On a structured multiscale model for acid-mediated tumor invasion: the effects of adhesion and proliferation

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Abstract

We propose a multiscale model for tumor cell migration in a tissue network. The system of equations involves a structured population model for the tumor cell density, which besides time and position depends on a further variable characterizing the cellular state with respect to the amount of receptors bound to soluble and insoluble ligands. Moreover, this equation features pH-taxis and adhesion, along with an integral term describing proliferation conditioned by receptor binding. The interaction of tumor cells with their surroundings calls for two more equations for the evolution of tissue fibers and acidity (expressed via concentration of extracellular protons), respectively. The resulting ODE-PDE system is highly nonlinear. We prove the global existence of a solution and perform numerical simulations to illustrate its behavior, paying particular attention to the influence of the supplementary structure and of the adhesion.

Keywords: cancer cell migration through tissue, multiscale model, structured population model, pH-taxis, cell-cell and cell-tissue adhesion, receptor binding, nonlocal PDE-ODE system, extracellular proton dynamics, nonlinear diffusion, global existence, integro-differential equations.

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1 Introduction

The migration of tumor cells and the consequent invasion and degradation of normal tissue leading to metastases constitute one of the hallmarks of cancer [30]. They are greatly influenced by the tumor microenvironment, of which the structure and composition of the extracellular matrix (ECM) plays a decisive role. From a simplified viewpoint, the ECM is made up of soluble (e.g., protons -buffered or not- in various chemical compounds, matrix degrading enzymes, proteolytic residuals resulting from degradation of the matrix fibers, etc.) and insoluble (e.g., fibrillar collagen or fibronectin) components, most of them being involved in cell survival, migration, and proliferation, see e.g., [42] and references

therein. At the onset of these processes is the binding of cell surface receptors to both types of ECM components. Thereby, the attachment of insoluble ligands to such receptors [1] is necessary for cell-tissue adhesions. When cells connect to each other via specific receptors (primarily cadherins, see e.g., [33]) cell-cell adhesions are established, the strength of which is essential among others for proliferation and determination of the migration phenotype (e.g., single cell vs. collective motions). The latter then leads to diversity of invasion patterns: those arising from individual cell migrations are diffusive and highly infiltrative, whereas tightly connected cells moving in groups form protruding sheets and strands that maintain contact with the primary site; they can also form 'islands' of cells [2] [25].

There is a plethora of mathematical models related to tumor invasion and accounting in a more or less direct way for cell-cell and cell-matrix adhesions. Most of them describe individual cell behavior and are discrete –in their majority lattice based (e.g., [29, 59], also see [15] for a comprehensive review) or off-lattice (see e.g., [18, 53]). The so-called hybrid models have a semidiscrete character: They specify the evolution of cells in a discrete, individual-based way and couple it to that of some tactic signal (e.g., chemoattractant concentration, density of ECM fibers), the latter being modeled in a continuous way via some reaction-(diffusion) equation, see e.g., [2, 36, 54]. (Semi)discrete models provide the framework for very detailed descriptions of the mechanical and biochemical processes involved in adhesion-mediated cell migration. Continuous models allow for less level of detail and make it rather difficult to explicitly include cell-cell and cell-tissue adhesion; however, they have the advantage of providing deeper insight into the mathematical analysis of the respective systems of equations and, moreover, of affording efficient numerical simulations.

There are different classes of fully continuous models involving cell adhesion; here we will only refer to those relating it to the space-time evolution of the cell density, some of them receiving a multiscale character by including subcellular dynamics in an explicit way. Among the first approaches we mention that in [51], where cell-cell adhesion is indirectly described by a certain kind of 'crowding', namely by letting the cell diffusion coefficient depend on the cell density. Another, still indirect way of investigating the effects of cell-cell adhesion on tumor growth via tumor surface tension has been proposed in [10] and further developed in [13, 43]. A further model class focuses on cell-tissue interactions, described by way of haptotaxis[3], see e.g. [12, 3]. Related multiscale settings also involving the integrin binding dynamics have been proposed in [44] and [45, 58], the latter also investigating the well-posedness of the obtained systems coupling PDEs for the macroscopic quantities (cell and tissue densities) with ODEs (receptor binding dynamics). Pure macroscopic models of tumor invasion featuring haptotaxis and diverse types of nonlinear (and possibly degenerate) diffusion have been investigated (also with respect to global well-posedness) in [65, 66, 67]. Directly incorporating cell-cell adhesion in a continuous, macroscopic formulation requires an adequate description of the mutual cell interactions; this is tightly related to the sensing region over which each cell is able to interact with its immediate and further-away neighbors. Similar considerations apply to cell-tissue interactions. The mentioned idea calls for nonlocal terms in the description of cell adhesions: such terms involve inte-

[1] primarily integrins, a family of heterodimeric transmembrane receptors providing the cell with signals from its surroundings, see e.g., [31, 32]

[2] cell aggregates situated some small distance away from the main tumor and presumably formed by detached cell clusters or cell 'seeding' and subsequent accumulation

[3] type of tactic cell motion biased in the direction of the gradient of some non-diffusing agent, in this context the density of ECM fibers

grals over all spatial points within the sensing region. This led to the model in [4] and its subsequent versions, see e.g., [27, 28, 47, 48]. The model in [37] considers haptotaxis in the 'classical' way (i.e., without integrating over the tissue-sensing region), while cell-cell interactions are described with the aid of such nonlocal terms. Hence, it can be seen as an intermediate setting between the two modeling approaches on the macroscale.

Works concerned with the mathematical analysis of nonlocal models of cell adhesion are less widespread than those addressing modeling and numerical simulations of such processes. In [56] the authors investigated the conditions ensuring boundedness of solutions to an integro-differential equation in 1D with cell-cell and cell-tissue adhesion, linear diffusion, and logistic type source term modeling the evolution of cancer cells invading and degrading the surrounding ECM. A system coupling a reaction-diffusion-haptotaxis equation with linear diffusion and nonlocal terms describing cell-cell and cell-ECM proliferative interactions has been proposed in [60], and the global existence of the solution was proved. Further analytical investigations of nonlocal models with cell-cell adhesion have been performed in [19, 20].

Since the population level behavior of cells is controled by and in turn influences cellular processes taking place on lower scales (individual and subcellular levels), multiscale continuous models connecting two or more of these scales would be desirable. The kinetic theory of active particles (KTAP, see e.g., [8]) offers a framework for addressing this issue. The corresponding models feature kinetic transport equations for the evolution of cell density functions depending on time, position, velocity, and possibly further variables relating to the cell condition and called in KTAP 'activity variables'. The integral terms included in those models describe changes in the (mesoscopic) cell density due to velocity innovations and proliferative actions via cell-cell interactions mediated by modifications of the activity variables. Hapto- and chemotaxis can be introduced on this mesoscopic level in an indirect way by using adequate integral terms accounting for the effects of activity variable dynamics, as in [41]. The resulting setting involves besides mesolevel cell and tissue dynamics also the subcellular receptor binding and the macroscopic evolution of some chemotactic signal, which makes it a three-scale model. While there the effects of cell-tissue reciprocities are described in an indirect way and have a local character, the model can be extended to allow for nonlocal interactions, with the therein proof for global well-posedness still functioning. Yet in the KTAP framework, we introduced in [22] a two-scale model for glioma invasion where the cell-tissue adhesion is characterized by interactions in the integral term featuring a cell turning rate depending on the binding of cell receptors to ECM fibers. The parabolic scaling led to effective equations for the macroscopic cell density involving haptotaxis and a supplementary advection term. The subsequent multiscale models in [24, 23] accounted for cell-tissue interactions in a more explicit way (via receptor-ECM binding), the latter also contributing to the cell proliferation.[4] In this work we retake that idea [5] in the general framework of a structured population model. Indeed, all previous settings can be cast in such a framework, in which the variables of interest (cell and tissue densities, concentrations of some chemicals influencing the cell motion) depend on time, position, and possibly further structure variables (e.g., cell velocity, fiber orientation, cell state: amount of bound receptors -as in this work, phenotype, etc.).

In [21] a cell migration model with cell-cell adhesion and structured by cell age has been proposed to extend previous nonlocal versions with linear diffusion and without further structures [19, 20] [6] and

[4] Cell-cell interactions could be presumably included as proposed in the more general KTAP mentioned above.

[5] see the second integral term on the right hand side of (2.1a)

[6] see also the references therein for further interesting models with nonlocal terms, those in [9, 39] even involving

analyzed with respect to well-posedness, positivity, and long-term behavior of the solution, thereby relying on the semigroup theory. The model proposed in [17] is a structured population model, as well, the variable of interest -cancer cell density- depending on time t, space x, and a further structure variable y, the latter representing the concentration of bound molecules on the cell surface. It is heuristically obtained by using -as e.g., in [4]- the equilibrium of (diffusive, taxis, and adhesion) fluxes, also obtaining as usually the transport term with respect to y which is typical for such structured models. By subsequent integration with respect to the y variable a non-structured, pure macroscopic model for cancer invasion with hapto- and chemotaxis was deduced and numerical simulations have been performed both for the structured and non-structured settings.
In this work we propose a multiscale model for acid-mediated tumor invasion in a tissue network, where the tumor cell density is also structured by the binding state of the cell surface receptors. Thereby, the receptors are assumed to bind both to soluble (to simplify we assume these are only protons) and insoluble components (tissue fibers) of the ECM, the respective concentrations making up the components of the vector of cell states, which constitutes at the same time the structure variable supplementary to space and position. The model includes cell-cell and cell-tissue adhesions, along with a so-called pH-taxis term to account for the bias in the cell motion introduced by the peritumoral acidity. The proliferation of tumor cells is included in a different way than in [17], rather relying on the KTAP approach and particularly on that in [24, 23]. The paper is organized as follows: In the subsequent Section 2 we introduce and explain our model. Section 3 follows, proving the global existence of weak solutions to the introduced system. In Section 4 we perform numerical simulations for a 1D version of the model, in order to illustrate the basic behavior of the solution. Eventually, Section 5 provides a discussion of the results and some comments of the problems which are still to be investigated in this context.

2 The model

We introduce the following model variables: $c(t,x,y)$ denotes the density of cancer cells, $v(t,x)$ represents the density of tissue fibers in the ECM, and $h(t,x)$ denotes the density of extracellular protons. Here $t \geq 0$ represents the time, $x \in \Omega$ the spatial position and $y \in Y$ the concentration of cell surface receptors[7] bound to ECM fibers (integrins) or occupied/activated by protons[8]. We consider the nonlocal PDE-ODE system

$$\begin{aligned}\partial_t c = \nabla\cdot(D(v,h)\nabla c) - \nabla\cdot(\chi(c,h)\nabla h) - \nabla\cdot(c\mathcal{A}) - \partial_y(g(t,x,y,h,v)c)\\ + \int_Y (1-\hat{c})\,\beta(y,\tilde{y})c(t,x,\tilde{y})d\tilde{y} \quad + v(t,x)\sigma(x,v(t,x))\int_Y \kappa(y,\tilde{y})c(t,x,\tilde{y})d\tilde{y}\\ - \delta_c(x,y,h)c, \qquad (t,x,y)\in(0,\infty)\times\Omega\times Y, \end{aligned} \tag{2.1a}$$

$$\partial_t v = -\delta_v v h + \mu_v v\,(1-v-\hat{c})\,, \quad (t,x)\in(0,\infty)\times\Omega, \tag{2.1b}$$

nonlinear and possibly degenerate diffusion

[7] by a slight abuse of definition we will call y an internal variable, which stresses out the fact that its dynamics is acting on the faster, subcellular scale

[8] usually proton dynamics refers to their shuttling across the cell membrane by several transporters like NHE (Na^+ and H^+ exchanger), NDBCE (Na^+ dependent Cl-HCO_3 exchanger), MCTs (monocarboxylate transporters) and AE (Cl-HCO_3 anion exchanger), however there have also been investigated cell receptors –so-called *proton sensing*– which can be activated by acidosis, see e.g., [14, 34, 55]

$$\partial_t h = D_h \Delta h + \frac{\alpha\, \hat{c}}{1+\hat{c}} - \lambda h, \quad (t,x) \in (0,\infty) \times \Omega, \tag{2.1c}$$

where $\Omega \subset \mathbb{R}^n$ is a bounded domain with smooth boundary, $n \in \{1,2,3\}$, and $Y := (0,1) \subset \mathbb{R}$. We denote the total cancer cell density with $\hat{c} = \int_Y c(t,x,\tilde{y})d\tilde{y}$. Throughout the paper, the operators ∇, $\nabla\cdot$, and Δ denote the gradient, divergence, and Laplacian, respectively, with respect to the spatial variable x. The first term on the right hand side of (2.1a) describes nonlinear diffusion, the coefficient of which is assumed to depend on the solution components v and h. Indeed, the way tissue fibers interact with (and are degraded by) soluble components of ECM does influence the motility (and in particular the diffusivity) of tumor cells. The second term on the right hand side in (2.1a) models pH-taxis hence it describes the directed motion of tumor cells towards the pH-gradient, as experimentally observed [5, 49]. A possible choice of the diffusion and pH-taxis coefficients is e.g.,

$$D(v,h) = \frac{hv + h_T}{h_T(1+v)^2} \quad \text{and} \quad \chi(c,h) = \frac{s\, h_T\, c}{(h_T+h)^2}, \tag{2.2}$$

ensuring that the diffusivity of tumor cells is enhanced upon contact between soluble and insoluble components of the ECM, however with a certain saturation with respect to the amount of tissue fibers available for influencing the spread of tumor cells; a too dense ECM is prone to inhibit motility. The concrete form of the pH-taxis coefficient is chosen, too, to account for the influence of cell density and the limitation imposed by the concentration of soluble components. Similar choices have been considered for haptotaxis in a different, but related context in [67, 66]; their particular form is motivated by the interactions between cells and tissue (here between cells and protons) taking place on a fast time scale. The next term in (2.1a) models adhesion, with the nonlocal flux term $c\mathcal{A}(c,v)$ including both cell-cell and cell-tissue interactions. The coefficient $\mathcal{A}(c,v)$ is called *adhesion velocity* and takes the form (see e.g. [27, 47])

$$\mathcal{A}(t,x,y,c,v) = \frac{1}{R}\int_{B_R(0)} F(|\xi|,\rho,h) G\big(t,y,c(t,x+\xi,\cdot),v(t,x+\xi)\big)\frac{\xi}{|\xi|}d\xi$$

with the definition $c(t,x,y) = v(t,x) = 0$ for $x \in \mathbb{R}^n \setminus \bar{\Omega}$ and $(t,y) \in [0,\infty) \times \bar{Y}$. Thereby, $R > 0$ denotes the sensing radius, $F(\cdot,\rho,\cdot)$ represents the interaction force depending on the interaction range ρ, and G gives the effective interactions, mutually between cells and with the surrounding tissue fibers:

$$\begin{aligned} &G(t,y,c(t,x+\xi,\cdot),v(t,x+\xi)) \\ &\quad = \left(\int_Y S_{cc}(t,y,\tilde{y})c(t,x+\xi,\tilde{y})d\tilde{y} + S_{cv}(t,y)v(t,x+\xi)\right)\Big(1-\hat{c}(t,x+\xi)-v(t,x+\xi)\Big)_+ \end{aligned}$$

Here, the coefficients S_{cc} and S_{cv} denote the self-population and the cross-population adhesion coefficients, respectively. They were previously [4, 27, 47, 48] taken to be constants or depend on time only [16]. In [17] they depend, too, on the supplementary structure variable y, however there the focus was not on effectively handling the structured population model, but on deducing a macroscopic description for the evolution of tumor cell density in interaction with tissue and MDEs. Therefore, the issue of these coefficients depending on y was not further addressed there. As in the present work we want to preserve the multiscale, structured setting for our investigations, we account for concrete such choices. They can take e.g., the form

$$S_{cc}(t,y,\tilde{y}) = \frac{y\tilde{y}}{1+y\tilde{y}}, \qquad S_{cv}(t,y) = \frac{y}{1+y},$$

characterizing the interactions between cells of internal state y with cells of internal state $\tilde{y}$, and between cells of internal state y and tissue, respectively. For the interaction force we choose as in [28, 47, 48] $F(r,\rho,h) = \gamma(h)\frac{r}{\rho^2}e^{-\frac{r^2}{2\rho^2}}$, where r denotes the distance from the cell and $\gamma(h)$ the interaction strength: for $\gamma > 0$ there is an attracting interaction, while $\gamma < 0$ means repelling. We also impose the condition $\int_0^\infty \gamma(h)\frac{r}{\rho^2}e^{-\frac{r^2}{2\rho^2}}dr = \rho$. The interaction strength depends on the (locally) available concentration of extracellular protons and is to be chosen nonnegative for $h \leq h_T$ (alcaline regime, attracting case) and negative for $h > h_T$ (acidic regime, repelling case), where h_T denotes an acidity threshold.[9]

The transport term (with respect to y) in (2.1a) originates in the receptor binding dynamics. A simple choice of the function g therein could be obtained by mass action kinetics for the binding of integrins to protons and to tissue fibers. However, in view of the conditions needed subsequently in the proof of the well-posedness we assume that the binding/detachment rates depend on time, position, and the receptor binding states; thus, in a scaled form these bindings are characterized by

$$(1-y) + h \underset{\kappa_h^-(t,x,y)}{\overset{\kappa_h^+(t,x,y)}{\rightleftharpoons}} y, \tag{2.3a}$$

$$(1-y) + v \underset{\kappa_v^-(t,x,y)}{\overset{\kappa_v^+(t,x,y)}{\rightleftharpoons}} y, \tag{2.3b}$$

with $\kappa_h^\pm(t,x,y) := k^\pm(t,x)r_h(y)$ and $\kappa_v^\pm(t,x,y) := K^\pm(t,x)r_v(y)$, with r_h and r_v chosen such that $r_h(0) = r_v(0) = 0$ and $ar_h(1) = br_v(1) = 0$, with $a > b \geq 0$ constants. Moreover, considering that the averaged subcellular dynamics (of receptor binding) happens very fast in comparison to the evolution of cells and tissue, we obtain for the coefficient function g involved in the term of (2.1a) modeling 'advection' with respect to y the form

$$g(t,x,y,h,v) = \frac{ak^+(t,x)r_h(y)h - bK^+(t,x)r_v(y)v}{a-b}(1-y) - \frac{ak^-(t,x)r_h(y)h - bK^-(t,x)r_v(y)v}{a-b}y,$$

The above choice has been made in order to comply with the conditions on the function g in Section 3. Other choices are possible, as well, and we will address in the numerical simulations an even simpler form, with constant attachment and detachment rates (for which, however, our proof below does not work). Notice that we lumped together both types of bound receptors, whether they are bound to soluble or insoluble components of the ECM. This simplification aims at having only a scalar internal variable y, allowing to operate in a more convenient way with the term modeling transport with respect to this variable. A more detailed modeling would have involved in (2.3) the 'reactant' $1-(y_1+y_2)$ on the left hand side and y_1, y_2 on the right hand sides, respectively, and consequently a vector function $g(t,x,y,h,v)$ and a transport term of the form $\nabla_y \cdot (gc)$, calling for corresponding conditions on the boundary of the set $Y = (0,1)\times(0,1)$. Moreover, we did not explicitly account for mutual receptor binding directly relating cell-cell interaction; indeed, the latter is indirectly addressed via bindings to ECM and soluble components (protons) in order to avoid inflating too much the setting; we recall

[9] E.g., one could choose the concentration of H^+ corresponding to a pH value below the normal one of $pH = 7.4$, as the cancer cells are able to survive at lower pH, however they start migrating when their surroundings become too acidic, see e.g. [63].

that our focus is on the joint effects of adhesion, pH-taxis, and nonlinear diffusion, thereby paying increased attention to the source terms in the PDEs under study and showing a way to include lower scale dynamics.

The cell proliferation is characterized by the integral terms on the right hand side of (2.1a). Unlike previous nonlocal models of cell migration (e.g., [27, 28, 47]) featuring logistic type terms or including positional nonlocality [60], it involves the supplementary structure variable y. The rate $\beta(y,\tilde{y})$ in (2.1a) denotes the average amount of cells with receptor binding state y produced per unit time by a cell of state $\tilde{y}$. A concrete form of it could be $\beta(y,\tilde{y}) = \mu_c \frac{1+y\tilde{y}}{1+y+\tilde{y}}$ accounting for the connection between the two types of cells and for a certain limiting of proliferation reported to the total receptor bindings. Further proliferative influences come from the cell-tissue reciprocity, as proposed in [23], where –relying on experimental evidence (see e.g., [31, 32])– we assumed that integrin binding to tissue fibers is at the onset of many processes including (besides motility, invasion, survival) cell division. These considerations lead to a further source term of the form given in the before-to-last term of (2.1a), with $\kappa(y,\tilde{y})$ denoting as in [23] a kernel characterizing the transition from the state $\tilde{y}$ to the state y during such a proliferative (inter)action. Thereby, we only take into account the binding of integrins to tissue fibers and omit any receptor occupancy with protons, as the latter rather impairs proliferation by proton transport across the cell membrane and intracellular acidification. The acid-induced decay is captured in the last term in (2.1a) in a very simplified way. The factor $\sigma(x,v)$ represents some further proliferation limitation when there are too many fibers surrounding the cancer cells, who are thus competing for space. Hence, $\sigma(x,\cdot)$ is supposed to be a decreasing function.

Equation (2.1c) describes the evolution of the extracellular proton concentration, which is produced (in a limited way) by all cells (regardless of their receptor binding states), diffuses, and is depleted (e.g., by buffering, uptake by vasculature, etc.). Notice that h could model other macroscopic concentrations of soluble ECM components, as well. For instance, it could represent the concentration of matrix degrading enzymes (MDEs) which are actually known to be enhanced by an acidic extracellular pH, see e.g., [11, 35] and references therein. Both MDEs and extracellular protons degrade the tissue, thus favorizing the invasion of tumor cells. Acidity-induced tissue degradation is modeled by the first term in (2.1b) for the evolution of tissue density; the second term therein characterizes the restructuring of the tissue in competition with both tissue and tumor cells.

In addition to the above PDEs we impose the boundary conditions

$$\begin{aligned} &D(v,h)\,\partial_\nu c - \chi(c,h)\,\partial_\nu h - c\mathcal{A}\cdot\nu = 0 = \partial_\nu h, \qquad (t,x,y)\in(0,\infty)\times\partial\Omega\times Y,\\ &g(t,x,0,h,v) = g(t,x,1,h,v) = 0, \qquad (t,x,h,v)\in(0,\infty)\times\Omega\times[0,\infty)^2, \end{aligned} \tag{2.4}$$

(where ν denotes the outer unit normal on $\partial\Omega$) and the initial conditions

$$c(0,x,y) = c_0(x,y), \quad v(0,x) = v_0(x), \quad h(0,x) = h_0(x), \qquad (x,y)\in\Omega\times Y. \tag{2.5}$$

3 Global existence of a weak solution

In this section we prove the existence of a global weak solution to (2.1),(2.4),(2.5). We assume that the initial data satisfy

$$c_0\in C^0(\bar{\Omega}\times\bar{Y}), \quad v_0\in C^0(\bar{\Omega}), \quad h_0\in C^1(\bar{\Omega}), \quad c_0\geq 0, \quad v_0\geq 0, \quad h_0\geq 0. \tag{3.1}$$

Moreover, for any $L > 0$ we require the existence of positive constants C_1 and C_2 such that

$$
\begin{aligned}
&D \in C^1([0,\infty)^2), \quad \chi \in C^1([0,\infty)^2) \cap W^{1,\infty}([0,\infty)\times[0,L]), \quad F \in C^1([0,R]\times(0,\infty)\times[0,\infty)),\\
&G \in W^{1,\infty}([0,L]\times\bar{Y}\times[0,\infty)\times[0,L]), \quad g \in C^2([0,\infty)\times\bar{\Omega}\times\bar{Y}\times[0,\infty)^2),\\
&\beta \in C^1(\bar{Y}^2), \quad \sigma \in C^1(\bar{\Omega}\times[0,\infty)), \quad \kappa \in C^1(\bar{Y}^2), \quad \delta_c \in C^1(\bar{\Omega}\times\bar{Y}\times[0,\infty)),\\
&0 < C_2 \le D(v,h) \le C_1 \quad \text{and} \quad \chi(0,h) = 0 \le \chi(c,h) \le C_1(1+c) \quad \text{for all } (c,v,h) \in [0,\infty)\times[0,L]^2,\\
&|G(t,y,c(t,x+\xi,\cdot),v(t,x+\xi))| + |\partial_y(G(t,y,c(t,x+\xi,\cdot),v(t,x+\xi)))|\\
&\le C_1\left(1 + \int_Y c(t,x+\xi,\tilde{y})d\tilde{y}\right) \quad \text{for all } (t,y,x,\xi,c(t),v) \in [0,L]\times\bar{Y}\times\bar{\Omega}\times L^1(\Omega\times Y)\times[0,L],\\
&\delta_c \ge 0, \quad \beta \ge 0, \quad \int_Y \beta(y,\hat{y})dy \ge \beta_2 > 0 \quad \text{for all } \hat{y} \in Y
\end{aligned}
\tag{3.2}
$$

with some constant $\beta_2 > 0$. We will use the following concept of weak solutions.

Definition 3.1 *Let $T \in (0,\infty)$. A weak solution to (2.1),(2.4),(2.5) consists of nonnegative functions*

$$c \in L^2((0,T);W^{1,2}(\Omega\times Y)), \quad v \in L^\infty((0,T)\times\Omega), \quad h \in L^\infty((0,T)\times\Omega)\cap L^2((0,T);W^{1,2}(\Omega))$$

which satisfy for all $\varphi \in C_0^\infty([0,T)\times\bar{\Omega}\times\bar{Y})$ and all $\psi \in C_0^\infty([0,T)\times\bar{\Omega})$ the equations

$$
\begin{aligned}
&-\int_0^T\int_\Omega\int_Y c\partial_t\varphi - \int_\Omega\int_Y c_0\varphi(0,\cdot,\cdot) = -\int_0^T\int_\Omega\int_Y D(v,h)\nabla c\cdot\nabla\varphi\\
&\qquad + \int_0^T\int_\Omega\int_Y \chi(c,h)\nabla h\cdot\nabla\varphi + \int_0^T\int_\Omega\int_Y c\mathcal{A}\cdot\nabla\varphi + \int_0^T\int_\Omega\int_Y g(t,x,y,h,v)c\partial_y\varphi\\
&\qquad + \int_0^T\int_\Omega\int_Y\int_Y\left(1 - \int_Y c(t,x,\tilde{y})d\tilde{y}\right)\beta(y,\hat{y})c(t,x,\hat{y})d\hat{y}\varphi(t,x,y)dydxdt\\
&\qquad + \int_0^T\int_\Omega\int_Y v(t,x)\sigma(x,v(t,x))\int_Y \kappa(y,\hat{y})c(t,x,\hat{y})d\hat{y}\varphi(t,x,y)dydxdt\\
&\qquad - \int_0^T\int_\Omega\int_Y \delta_c(x,y,h)c\varphi,
\end{aligned}
\tag{3.3}
$$

$$
\begin{aligned}
&-\int_0^T\int_\Omega v\partial_t\psi - \int_\Omega v_0\psi(0,\cdot)\\
&\qquad = \int_0^T\int_\Omega\left\{-\delta_v vh + \mu_v v\left(1 - v - \int_Y c(t,x,y)dy\right)\right\}\psi,
\end{aligned}
\tag{3.4}
$$

$$
\begin{aligned}
&-\int_0^T\int_\Omega h\partial_t\psi - \int_\Omega h_0\psi(0,\cdot)\\
&\qquad = -\int_0^T\int_\Omega D_h\nabla h\cdot\nabla\psi + \int_0^T\int_\Omega\left\{\frac{\alpha\int_Y c(t,x,y)dy}{1+\int_Y c(t,x,y)dy} - \lambda h\right\}\psi.
\end{aligned}
\tag{3.5}
$$

(c,v,h) is a global weak solution to (2.1),(2.4),(2.5) if it is a weak solution in $(0,T)\times\Omega\times Y$ for all $T > 0$.

The main result of this section is the existence of a global weak solution.

Theorem 3.2 *Let $n \in \mathbb{N}$, $\Omega \subset \mathbb{R}^n$ be a bounded domain with smooth boundary, and $Y = (0,1) \subset \mathbb{R}$. Assume further that (3.1) and (3.2) are fulfilled. Then there exists a global weak solution to (2.1),(2.4),(2.5) in the sense of Definition 3.1 satisfying in addition*

$$c \in L^\infty_{loc}([0,\infty); L^p(\Omega \times Y)) \cap L^\infty_{loc}([0,\infty) \times \bar{\Omega}; L^1(Y)) \cap L^\infty((0,\infty); L^1(\Omega \times Y)),$$
$$v \in L^\infty((0,\infty) \times \Omega), \quad h \in L^\infty((0,\infty); W^{1,\infty}(\Omega))$$

for all $p \in (1,\infty)$.

We prove this result by adapting the method used in [57]. Namely, for suitable regularizations of (2.1) we prove the existence of global classical solutions by the theory of parabolic equations and a series of estimates in Lebesgue- and Sobolev-spaces. Finally, the Aubin-Lions lemma allows us to deduce appropriate compactness properties which lead to the existence of a global weak solution to the original problem. The main additional difficulty is to adapt the method to cover also (2.1a), which is parabolic in x, but only of first order in y, and contains the nonlocal term $\nabla \cdot (c\mathcal{A})$ (see in particular Lemmas 3.3, 3.7, and 3.8). Unlike most methods for equations of this type, we neither use the theory of semigroups nor the method of characteristics. However, the condition on g in (2.4), the growth conditions on χ and G as well as the positivity of the diffusion coefficient D and its independence of c in (3.2) are important in our proof. It remains an open problem to prove the global existence for weaker conditions on these functions.
For the proof of this result, we approximate (2.1),(2.4),(2.5) for $\varepsilon \in (0,1)$ with the regularized problems

$$\begin{cases} \partial_t c_\varepsilon = \nabla \cdot (D_\varepsilon(v_\varepsilon, h_\varepsilon)\nabla c_\varepsilon) + \varepsilon \partial_y^2 c_\varepsilon - \nabla \cdot (\chi_\varepsilon(c_\varepsilon, h_\varepsilon)\nabla h_\varepsilon) - \nabla \cdot (c_\varepsilon \mathcal{A}_\varepsilon) \\ \qquad -\partial_y(g_\varepsilon(t,x,y,h_\varepsilon,v_\varepsilon)c_\varepsilon) + \int_Y \left(1 - \int_Y c_\varepsilon(t,x,\tilde{y})d\tilde{y}\right)\beta(y,\hat{y})c_\varepsilon(t,x,\hat{y})d\hat{y} \\ \qquad +v_\varepsilon(t,x)\sigma(x,v_\varepsilon(t,x))\int_Y \kappa(y,\hat{y})c_\varepsilon(t,x,\hat{y})d\hat{y} \\ \qquad -\delta_c(x,y,h_\varepsilon)c_\varepsilon, \quad (t,x,y) \in (0,\infty) \times \Omega \times Y, \\ \partial_t v_\varepsilon = -\delta_v v_\varepsilon h_\varepsilon + \mu_v v_\varepsilon \left(1 - v_\varepsilon - \int_Y c_\varepsilon(t,x,y)dy\right), \quad (t,x) \in (0,\infty) \times \Omega, \\ \partial_t h_\varepsilon = D_h \Delta h_\varepsilon + \frac{\alpha \int_Y c_\varepsilon(t,x,y)dy}{1+\int_Y c_\varepsilon(t,x,y)dy} - \lambda h_\varepsilon, \quad (t,x) \in (0,\infty) \times \Omega, \\ D_\varepsilon(v_\varepsilon,h_\varepsilon)\,\partial_\nu c_\varepsilon - \chi_\varepsilon(c_\varepsilon,h_\varepsilon)\,\partial_\nu h_\varepsilon - c_\varepsilon \mathcal{A}_\varepsilon \cdot \nu = 0 = \partial_\nu h_\varepsilon, \qquad (t,x,y) \in (0,\infty) \times \partial\Omega \times Y, \\ \partial_y c_\varepsilon = 0, \qquad (t,x,y) \in (0,\infty) \times \Omega \times \{0,1\}, \\ c_\varepsilon(0,x,y) = c_{0\varepsilon}(x,y), \quad v_\varepsilon(0,x) = v_{0\varepsilon}(x), \quad h_\varepsilon(0,x) = h_{0\varepsilon}(x), \qquad (x,y) \in \Omega \times Y. \end{cases} \tag{3.6}$$

Here, we choose families of functions $c_{0\varepsilon}$, $v_{0\varepsilon}$, $h_{0\varepsilon}$, D_ε, χ_ε, F_ε, G_ε, and g_ε, $\varepsilon \in (0,1)$, such that for any $L > 0$

$$c_{0\varepsilon} \in C^3(\bar{\Omega} \times \bar{Y}), \quad v_{0\varepsilon}, h_{0\varepsilon} \in C^3(\bar{\Omega}), \quad c_{0\varepsilon} \geq 0, \quad v_{0\varepsilon} \geq 0, \quad h_{0\varepsilon} \geq 0,$$
$$D_\varepsilon(v_{0\varepsilon},h_{0\varepsilon})\,\partial_\nu c_{0\varepsilon} - \chi_\varepsilon(c_{0\varepsilon},h_{0\varepsilon})\,\partial_\nu h_{0\varepsilon} - c_{0\varepsilon}\mathcal{A}_\varepsilon \cdot \nu = 0 = \partial_\nu h_{0\varepsilon}, \quad (t,x,y) \in \{0\} \times \partial\Omega \times Y,$$
$$\partial_y c_{0\varepsilon} = 0, \qquad (t,x,y) \in \{0\} \times \Omega \times \{0,1\},$$
$$D_\varepsilon \in C^3([0,\infty)^2), \quad \chi_\varepsilon \in C^3([0,\infty)^2) \cap W^{2,\infty}([0,\infty) \times [0,L]), \quad F_\varepsilon \in C^3([0,R] \times (0,\infty) \times [0,\infty)),$$
$$G_\varepsilon \in C^3([0,\infty) \times \bar{Y} \times [0,\infty)^2) \cap W^{1,\infty}([0,L] \times \bar{Y} \times [0,\infty) \times [0,L]),$$
$$g_\varepsilon \in C^3([0,\infty) \times \bar{\Omega} \times \bar{Y} \times [0,\infty)^2),$$
$$0 < C_4 \leq D_\varepsilon(v,h) \leq C_3 \quad \text{and} \quad \chi_\varepsilon(0,h) = 0 \leq \chi_\varepsilon(c,h) \leq C_3(1+c) \text{ for all } (c,v,h) \in [0,\infty) \times [0,L]^2,$$

$$
\begin{aligned}
&|G_\varepsilon(t,y,c(t,x+\xi,\cdot),v(t,x+\xi))| + |\partial_y(G_\varepsilon(t,y,c(t,x+\xi,\cdot),v(t,x+\xi)))|\\
&\le C_3\left(1+\int_Y c(t,x+\xi,\tilde{y})d\tilde{y}\right) \quad \text{for all } (t,y,x,\xi,c,v)\in[0,L]\times\bar{Y}\times\bar{\Omega}\times L^1(\Omega\times Y)\times[0,L],\\
&g_\varepsilon(t,x,0,h_\varepsilon,v_\varepsilon) = g_\varepsilon(t,x,1,h_\varepsilon,v_\varepsilon) = 0 \quad \text{for all } (t,x,h_\varepsilon,v_\varepsilon)\in(0,\infty)\times\Omega\times[0,\infty)^2,\\
&\mathcal{A}_\varepsilon(t,x,y,c_\varepsilon,v_\varepsilon) = \frac{1}{R}\int_{B_R(0)} F_\varepsilon(|\xi|,\rho,h)G_\varepsilon(t,y,c_\varepsilon(t,x+\xi,\cdot),v_\varepsilon(t,x+\xi))\frac{\xi}{|\xi|}d\xi
\end{aligned}
\tag{3.7}
$$

are satisfied with some positive constants C_3 and C_4 for all $\varepsilon\in(0,1)$, where again we set $c_\varepsilon(t,x,y) = v_\varepsilon(t,x) = 0$ for $x\in\mathbb{R}^n\setminus\bar{\Omega}$ and $(t,y)\in[0,\infty)\times\bar{Y}$ in the definition of $\mathcal{A}_\varepsilon$. In addition, we assume that

$$
\begin{aligned}
&c_{0\varepsilon}\to c_0 \quad \text{in } C^0(\bar{\Omega}\times\bar{Y}), \quad v_{0\varepsilon}\to v_0 \quad \text{in } C^0(\bar{\Omega}), \quad h_{0\varepsilon}\to h_0 \quad \text{in } W^{1,\infty}(\Omega),\\
&D_\varepsilon\to D \quad \text{in } C^1([0,L]^2), \quad \chi_\varepsilon\to\chi \quad \text{in } C^1([0,L]^2)\cap W^{1,\infty}([0,\infty)\times[0,L]),\\
&G_\varepsilon\to G \quad \text{in } W^{1,\infty}([0,T]\times\bar{Y}\times[0,\infty)\times[0,L]),\\
&F_\varepsilon\to F \quad \text{in } C^1([0,R]\times[l,L]\times[0,L]), \quad g_\varepsilon\to g \quad \text{in } C^2([0,T]\times\bar{\Omega}\times\bar{Y}\times[0,L]^2)
\end{aligned}
\tag{3.8}
$$

as $\varepsilon\searrow 0$ for any $0<l<L$ and any $T>0$.

3.1 Global existence for the regularized problems

By adapting the method from [57] we prove the global existence of a classical solution for the approximate problems (3.6) for any $\varepsilon\in(0,1)$. We first show the local existence with a proof similar to [57, Lemma 3.3].

Lemma 3.3 *Let $\varepsilon\in(0,1)$ and assume that (3.2) and (3.7) are fulfilled. Then there exists a maximal existence time $T_\varepsilon\in(0,\infty]$ and functions $c_\varepsilon\in C^{1,2,2}([0,T_\varepsilon)\times\bar{\Omega}\times\bar{Y})$, $v_\varepsilon,h_\varepsilon\in C^{1,2}([0,T_\varepsilon)\times\bar{\Omega})$ solving (3.6) in the classical sense and satisfying*

$$
c_\varepsilon(t,x,y)\ge 0, \quad 0\le v_\varepsilon(t,x)\le\max\left\{\|v_{0\varepsilon}\|_{L^\infty(\Omega)},1\right\}, \quad 0\le h_\varepsilon(t,x)\le\max\left\{\|h_{0\varepsilon}\|_{L^\infty(\Omega)},\frac{\alpha}{\lambda}\right\}
\tag{3.9}
$$

for $(t,x,y)\in[0,T_\varepsilon)\times\bar{\Omega}\times\bar{Y}$. Furthermore, in case of $T_\varepsilon<\infty$

$$
\limsup_{t\nearrow T_\varepsilon}\left(\|c_\varepsilon(t,\cdot,\cdot)\|_{C^0(\bar{\Omega}\times\bar{Y})}+\|h_\varepsilon(t,\cdot)\|_{W^{1,\infty}(\Omega)}\right)=\infty
\tag{3.10}
$$

is fulfilled.

Proof. We fix $\eta\in(0,1)$, $T:=1$, and

$$
A := \|c_{0\varepsilon}\|_{C^{2+\eta}(\bar{\Omega}\times\bar{Y})}+\|v_{0\varepsilon}\|_{C^{2+\eta}(\bar{\Omega})}+\|h_{0\varepsilon}\|_{C^{2+\eta}(\bar{\Omega})}<\infty.
$$

Denoting by $c_{0\varepsilon t}(x,y)$, $v_{0\varepsilon t}(x)$, and $h_{0\varepsilon t}(x)$ the right hand side of the first, second, and third equation of (3.6), respectively, evaluated at $(x,y,t)=(x,y,0)$, we observe that there is a positive constant $C_5(A)$ depending on A such that

$$
B := \|c_{0\varepsilon}\|_{C^\eta(\bar{\Omega}\times\bar{Y})}+\|c_{0\varepsilon t}\|_{C^0(\bar{\Omega}\times\bar{Y})}+\|v_{0\varepsilon}\|_{C^{1+\eta}(\bar{\Omega})}+\|v_{0\varepsilon t}\|_{C^1(\bar{\Omega})}
$$

$$+\|h_{0\varepsilon}\|_{C^\eta(\bar\Omega)} + \|h_{0\varepsilon t}\|_{C^0(\bar\Omega)} \le C_5(A) < \infty \tag{3.11}$$

is fulfilled. We further define

$$\begin{aligned} X \;:=\; \Big\{ & (c_\varepsilon, v_\varepsilon, h_\varepsilon) \in C^{\frac{\eta}{2},\eta,\eta}([0,T]\times\bar\Omega\times\bar Y) \times C^{\frac{1+\eta}{2},1+\eta}([0,T]\times\bar\Omega) \times C^{\frac{\eta}{2},\eta}([0,T]\times\bar\Omega) \;: \\ & c_\varepsilon(0,x,y) = c_{0\varepsilon}(x,y), \quad v_\varepsilon(0,x) = v_{0\varepsilon}(x), \quad h_\varepsilon(0,x) = h_{0\varepsilon}(x), \quad (x,y)\in\Omega\times Y, \\ & \|c_\varepsilon\|_{C^{\frac{\eta}{2},\eta,\eta}([0,T]\times\bar\Omega\times\bar Y)} + \|v_\varepsilon\|_{C^{\frac{1+\eta}{2},1+\eta}([0,T]\times\bar\Omega)} + \|h_\varepsilon\|_{C^{\frac{\eta}{2},\eta}([0,T]\times\bar\Omega)} \le B+3 \Big\} \end{aligned}$$

and choose a function $H\in C^3(\mathbb{R})$ such that

$$H(z) \ge \frac14 \quad \text{for all } z\in\mathbb{R}, \qquad H(z) = 1+z \quad \text{for all } z \ge -\frac12. \tag{3.12}$$

Given fixed $(c_\varepsilon, v_\varepsilon, h_\varepsilon)\in X$, we use (3.2) and (3.7) to deduce from [38, Theorem IV.5.3] and the parabolic comparison principle that there exists a solution $\tilde h_\varepsilon \in C^{1+\frac{\eta}{2},2+\eta}([0,T]\times\bar\Omega)$ to

$$\partial_t \tilde h_\varepsilon = D_h \Delta \tilde h_\varepsilon + \frac{\alpha \int_Y c_\varepsilon(t,x,y)dy}{H\left(\int_Y c_\varepsilon(t,x,y)dy\right)} - \lambda \tilde h_\varepsilon, \quad (t,x)\in(0,\infty)\times\Omega, \tag{3.13}$$

with the homogeneous Neumann boundary condition and initial data $h_{0\varepsilon}$ so that

$$\|\tilde h_\varepsilon\|_{C^{1+\frac{\eta}{2},2+\eta}([0,T]\times\bar\Omega)} \le C_6(A) \tag{3.14}$$

holds with some constant $C_6(A)$. Next, by (3.2), (3.7), [38, Theorem III.5.1], and [40, Theorem 1.1], there exists some $\eta_1\in(0,\eta]$ and a weak solution $\tilde c_\varepsilon \in C^{\frac{1+\eta_1}{2},1+\eta_1,1+\eta_1}([0,T]\times\bar\Omega\times\bar Y)\cap W_2^{\frac12,1,1}([0,T]\times\bar\Omega\times\bar Y)$ of the problem

$$\begin{cases} \partial_t \tilde c_\varepsilon = \nabla\cdot\Big(D_\varepsilon(v_\varepsilon,\tilde h_\varepsilon)\nabla\tilde c_\varepsilon\Big) + \varepsilon\partial_y^2\tilde c_\varepsilon - \chi_\varepsilon(c_\varepsilon,\tilde h_\varepsilon)\Delta\tilde h_\varepsilon - \partial_c(\chi_\varepsilon)(c_\varepsilon,\tilde h_\varepsilon)\nabla\tilde c_\varepsilon\cdot\nabla\tilde h_\varepsilon \\ \qquad -\partial_h(\chi_\varepsilon)(c_\varepsilon,\tilde h_\varepsilon)|\nabla\tilde h_\varepsilon|^2 - \nabla\tilde c_\varepsilon\cdot\mathcal{A}_\varepsilon(t,x,y,c_\varepsilon,v_\varepsilon) - c_\varepsilon\partial_c(\mathcal{A}_\varepsilon)(t,x,y,c_\varepsilon,v_\varepsilon)\cdot\nabla\tilde c_\varepsilon \\ \qquad -c_\varepsilon\partial_v(\mathcal{A}_\varepsilon)(t,x,y,c_\varepsilon,v_\varepsilon)\cdot\nabla v_\varepsilon - \partial_y(g_\varepsilon(t,x,y,\tilde h_\varepsilon,v_\varepsilon)\tilde c_\varepsilon) \\ \qquad +\int_Y\left(1-\int_Y c_\varepsilon(t,x,\tilde y)d\tilde y\right)\beta(y,\hat y)c_\varepsilon(t,x,\hat y)d\hat y \\ \qquad +v_\varepsilon(t,x)\sigma(x,v_\varepsilon(t,x))\int_Y\kappa(y,\hat y)c_\varepsilon(t,x,\hat y)d\hat y - \delta_c(x,y,\tilde h_\varepsilon)\tilde c_\varepsilon, \quad (t,x,y)\in(0,T]\times\Omega\times Y, \\ D_\varepsilon(v_\varepsilon,\tilde h_\varepsilon)\,\partial_\nu\tilde c_\varepsilon - \chi_\varepsilon(c_\varepsilon,\tilde h_\varepsilon)\,\partial_\nu\tilde h_\varepsilon - \tilde c_\varepsilon\mathcal{A}_\varepsilon(t,x,y,c_\varepsilon,v_\varepsilon)\cdot\nu = 0, \qquad (t,x,y)\in(0,\infty)\times\partial\Omega\times Y, \\ \partial_y\tilde c_\varepsilon = 0, \qquad (t,x,y)\in(0,\infty)\times\Omega\times\{0,1\}, \\ \tilde c_\varepsilon(0,x,y) = c_{0\varepsilon}(x,y), \qquad (x,y)\in\Omega\times Y. \end{cases}$$

Applying [40, Theorem 1.1], [38, Theorem IV.5.3], and the comparison principle, we further deduce that $\tilde c_\varepsilon \in C^{1+\frac{\eta_1}{2},2+\eta_1,2+\eta_1}([0,T]\times\bar\Omega\times\bar Y)$ is a classical solution of the latter problem and satisfies

$$\|\tilde c_\varepsilon\|_{C^{1+\frac{\eta_1}{2},2+\eta_1,2+\eta_1}([0,T]\times\bar\Omega\times\bar Y)} \le C_7(A) \tag{3.15}$$

with some constant $C_7(A)$. Moreover, by (3.14), (3.15), the theory of ODEs (see e.g. [50, Section 2.3]), and the comparison principle we get a solution $\tilde v_\varepsilon \in C^{1+\frac{\eta_1}{2},2+\eta_1}([0,T]\times\bar\Omega)$ to the second equation of (3.6) (with $\tilde c_\varepsilon$ and $\tilde h_\varepsilon$ instead of c_ε and h_ε) with initial data $v_{0\varepsilon}$ which fulfills

$$\tilde v_\varepsilon \ge 0 \quad \text{in } [0,T]\times\bar\Omega, \qquad \|\tilde v_\varepsilon\|_{C^{1+\frac{\eta_1}{2},2+\eta_1}([0,T]\times\bar\Omega)} + \|\partial_t\tilde v_\varepsilon\|_{C^{\frac{1+\eta_1}{2},1+\eta_1}([0,T]\times\bar\Omega)} \le C_8(A) \tag{3.16}$$

with some constant $C_8(A)$. Here, the Hölder estimates with respect to x follow from the regularity of $\tilde{c}_\varepsilon$ and $\tilde{h}_\varepsilon$, an application of Gronwall's inequality to $\tilde{v}_\varepsilon(t,x_1)-\tilde{v}_\varepsilon(t,x_2)$, and similar applications of Gronwall's inequality for derivatives of $\tilde{v}_\varepsilon$. In particular, in view of the definitions of $c_{0\varepsilon t}(x,y)$, $v_{0\varepsilon t}(x)$, and $h_{0\varepsilon t}(x)$ before (3.11), the estimates (3.14)–(3.16) together with (3.12) imply that $c_{0\varepsilon t}(x,y)=\partial_t\tilde{c}_\varepsilon(0,x,y)$, $v_{0\varepsilon t}(x)=\partial_t\tilde{v}_\varepsilon(0,x)$, and $h_{0\varepsilon t}(x)=\partial_t\tilde{h}_\varepsilon(0,x)$ hold for $(x,y)\in\bar{\Omega}\times\bar{Y}$ and that there is $T_0\in(0,T]$ depending only on A such that

$$\|\tilde{c}_\varepsilon\|_{C^{\frac{\eta}{2},\eta,\eta}([0,T_0]\times\bar{\Omega}\times\bar{Y})}+\|\tilde{v}_\varepsilon\|_{C^{\frac{1+\eta}{2},1+\eta}([0,T_0]\times\bar{\Omega})}+\|\tilde{h}_\varepsilon\|_{C^{\frac{\eta}{2},\eta}([0,T_0]\times\bar{\Omega})}\le B+3 \tag{3.17}$$

is fulfilled. For the latter estimate we used that $T_0\le 1$ implies that $\|\psi\|_{C^{\frac{\eta}{2}}([0,T_0])}\le\|\psi\|_{C^1([0,T_0])}$ holds for any $\psi\in C^1([0,T_0])$. Now, setting $T:=T_0$ and using (3.14)–(3.17), we conclude that $\mathcal{F}:X\to X,\mathcal{F}(c_\varepsilon,v_\varepsilon,h_\varepsilon):=(\tilde{c}_\varepsilon,\tilde{v}_\varepsilon,\tilde{h}_\varepsilon)$ is a well defined and compact map. Therefore, in view of Schauder's fixed point theorem $\mathcal{F}$ has a fixed point $(c_\varepsilon,v_\varepsilon,h_\varepsilon)$. By the above reasoning, c_ε is a classical solution to the first equation of (3.6) with the respective boundary and initial conditions so that the parabolic comparison principle implies

$$c_\varepsilon(t,x,y)\ge 0,\quad (t,x,y)\in[0,T)\times\bar{\Omega}\times\bar{Y}.$$

Hence, in view of (3.12) and (3.13), h_ε is a solution to the third equation of (3.6). Therefore, by the above reasoning, the fixed point $(c_\varepsilon,v_\varepsilon,h_\varepsilon)$ of $\mathcal{F}$ is a classical solution to (3.6) in $(0,T)\times\Omega\times Y$, has the claimed regularity properties, and satisfies (3.9), where the remaining estimates

$$v_\varepsilon(t,x)\le\max\left\{\|v_{0\varepsilon}\|_{L^\infty(\Omega)},1\right\},\quad 0\le h_\varepsilon(t,x)\le\max\left\{\|h_{0\varepsilon}\|_{L^\infty(\Omega)},\frac{\alpha}{\lambda}\right\}$$

for $(t,x)\in[0,T)\times\bar{\Omega}$ are consequences of standard comparison principles.
Finally, in order to prove (3.10), suppose that $T_\varepsilon<\infty$ and assume for contradiction that there is $C_9>0$ such that

$$\|c_\varepsilon\|_{L^\infty((0,T_\varepsilon)\times\Omega\times Y)}+\|h_\varepsilon\|_{L^\infty((0,T_\varepsilon);W^{1,\infty}(\Omega))}\le C_9. \tag{3.18}$$

In conjunction with (3.2), (3.7), (3.9), and (3.6), this implies that

$$\partial_t c_\varepsilon=\nabla_{\hat{x}}\cdot a_\varepsilon(\hat{x},t,\nabla_{\hat{x}}c_\varepsilon)+b_\varepsilon(\hat{x},t)\quad\text{in }(\Omega\times Y)\times(0,T_\varepsilon),$$

where $\hat{x}:=(x,y)\in\mathbb{R}^{n+1}$,

$$a_\varepsilon(\hat{x},t,\xi)\cdot\xi\ge\frac{1}{2}\min\{C_4,\varepsilon\}|\xi|^2-\psi_0(\hat{x},t),\quad |a_\varepsilon(\hat{x},t,\xi)|\le(C_3+1)|\xi|+\psi_1(\hat{x},t)$$

is fulfilled for all $(\hat{x},t,\xi)\in(\Omega\times Y)\times(0,T_\varepsilon)\times\mathbb{R}^{n+1}$ with $\psi_0,\psi_1,b_\varepsilon\in L^\infty((0,T_\varepsilon)\times\Omega\times Y)$. Hence, by [52, Theorem 1.3 and Remark 1.4] and (3.7), we have

$$\|c_\varepsilon\|_{C^{\frac{\eta_2}{2},\eta_2,\eta_2}([0,T_\varepsilon]\times\bar{\Omega}\times\bar{Y})}\le C_{10} \tag{3.19}$$

with some constants $C_{10}>0$ and $\eta_2\in(0,1)$. Then, by [38, Theorem IV.5.3],

$$\|h_\varepsilon\|_{C^{1+\frac{\eta_2}{2},2+\eta_2}([0,T_\varepsilon]\times\bar{\Omega})}\le C_{11}$$

holds with some $C_{11} > 0$. In conjunction with (3.19) and Gronwall's inequality, this implies like in (3.16) that

$$\|v_\varepsilon\|_{C^{\frac{\eta_2}{2},\eta_2}([0,T_\varepsilon]\times\bar{\Omega})} \le C_{12}$$

with some constant C_{12}. Using next [40, Theorem 1.1] for c_ε and afterwards [50, Theorem 2 in Section 2.3] for v_ε, we deduce that

$$\|c_\varepsilon\|_{C^{\frac{1+\eta_3}{2},1+\eta_3,1+\eta_3}([0,T_\varepsilon]\times\bar{\Omega}\times\bar{Y})} + \|v_\varepsilon\|_{C^{\frac{1+\eta_3}{2},1+\eta_3}([0,T_\varepsilon]\times\bar{\Omega})} \le C_{13}$$

is fulfilled with some constants $C_{14} > 0$ and $\eta_3 \in (0, \eta_2]$. Since in addition A with $\eta = \eta_3$ is finite, (3.14)–(3.16) imply that

$$A_1 := \|c_\varepsilon\|_{C^{1+\frac{\eta_4}{2},2+\eta_4,2+\eta_4}([0,T_\varepsilon]\times\bar{\Omega}\times\bar{Y})} + \|v_\varepsilon\|_{C^{1+\frac{\eta_4}{2},2+\eta_4}([0,T_\varepsilon]\times\bar{\Omega})} + \|h_\varepsilon\|_{C^{1+\frac{\eta_4}{2},2+\eta_4}([0,T_\varepsilon]\times\bar{\Omega})} < \infty$$

is satisfied with some $\eta_4 \in (0, \eta_3]$. By using the first part of this proof, this solution can be extended to a classical solution of (3.6) in $(0, T_\varepsilon + \frac{T_0}{2}) \times \Omega \times Y$ with some $T_0 = T_0(A_1) > 0$. Since this contradicts the maximality of T_ε, (3.10) is proved. □

In order to prove the global existence for (3.6) we will show appropriate estimates for c_ε and h_ε which are independent of $\varepsilon \in (0,1)$. To this end, the heat semigroup in Ω with homogeneous Neumann boundary conditions is denoted by $(e^{t\Delta})_{t\ge 0}$ and $\lambda_1 > 0$ is the corresponding first non-zero eigenvalue of $-\Delta$ in Ω. Then there exists a constant $C_5 > 0$ such that

$$\|\nabla e^{t\Delta} v\|_{L^\rho(\Omega)} \le C_5 \left(1 + t^{-\frac{1}{2}-\frac{N}{2}(\frac{1}{r}-\frac{1}{\rho})}\right) e^{-\lambda_1 t}\|v\|_{L^r(\Omega)} \qquad \text{for all } t > 0 \tag{3.20}$$

$$\|\nabla e^{t\Delta} w\|_{L^p(\Omega)} \le C_5 \|w\|_{W^{1,p}(\Omega)} \qquad \text{for all } t > 0 \tag{3.21}$$

are fulfilled for any $v \in L^r(\Omega)$, $w \in C^1(\bar{\Omega})$ with $\partial_\nu w = 0$ on $\partial\Omega$, $1 \le r \le \rho \le \infty$ and $p \in [2, \infty]$. (3.21) for $p < \infty$ and (3.20) are proved e.g. in [64, Lemma 1.3], while (3.21) for $p = \infty$ follows from [46, (2.39)] for $t \le 1$ and from (3.20) for $t \ge 1$.
As a first step, we have the following elementary estimates by slightly adapting the method from [57, Lemma 3.4].

Lemma 3.4 *Assume that (3.1), (3.2), (3.7), and (3.8) are satisfied. Then there exists $C > 0$ such that for all $\varepsilon \in (0,1)$ the solution to (3.6) from Lemma 3.3 fulfills for all $t \in (0, T_\varepsilon)$*

$$\int_Y \int_\Omega c_\varepsilon(t,x,y)\,dxdy$$

$$\le m := \max\left\{ \sup_{\varepsilon\in(0,1)} \int_Y \int_\Omega c_{0\varepsilon}\,dxdy, \frac{|\Omega|\left(\|\beta\|_{L^\infty(\bar{Y}^2)} + L_1\|\sigma\|_{L^\infty(\bar{\Omega}\times[0,L_1])}\|\kappa\|_{L^\infty(\bar{Y}^2)}\right)}{\beta_2} \right\}, \tag{3.22}$$

$$\|h_\varepsilon(t,\cdot)\|_{W^{1,\infty}(\Omega)} \le C, \tag{3.23}$$

where $L_1 := \max\left\{ \sup_{\varepsilon\in(0,1)} \|v_{0\varepsilon}\|_{L^\infty(\Omega)}, 1 \right\} < \infty.$

Proof. In view of the boundary conditions in (3.6) and the condition on g_ε in (3.7), an integration of the first equation of (3.6) in conjunction with (3.2), (3.9), $Y=(0,1)$, and Hölder's inequality implies

$$\begin{aligned}
&\frac{d}{dt}\int_Y\int_\Omega c_\varepsilon dxdy\\
&\quad=\int_Y\int_\Omega\int_Y\left(1-\int_Y c_\varepsilon(t,x,\tilde{y})d\tilde{y}\right)\beta(y,\hat{y})c_\varepsilon(t,x,\hat{y})d\hat{y}dxdy\\
&\qquad+\int_Y\int_\Omega v_\varepsilon(t,x)\sigma(x,v_\varepsilon(t,x))\int_Y\kappa(y,\hat{y})c_\varepsilon(t,x,\hat{y})d\hat{y}dxdy-\int_Y\int_\Omega\delta_c(x,y,h_\varepsilon)c_\varepsilon dxdy\\
&\quad\le\left(\|\beta\|_{L^\infty(\bar{Y}^2)}+L_1\|\sigma\|_{L^\infty(\bar{\Omega}\times[0,L_1])}\|\kappa\|_{L^\infty(\bar{Y}^2)}\right)\int_Y\int_\Omega c_\varepsilon(t,x,y)dxdy\\
&\qquad-\beta_2\int_\Omega\left(\int_Y c_\varepsilon(t,x,y)dy\right)^2dx\\
&\quad\le\left(\|\beta\|_{L^\infty(\bar{Y}^2)}+L_1\|\sigma\|_{L^\infty(\bar{\Omega}\times[0,L_1])}\|\kappa\|_{L^\infty(\bar{Y}^2)}\right)\int_Y\int_\Omega c_\varepsilon(t,x,y)dxdy\\
&\qquad-\frac{\beta_2}{|\Omega|}\left(\int_\Omega\int_Y c_\varepsilon(t,x,y)dydx\right)^2,\quad t\in(0,T_\varepsilon).
\end{aligned}$$

Using an ODE comparison argument along with (3.8), we deduce that (3.22) is valid.
Next, the third equation of (3.6) and Lemma 3.3 yield

$$h_\varepsilon(t,\cdot)=e^{tD_h\Delta}h_{0\varepsilon}+\int_0^t e^{(t-s)D_h\Delta}\left(\frac{\alpha\int_Y c_\varepsilon(s,\cdot,y)dy}{1+\int_Y c_\varepsilon(s,\cdot,y)dy}-\lambda h_\varepsilon(s,\cdot)\right)ds,\quad t\in(0,T_\varepsilon).$$

Combining this with (3.20), (3.21), and (3.9), we obtain

$$\begin{aligned}
&\|\nabla h_\varepsilon(t,\cdot)\|_{L^\infty(\Omega)}\\
&\quad\le\left\|\nabla e^{tD_h\Delta}h_{0\varepsilon}\right\|_{L^\infty(\Omega)}+\int_0^t\left\|\nabla e^{(t-s)D_h\Delta}\left(\frac{\alpha\int_Y c_\varepsilon(s,\cdot,y)dy}{1+\int_Y c_\varepsilon(s,\cdot,y)dy}-\lambda h_\varepsilon(s,\cdot)\right)\right\|_{L^\infty(\Omega)}ds\\
&\quad\le C_5\|h_{0\varepsilon}\|_{W^{1,\infty}(\Omega)}\\
&\qquad+C_5\int_0^t\left(1+(D_h(t-s))^{-\frac{1}{2}}\right)e^{-\lambda_1 D_h(t-s)}\left\|\frac{\alpha\int_Y c_\varepsilon(s,\cdot,y)dy}{1+\int_Y c_\varepsilon(s,\cdot,y)dy}-\lambda h_\varepsilon(s,\cdot)\right\|_{L^\infty(\Omega)}ds\\
&\quad\le C_5\sup_{\varepsilon\in(0,1)}\|h_{0\varepsilon}\|_{W^{1,\infty}(\Omega)}\\
&\qquad+C_5\left(\alpha+\lambda\sup_{\varepsilon\in(0,1)}\|h_\varepsilon\|_{L^\infty((0,T_\varepsilon)\times\Omega)}\right)\int_0^\infty\left(1+(D_h\sigma)^{-\frac{1}{2}}\right)e^{-\lambda_1 D_h\sigma}d\sigma
\end{aligned}$$

for all $t\in(0,T_\varepsilon)$. In view of (3.1), (3.8), and (3.9), this proves (3.23). □

Next we prove bounds on c_ε in $L^\infty((0,T);L^p(\Omega\times Y))$ for any $p\in(1,\infty)$. This is an important step towards the global existence for (3.6).

Lemma 3.5 *Let (3.1), (3.2), (3.7), and (3.8) be fulfilled and $T \in (0,\infty)$ such that $T \leq T_\varepsilon$. For any $p \in (1,\infty)$ there exists a constant $C_p(T) > 0$ such that for any $\varepsilon \in (0,1)$ the solution to (3.6) from Lemma 3.3 satisfies*

$$\|c_\varepsilon(t,\cdot,\cdot)\|_{L^p(\Omega\times Y)} \leq C_p(T) \qquad \text{for all } t \in (0,T), \tag{3.24}$$

$$\int_0^T \int_Y \int_\Omega (c_\varepsilon+1)^{p-2} |\nabla c_\varepsilon|^2 \, dxdydt \leq C_p(T). \tag{3.25}$$

Proof. We fix $p \in (1,\infty)$ and multiply the first equation of (3.6) by $(c_\varepsilon+1)^{p-1}$. By using integration by parts, the boundary conditions in (3.6), Hölder's and Young's inequality along with (3.2), (3.7), (3.8), and Lemma 3.4, we have

$$\begin{aligned}
&\frac{d}{dt}\frac{1}{p}\int_Y\int_\Omega (c_\varepsilon+1)^p dxdy \\
&\quad = \int_Y\int_\Omega (c_\varepsilon+1)^{p-1}\partial_t c_\varepsilon \, dxdy \\
&\quad = -(p-1)\int_Y\int_\Omega D_\varepsilon(v_\varepsilon,h_\varepsilon)(c_\varepsilon+1)^{p-2}|\nabla c_\varepsilon|^2 \, dxdy - \varepsilon(p-1)\int_Y\int_\Omega (c_\varepsilon+1)^{p-2}|\partial_y c_\varepsilon|^2 \, dxdy \\
&\qquad + (p-1)\int_Y\int_\Omega \chi_\varepsilon(c_\varepsilon,h_\varepsilon)(c_\varepsilon+1)^{p-2}\nabla h_\varepsilon\cdot\nabla c_\varepsilon \, dxdy \\
&\qquad + (p-1)\int_Y\int_\Omega c_\varepsilon(c_\varepsilon+1)^{p-2}\mathcal{A}_\varepsilon\cdot\nabla c_\varepsilon \, dxdy \\
&\qquad - (p-1)\int_Y\int_\Omega \left(\partial_y g_\varepsilon(t,x,y,h_\varepsilon,v_\varepsilon)c_\varepsilon + g_\varepsilon(t,x,y,h_\varepsilon,v_\varepsilon)\partial_y c_\varepsilon\right)(c_\varepsilon+1)^{p-1} \, dxdy \\
&\qquad + \int_Y\int_\Omega\int_Y \left(1-\int_Y c_\varepsilon(t,x,\tilde{y})d\tilde{y}\right)\beta(y,\hat{y})c_\varepsilon(t,x,\hat{y})d\hat{y}(c_\varepsilon(t,x,y)+1)^{p-1} \, dxdy \\
&\qquad + \int_Y\int_\Omega v_\varepsilon(t,x)\sigma(x,v_\varepsilon(t,x))\int_Y \kappa(y,\hat{y})c_\varepsilon(t,x,\hat{y})d\hat{y}(c_\varepsilon(t,x,y)+1)^{p-1} \, dxdy \\
&\qquad - \int_Y\int_\Omega \delta_c(x,y,h_\varepsilon)c_\varepsilon(c_\varepsilon+1)^{p-1} \, dxdy \\
&\quad \leq -(p-1)C_4\int_Y\int_\Omega (c_\varepsilon+1)^{p-2}|\nabla c_\varepsilon|^2 \, dxdy \\
&\qquad + (p-1)C_3\int_Y\int_\Omega (c_\varepsilon+1)^{p-1}|\nabla h_\varepsilon|\,|\nabla c_\varepsilon| \, dxdy \\
&\qquad + (p-1)C_6(T)(1+m)\int_Y\int_\Omega (c_\varepsilon+1)^{p-1}|\nabla c_\varepsilon| \, dxdy \\
&\qquad + (p-1)C_6(T)\int_Y\int_\Omega (c_\varepsilon+1)^p \, dxdy + \frac{p-1}{p}\int_Y\int_\Omega \partial_y g_\varepsilon(t,x,y,h_\varepsilon,v_\varepsilon)(c_\varepsilon+1)^p \, dxdy \\
&\qquad + C_7\int_Y\int_\Omega (c_\varepsilon(t,x,y)+1)^p \, dxdy + C_7\int_Y (c_\varepsilon+1)^p \, dxdy \\
&\quad \leq -\frac{(p-1)C_4}{2}\int_Y\int_\Omega (c_\varepsilon+1)^{p-2}|\nabla c_\varepsilon|^2 \, dxdy + \frac{(p-1)C_3^2}{C_4}\int_Y\int_\Omega (c_\varepsilon+1)^p|\nabla h_\varepsilon|^2 \, dxdy
\end{aligned}$$

$$+\frac{(p-1)C_6^2(T)(1+m)^2}{C_4}\int_Y\int_\Omega (c_\varepsilon+1)^p\,dxdy + C_8(T)\int_Y\int_\Omega (c_\varepsilon+1)^p\,dxdy$$
$$\le -\frac{(p-1)C_4}{2}\int_Y\int_\Omega (c_\varepsilon+1)^{p-2}|\nabla c_\varepsilon|^2\,dxdy + C_9(T)\int_Y\int_\Omega (c_\varepsilon+1)^p\,dxdy \tag{3.26}$$

for all $t\in(0,T)$ with positive constants $C_6(T), C_7, C_8(T), C_9(T)$ which do not depend on $\varepsilon\in(0,1)$ and $t\in(0,T)$. Then by Gronwall's inequality along with (3.1) and (3.8) we deduce that (3.24) is valid, while (3.25) follows from (3.24) by integrating (3.26) with respect to $t\in(0,T)$. □

Now we are in a position to prove the global existence for each of the approximate problems (3.6) by standard Hölder estimates.

Lemma 3.6 *Assume that (3.1), (3.2), (3.7), and (3.8) are satisfied. Then for each $\varepsilon\in(0,1)$ the solution to (3.6) from Lemma 3.3 exists globally in time and we have $T_\varepsilon=\infty$.*

Proof. We fix $\varepsilon\in(0,1)$ and assume for contradiction that $T_\varepsilon\in(0,\infty)$. Then (3.2), (3.7), (3.9), (3.23), (3.24), and (3.6) imply that

$$\partial_t c_\varepsilon = \nabla_{\hat{x}}\cdot a_\varepsilon(\hat{x},t,\nabla_{\hat{x}}c_\varepsilon)+b_\varepsilon(\hat{x},t)\quad \text{in } (\Omega\times Y)\times(0,T_\varepsilon),$$

where $\hat{x}:=(x,y)\in\mathbb{R}^{n+1}$,

$$a_\varepsilon(\hat{x},t,\xi)\cdot\xi\ge\frac{1}{2}\min\{C_4,\varepsilon\}|\xi|^2-\psi_0(\hat{x},t),\quad |a_\varepsilon(\hat{x},t,\xi)|\le(C_3+1)|\xi|+\psi_1(\hat{x},t)$$

is fulfilled for all $(\hat{x},t,\xi)\in(\Omega\times Y)\times(0,T_\varepsilon)\times\mathbb{R}^{n+1}$ with $\psi_0,\psi_1,b_\varepsilon\in L^\infty((0,T_\varepsilon);L^p(\Omega\times Y))$ for any $p\in(1,\infty)$. Hence, by [52, Theorem 1.3 and Remark 1.4] and (3.7), we have

$$\|c_\varepsilon\|_{C^{\frac{\eta}{2},\eta,\eta}([0,T_\varepsilon]\times\bar{\Omega}\times\bar{Y})}\le C_6$$

with some constants $C_6>0$ and $\eta\in(0,1)$. In view of (3.23) and (3.10), this contradicts the assumption that T_ε is finite and proves the lemma. □

3.2 Global weak solution to the original problem

In this subsection we prove the existence of a global weak solution to (2.1),(2.4),(2.5) with the help of appropriate compactness properties of the solutions to (3.6). In addition to Lemma 3.5 we first need bounds on the derivative $\partial_y c_\varepsilon$.

Lemma 3.7 *Let (3.1), (3.2), (3.7), and (3.8) be satisfied and $T\in(0,\infty)$. Then for any $p\in(1,\infty)$ there exists a constant $C_p(T)>0$ such that for all $\varepsilon\in(0,1)$ the solution to (3.6) from Lemma 3.3 fulfills*

$$\int_0^T\int_Y\int_\Omega |\partial_y c_\varepsilon|^p\,dxdydt\le C_p(T). \tag{3.27}$$

Proof. We fix $p\in(3,\infty)$ and remark that parabolic regularity theory (see [38]) applied to the first equation of (3.6) implies that $c_\varepsilon\in C^\infty((0,\infty)\times\Omega\times Y)$. Hence, we may use (3.6), the condition on

g_ε in (3.7), integration by parts, (3.2), (3.7), (3.8), (3.22), (3.23), Young's and Hölder's inequality to obtain

$$
\begin{aligned}
&\frac{d}{dt}\frac{1}{p}\int_Y\int_\Omega |\partial_y c_\varepsilon|^p\,dxdy\\
&\quad=\int_Y\int_\Omega |\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon\,\partial_y(\partial_t c_\varepsilon)\,dxdy\\
&\quad=\int_Y\int_\Omega \partial_y\left(\nabla\cdot(D_\varepsilon(v_\varepsilon,h_\varepsilon)\nabla c_\varepsilon)\right)|\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon\,dxdy+\varepsilon\int_Y\int_\Omega \partial_y^3 c_\varepsilon|\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon\,dxdy\\
&\qquad-\int_Y\int_\Omega \partial_y\left(\nabla\cdot(\chi_\varepsilon(c_\varepsilon,h_\varepsilon)\nabla h_\varepsilon)\right)|\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon\,dxdy\\
&\qquad-\int_Y\int_\Omega \partial_y\left(\nabla\cdot(c_\varepsilon\mathcal{A}_\varepsilon)\right)|\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon\,dxdy\\
&\qquad-\int_Y\int_\Omega \partial_y^2(g_\varepsilon(t,x,y,h_\varepsilon,v_\varepsilon)c_\varepsilon)|\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon\,dxdy\\
&\qquad+\int_Y\int_\Omega\int_Y\left(1-\int_Y c_\varepsilon(t,x,\tilde{y})d\tilde{y}\right)\partial_y\beta(y,\hat{y})c_\varepsilon(t,x,\hat{y})d\hat{y}|\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon\,dxdy\\
&\qquad+\int_Y\int_\Omega v_\varepsilon(t,x)\sigma(x,v_\varepsilon(t,x))\int_Y\partial_y\kappa(y,\hat{y})c_\varepsilon(t,x,\hat{y})d\hat{y}|\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon\,dxdy\\
&\qquad-\int_Y\int_\Omega \partial_y(\delta_c(x,y,h_\varepsilon)c_\varepsilon)|\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon\,dxdy\\
&\quad\le-(p-1)\int_Y\int_\Omega D_\varepsilon(v_\varepsilon,h_\varepsilon)|\partial_y c_\varepsilon|^{p-2}|\nabla(\partial_y c_\varepsilon)|^2\,dxdy-\varepsilon(p-1)\int_Y\int_\Omega|\partial_y c_\varepsilon|^{p-2}(\partial_y^2 c_\varepsilon)^2\,dxdy\\
&\qquad+(p-1)\int_Y\int_\Omega \partial_c\chi_\varepsilon(c_\varepsilon,h_\varepsilon)|\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon\nabla h_\varepsilon\cdot\nabla(\partial_y c_\varepsilon)\,dxdy\\
&\qquad+(p-1)\int_Y\int_\Omega |\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon\,\mathcal{A}_\varepsilon\cdot\nabla(\partial_y c_\varepsilon)\,dxdy\\
&\qquad+(p-1)\int_Y\int_\Omega c_\varepsilon|\partial_y c_\varepsilon|^{p-2}\partial_y\mathcal{A}_\varepsilon\cdot\nabla(\partial_y c_\varepsilon)\,dxdy\\
&\qquad-\int_Y\int_\Omega\left(\partial_y^2 g_\varepsilon\,c_\varepsilon|\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon+2\partial_y g_\varepsilon|\partial_y c_\varepsilon|^p+g_\varepsilon\partial_y^2 c_\varepsilon|\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon\right)dxdy\\
&\qquad+C_6\int_Y\int_\Omega\left(1+\left(\int_Y c_\varepsilon(t,x,\tilde{y})d\tilde{y}\right)^2\right)|\partial_y c_\varepsilon|^{p-1}\,dxdy\\
&\qquad-\int_Y\int_\Omega\left(\partial_y\delta_c(x,y,h_\varepsilon)\,c_\varepsilon|\partial_y c_\varepsilon|^{p-2}\partial_y c_\varepsilon+\delta_c(x,y,h_\varepsilon)|\partial_y c_\varepsilon|^p\right)dxdy\\
&\quad\le-(p-1)C_4\int_Y\int_\Omega|\partial_y c_\varepsilon|^{p-2}|\nabla(\partial_y c_\varepsilon)|^2\,dxdy+(p-1)C_7\int_Y\int_\Omega|\partial_y c_\varepsilon|^{p-1}|\nabla(\partial_y c_\varepsilon)|\,dxdy\\
&\qquad+(p-1)(1+m)C_8(T)\int_Y\int_\Omega|\partial_y c_\varepsilon|^{p-1}|\nabla(\partial_y c_\varepsilon)|\,dxdy\\
&\qquad+(p-1)(1+m)C_8(T)\int_Y\int_\Omega c_\varepsilon|\partial_y c_\varepsilon|^{p-2}|\nabla(\partial_y c_\varepsilon)|\,dxdy
\end{aligned}
$$

$$
\begin{aligned}
&+ C_8(T) \int_Y \int_\Omega \left(c_\varepsilon |\partial_y c_\varepsilon|^{p-1} + |\partial_y c_\varepsilon|^p \right) \, dxdy + \frac{1}{p} \int_Y \int_\Omega \partial_y g_\varepsilon |\partial_y c_\varepsilon|^p \, dxdy \\
&+ C_6 \int_Y \int_\Omega \left(1 + \left(\int_Y c_\varepsilon(t,x,\tilde{y}) d\tilde{y} \right)^2 \right)^p \, dxdy + C_6 \int_Y \int_\Omega |\partial_y c_\varepsilon|^p \, dxdy \\
&+ C_7 \int_Y \int_\Omega \left(c_\varepsilon |\partial_y c_\varepsilon|^{p-1} + |\partial_y c_\varepsilon|^p \right) \, dxdy \\
\leq & - \frac{(p-1)C_4}{4} \int_Y \int_\Omega |\partial_y c_\varepsilon|^{p-2} |\nabla(\partial_y c_\varepsilon)|^2 \, dxdy \\
&+ \frac{(p-1)(C_7^2 + (1+m)^2 C_8^2(T))}{C_4} \int_Y \int_\Omega |\partial_y c_\varepsilon|^p \, dxdy \\
&+ \frac{(p-1)(1+m)^2 C_8^2(T)}{C_4} \int_Y \int_\Omega c_\varepsilon^2 |\partial_y c_\varepsilon|^{p-2} \, dxdy \\
&+ C_8(T) \int_Y \int_\Omega c_\varepsilon^p \, dxdy + 2C_8(T) \int_Y \int_\Omega |\partial_y c_\varepsilon|^p \, dxdy + \frac{C_9(T)}{p} \int_Y \int_\Omega |\partial_y c_\varepsilon|^p \, dxdy \\
&+ C_{10} \left(1 + \int_\Omega \int_Y c_\varepsilon^{2p}(t,x,\tilde{y}) d\tilde{y} dx \right) + C_6 \int_Y \int_\Omega |\partial_y c_\varepsilon|^p \, dxdy \\
&+ C_7 \int_Y \int_\Omega c_\varepsilon^p \, dxdy + 2C_7 \int_Y \int_\Omega |\partial_y c_\varepsilon|^p \, dxdy \\
\leq & - \frac{(p-1)C_4}{4} \int_Y \int_\Omega |\partial_y c_\varepsilon|^{p-2} |\nabla(\partial_y c_\varepsilon)|^2 \, dxdy + (p-1) C_{11}(T) \int_Y \int_\Omega |\partial_y c_\varepsilon|^p \, dxdy \\
&\frac{(p-1)(1+m)^2 C_8^2(T)}{C_4} \int_Y \int_\Omega \left(c_\varepsilon^p + |\partial_y c_\varepsilon|^p \right) \, dxdy \\
&+ C_{11}(T) \int_Y \int_\Omega c_\varepsilon^p \, dxdy + C_{10} + C_{10} \int_Y \int_\Omega c_\varepsilon^{2p} \, dxdy \\
\leq & - \frac{(p-1)C_4}{4} \int_Y \int_\Omega |\partial_y c_\varepsilon|^{p-2} |\nabla(\partial_y c_\varepsilon)|^2 \, dxdy + (p-1) C_{12}(T) \int_Y \int_\Omega |\partial_y c_\varepsilon|^p \, dxdy \\
&+ C_{12}(T) \int_Y \int_\Omega c_\varepsilon^p \, dxdy + C_{10} + C_{10} \int_Y \int_\Omega c_\varepsilon^{2p} \, dxdy
\end{aligned} \tag{3.28}
$$

for all $t \in (0,T)$ with positive constants C_6, C_7, $C_8(T)$, $C_9(T)$, C_{10}, $C_{11}(T)$, and $C_{12}(T)$, which may depend on p, but are independent of $\varepsilon \in (0,1)$. In view of Lemmas 3.5 and 3.6, an application of Gronwall's inequality to (3.28) along with (3.1) and (3.8) implies (3.27) for $p > 3$. Since $(0,T) \times \Omega \times Y$ is bounded, the lemma is proved for any $p \in (1,\infty)$. □

A final preparation for the compactness of $(v_\varepsilon)_{\varepsilon \in (0,1)}$ is the following L^∞ bound for $\int_Y c \, dy$ locally in time which is also of interest on its own.

Lemma 3.8 *Assume that (3.1), (3.2), (3.7), and (3.8) are fulfilled and $T \in (0,\infty)$. Let further $u_\varepsilon(t,x) := \int_Y c_\varepsilon(t,x,y) \, dy$ for $(t,x) \in [0,\infty) \times \bar{\Omega}$, where c_ε is the function from Lemma 3.3. Then there exists a constant $C(T) > 0$ such that for any $\varepsilon \in (0,1)$ we have*

$$
\|u_\varepsilon\|_{L^\infty((0,T)\times\Omega)} \leq C(T). \tag{3.29}
$$

Proof. By integrating the first equation of (3.6) with respect to $y \in Y$ and using the boundary conditions for c_ε as well as the condition on g_ε in (3.7), we obtain

$$\begin{aligned}
\partial_t u_\varepsilon &= \int_Y \partial_t c_\varepsilon \, dy \\
&= \nabla \cdot (D_\varepsilon(v_\varepsilon, h_\varepsilon)\nabla u_\varepsilon) - \nabla \cdot \int_Y (\chi_\varepsilon(c_\varepsilon, h_\varepsilon)\nabla h_\varepsilon + c_\varepsilon \mathcal{A}_\varepsilon) \, dy \\
&\quad + \int_Y \int_Y \left(1 - \int_Y c_\varepsilon(t,x,\tilde{y}) d\tilde{y}\right) \beta(y,\hat{y}) c_\varepsilon(t,x,\hat{y}) \, d\hat{y} dy \\
&\quad + \int_Y v_\varepsilon(t,x)\sigma(x, v_\varepsilon(t,x)) \int_Y \kappa(y,\hat{y}) c_\varepsilon(t,x,\hat{y}) d\hat{y} dy - \int_Y \delta_c(x,y,h_\varepsilon) c_\varepsilon \, dy
\end{aligned} \tag{3.30}$$

for $(t,x) \in (0,\infty)\times\Omega$. Hence, in view of (3.6), (3.2), (3.7), and Lemmas 3.3–3.6, $u_\varepsilon \in C^{1,2}([0,\infty)\times\bar{\Omega})$ is a solution to

$$\begin{cases} \partial_t u_\varepsilon = \nabla \cdot (\tilde{D}_\varepsilon(t,x)\nabla u_\varepsilon) + \nabla \cdot (\tilde{f}_\varepsilon(t,x)) + \tilde{g}_\varepsilon(t,x), & (t,x) \in (0,\infty)\times\Omega, \\ \left(\tilde{D}_\varepsilon(t,x)\nabla u_\varepsilon + \tilde{f}_\varepsilon(t,x)\right)\cdot \nu = 0, & (t,x) \in (0,\infty)\times\partial\Omega, \end{cases} \tag{3.31}$$

where $\tilde{D}_\varepsilon$ and $\tilde{f}_\varepsilon$ are C^1-functions and $\tilde{g}_\varepsilon$ is continuous. In addition, we have $\tilde{D}_\varepsilon \geq C_4 > 0$ and, for any fixed $T \in (0,\infty)$ and $p_0, q_1, q_2 \in (1,\infty)$, there are appropriate constants such that $\|\tilde{f}_\varepsilon\|_{L^\infty((0,T);L^{q_1}(\Omega))} \leq C_{q_1}(T)$, $\|\tilde{g}_\varepsilon\|_{L^\infty((0,T);L^{q_2}(\Omega))} \leq C_{q_2}(T)$, and $\|u_\varepsilon\|_{L^\infty((0,T);L^{p_0}(\Omega))} \leq C_{p_0}(T)$ are satisfied. Hence, we first fix $m = 1$, $q_1 > n+2$, and $q_2 > \frac{n+2}{2}$, and then apply [61, Lemma A.1] with some $p_0 > 1$ large enough to conclude that (3.29) is valid with some constant $C(T) > 0$ for all $\varepsilon \in (0,1)$. We remark that the proof of [61, Lemma A.1] is still valid for the boundary condition in (3.31) (the original proof is given for $\nabla u_\varepsilon \cdot \nu = 0 = \tilde{f}_\varepsilon \cdot \nu$ on $(0,T)\times\partial\Omega$). As $C(T)$ only depends on Ω, C_4, $C_{q_1}(T)$, $C_{q_2}(T)$, $C_{p_0}(T)$, and $\sup_{\varepsilon\in(0,1)} \|u_\varepsilon(0,\cdot)\|_{L^\infty(\Omega)}$, we deduce from (3.1) and (3.8) that $C(T)$ does not depend on $\varepsilon \in (0,1)$. □

Now we are in a position to prove the announced precompactness of the solution components with a method similar to [57, Lemma 3.8].

Lemma 3.9 *Let (3.1), (3.2), (3.7), and (3.8) be fulfilled and $T \in (0,\infty)$. Then for the solution to (3.6) from Lemma 3.3 we have that $(c_\varepsilon)_{\varepsilon\in(0,1)}$ is strongly precompact in $L^2((0,T)\times\Omega\times Y)$, while $(v_\varepsilon)_{\varepsilon\in(0,1)}$ and $(h_\varepsilon)_{\varepsilon\in(0,1)}$ are strongly precompact in $L^2((0,T)\times\Omega)$.*

Proof. By (3.2), (3.7), and Lemmas 3.3–3.6 there exists a constant $C_6(T) > 0$ such that for any $\varphi \in C_0^\infty(\Omega\times Y)$ and each $\varepsilon \in (0,1)$ we have

$$\begin{aligned}
&\int_Y \int_\Omega \partial_t c_\varepsilon \varphi \, dxdy \\
&\quad = -\int_Y \int_\Omega D_\varepsilon(v_\varepsilon, h_\varepsilon)\nabla c_\varepsilon \cdot \nabla\varphi \, dxdy - \varepsilon \int_Y \int_\Omega \partial_y c_\varepsilon \, \partial_y \varphi \, dxdy \\
&\qquad + \int_Y \int_\Omega \chi_\varepsilon(c_\varepsilon, h_\varepsilon)\nabla h_\varepsilon \cdot \nabla\varphi \, dxdy + \int_Y \int_\Omega c_\varepsilon \mathcal{A}_\varepsilon \cdot \nabla\varphi \, dxdy \\
&\qquad + \int_Y \int_\Omega g_\varepsilon(t,x,y,h_\varepsilon,v_\varepsilon) c_\varepsilon \partial_y \varphi \, dxdy
\end{aligned}$$

$$
\begin{aligned}
&+\int_Y\int_\Omega\int_Y\left(1-\int_Y c_\varepsilon(t,x,\tilde{y})d\tilde{y}\right)\beta(y,\hat{y})c_\varepsilon(t,x,\hat{y})\,d\hat{y}\varphi(x,y)\,dxdy\\
&+\int_Y\int_\Omega v_\varepsilon(t,x)\sigma(x,v_\varepsilon(t,x))\int_Y\kappa(y,\hat{y})c_\varepsilon(t,x,\hat{y})\,d\hat{y}\varphi(x,y)\,dxdy-\int_Y\int_\Omega\delta_c(x,y,h_\varepsilon)c_\varepsilon\varphi\,dxdy\\
&\le\left[C_6(T)+C_3\left(\int_Y\int_\Omega|\nabla c_\varepsilon|^2\,dxdy\right)^{\frac{1}{2}}+\left(\int_Y\int_\Omega|\partial_y c_\varepsilon|^2\,dxdy\right)^{\frac{1}{2}}\right]\|\varphi\|_{W_0^{1,2}(\Omega\times Y)}
\end{aligned}
$$

for all $t\in(0,T)$. In conjunction with (3.25) and (3.27), this implies the uniform boundedness of $(\partial_t c_\varepsilon)_{\varepsilon\in(0,1)}$ in $L^2((0,T);(W_0^{1,2}(\Omega\times Y))^*)$. Moreover, $(c_\varepsilon)_{\varepsilon\in(0,1)}$ is uniformly bounded in $L^2((0,T);W^{1,2}(\Omega\times Y))$ by Lemmas 3.5 and 3.7, $W^{1,2}(\Omega\times Y)$ is compactly embedded into $L^2(\Omega\times Y)$, and $L^2(\Omega\times Y)\subset W_0^{1,2}(\Omega\times Y))^*$. Hence, the Aubin-Lions lemma (see e.g. [62, Theorem 2.1 in Chapter III]) yields the strong precompactness of $(c_\varepsilon)_{\varepsilon\in(0,1)}$ in $L^2((0,T);L^2(\Omega\times Y))$.
In a similar way we obtain from Lemmas 3.4 and 3.5 that $(\partial_t h_\varepsilon)_{\varepsilon\in(0,1)}$ and $(h_\varepsilon)_{\varepsilon\in(0,1)}$ are uniformly bounded in $L^2((0,T);(W_0^{1,2}(\Omega))^*)$ and in $L^2((0,T);W^{1,2}(\Omega))$, respectively. Therefore, we deduce the strong precompactness of $(h_\varepsilon)_{\varepsilon\in(0,1)}$ in $L^2((0,T);L^2(\Omega))$ due to the Aubin-Lions lemma.
Next, let $\mathcal{D}\subset\mathbb{R}^s$ be a bounded domain with some $s\in\mathbb{N}$. We recall that by Kolmogorov-Riesz a set $\mathcal{M}\subset L^2(\mathcal{D})$ is strongly precompact in $L^2(\mathcal{D})$ if and only if

$$
\sup_{f\in\mathcal{M}}\|f\|_{L^2(\mathcal{D})}<\infty\quad\text{and}\quad\lim_{z\to 0}\left(\sup_{f\in\mathcal{M}}\|f^z-f\|_{L^2(\mathcal{D})}\right)=0,
$$

where $z\in\mathbb{R}^s$ and $f^z(\zeta):=f(\zeta+z)$ for $\zeta\in\mathcal{D}$ such that $(\zeta+z)\in\mathcal{D}$ and $f^z(\zeta):=0$ if $(\zeta+z)\in\mathbb{R}^s\setminus\mathcal{D}$.
In order to prove the claimed precompactness of $(v_\varepsilon)_{\varepsilon\in(0,1)}$ we set $\mathcal{D}:=(0,T)\times\Omega$ and $\zeta:=(t,x)\in\mathcal{D}$. Integrating the second equation of (3.6), recalling the definition of u_ε in Lemma 3.8, and using (3.9) and (3.29), we obtain constants $C_7(T)$ and $C_8(T)$ such that

$$
\begin{aligned}
&\frac{d}{dt}\int_\Omega(v_\varepsilon^z-v_\varepsilon)^2(t,x)\,dx\\
&\qquad\le C_7(T)\int_\Omega\left[\left(|v_\varepsilon^z-v_\varepsilon|+|u_\varepsilon^z-u_\varepsilon|+|h_\varepsilon^z-h_\varepsilon|\right)|v_\varepsilon^z-v_\varepsilon|\right](t,x)\,dx\\
&\qquad\le C_8(T)\int_\Omega\left(|v_\varepsilon^z-v_\varepsilon|^2+|u_\varepsilon^z-u_\varepsilon|^2+|h_\varepsilon^z-h_\varepsilon|^2\right)(t,x)\,dx
\end{aligned}
$$

is fulfilled for all $t\in(0,T)$, $\varepsilon\in(0,1)$ and $z\in\mathbb{R}^{n+1}$. Thus, Gronwall's inequality yields the existence of $C_9(T)>0$ such that

$$
\begin{aligned}
&\sup_{\varepsilon\in(0,1)}\|v_\varepsilon^z-v_\varepsilon\|_{L^2((0,T)\times\Omega)}\\
&\qquad\le C_9(T)\sup_{\varepsilon\in(0,1)}\left(\|v_{0\varepsilon}^z-v_{0\varepsilon}\|_{L^2(\Omega)}+\|c_\varepsilon^z-c_\varepsilon\|_{L^2((0,T)\times\Omega\times Y)}+\|h_\varepsilon^z-h_\varepsilon\|_{L^2((0,T)\times\Omega)}\right)
\end{aligned}
\tag{3.32}
$$

for all $\varepsilon\in(0,1)$ and $z\in\mathbb{R}^{n+1}$. In view of the strong precompactness of $(c_\varepsilon)_{\varepsilon\in(0,1)}$ in $L^2((0,T)\times\Omega\times Y)$, of $(h_\varepsilon)_{\varepsilon\in(0,1)}$ in $L^2((0,T)\times\Omega)$ and of $(v_{0\varepsilon})_{\varepsilon\in(0,1)}$ in $L^2(\Omega)$ by (3.8), we deduce from Kolmogorov-Riesz that the right hand side of (3.32) converges to 0 as $z\to 0$. As $(v_\varepsilon)_{\varepsilon\in(0,1)}$ is uniformly bounded in $L^2((0,T)\times\Omega)$ by (3.9), its strong precompactness in $L^2((0,T)\times\Omega)$ follows from Kolmogorov-Riesz.

□

Finally, we are in a position to prove our main result, namely the existence of a global weak solution to (2.1),(2.4),(2.5).

Proof of Theorem 3.2. By Lemma 3.9 along with Lemmas 3.3–3.8 there exist a sequence $(\varepsilon_j)_{j\in\mathbb{N}} \subset (0,1)$ with $\varepsilon_j \searrow 0$ as $j \to \infty$ and functions

$$c \in L^\infty_{loc}([0,\infty); L^p(\Omega \times Y)) \cap L^\infty_{loc}([0,\infty) \times \bar{\Omega}; L^1(Y)) \cap L^\infty((0,\infty); L^1(\Omega \times Y))$$
$$\cap L^2_{loc}([0,\infty); W^{1,2}(\Omega \times Y)), \quad v \in L^\infty((0,\infty) \times \Omega), \quad h \in L^\infty((0,\infty); W^{1,\infty}(\Omega))$$

for all $p \in (1,\infty)$ such that

$$c_\varepsilon \to c \quad \text{strongly in } L^2_{loc}([0,\infty); L^2(\Omega \times Y)) \text{ and a.e. in } (0,\infty) \times \Omega \times Y,$$
$$v_\varepsilon \to v \quad \text{and} \quad h_\varepsilon \to h \quad \text{strongly in } L^2_{loc}([0,\infty); L^2(\Omega)) \text{ and a.e. in } (0,\infty) \times \Omega,$$
$$\nabla c_\varepsilon \rightharpoonup \nabla c \quad \text{and} \quad \partial_y c_\varepsilon \rightharpoonup \partial_y c \quad \text{weakly in } L^2_{loc}([0,\infty); L^2(\Omega \times Y)),$$
$$\nabla h_\varepsilon \rightharpoonup \nabla h \quad \text{weakly in } L^2_{loc}([0,\infty); L^2(\Omega))$$

are fulfilled as $\varepsilon = \varepsilon_j \searrow 0$. When combined with (3.1), (3.2), (3.7), (3.8), and the dominated convergence theorem, these properties allow us to pass to the limit as $\varepsilon = \varepsilon_j \searrow 0$ in the weak formulation of (3.6) corresponding to (3.3)–(3.5). We conclude that (c, v, h) is a global weak solution to (2.1),(2.4),(2.5) in the sense of Definition 3.1 which satisfies the additional regularity properties claimed in Theorem 3.2. □

4 Numerical simulations

We carried out the numerical simulations by using the DUNE framework [6, 7]. The implementation allows for simulations in different space dimensions, but in the following we only consider the 1D case. Using a structured grid with meshwidth h, we first discretize in space using (similarly to [28]) a finite volume formulation, where we discretize the advective terms by using upwind stabilization. In the same way we discretize the structure variable $y \in Y$ by using finite volumes, which is equivalent to a binning of the structure variable y and then treating the classes as individual species.

To incorporate the nonlocal evaluation of the adhesion velocity $\mathcal{A}$ we employ an IMEX approach, where $\mathcal{A}$ is evaluated explicitly with respect to the previous time step, while the coupled nonlinear reaction-diffusion-advection system is solved implicitly. The resulting nonlinear system is solved using a Newton scheme and an ILU preconditioned CG solver for the linearized problem.

We compute on a 1D domain of length $h = 0.6\ mm$ with a resolution of 400 discretization cells. The time step size is controlled depending on the convergence of the Newton scheme and is at most $\tau = 10s$, which allows to keep the splitting error small and to capture the fast dynamics, in particular in the first time steps. The total simulation time covers $172800\,s = 48\,h$. If not indicated differently we use a resolution of $\frac{1}{9}$ in Y.

For the initial conditions we chose a total tumor population of $\hat{c} = 0.7$ in the interval $x = 0 \ldots 0.1\ mm$ and a homogeneous distribution along Y. The tissue fiber density v is chosen such that $v + \hat{c} \leq 1$; in particular we set $v = (1-\hat{c})^{1.2}$, and h is chosen as $10^{-1.4+\hat{c}} kMol/cm^3$, which means that the pH value ranges between 6.6 and 7.4. The model functions and coefficients are summarized in Table 1 below.

Model functions
$D(v,h) \coloneqq D_c \frac{hv+h_T}{h_T(1+v)}$
$\chi(c,h) \coloneqq \tilde{s}_h \frac{h_T c}{(h_T+h)^2}$
$g(t,x,y,h,v) \coloneqq \frac{1}{2}(k^+ \frac{h}{h_T} + K^+ v)(1-y) - \frac{1}{2}(k^- + K^-)y$
$\beta(y,\tilde{y}) \coloneqq \mu_c \frac{1+y\tilde{y}}{1+y+\tilde{y}}$
$\kappa(y,\tilde{y}) \coloneqq \mu_c \frac{y}{2} e^{-\frac{y}{2}}$
$\sigma(x,v) \coloneqq (1-v)$
$\delta_c(x,y,h) \coloneqq \tilde{\delta}_c y \frac{h}{h_T}$
$\delta_v \coloneqq \tilde{\delta}_v \frac{1}{h_T}$
$\alpha \coloneqq 2\lambda h_T$
$S_{cc}(t,y,\tilde{y}) \coloneqq \tilde{S}_{cc} \frac{y\tilde{y}}{1+y\tilde{y}}$
$S_{cv}(t,y) \coloneqq \tilde{S}_{cv} \frac{y}{1+y}$
$\gamma(h) \coloneqq -\log_{10}(h/h_T)$

Constant	*Value*	*Unit*
D_c	$2.1 \cdot 10^{-11}$	$\frac{cm^2}{s}$
$\tilde{s}_h$	$1.6 \cdot 10^{-9}$	$\frac{cm}{s}$
k^+, k^-	$3 \cdot 10^{-4}$	s^{-1}
K^+, K^-	0.1	s^{-1}
μ_c	$2 \cdot 10^{-5}$	s^{-1}
μ_v	$5 \cdot 10^{-7}$	s^{-1}
$\tilde{\delta}_c$	$5 \cdot 10^{-10}$	s^{-1}
$\tilde{\delta}_v$	$5 \cdot 10^{-9}$	s^{-1}
h_T	0.1	$\frac{kMol}{cm^3}$
λ	$5 \cdot 10^{-7}$	s^{-1}
ρ	$3 \cdot 10^{-3}$	cm
R	$5 \cdot 10^{-3}$	cm
$\tilde{S}_{cc}$	0.1	
$\tilde{S}_{cv}$	2.0	

Table 1: Choice of model functions (left) and constants (right).

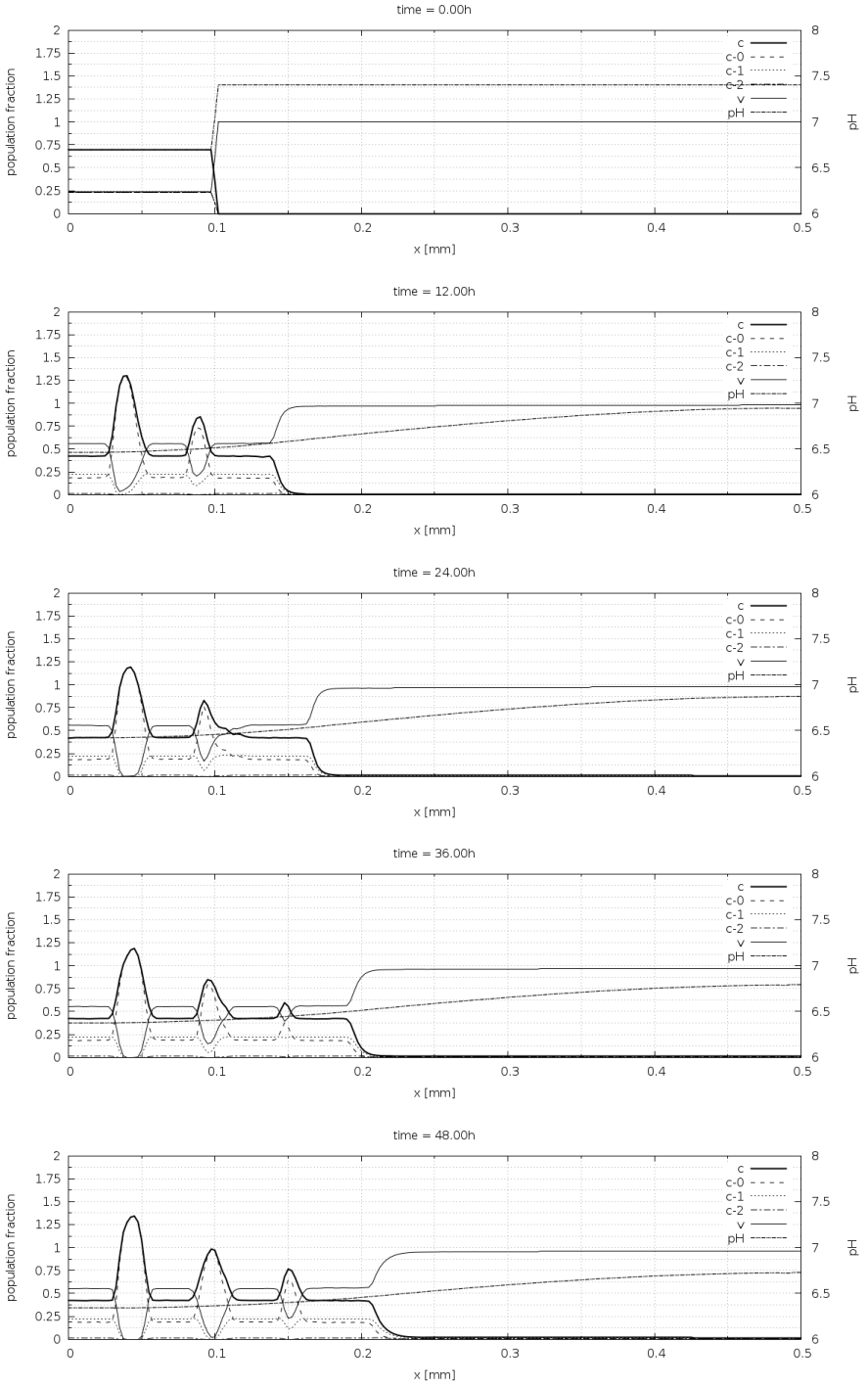

Figure 1: Simulation results of tumor invasion at different time steps. An oscillatory pattern formation due to adhesion is visible.

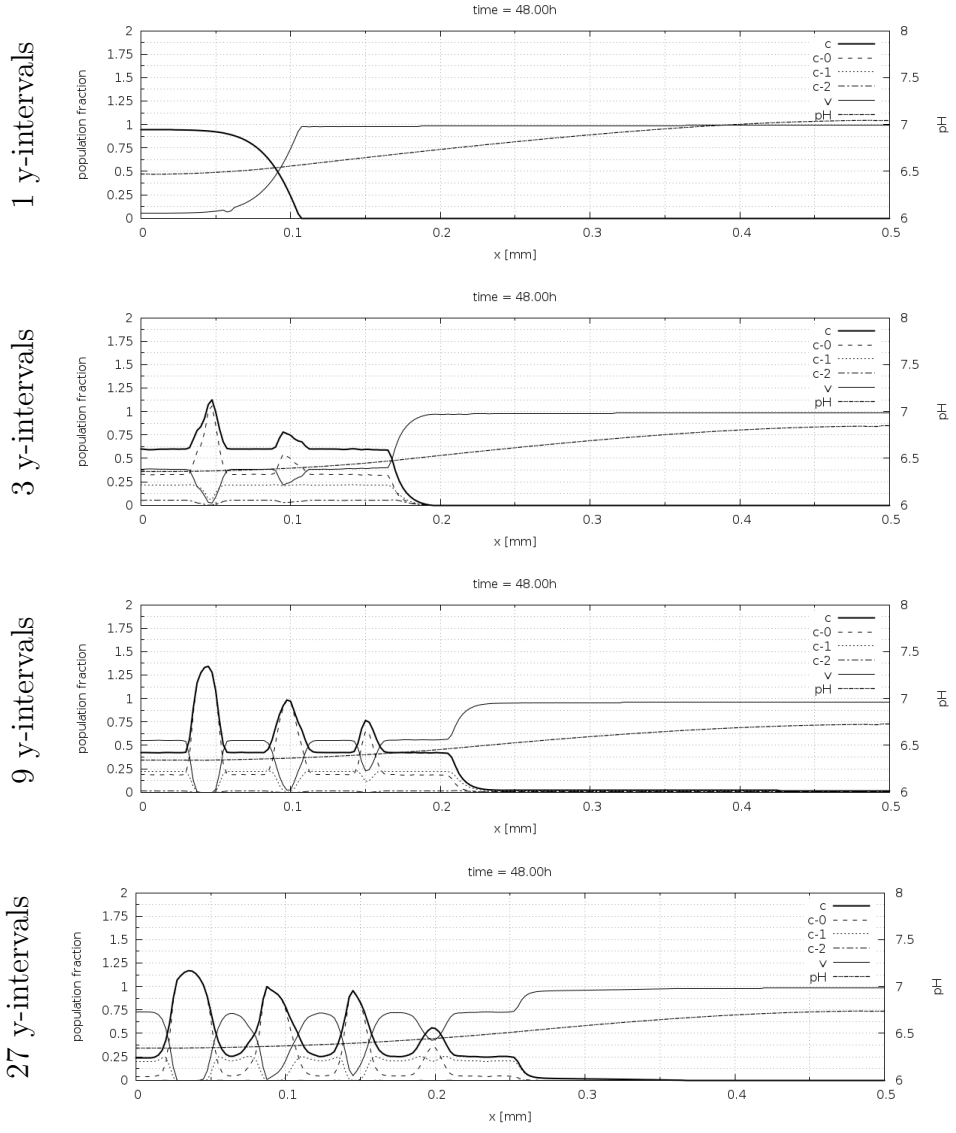

Figure 2: Comparison of different resolutions of Y at the final timestep $T = 48h$. Depending on the number of y-intervals the oscillatory pattern becomes more visible.

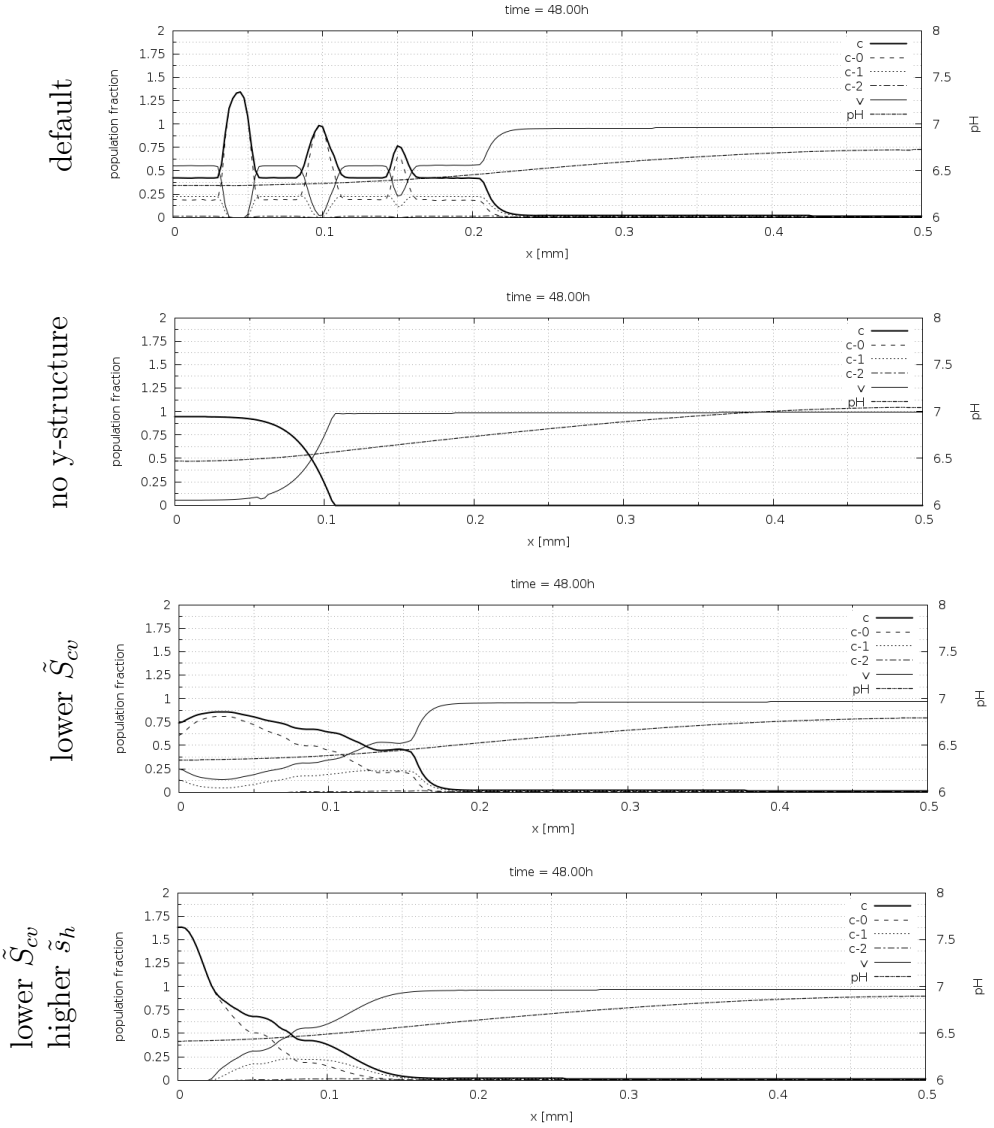

Figure 3: Comparison of different simulation scenarios. The default scenario is the one corresponding to the choice of functions and coefficients in Table 1. In scenario 3 we use a reduced value of $\tilde{S}_{cv} = 0.1$. In the last scenario we increased $\tilde{s}_h = 8 \cdot 10^{-4}$ to compensate for the reduced $\tilde{S}_{cv}$, but clearly the effects of adhesion and pH-taxis lead to different patterns.

Results The numerical experiments show the evolution of a spatial pattern behind an advancing tumor front (see Figure 1). In order to assess the influence of the supplementary structure variable y we consider several regimes for the receptor binding states; correspondingly, we represent the cancer cell densities $c_i(t,x) = \int_{\frac{i}{3}}^{\frac{i+1}{3}} c(t,x,y)dy$ $(i = 0,1,2)$. A somewhat periodic structure is observable, whereby the length of a single phase corresponds approximately to the sensing radius R. Notice that the main part of the tumor mass is made up of cells with low or moderate amounts of bound receptors, since too large such amounts indicate cells tightly packed between tissue fibers and/or binding lots of protons, both situations being impedimental for proliferation.

It is interesting to observe that the infiltration speed of cells into the tissue is dramatically influenced by the Y-structure, as cells with lower receptor binding state are faster invading the surrounding ECM, thus leading to enhanced tumor expansion. Figure 2 compares simulation results featuring different resolutions of the Y domain; thereby, we considered several intermediate intervals for the variable y, by further dividing each of the subintervals $(i/3,(i+1)/3)$ $(i = 0,1,2)$ into 3, 9, etc. parts and computing c_0, c_1, and c_2 accordingly [10]. Looking at the simulation results it becomes obvious that a sufficient resolution of Y is required at all to obtain an expansion speed of approximately 4 cm per year. Comparing the third and the fourth simulation scenarios in Figure 2 indicates that a resolution of 9 intervals for the Y domain seems to be sufficient to capture the dynamics; in order to get completely reliable quantitative results the resolution might need to be further increased and proper convergence studies ought to be carried out. This is an important issue, as an incorrect resolution might lead to under- or overestimation of the tumor invasion.

Furthermore, looking at the first row in Figure 2 it can be seen that without any Y-structure the tumor expansion is very much limited (and actually, hardly taking place), let alone the patterning.

The diffusion of tumor cells is relatively slow (e.g., with respect to that of protons), thus advection via pH-taxis and adhesion $\nabla\cdot(\mathcal{A}c)$ has significant impact. In particular, cell-cell and especially cell-tissue adhesion play a dominant role, as shown by the third simulation scenario in Figure 3, where the cell-tissue adhesion $\tilde{S}_{cv}$ coefficient was reduced to $\tilde{S}_{cv} = 0.1$, leading to a slower expansion of the tumor. Varying the cell-cell adhesion coefficient $\tilde{S}_{cc}$ led to less prominent changes in the tumor behavior (not shown). The enhancement of pH-tactic effects (still in the case of reduced cell-tissue interactions) causes less tumor expansion than in the case with increased $\tilde{S}_{cv}$, thus endorsing the surmise that cell-ECM adhesion is a crucial factor for tumor advancement, even more important than cell-cell adhesion.[11] For the pure macroscopic cell adhesion model considered in [26] and featuring similar PDEs[12] and constant cell-cell and cell-ECM adhesion coefficients it was found that a substantial increase in the former coefficient led to an oscillatory pattern, while a similar increase in cell-ECM adhesion only led to an accumulation of cells at a specific site depending on the density of the surrounding substrate. Since the pH-taxis does not seem to play a decisive role in the simulation outcome we believe that it is the supplementary structure variable and the afferent terms (in particular, y-dependent adhesion coefficients and the transport term $\partial_y(g(t,x,y,h,v)c)$) which greatly contribute to the different qualitative behavior of the cell population.

[10] e.g., for 9 y-intervals we compute $c_i(t,x) = \int_{\frac{i}{3}}^{\frac{i+1}{3}} c(t,x,y)dy = \sum_{k=0}^{2} \int_{\frac{i}{3}+\frac{k}{9}}^{\frac{i}{3}+\frac{k+1}{9}} c(t,x,y)dy$

[11] at least as far as our model is concerned

[12] however without taxis and further structure variables

5 Discussion

We proposed and analyzed a novel multiscale model for tumor invasion into a tissue network, thereby paying particular attention to cell-cell and cell-tissue adhesion, but also to the effects of receptor binding, hence to subcellular dynamics. The latter is captured by way of a supplementary structure variable, which led to a structured PDE for the density of cancer cells and which also controls both the adhesion and proliferation terms, in agreement to known biological facts. We proved the global existence of a weak solution as defined in Section 3, the boundedness and uniqueness of which remain open. The numerical simulations elicited -as was the case with previous models involving adhesion- the crucial role of adhesion terms involving spatial nonlocality, but beyond that also the vast importance of the new structure variable, which led to irregular infiltrative patterns as they are often observed in vivo (see e.g. [1]). Interestingly, the simulations of our structured multiscale model with adhesion coefficients depending on the subcellular dynamics highlighted the dominance of cell-tissue over cell-cell adhesions.

Observe as in [47] that the form of the adhesion velocity in Section 2 (in particular the part describing cell-tissue interactions) points on an ECM gradient across the sensitivity radius, which can determine cell motility in the direction of such gradient, hence haptotaxis. A characterization of tumor invasion by way of a continuous model involving a haptotaxis term of the form $\nabla \cdot (\Psi(c, v, h)\nabla v)$ has its advantages, among others the fact that it avoids the integrals inherent to the adhesion term and is actually obtained in a framework where the solution depends on time and space only, thus not involving further structure variables and hence also not the additional transport term w.r.t. y. This simplifies not only the setting, but also the analysis and numerics; however there are still plenty of mathematical challenges for that type of models as well, see [58, 66, 67]. In [45, 58] we proposed a multiscale model for cancer invasion with chemo- and haptotaxis, where the subcellular scale was represented, too, by the dynamics of receptor binding; however, the connection between the scales was different and the amount y of bound receptors did not act as another structure variable. As one of the main purposes of this work is to model multiscale cancer invasion (migration and proliferation) through adhesive binding and acid-mediated receptor activation, we kept the structured population framework and the corresponding integral terms.

The model introduced here gives rise to challenges both from the analytical and the numerical viewpoint; the former relates to less regular data requirements and more information about the qualitative (long time) behavior of the solution, while in the numerical framework there is an obvious need for investigating the mathematical properties of adequate procedures, also in higher dimensions.

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References

[1] Japanese classification of gastric carcinoma: 3rd english edition. Gastric Cancer **14** (2011), 101–112.

[2] A.R.A. Anderson, *A hybrid multiscale model of solid tumour growth and invasion: Evolution and the microenvironment*, A.R.A. Anderson, M.A.J. Chaplain and K.A. Rejniak (eds.), *Single-Cell-Based Models in Biology and Medicine*, Birkhäuser, Basel, 2007, pp. 3–28.

[3] A.R.A. Anderson, M.A.J. Chaplain, E.L. Newman, R.J.C. Steele and A.M. Thompson, *Mathematical modelling of tumour invasion and metastasis*, J. Theor. Med. **2** (2000), 129–154.

[4] N.J. Armstrong, K.J. Painter and J.A. Sherratt, *A continuum approach to modelling cell-cell adhesion*, J. Theor. Biol. **243** (2006), 98–113.

[5] P. Bartel, F.T. Ludwig, A. Schwab and C. Stock, *pH-taxis: Directional tumor cell migration along pH-gradients*, Acta Physiol. **204** (2012), 113.

[6] P. Bastian, M. Blatt, A. Dedner, C. Engwer, R. Klöfkorn, M. Ohlberger and O. Sander, *A generic grid interface for parallel and adaptive scientific computing. Part I: Abstract framework.* Computing **82** (2008) 103–119.

[7] P. Bastian, M. Blatt, A. Dedner, C. Engwer, R. Klöfkorn, R. Kornhuber, M. Ohlberger and O. Sander, *A generic grid interface for parallel and adaptive scientific computing. Part II: Implementation and tests in DUNE.* Computing **82** (2008) 121–138.

[8] N. Bellomo, *Modeling Complex Living Systems – A Kinetic Theory and Stochastic Game Approach*, Modeling and Simulation in Science, Engineering and Technology, Birkhäuser, Boston, 2008.

[9] M. Burger, V. Capasso and D. Morale, *On an aggregation model with long and short range interactions*, Nonlinear Anal. Real World Appl. **8** (2007), 939–958.

[10] H.M. Byrne and M.A.J. Chaplain, *Modelling the role of cell-cell adhesion in the growth and development of carcinomas*, Math. Comput. Modelling **24** (1996), 1–17.

[11] L. Calorini, S. Peppicelli and F. Bianchini, *Extracellular acidity as favouring factor of tumor progression and metastatic dissemination*, Exp. Oncol. **34** (2012), 79–84.

[12] M.A.J. Chaplain and G. Lolas, *Mathematical modelling of cancer invasion of tissue: Dynamic heterogeneity*, Netw. Heterog. Media **1** (2006), 399–439.

[13] V. Cristini, J. Lowengrub and Q. Nie, *Nonlinear simulation of tumor growth*, J. Math. Biol. **46** (2003), 191–224.

[14] M. Damaghi, J.W. Wojtkowiak and R.J. Gillies, *pH sensing and regulation in cancer*, Front. Physiol. **4** (2013), article 370, 1–10.

[15] A. Deutsch and S. Dormann, *Cellular Automaton Modeling of Biological Pattern Formation. Characterization, Applications, and Analysis*, Birkhäuser, Boston, 2005.

[16] P. Domschke, D. Trucu, A. Gerisch and M.A.J. Chaplain, *Mathematical modelling of cancer invasion: Implications of cell adhesion variability for tumour infiltrative growth patterns*, J. Theor. Biol. **361** (2014), 41–60.

[17] P. Domschke, D. Trucu, A. Gerisch and M.A.J. Chaplain, *Structured models of cell migration incorporating molecular binding processes*, arxiv:1607.05353, 2016.

[18] D. Drasdo, *Center-based single-cell models: An approach to multicellular organization based on a conceptual analogy to colloidal particles*, in A.R.A. Anderson, M.A.J. Chaplain and K.A. Rejniak (eds.), *Single-Cell-Based Models in Biology and Medicine*, Birkhäuser, Basel, 2007, pp. 171–196.

[19] J. Dyson, S.A. Gourley, R. Villella-Bressan and G.F. Webb, *Existence and asymptotic properties of solutions of a nonlocal evolution equation modeling cell-cell adhesion*, SIAM J. Math. Anal. **42** (2010), 1784–1804.

[20] J. Dyson, S.A. Gourley and G.F. Webb, *A non-local evolution equation model of cell-cell adhesion in higher dimensional space*, J. Biol. Dyn. **7** (2013), 68–87.

[21] J. Dyson and G.F. Webb, *A cell population model structured by cell age incorporating cell-cell adhesion*, in A. d'Onofrio and A. Gandolfi (eds.), Mathematical Oncology 2013, Modeling and Simulation in Science, Engineering, and Technology, Springer, New York, 2014, pp. 109–149.

[22] C. Engwer, T. Hillen, M. Knappitsch and C. Surulescu, *Glioma follow white matter tracts: A multiscale DTI-based model*, J. Math. Biol. **71** (2015), 551–582.

[23] C. Engwer, A. Hunt and C. Surulescu, *Effective equations for anisotropic glioma spread with proliferation: A multiscale approach and comparisons with previous settings*, Math. Med. Biol. (2015), Epub ahead of print, DOI: 10.1093/imammb/dqv030.

[24] C. Engwer, M. Knappitsch and C. Surulescu, *A multiscale model for glioma spread including cell-tissue interactions and proliferation*, Math. Biosc. Eng. **13** (2016), 443-460.

[25] P. Friedl and K. Wolf, *Tumour-cell invasion and migration: Diversity and escape mechanisms*, Nature Rev. Cancer **3** (2003), 362–374.

[26] L. Geris and A. Gerisch, *Mathematical modelling of cell adhesion in tissue engineering using continuum models*, in A. Gefen (ed.), *Cellular and Biomolecular Mechanics and Mechanobiology*, Springer, Heidelberg, 2011, pp. 431–450.

[27] A. Gerisch and M.A.J. Chaplain, *Mathematical modelling of cancer cell invasion of tissue: Local and non-local models and the effect of adhesion*, J. Theor. Biol. **250** (2008), 684–704.

[28] A. Gerisch and K.J. Painter, *Mathematical modeling of cell adhesion and its applications to developmental biology and cancer invasion*, in A. Chauviere, L. Preziosi, and C. Verdier (eds.), *Cell Mechanics. From Single Scale-Based Models to Multiscale Modeling*, Chapman and Hall/CRC, 2010, pp. 319–349.

[29] C. Giverso. M. Scianna, L. Preziosi, N. Lo Buono and A. Funaro, *Individual cell-based model for in-vitro mesothelial invasion of ovarian cancer*, Math. Model. Nat. Phenom. **5** (2010), 203–223.

[30] D. Hanahan and R.A. Weinberg, *Hallmarks of cancer: The next generation*, Cell **144** (2011), 646–674.

[31] J.D. Hood and D.A. Cheresh, *Role of integrins in cell invasion and migration*, Nature Rev. Cancer **2** (2002), 91–100.

[32] A. Huttenlocher and A.R. Horwitz, *Integrins in cell migration*, Cold Spring Harb. Perspect. Biol. **3** (2011), a005074.

[33] A. Jeanes, C.J. Gottardi and A.S. Yap, *Cadherins and cancer: How does cadherin dysfunction promote tumor progression?*, Oncogene **27** (2008), 6920–6929.

[34] Z. Jing, H. Xu, X. Chen, Q. Zhong, J. Huang, Y. Zhang, W. Guo, Z. Yang, S. Ding, P. Chen and Z. Huang, *The proton-sensing G-protein coupled receptor GPR4 promotes angiogenesis in head and neck cancer*, PLoS ONE **11** (2016), e0152789.

[35] Y. Kato, S. Ozawa, C. Miyamoto, Y. Maehata, A. Suzuki, T. Maeda and Y. Baba, *Acidic extracellular microenvironment and cancer*, Cancer Cell International **13** (2013), 8 pages.

[36] Y. Kim and H.G. Othmer, *Hybrid models of cell and tissue dynamics in tumor growth*, Math. Biosc. Eng. **12** (2015), 1141–1156.

[37] Y. Kim, S. Lawler, M.O. Nowicki, E.A. Chiocca and A. Friedman, *A mathematical model for pattern formation of glioma cells outside the tumor spheroid core*, J. Theor. Biol. **260** (2009), 359–371.

[38] O.A. Ladyženskaja, V.A. Solonnikov and N.N. Ural'ceva, *Linear and Quasi-Linear Equations of Parabolic Type,* Amer. Math. Soc. Transl., Vol. 23, Providence, RI, 1968.

[39] D. Li and J.L. Rodrigo, *Wellposedness and regularity of solutions of an aggregation equation*, Rev. Mat. Iberoamericana **26** (2010), 261–294.

[40] G.M. Lieberman, *Hölder continuity of the gradient of solutions of uniformly parabolic equations with conormal boundary conditions*, Ann. Mat. Pura Appl. **148** (1987), 77–99.

[41] T. Lorenz and C. Surulescu, *On a class of multiscale cancer cell migration models: Well-posedness in less regular function spaces*, Math. Models Methods Appl. Sci. **24** (2014), 2383–2436.

[42] P. Lu, V.M. Weaver and Z. Werb, *The extracellular matrix: A dynamic niche in cancer progression*, J. Cell Biol. **196** (2012), 395–406.

[43] P. Macklin and J.Lowengrub, *Nonlinear simulation of the effect of microenvironment on tumor growth*, J. Theor. Biol. **245** (2007), 677–704.

[44] D.G. Mallet and G.J. Pettet, *A mathematical model of integrin-mediated haptotactic cell migration*, Bull. Math. Biol. **68** (2006), 231–253.

[45] G. Meral, C. Stinner and C. Surulescu, *On a multiscale model involving cell contractivity and its effects on tumor invasion*, Discrete Cont. Dyn. Syst. Ser. B **20** (2015), 189–213.

[46] X. Mora, *Semilinear parabolic problems define semiflows on C^k spaces,* Trans. Amer. Math. Soc. **278** (1983), 21–55.

[47] K.J. Painter, N.J. Armstrong and J.A. Sherratt, *The impact of adhesion on cellular invasion processes in cancer and development*, J. Theor. Biol. **264** (2010), 1057–1067.

[48] K.J. Painter, J.M. Bloomfield, J.A. Sherratt and A. Gerisch, *A nonlocal model for contact attraction and repulsion in heterogeneous cell populations*, Bull. Math. Biol. **77** (2015), 1132-1165.

[49] R.K. Paradise, M.J. Whitfield, D.A. Lauffenburger and K.J. Van Vliet, *Directional cell migration in an extracellular pH gradient: A model study with an engineered cell line and primary microvascular endothelial cells*, Exp. Cell Res. **319** (2013), 487–497.

[50] L. Perko, *Differential Equations and Dynamical Systems, Third edition,* Texts in Applied Mathematics 7, Springer, New York, 2001.

[51] A.J. Perumpanani, J.A. Sherratt, J. Norbury and H.M. Byrne, *Biological inferences from a mathematical model for malignant invasion*, Invasion Metastasis **16** (1996), 209–221.

[52] M.M. Porzio and V. Vespri, *Holder estimates for local solutions of some doubly nonlinear degenerate parabolic equations,* J. Differential Equations **103** (1993), 146–178.

[53] I. Ramis-Conde, D. Drasdo, A.R.A. Anderson and M.A.J. Chaplain, *Modeling the influence of the E-cadherin-β-catenin pathway in cancer cell invasion: A multiscale approach*, Biophys. J. **95** (2008), 155–165.

[54] M. Scianna and L. Preziosi, *A hybrid model describing different morphologies of tumor invasion fronts*, Math. Model. Nat. Phenom. **7** (2012), 78–104.

[55] K. Seuwen, M.-G. Ludwig and R.M. Wolf, *Receptors for protons or lipid messengers or both?*, Journal of Receptors and Signal Transduction **26** (2006), 599–610.

[56] J.A. Sherratt, S.A. Gourley, N.J. Armstrong and K.J. Painter, *Boundedness of solutions of a non-local reaction-diffusion model for adhesion in cell aggregation and cancer invasion*, Eur. J. Appl. Math. **20** (2009), 123–144.

[57] C. Stinner, C. Surulescu and G. Meral, *A multiscale model for pH-tactic invasion with time-varying carrying capacities,* IMA J. Appl. Math. **80** (2015), 1300–1321.

[58] C. Stinner, C. Surulescu and M. Winkler, *Global weak solutions in a PDE-ODE system modeling multiscale cancer cell invasion*, SIAM J. Math. Anal. **46** (2014), 1969-2007.

[59] A. Szabó and R.M.H. Merks, *Cellular Potts modeling of tumor growth, tumor invasion, and tumor evolution*, Front Oncol. **3** (2013), article 87, 1–12.

[60] Z. Szymańska, C. Morales Rodrigo, M. Lachowicz and M.A.J. Chaplain, *Mathematical modelling of cancer invasion of tissue: The role and effect of nonlocal interactions*, Math. Models Methods Appl. Sci. **19** (2009), 257–281.

[61] Y. Tao and M. Winkler, *Boundedness in a quasilinear parabolic-parabolic Keller-Segel system with subcritical sensitivity,* J. Differential Equations **252** (2012), 692–715.

[62] R. Temam, *Navier-Stokes Equations. Theory and Numerical Analysis,* Studies in Mathematics and its Applications, Vol. 2, North-Holland, Amsterdam, 1977.

[63] B.A. Webb, M. Chimenti, M.P. Jacobson and D.L. Barber, *Dysregulated pH: A perfect storm for cancer progression*, Nature Rev. Cancer **11** (2011), 671–677.

[64] M. Winkler, *Aggregation vs. global diffusive behavior in the higher-dimensional Keller-Segel model,* J. Differential Equations **248** (2010), 2889–2905.

[65] M. Winkler and C. Surulescu, *Global weak solutions to a strongly degenerate haptotaxis model*, arXiv:1603.04233, 2016, submitted.

[66] A. Zhigun, C. Surulescu and A. Hunt, *Global existence for a degenerate haptotaxis model of tumor invasion under the go-or-grow dichotomy hypothesis*, arXiv:1605.09226, 2016, submitted.

[67] A. Zhigun, C. Surulescu and A. Uatay, *Global existence for a degenerate haptotaxis model of cancer invasion*, arXiv:1512.04287, accepted by Z. Angew. Math. Phys.