$$

For $t \to 0$ we can consider the equation (30). It has the solution

$$\tilde{H}^0(t,\boldsymbol{x}) = \frac{1}{2\sqrt{\pi D_H t}} \int_\Omega e^{-\frac{(\boldsymbol{x}-\boldsymbol{y})^2}{4D_H t}} H_0(\boldsymbol{y}) dy \qquad (\boldsymbol{x} \in \Omega,\, t > 0)$$

and it holds (see e.g., [5]) that

$$\lim_{(t,\boldsymbol{x})\to(0,\boldsymbol{x}^0)} \tilde{H}^0(t,\boldsymbol{x}) = H_0(\boldsymbol{x}^0) \quad \text{for every } \boldsymbol{x}^0 \in \Omega\,.$$

Therefore,

$$\lim_{(t,\boldsymbol{x})\to(0,\boldsymbol{x}^0)} H^0(t,\boldsymbol{x}) = \lim_{(t,\boldsymbol{x})\to(0,\boldsymbol{x}^0)} \tilde{H}^0(t,\boldsymbol{x}) e^{d_H t} = H_0(\boldsymbol{x}^0)$$

and finally (34), thus also (23) for $m = 0$.

The following proof of (24), (25), (28) upon starting from (19) relies on Theorem 7.1.5 in Evans [5]. However, that result cannot be directly applied to the present case, since the coefficient $a(t,\boldsymbol{x}) = D_K\left(1 - \frac{N^0(t,\boldsymbol{x})}{K_N}\right)$ in (19) depends on time, therefore the proof has to be modified.

Let

$$k_m(t) := \sum_{i=1}^m d_m^i(t) w_i$$

with smooth functions $w_i = w_i(\boldsymbol{x})$ such that

$$\{w_i\}_{i=1}^\infty \text{ is an orthogonal basis of } H^1(\Omega)$$

and

$$\{w_i\}_{i=1}^\infty \text{ is an orthonormal basis of } L^2(\Omega).$$

Considering the symmetric bilinear form

$$A[k_m, k_m] := \int_\Omega a(t,\boldsymbol{x})(\nabla k_m)^2 d\boldsymbol{x},$$

the dependence of the coefficient $a(t,\boldsymbol{x})$ on t leads in its time derivative

$$\frac{d}{dt}A[k_m,k_m] = \int\limits_\Omega a'(t,\boldsymbol{x})(\nabla k_m)^2 d\boldsymbol{x} + 2\int\limits_\Omega a(t,\boldsymbol{x})(\nabla k_m)'\nabla k_m d\boldsymbol{x}$$

to a supplementary summand

$$\int\limits_\Omega a'(t,\boldsymbol{x})(\nabla k_m)^2 d\boldsymbol{x} = -\int\limits_\Omega \frac{D_K}{K_N}(N^0)'(t,\boldsymbol{x})(\nabla k_m)^2 d\boldsymbol{x}, \tag{35}$$

where for shortnes we denoted by $'$ the derivative w.r.t. t.

The rest of the proof of Theorem 7.1.5 in [5] can now be adapted to obtain for an arbitrary $\zeta > 0$ the estimate

$$\begin{aligned}&\left\|k_m'\right\|^2_{L^2(\Omega)} + \frac{d}{dt}\left(\frac{1}{2}A[k_m,k_m]\right)\\ &\quad\leq\ \frac{C}{\zeta}\left(\|k_m\|^2_{H^1(\Omega)} + \|f\|^2_{L^2(\Omega)}\right) + 2\zeta\left\|k_m'\right\|^2_{L^2(\Omega)} + \frac{1}{2}\int\limits_\Omega \frac{D_K}{K_N}(N^0)'(\nabla k_m)^2 d\boldsymbol{x}\,.\end{aligned}$$

Now let (recall (34))

$$M_{N^0} := \frac{D_K}{K_N}\left\|N^0_t\right\|_{L^\infty((0,T]\times\Omega)}\,.$$

Upon integrating with respect to t one can majorize

$$\begin{aligned}\int\limits_0^T\int\limits_\Omega \frac{D_K}{K_N}(N^0)'(\nabla k_m)^2 d\boldsymbol{x}dt &\leq M_{N^0}\int\limits_0^T \|\nabla k_m\|^2_{L^2(\Omega)}dt\\ &\leq M_{N^0}\|k_m\|^2_{L^2(0,T;H^1(\Omega))} \leq \gamma(\Omega,T) < \infty\,,\end{aligned}$$

with $\gamma(\Omega,T)$ an adequate constant. The rest of the proof can be done as in Theorem 7.1.5 in [5], upon taking into account (33) and $K_0 \in H^1(\Omega)$ in order to show that there exists a unique weak solution $K^0(t,\boldsymbol{x})$ to (19) such that

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

and

$$\left\|K^0\right\|_X + \left\|K^0\right\|_{L^2(0,T;H^2(\Omega))} \leq C(\Omega,T)\,\|K_0\|_{H^1(\Omega)}\,.$$

Since

$$K^0_0(\boldsymbol{x}) > 0\,,$$

it follows from the weak maximum principle (see e.g., [5]) that $K^0(t,\boldsymbol{x}) > 0$ and thus also the positivity of $K^0(t,\boldsymbol{x})$.

With **(a)** - **(c)** we proved all statements of Lemma 3.1 for $m = 0$.

Induction hypothesis:

Assume the assertions of the lemma hold for an arbitrary $m \in \mathbb{N}_0$.

Inductive step:

The proof for $m+1$ is to be done separately for each of the three equations (20) - (22). Since for a corresponding embedding constant $c_1 := c_1(\Omega, T)$

$$\begin{aligned}\int_0^T \|K^m\|^2_{L^2(\Omega)} dt \quad &\leq \quad c_1 \int_0^T \|K^m\|^2_{H^1(\Omega)} dt \\ &\overset{\text{ind. hyp.}}{\underset{(28)}{\leq}} \quad 4c_1 C^2(\Omega,T) T \|K_0\|^2_{H^1(\Omega)} < \infty\end{aligned}$$

und thus

$$K^m \in L^2(0,T;L^2(\Omega)),$$

the existence of a unique weak solution to (20), (4), (5) follows from the theory of linear parabolic differential equations. The solution $H^{m+1}(t,\boldsymbol{x})$ satisfies

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

and

$$\begin{aligned}\left\|H^{m+1}\right\|_X \quad + \quad &\left\|H^{m+1}\right\|_{L^2(0,T;H^2(\Omega))} \\ &\leq C_1(\Omega,T)\left((4w_H^2 c_1 C^2(\Omega,T)T\|K_0\|^2_{H^1(\Omega)})^{\frac{1}{2}} + \|H_0\|_{H^1(\Omega)}\right) \\ &\leq \mathcal{C}(\Omega,T)\left(\|K_0\|_{H^1(\Omega)} + \|H_0\|_{H^1(\Omega)}\right).\end{aligned}$$

with $\mathcal{C}(\Omega,T) = \max\{C_1(\Omega,T), C_1(\Omega,T)2w_H C(\Omega,T)\sqrt{c_1 T}\}$.

With the substitution

$$\tilde{H}^{m+1}(t,\boldsymbol{x}) = H^{m+1}(t,\boldsymbol{x})e^{-d_H t},$$

equation (20) ca be reduced to the heat equation

$$\tilde{H}_t^{m+1} - D_H \Delta \tilde{H}^{m+1} = w_H K^m. \tag{36}$$

With

$$K^m(t,\boldsymbol{x}) > 0 \quad \text{and} \quad H_0^{m+1}(\boldsymbol{x}) > 0$$

it follows from the weak maximum principle (see e.g., [5]) that $\tilde{H}^{m+1}(t,\boldsymbol{x}) > 0$ and thus the positivity of $H^{m+1}(t,\boldsymbol{x})$.

Now (21) is a linear, inhomogeneous differential equation, with solution

$$N^{m+1}(t,\boldsymbol{x}) = e^{-\alpha(t,\boldsymbol{x})}(N_0(\boldsymbol{x}) + \int_0^t \beta(s,\boldsymbol{x})e^{\alpha(s,\boldsymbol{x})}ds), \tag{37}$$

where

$$\alpha(t,\boldsymbol{x}) = \int_0^t d_N H^{m+1}(v,\boldsymbol{x})dv$$

and

$$\beta(s,\boldsymbol{x}) = w_N N^m(s,\boldsymbol{x}) - w_N \frac{(N^m(s,\boldsymbol{x}))^2}{K_N}.$$

In order to prove (23) for $m+1$ we have to show that

$$N^{m+1} \in L^\infty((0,T]\times\Omega) \tag{38}$$

and

$$N_t^{m+1} \in L^\infty((0,T]\times\Omega). \tag{39}$$

We now estimate

$$\begin{aligned}
&\left\|N^{m+1}\right\|_{L^\infty((0,T]\times\Omega)}\\
&= \left\|e^{-\alpha(t)}N_0 + e^{-\alpha(t)}\int_0^t \beta(s)e^{\alpha(s)}ds\right\|_{L^\infty((0,T]\times\Omega)}\\
&\le \left\|N_0 + \int_0^t w_N N^m ds - \int_0^t w_N \frac{(N^m)^2}{K_N}ds\right\|_{L^\infty((0,T]\times\Omega)}\\
&\le \|N_0\|_{L^\infty((0,T]\times\Omega)} + \left\|\int_0^t w_N N^m ds\right\|_{L^\infty((0,T]\times\Omega)} + \left\|\int_0^t w_N \frac{(N^m)^2}{K_N}ds\right\|_{L^\infty((0,T]\times\Omega)} < \infty,
\end{aligned}$$

by (23) and the induction hypothesis and thus (38) follows.

Let now (remember (37))

$$M_{N^{m+1}} := \left\|N^{m+1}\right\|_{L^\infty((0,T]\times\Omega)}.$$

Since

$$\begin{aligned}
&\left\|N_t^{m+1}\right\|_{L^\infty((0,T]\times\Omega)}\\
&= \left\|w_N N^m(1-\frac{N^m}{K_N}) - d_N H^{m+1}N^{m+1}\right\|_{L^\infty((0,T]\times\Omega)}\\
&\le \|w_N N^m\|_{L^\infty((0,T]\times\Omega)} + \left\|\frac{w_N}{K_N}(N^m)^2\right\|_{L^\infty((0,T]\times\Omega)} + d_N M_{N^{m+1}}\left\|H^{m+1}\right\|_{L^\infty((0,T]\times\Omega)} < \infty,
\end{aligned}$$

due to (23).

We still have to prove $\|H^{m+1}\|_{L^\infty((0,T]\times\Omega)} < \infty$ in order to show (39) .

Due to

$$H_0^{m+1} \in L^\infty(\Omega),$$

and applying the maximum principle for the heat equation it follows that

$$\left\|H^{m+1}\right\|_{L^\infty((0,T]\times\Omega)} = \left\|\tilde{H}^{m+1}e^{-d_h t}\right\|_{L^\infty((0,T]\times\Omega)} < \infty\,.$$

This leads to

$$\left\|N_t^{m+1}\right\|_{L^\infty((0,T]\times\Omega)} < \infty$$

and thus (39) is proved.

Since for all $m \in \mathbb{N}$ we have $\|N^m\|_{L^\infty((0,T]\times\Omega)} < \infty$, it follows that there exists an upper bound for the normal cells. This can be (biologically meaningful) chosen to be their carrying capacity

$$K_N = \|N^m\|_{L^\infty((0,T]\times\Omega)}\,. \tag{40}$$

With this assumption we get for all $m \in \mathbb{N}$ that $N^m(t,\boldsymbol{x}) \leq K_N$ and thus

$$0 \leq w_N N^m(s,\boldsymbol{x})\left(1 - \frac{N^m(s,\boldsymbol{x})}{K_N}\right) = \beta(s,\boldsymbol{x})\,.$$

This leads to

$$N^{m+1}(t,\boldsymbol{x}) = e^{-a(t,\boldsymbol{x})}(N_0(\boldsymbol{x}) + \int_0^t b(s,\boldsymbol{x})e^{a(s,\boldsymbol{x})}ds) \geq 0,$$

which implies the positivity of N^{m+1}.

In the next step we prove the estimate (27) for $N^{m+1}(t,\boldsymbol{x})$.

Due to (37) we get

$$\begin{aligned}
&\left\|N^{m+1}(t)\right\|_{H^1(\Omega)}^2 \\
&= \left\|e^{-\alpha(t)}N_0 + e^{-\alpha(t)}\int_0^t \beta(s)e^{\alpha(s)}ds\right\|_{H^1(\Omega)}^2 \leq \left\|N_0 + \int_0^t w_N N^m(s) - w_N\frac{(N^m(s))^2}{K_N}ds\right\|_{H^1(\Omega)}^2 \\
&\leq 2\left\|N_0\right\|_{H^1(\Omega)}^2 + 2w_N^2\left\|\int_0^t N^m(s)\left(1 - \frac{N^m(s)}{K_N}\right)ds\right\|_{H^1(\Omega)}^2 \\
&\leq 2\left\|N_0\right\|_{H^1(\Omega)}^2 + 4w_N^2\left\|\int_0^t N^m(s)ds\right\|_{H^1(\Omega)}^2 + \frac{w_N^2}{K_N^2}\left\|\int_0^t (N^m(s))^2 ds\right\|_{H^1(\Omega)}^2 \\
&\overset{(40)}{\leq} 2\left\|N_0\right\|_{H^1(\Omega)}^2 + 4w_N^2\Big(\int_0^t \|N^m(s)\|_{H^1(\Omega)}ds\Big)^2 + \frac{w_N^2K_N^2}{K_N^2}\Big(\int_0^t \left\|(N^m(s))_{H^1(\Omega)}\right\|ds\Big)^2
\end{aligned}$$

$$\leq \quad \|N_0\|^2_{H^1(\Omega)} \left[2 + 4w_N^2 C(\Omega,T)T^2\right] \leq \mathcal{C}(\Omega,T)\,\|N_0\|^2_{H^1(\Omega)}\,,$$

by (27) and the induction hypothesis.

In order to prove the assertions of Lemma 3.1 for $K^{m+1}(t,\boldsymbol{x})$ one can apply Theorem 7.1.5 in [5], with (38), (39) and the same justification as for the induction start at (c).

With an adequate embedding constant $c_2 := c_2(\Omega,T)$

$$\begin{aligned}
&\int_0^T \left\| K^m\left(1-\frac{K^m}{K_K}\right)\right\|^2_{L^2(\Omega)} dt \\
&\leq \int_0^T \left(\|K^m\|_{L^2(\Omega)} + \left\|\frac{(K^m)^2}{K_K}\right\|_{L^2(\Omega)}\right)^2 dt \leq 2\int_0^T \|K^m\|^2_{L^2(\Omega)} dt + 2\int_0^T \left\|\frac{(K^m)^2}{K_K}\right\|^2_{L^2(\Omega)} dt \\
&\leq 2c_1^2 \int_0^T \|K^m\|^2_{H^1(\Omega)} dt + 2\frac{c_2^4}{K_K^2}\int_0^T \|K^m\|^4_{H^1(\Omega)} dt \\
&\leq 8c_1^2 C^2(\Omega,T)\,\|K_0\|^2_{H^1(\Omega)}\,T_1T_2 + 32\frac{c_2^4}{K_K^2} C^4(\Omega,T)\,\|K_0\|^4_{H^1(\Omega)}\,T_1T_2 < \infty,
\end{aligned}$$

by (28) and the induction hypothesis; therefore $K^m(1-\frac{K^m}{K_K}) \in L^2(0,T;L^2(\Omega))$ and $K_0(\boldsymbol{x}) \in H^1(\Omega)$. By applying Theorem 7.1.5 in [5] it follows that equation (22) has a unique weak solution $K^{m+1}(t,\boldsymbol{x})$ with

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

Now choose T_1 such that $\max\{T_1C^2(\Omega,T), T_1C^4(\Omega,T)\} \leq 1$ and

$$T_2 := \min\left\{\frac{1}{2}, \frac{1}{16w_K^2c_1^2\,\|K_0\|}, \frac{K_K^2}{64w_K^2c_2^4\,\|K_0\|^3}\right\}.$$

Then

$$\int_0^T \left\| w_K K^m\left(1-\frac{K^m}{K_K}\right)\right\|^2_{L^2(\Omega)} dt \leq \|K_0\|_{H^1(\Omega)}$$

and thus the estimate

$$\left\|K^{m+1}\right\|_X + \left\|K^{m+1}\right\|_{L^2(0,T;H^2(\Omega))} \leq 2C(\Omega,T)\,\|K_0\|_{H^1(\Omega)}$$

holds.

In order to prove the positivity of K^{m+1} we introduce an auxiliary function

$$\xi^m(t,\boldsymbol{x}) := \frac{\eta t + K_K}{2} - K^m(t,\boldsymbol{x}), \tag{41}$$

which -via mathematical induction- will lead to the proof that for all $m \in \mathbb{N}_0$ there exists $T_3 > 0$ such that

$$K^m \leq K_K. \tag{42}$$

Proof. (of the statement (42))

Induction start:

The proof of (42) for $m = 0$ is identical to the one for $m + 1$.

Induction hypothesis:

Assume assertion (42) holds for an arbitrary $m \in \mathbb{N}_0$.

Inductive step:

Upon (41) in (22) we get

$$\frac{\partial \xi^{m+1}}{\partial t} - \nabla \cdot \left(D_K \left(1 - \frac{N^{m+1}}{K_N} \right) \nabla \xi^{m+1} \right) = \frac{\eta}{2} - w_K K^m \left(1 - \frac{K^m}{K_K} \right) . \tag{43}$$

Let

$$\eta = \frac{K_K}{T_3} \qquad \text{and} \qquad T_3 \leq \frac{1}{w_K} .$$

Since

$$K^m \left(1 - \frac{K^m}{K_K} \right) \leq \frac{K_K}{2} ,$$

for the right hand side of (43) it follows that

$$\frac{\eta}{2} - w_K K^m \left(1 - \frac{K^m}{K_K} \right) \geq w_K \left(\frac{K_K}{2} - K^m \left(1 - \frac{K^m}{K_K} \right) \right) \geq 0.$$

Since by construction $\xi^{m+1}(0, \boldsymbol{x}) \geq 0$, we can apply the weak maximum principle for $T \leq 1/w_K$ to show that

$$\frac{\eta t + K_K}{2} - K^{m+1}(t, \boldsymbol{x}) = \xi^{m+1} \geq 0 ,$$

from which follows also

$$K^{m+1} \leq K_K .$$

□

In virtue of (42), for $T \leq 1/w_K$ the right hand side in (22) is positive. Since by hypothesis $K_0^{m+1} > 0$, the weak maximum principle implies the positivity of K^{m+1}. This ends the proof of all statements in Lemma 3.1 for an arbitrary $m \in \mathbb{N}_0$ and therefore the proof of the lemma itself. □

Now we are able to prove Theorem 3.1.

Proof. (of Theorem 3.1)

Existence. In order to prove the existence of a weak solution to (1)-(4) we show that the iterative sequence $(N^m, K^m, H^m)_{m\in\mathbb{N}_0}$ is a Cauchy sequence.

Due to the completeness of $H^1(\Omega)$ and $L^2(\Omega)$, this will imply the convergence of the sequence to some limit functions N, K and H, these being solutions to (1)-(4).

Consider an arbitrary $m \in \mathbb{N}_0$. Since $H_0^m, H_0^{m+1} \in H^1(\Omega)$ and $K^m, K^{m+1} \in L^2(0,T;L^2(\Omega))$

$$H_0^{m+1} - H_0^m \in H^1(\Omega) \quad \text{and} \quad K^{m+1} - K^m \in L^2(0,T;L^2(\Omega))$$

one can apply Theorem 7.1.5 in [5] to the difference $H^{m+1} - H^m$ to deduce the estimate

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

The right hand side can be further estimated and with the embedding constant $c_3 := c_3(\Omega,T)$ it follows that

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

where

$$T_4 = \min\left\{\frac{1}{4}, \frac{1}{4C(\Omega,T)w_H^2 c_3^2}\right\}.$$

In order to obtain a corresponding estimate for the sequence $(N^m)_{m\in\mathbb{N}}$, replace two arbitrary terms N^m and N^{m+1} in equation (21) and substract. This leads to

$$\frac{\partial(N^{m+1}-N^m)}{\partial t} + d_N(H^{m+1}N^{m+1} - H^m N^m) = \underbrace{w_N\left(N^m(1-\frac{N^m}{K_N}) - N^{m-1}(1-\frac{N^{m-1}}{K_N})\right)}_{=:h(N^m,N^{m-1})}.$$

Now multiply with $(N^{m+1} - N^m)$ and integrate w.r.t. $\boldsymbol{x}$ to infer

$$\begin{aligned}&\frac{1}{2}\int_\Omega \frac{\partial}{\partial t}(N^{m+1}-N^m)^2 d\boldsymbol{x} + d_N \int_\Omega (N^{m+1}-N^m)^2 H^{m+1} d\boldsymbol{x} \\ &\qquad = \int_\Omega (h(N^m,N^{m-1}) - d_N N^m(H^{m+1}-H^m))(N^{m+1}-N^m) d\boldsymbol{x}\,.\end{aligned}$$

Thus

$$\begin{aligned}
&\frac{d}{dt}\left\|N^{m+1}-N^m\right\|^2_{L^2(\Omega)}\\
&\leq\ 2w_N\int\limits_\Omega\left|\left(N^m\left(1-\frac{N^m}{K_N}\right)-N^{m-1}\left(1-\frac{N^{m-1}}{K_N}\right)\right)(N^{m+1}-N^m)\right|d\boldsymbol{x}\\
&\qquad\qquad +2d_N\int\limits_\Omega|N^m(H^{m+1}-H^m)(N^{m+1}-N^m)|d\boldsymbol{x}\\
&\leq\ \Big[2w_N\left\|N^m\left(1-\frac{N^m}{K_N}\right)-N^{m-1}\left(1-\frac{N^{m-1}}{K_N}\right)\right\|_{L^2(\Omega)}\\
&\qquad\qquad +2d_N\left\|N^m(H^{m+1}-H^m)\right\|_{L^2(\Omega)}\Big]\left\|N^{m+1}-N^m\right\|_{L^2(\Omega)}.
\end{aligned}$$

Next we estimate the above terms.

Let (recall (23))

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

With the embedding constant $c_4:=c_4(\Omega,T)$ we obtain

$$\begin{aligned}
&2w_N\left\|N^m-N^{m-1}-\frac{(N^m)^2}{K_N}+\frac{(N^{m-1})^2}{K_N}\right\|_{L^2(\Omega)}\\
&\leq\ 2w_N\left\|N^m-N^{m-1}\right\|_{L^2(\Omega)}+\frac{2w_N}{(K_N)^2}\left\|(N^m-N^{m-1})2M_{max})\right\|_{L^2(\Omega)}\\
&\leq\ C_{\tilde{a}}\left\|N^m-N^{m-1}\right\|_{L^2(\Omega)}
\end{aligned}$$

with $C_{\tilde{a}}:=2w_N+\dfrac{4w_NM_{max}}{(K_N)^2}$.

$$\begin{aligned}
2d_N\left\|N^m(H^{m+1}-H^m)\right\|_{L^2(\Omega)}&\leq\ 2d_NM_{N^m}c_4\left\|H^{m+1}-H^m\right\|_{H^1(\Omega)}\\
&=\ C_{\tilde{b}}\left\|H^{m+1}-H^m\right\|_{H^1(\Omega)},
\end{aligned}$$

with $C_{\tilde{b}}:=2d_NM_{N^m}c_4$. The two estimates above thus lead to

$$\begin{aligned}
&\frac{d}{dt}\left\|N^{m+1}-N^m\right\|^2_{L^2(\Omega)}\\
&\leq\ \frac{1}{2}\Big(C_{\tilde{a}}\left\|N^m-N^{m-1}\right\|_{L^2(\Omega)}+C_{\tilde{b}}\left\|H^{m+1}-H^m\right\|_{H^1(\Omega)}\Big)^2+\frac{1}{2}\left\|N^{m+1}-N^m\right\|^2_{L^2(\Omega)}\\
&\leq\ C^2_{\tilde{a}}\left\|N^m-N^{m-1}\right\|^2_{L^2(\Omega)}+C^2_{\tilde{b}}\left\|H^{m+1}-H^m\right\|^2_{H^1(\Omega)}+\frac{1}{2}\left\|N^{m+1}-N^m\right\|^2_{L^2(\Omega)}.
\end{aligned}$$

Applying Gronwall's inequality we deduce

$$\left\|N^{m+1}-N^m\right\|^2_{L^2(\Omega)} \leq e^{\int_0^t \frac{1}{2}ds} \int_0^t C_{\tilde{a}}^2 \left\|N^m-N^{m-1}\right\|^2_{L^2(\Omega)} + C_{\tilde{b}}^2 \left\|H^{m+1}-H^m\right\|^2_{H^1(\Omega)} ds$$

and finally with $D(\Omega,T) = \max\left\{C_{\tilde{a}}^2 exp(\int_0^t \frac{1}{2}ds)\,, C_{\tilde{b}}^2 exp(\int_0^t \frac{1}{2}ds)\right\}$

$$\begin{aligned}
&\left\|N^{m+1}-N^m\right\|^2_{L^\infty(0,T;L^2(\Omega))} \\
&\qquad \leq \quad D(\Omega,T)\Big(\left\|N^m-N^{m-1}\right\|^2_{L^\infty(0,T;L^2(\Omega))} + \left\|H^{m+1}-H^m\right\|^2_X \Big) T_5 \\
&\qquad \leq \quad \frac{1}{4}\Big(\left\|N^m-N^{m-1}\right\|^2_{L^\infty(0,T;L^2(\Omega))} + \left\|H^{m+1}-H^m\right\|^2_X \Big) \\
&\qquad \leq \quad \frac{1}{4}\Big(\left\|N^m-N^{m-1}\right\|^2_{L^\infty(0,T;L^2(\Omega))} + \frac{1}{4}\left\|K^m-K^{m-1}\right\|^2_X \Big)\,.
\end{aligned}$$

T_5 is chosen such that

$$D(\Omega,T)T_5 \leq \frac{1}{4}\,.$$

Now since $K_0^m, K_0^{m+1} \in H^1(\Omega)$ and $K^m\left(1-\frac{K^m}{K_K}\right), K^{m+1}\left(1-\frac{K^{m+1}}{K_K}\right) \in L^2(0,T;L^2(\Omega))$, we get

$$(K_0^{m+1}-K_0^m) \in H^1(\Omega)$$

and

$$\left[w_K K^{m+1}\left(1-\frac{K^{m+1}}{K_K}\right) - w_K K^m\left(1-\frac{K^m}{K_K}\right)\right] \in L^2(0,T;L^2(\Omega)).$$

Theorem 7.1.5 in [5] can be applied to the difference $K^{m+1}-K^m$, leading to

$$\left\|K^{m+1}-K^m\right\|^2_X \leq C(\Omega,T)\int_0^T \left\| w_K K^m\left(1-\frac{K^m}{K_K}\right) - w_K K^{m-1}\left(1-\frac{K^{m-1}}{K_K}\right)\right\|^2_{L^2(\Omega)} dt\,.$$

The right hand side of this inequality can further be majorized and with the embedding constants $c_5 := c_5(\Omega,T)$ and $c_6 := c_6(\Omega,T)$ it follows that

$$\begin{aligned}
&\int_0^T \left\| w_K K^m\left(1-\frac{K^m}{K_K}\right) - w_K K^{m-1}\left(1-\frac{K^{m-1}}{K_K}\right)\right\|^2_{L^2(\Omega)} dt \\
&\leq \quad 2\int_0^T \frac{w_K^2}{K_K^2}\left\|(K^m)^2-(K^{m-1})^2\right\|^2_{L^2(\Omega)} + w_K^2\left\|K^m-K^{m-1}\right\|^2_{L^2(\Omega)} dt
\end{aligned}$$

$$
\begin{aligned}
&\leq 2\int_0^T c_5^4 \frac{w_K^2}{K_K^2} \left\|K^m - K^{m-1}\right\|_{H^1(\Omega)}^2 \left\|K^m + K^{m-1}\right\|_{H^1(\Omega)}^2 + w_K^2 c_6^2 \left\|K^m - K^{m-1}\right\|_{H^1(\Omega)}^2 dt \\
&\leq \left(\int_0^T \left(4c_5^4 \frac{w_K^2}{K_K^2}\left[\|K^m\|_{H^1(\Omega)}^2 + \left\|K^{m-1}\right\|_{H^1(\Omega)}^2\right] + 2w_K^2 c_6^2\right) dt\right) \left\|K^m - K^{m-1}\right\|_X^2 \\
&\leq \left(32C^2(\Omega,T) c_5^4 \frac{w_K^2}{K_K^2} T_6 \|K_0\|_{H^1(\Omega)}^2 + 2w_K^2 c_6^2 T_6\right) \left\|K^m - K^{m-1}\right\|_X^2 \\
&\leq \frac{1}{4}\left\|K^m - K^{m-1}\right\|_X^2 ,
\end{aligned}
$$

where

$$
T_6 := \min\left\{\frac{1}{8}, \frac{1}{8\kappa}, \frac{1}{8\lambda}\right\}, \quad k := 32C^2(\Omega,T) c_5^4 \frac{w_K^2}{K_K^2} \|K_0\|_{H^1(\Omega)}^2 , \quad \lambda := 2w_K^2 c_6^2.
$$

Thus, putting all together

$$
\begin{aligned}
&\left\|K^{m+1} - K^m\right\|_X^2 + \left\|N^{m+1} - N^m\right\|_{L^\infty(0,T;L^2(\Omega))}^2 + \left\|H^{m+1} - H^m\right\|_X^2 \\
&\qquad \leq \frac{1}{4}\left(3\left\|K^m - K^{m-1}\right\|_X^2 + \left\|N^m - N^{m-1}\right\|_{L^\infty(0,T;L^2(\Omega))}^2\right) .
\end{aligned}
$$

Therefore, (H^m, N^m, K^m) is a Cauchy sequence in $X \times L^\infty(0,T;L^2(\Omega)) \times X$, from which the existence of a weak solution follows.

Uniqueness. Let (K_1, N_1, H_1) and (K_2, N_2, H_2) be two solutions to (1) - (5). Due to the previous estimates

$$
\|K_1 - K_2\|_X^2 \leq \frac{1}{4}\|K_1 - K_2\|_X^2 \tag{44}
$$

$$
\|H_1 - H_2\|_X^2 \leq \frac{1}{4}\|K_1 - K_2\|_X^2 \tag{45}
$$

$$
\|N_1 - N_2\|_{L^\infty(0,T;L^2(\Omega))}^2 \leq \frac{1}{4}\|N_1 - N_2\|_{L^\infty(0,T;L^2(\Omega))}^2 + \frac{1}{4}\|H_1 - H_2\|_X^2 , \tag{46}
$$

thus $K_1 = K_2$ (44) and with (45) it follows that $H_1 = H_2$. Finally, (46) implies that $N_1 = N_2$. This completes the proof of the uniqueness.

Regularity of the solution. From (24) and (25) follows that (K^m, H^m) is uniformly bounded w.r.t. m in $Y \times Y$, therefore Y is compactly embedded in $L^2(0,T;H^1(\Omega))$. This implies that for $m \to \infty$ we have $(K, H) \in Y \times Y$. □

4. Numerical Simulations

In this section we perform the numerical simulation of the system (6), (7), (8) with the corresonding initial and boundary conditions. We assume the existence of the three involved functions N, K, H in $L^2(0,T;H^1(\Omega))$.

For the space discretisation of the dimensionless system

$$\begin{aligned}
\int_\Omega (N(1-N)-\delta_N NH)\phi d\boldsymbol{x} &= \int_\Omega N_t\phi d\boldsymbol{x}\\
\int_\Omega \rho_K K(1-K)\phi d\boldsymbol{x} &= \int_\Omega K_t\phi d\boldsymbol{x}+\int_\Omega \Delta_K(1-N)\nabla K\nabla\phi d\boldsymbol{x}\\
\int_\Omega \delta_H(K-H)\phi d\boldsymbol{x} &= \int_\Omega H_t\phi d\boldsymbol{x}+\Delta_H\int_\Omega \nabla H\nabla\phi d\boldsymbol{x}
\end{aligned}$$

we use a finite element method. Recall the way in which the constants of the dimensionless system have been defined:

$$\delta_N=\frac{d_N w_H K_K}{d_H w_N},\qquad \rho_K=\frac{w_K}{w_N},\qquad \Delta_K=\frac{D_K}{D_H},\qquad \delta_H=\frac{d_H}{w_N}.$$

Remark 4.1. *The parameter δ_N plays a crucial role. One can show* [8] *that it can characterize the aggressivity of the tumor (also whether it is benign or malign). This will be an important fact for the simulations to follow.*

For the space discretization we approximate the underlying Sobolev space $H^1(\Omega)$ by a finite dimensional subspace $U_n\subset H^1(\Omega)$. Then the solutions to be approximated can be expressed with the aid of basis functions of the subspace.

Let $(b_1,b_2,...,b_n)$ be a basis of U_n. Then the problem reduces to determine functions

$$(N(t,\boldsymbol{x}),K(t,\boldsymbol{x}),H(t,\boldsymbol{x}))\in L^2(0,T;U_n)\times L^2(0,T;U_n)\times L^2(0,T;U_n)$$

which are solutions to the system

$$r_i^N(t) = BN_t \tag{47}$$

$$r_i^K(t) = BK_t+\Delta_K(M-M^*)K(t) \tag{48}$$

$$r_i^H(t) = BH_t+\Delta_H MH(t)\,. \tag{49}$$

Define the matrices $B,M,M^*\in\mathbb{R}^{n\times n}$ by

$$M_{j,k}=\int_\Omega \bigtriangledown b_j\bigtriangledown b_k\,,\qquad M^*_{j,k}=M_{j,k}\cdot N^*\,,\qquad B_{j,k}=\int_\Omega b_jb_k \tag{50}$$

and the left hand sides $r_i^N(t),r_i^K(t),r_i^H(t)\in\mathbb{R}^n$ by

$$r_i^N(t)=\int_\Omega a(N,H)b_i d\boldsymbol{x}\,,\quad r_i^K(t)=\int_\Omega b(K)b_i d\boldsymbol{x}\,,\quad r_i^H(t)=\int_\Omega c(K,H)b_i d\boldsymbol{x}. \tag{51}$$

N^* denotes here an approximation of the function $N(t, \boldsymbol{x})$.

For the time discretization we use the so-called IMEX (implicit-explicit) method (see, e.g. [16], [12]), which allows to rewrite the equations (47) - (49) as a system of linear equations

$$BN(t+\Delta t) = BN(t) + \Delta t r_i^N(t) \tag{52}$$

$$(B + \Delta t \Delta_K (M - M^*))K(t+\Delta t) = BK(t) + \Delta t r_i^K(t) \tag{53}$$

$$(B + \Delta t \Delta_K M)H(t+\Delta t) = BH(t) + \Delta t r_i^H(t), \tag{54}$$

where Δt denotes the magnitude of the time step. This system is numerically solved by using the conjugate gradient procedure.

4.1. **The one dimensional case.**

4.1.1. *Dependence of the system on the normal cells' death rate.*

We choose for the simulation the following parameters:

$$K_N = K_K = 5 \cdot 10^7/cm^3, \quad w_N = w_K = 10^{-6}/s, \quad w_H = 2.2 \cdot 10^{-17}/s$$
$$D_K = 2 \cdot 10^{-10} cm^2/s, \quad D_H = 5 \cdot 10^{-6} cm^2/s, \quad d_H = 7 \cdot 10^{-7}/s$$
$$d_N \in [1.27 \cdot 10^{-4}/M \cdot s, 3.2 \cdot 10^{-3}/M \cdot s],$$

respectively

$$\delta_N \in [0.2, 5], \quad \rho_K = 1.0, \quad \Delta_K = 4 \cdot 10^{-5}, \quad \Delta_H = 1, \quad \delta_H = 0.7 \tag{55}$$

along with the initial values

$$N_0 = 5 \cdot 10^7/cm^3, \quad K_0 = 10^7/cm^3, \quad H_0 = 10^{-6} M,$$

respectively

$$\tilde{N}_0 = 1, \quad \tilde{K}_0 = 0.2, \quad \tilde{H}_0 = 0.1, \tag{56}$$

in accordance to [8]. We also choose a relatively small reabsorption rate d_H, in order to better represent the dependence of normal cell density on their death rate d_N.

4.1.2. *The normal cell density: evolution and dependence on the concentration of H^+ ions.*

The parameter δ_N is a measure of the tumor aggressivity against the normal cells and it is proportional to the death rate d_N of normal cells.

Figure 1a shows the evolution of the normal cell density w.r.t. δ_N. Observe that an aggressive tumor (larger δ_N respectively larger d_N) leads to a faster decay of the normal cell density.

Figure 1b shows the normal cell density depending on the concentration of H^+ ions for several different values of δ_N respectively d_N. In an organism whose

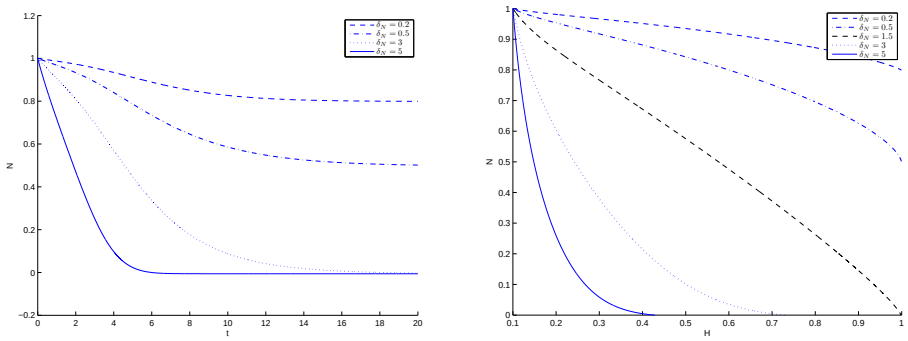


Figure 1: 1a Evolution of the normal cell density for several different values of δ_N. 1b Normal cell density w.r.t. the H^+ ions concentration for several different values of δ_N.

normal cells are more sensitive to pH variations (larger d_N) the density of these cells will decay faster for the same concentration of H^+ ions.

4.1.3. *Dependence of the concentration of H^+ ions on the density of tumor cells.*

Figure 2 shows the dependence of the H^+ ions concentration on the tumor cell density. The production rate of the protons is independent of δ_N.

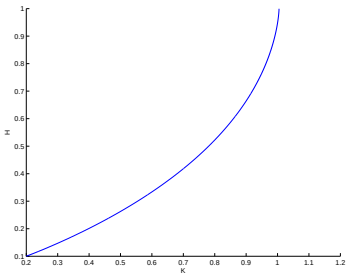


Figure 2: Concentration of H^+ ions w.r.t. tumor cell density

The concentration of H^+ ions grows with the tumor cell density. A detailed investigation of this dependency will be done in the next subsection.

Figures 1 and 2 intuitively endorse the biologically meaningful predictions of the model.

4.1.4. *Dependence of the system on the reabsorption rate of H^+ ions.*

In this subsection we use for the simulations the same parameters as in 4.1.1, however we vary now the reabsorption rate d_H of the protons (and thus the factor

δ_N). The death rate d_N is now fixed. This allows to represent the evolution of normal cell density for various reabsorption rates w.r.t. time and to the concentration of H^+ ions.

Furthermore, we represent the dependence of H^+ ion concentration on the tumor cell density.

The simulation has been performed with the parameters

$$K_N = K_K = 5 \cdot 10^7/\text{cm}^3, \quad w_N = w_K = 10^{-6}/s, \quad w_H = 2.2 \cdot 10^{-17}/\text{s}$$
$$D_K = 2 \cdot 10^{-10}\text{cm}^2/\text{s}, \quad D_H = 5 \cdot 10^{-6}\text{cm}^2/\text{s}, \quad d_N = 9.5 \cdot 10^{-4}/m \cdot s$$
$$d_H \in [5.25 \cdot 10^{-6}/s, 2.1 \cdot 10^{-7}/s],$$

respectively

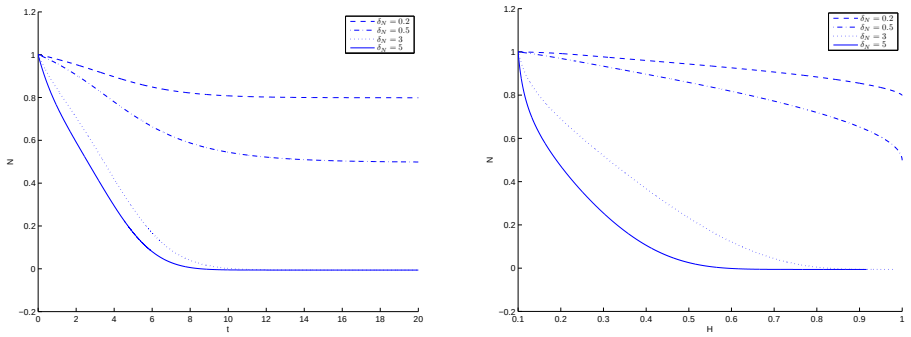
$$\delta_N \in [0.2, 5], \quad \rho_K = 1.0, \quad \Delta_K = 4 \cdot 10^{-5}, \quad \Delta_H = 1, \quad \delta_H \in [5.25, 0.21]$$

and the initial data (56) from [8].

We chose a relatively small death rate d_N in order to provide a more clear picture for the dependence of the normal cell density on the reabsorption rate d_H.

4.1.5. *The normal cell density: time evolution and dependence on the concentration of excessive protons.*

The parameter δ_N provides a measure of tumor aggressivity against normal cells. It is inversely proportional to the proton reabsorption rate d_H.



(a) (b)

Figure 3: 3a: Evolution of the normal cell density for several values of δ_N. 3b: Dependence of the normal cell density on the concentration of excessive proteins for several values of δ_N.

Figure 3a supports the intuitive fact that in an organism which can poorly buffer the issuing excessive protons (smaller d_H, respectively larger δ_N), the pH value -and thus the normal cell density- will decay faster.

Figure 3b shows the normal cell density in dependence on the excessive proton concentration H^+ for several values of δ_N, respectively for various reabsorption

rates d_H. Observe the faster decay of normal cell density (for the same concentration of H^+ ions) relatively to a smaller reabsorption rate of excessive protons.

4.1.6. *Dependence of the concentration of H^+ ions on the tumor cell density.*
Figure 4 illustrates the dependence of the H^+ ion concentration on the cancer cell density for several values of d_H, respectively δ_N.

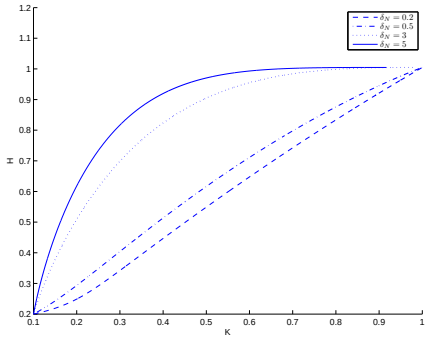


Figure 4: Excessive proton concentration w.r.t. cancer cell density for various δ_N.

Observe the increase in H^+ ion concentration for increasing tumor cell density. In a weaker organism (smaller reabsorption rate d_H/ larger δ_N) this increase is steeper than in a stronger organism (for the same tumor cell density).

Figures 3 and 4 make clear the crucial effect of proton reabsorption rate on the H^+ ion concentration and the normal cell density. In a certain domain with a given proton reabsorption rate one can achieve an artificial increase of this reabsorption rate by administration of substances which increase the pH value. The effect of this would be to slow down the decay of normal cell density; in particular, this can prevent the normal cells to die off. This treatment can therefore operate tumor reduction and constriction of tumor growth. This confirms the cancer treatment approach proposed by Gatenby [8], whereby the patients are given sodium bicarbonate (known to reduce acidity) instead of the much more aggressive chemoterapy.

4.2. **The two dimensional case.** For the 2D simulations we choose the parameters $\delta_N = 2.1$, $\rho_K = 1$, $\Delta_K = 1$, $\Delta_H = 5$, $\delta_H = 2$ and the initial values $K_0 = 0.1 + 0.01\xi(\boldsymbol{x})$, $N_0 = 0.9$, $H_0 = 0.05$.

$\xi(\boldsymbol{x})$ denotes here a standard normal density. The term $0.01\xi(\boldsymbol{x})$ has been introduced in order to provide at the beginning of the simulation a (biologically meaningful) rather irregular tumor cell density in the domain of interest. The latter has been chosen to be the rectangle $[-1, 0] \times [0, 1]$.

The following pictures show the cell density, respectively the concentration of excessive protons in the domain $[-1,0]\times[0,1]$ at several (chronologically ordered) time moments.

Observe how the proton concentration varies proportionally to the tumor cell density, respectively inversely proportional to the normal cell density.

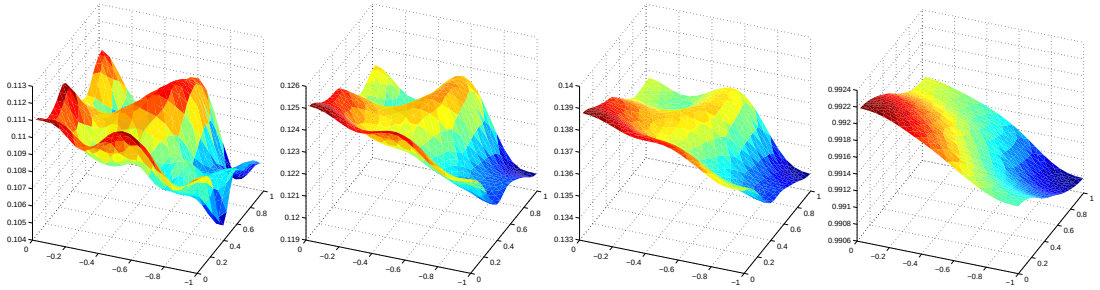


Figure 5: Evolution of tumor cell density at several time moments.

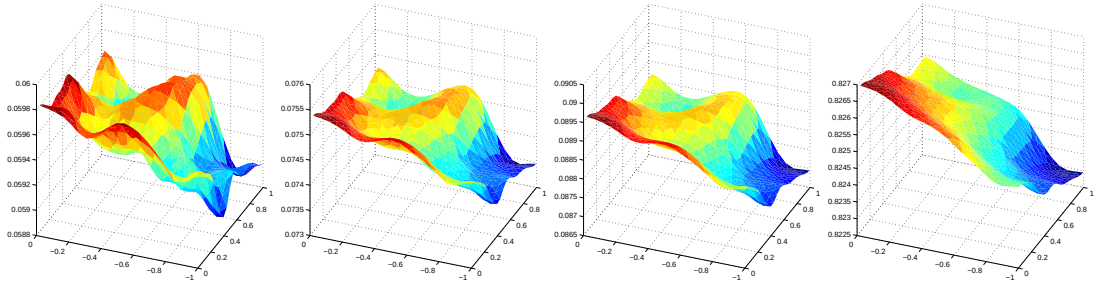


Figure 6: Evolution of excessive proton concentration at several time moments.

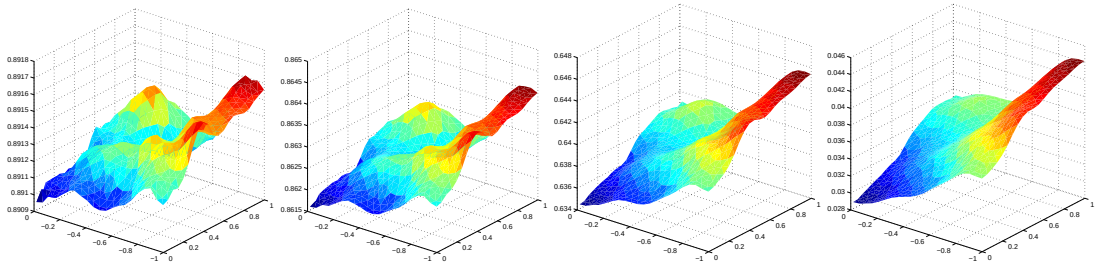


Figure 7: Evolution of normal cell density at several time moments.

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REFERENCES

[1] A.R.A. Anderson, M.A.J. Chaplain, E.L. Newman, R.J.C. Steele, A.M. Thompson, *Mathematical modeling of tumor invasion and metastasis*, J. Theoretical Med. 2 (2000) 129-154.
[2] A. Ashkenazi, W.M. Dixit, *Death receptor: signaling and modulation*, Science 281 (1998) 1305-1308.
[3] L. Bianchini, A. Fasano, *A model combining acid-mediated tumor invasion and nutrient dynamics*, Nonlinear Analysis. Real World Applications 10 (2009) 1955-1975.
[4] Chauviere A, Hillen T, Preziosi L (2007), *Modeling cell movement in anisotropic and heterogeneous tissue: dynamic heterogeneity*, Networks and Heterogeneous Media 2: 333-357.
[5] L. C. Evans, **Partial Differential Equations**. AMS, 1998.
[6] R. A. Gatenby, R.J. Gillies, *Glycolysis in cancer: a potential target for therapy*, Int. J. Biochem. Cell Biol. 39 (2007) 1358-1366.
[7] R. A. Gatenby, *A Change of strategy in the war on cancer*, Nature 459 (2009) 508-509.
[8] R. A. Gatenby, E. T. Gawlinski, *A Reaction-Diffusion Model of Cancer Invasion*, Cancer Research 56 (1996), 5745-5753.
[9] R. A. Gatenby, E. T. Gawlinski, The glycolytic phenotype in carcinogenesis and tumor invasion: insights through mathematical models. Cancer Res. 63 (2003) 3847-3854.
[10] T. Hillen, *(M5) Mesoscopic and macroscopic models for mesenchymal motion.* J. Math. Biol. 53 (2006), 585-616.
[11] H. Izumi, T. Torigoe, H. Ishiguchi, H. Uramoto, Y. Yoshida, M. Tanabe, T. Ise, T. Murakami, T. Yoshida, M. Nomoto, K. Khono, *Cellular pH regulators: potentially promising molecular targets for cancer chemotherapy*, Cancer Treat. Rev. 29 (2003) 541-549.
[12] J. Kelkel, C. Surulescu, *A weak solution approach to a reaction-diffusion system modeling pattern formation on seashells*, Mathematical Methods in the Applied Sciences 32 (2009) 2267-2286.
[13] J. Kelkel, C. Surulescu, *On a stochastic reaction-diffusion system modeling pattern formation on seashells*, J. of Math. Biology 60 (2010) 765-796.
[14] J. Kelkel and C. Surulescu, *On some models for cancer cell migration through tissue*, submitted.
[15] J. Kelkel, C. Surulescu, *A multiscale approach to cell migration in tissue networks*, preprint 03/2010, IANS, University of Stuttgart (submitted).
[16] T. Koto, *Stability of implicit-explicit linear multistep methods for ordinary and delay differential equations*, Frontiers of Mathematics in China 4(1) (2009) 113-129.
[17] J. Morgenroth, *Die Begründung der experimentellen Chemotherapie durch Paul Ehrlich*, Naturwissenschaften 2 (1914) 251-259.
[18] C.-D. Munz, T. Westermann, **Numerische Behandlung gewöhnlicher und partieller Differenzialgleichungen**, Springer, 2009.
[19] A. D. Polyanin, **Handbook of Linear Partial Differential Equations for Engineers and Scientists**, Chapman & Hall, 2001.
[20] K. Smallbone, D.J. Gavaghan, R.A. Gatenby, P.K. Maini, *The role of acidity in solid tumor growth and invasion*, J. of Theoretical Biology 235 (2005) 476-484.
[21] H. Yamaguchi, F. Pixley, J. Condeelis, *Invadopodia and podosomes in tumor invasion*, European J. of Cell Biology 85 (2006) 213-218.

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