Global existence for a go-or-grow multiscale model for tumor invasion with therapy

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Abstract

We investigate a PDE-ODE system describing cancer cell invasion in a tissue network. The model is an extension of the multiscale setting in [28, 40], by considering two subpopulations of tumor cells interacting mutually and with the surrounding tissue. According to the go-or-grow hypothesis, these subpopulations consist of moving and proliferating cells, respectively. The mathematical setting also accommodates the effects of some therapy approaches. We prove the global existence of weak solutions to this model and perform numerical simulations to illustrate its behavior for different therapy strategies.

Keywords: tumor cell invasion; haptotaxis; asymptotic behavior; multiscale model; go-or-grow; delay.

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1 Introduction

The heterogeneity of tumors is a known fact, which plays a crucial role in the response of cancer cells to the applied therapies. Indeed, evidence has been found that cancer cells exhibit differentiated sensitivity against ionizing radiation or chemotherapy [23, 38], and slowly cycling cells are more resistant than their highly proliferating neighbor cells [32, 37]. A further widely accepted fact is that cancer cells can either migrate or proliferate; this is the so-called go-or-grow dichotomy [4, 12]. Thereby, the migrating cells are less sensitive against therapy than the proliferating ones. When modeling tumor growth and invasion in the surrounding tissue it is therefore desirable to account for two subpopulations of cancer cells, one of which is migrating and the other is performing mitosis.
Another relevant feature of tumor migration is its multiscality: the macroscopic behavior of the whole cell population is conditioned by processes taking place on the individual cell level and on the subcellular scale and influences, in turn, these processes. Apart from discrete or hybrid settings (see e.g., [3] and the references therein), several continuum models connecting the subcellular and

the population scales or also accounting for the mesoscopic individual level dynamics of cells have been recently proposed and analyzed e.g., in [14, 28, 39, 40] and [20, 26, 5], respectively. Newer multiscale models also accounting for the tumor heterogeneity in the sense mentioned above (go-or-grow dichotomy) were proposed in [6, 17, 43] and in the context of acid-mediated tumor invasion (active vs. quiescent cells) in [29]. Here we reconsider the model in [43] (for which well-posedness was shown locally in time) with some slight modifications and investigate the global existence of a weak solution. The main challenge thereby comes from the splitting into the two subpopulations of moving and proliferating tumor cells: due to the switching between the two populations, the moving cells act on the one side as source for the proliferating ones (when they stop and advance through the cell cycle, see Section 2), and on the other side as decay term for themselves and for the tissue. This makes it insufficient to directly apply the method used in [40] to handle the usual difficulty coming from the lack of derivatives in one of the equations characterizing the macroscale dynamics with haptotaxis; in this work there will be one more equation without space derivatives, namely that for the evolution of proliferating tumor cells, while the diffusion of the moving cells is nonlinear, its coefficient depending on all macroscopic variables of the model.
The paper is organized as follows: Section 2 introduces the model for the dynamics of the two subpopulations of tumor cells (migrating and proliferating, respectively) and of the normal tissue, supplemented by the integrin binding dynamics on the subcellular level. The analysis of the model is done in Section 3, where the global existence of weak solutions is proved with the aid of an entropy functional constructed upon relying on the idea in [40]. In Section 4 we perform numerical simulations to illustrate the behavior of the model predicting the evolution of the three cell populations under several therapy strategies. Eventually, Section 5 provides a discussion of the results and some further related issues to be addressed in future work.

2 The model

We introduce the following model variables: $m(x,t)$ denotes the density of migrating cancer cells, $q(x,t)$ is that of proliferating cancer cells, and $v(x,t)$ represents the density of tissue fibers in the ECM. Moreover, let us denote by $y(x,t)$ the concentration of integrins bound to ECM fibers and by $\kappa(x,t)$ the contractivity function of cancer cells. Then we consider the PDE-ODE system

$$\partial_t m = \nabla \cdot (\phi(\kappa, m, q, v)\nabla m) - \nabla \cdot (\psi(\kappa, v) m \nabla v) + \lambda(y) q - \gamma(y) m - \Gamma_m R_m(d_r) m \tag{2.1a}$$

$$\partial_t q = \mu_q q \left(1 - \frac{m+q}{K_c} - \eta_1 \frac{v}{K_v}\right) - \lambda(y) q + \gamma(y) m - \Gamma_q R_q(d_r) q \tag{2.1b}$$

$$\partial_t v = -\delta_v (m + \delta_q q) v + \mu_v v \left(1 - \eta_2 \frac{m+q}{K_c} - \frac{v}{K_v}\right) - \Gamma_v R_v(d_r) v \tag{2.1c}$$

$$\partial_t y = k_1(d_c)(R_0 - y) v - k_{-1}(d_c) y \tag{2.1d}$$

$$\partial_t \kappa = -\delta_\kappa \kappa + H(y(\cdot, t-\tau)) \tag{2.1e}$$

in $\Omega \times (0,\infty)$, where $\Omega \subset \mathbb{R}^n$ is a bounded domain with smooth boundary, $n \in \{1,2,3\}$ and we impose no-flux boundary conditions and appropriate initial conditions.
Equation (2.1a) above characterizes the evolution of the density of migrating cancer cells, with diffusion and taxis driving the motility. Thereby, both diffusion and haptotaxis coefficients depend on the

solution in a nonlinear way. Concrete choices of these and the other coefficients of the model will be provided in Section 4. The rest of the terms describe the exchange between the two subpopulations of tumor cells and the therapy effects. Thereby, $\lambda(y)$ denotes the rate with which proliferating (i.e., resting) cells advance in their cycle towards non-proliferative phases and start to move, while $\gamma(y)$ is the rate with which the moving cells stop and start proliferating. Both rates naturally depend on the subcellular dynamics, featured here by the amount of cell surface receptors (in this work we concentrate on integrins, a class of heterodimeric transmembrane surface proteins) binding to their insoluble ligands in the ECM and characterized by the equation (2.1d). These dependences are motivated by the fact that integrin activation (binding) is at the onset of a plethora of intracellular events leading among others to cell survival, division, and motility [15, 18, 24]. The coefficients k_1 and k_{-1} in (2.1d) denote the binding and detachment rates, respectively. Thereby, R_0 denotes the total (average) amount of integrins of the relevant type on a cell surface, and we assume it to be constant. The density of dividing cells evolves according to (2.1b), which contains beside the exchange and therapy terms only a source term modeling proliferation restricted by crowding. Equation (2.1c) describes the dynamics of the density v of ECM fibers, which are degraded upon interacting with the tumor cells and are (partially) recovered, a process triggered by the normal tissue and limited, too, by crowding. The decay of v is also due to the side effects of radiotherapy. Eventually, (2.1e) characterizes the evolution of the hypothetic contractivity function depending on the variable y which as in [28, 40] connects the subcellular level of receptor binding dynamics with the macroscopic level of population dynamics.
The applied therapy involves consecutive or concurrent radiotherapy and the administration of a chemical agent. As in [17], the latter has the role of inhibiting integrin binding and thus negatively influence the motility and proliferation of the tumor cells. Several integrin-targeted drugs are already in clinical use and many others are in clinical trials or preclinical development, see e.g., [30] for a review. In the following we will refer to the drug administration as chemotherapy, although its aim is to inhibit integrin binding (and thus mainly reduce migration) and not necessarily to (directly) kill the tumor cells. The effects of this chemotherapy are captured by the rates k_1 and k_{-1} in (2.1d), both depending on the dose d_c of the drug. The radiotherapy is aimed at depleting the tumor cells in both subpopulations, but its side effects are also decaying the normal tissue. The impact of ionizing radiation is modeled by the terms $\Gamma_i R_i(d_r)i$, with $i \in \{m, q, v\}$, Γ_i constants, and R_i being functions depending on the applied radiation dose d_r. As mentioned in Section 1, the cells exhibit different sensitivities (among others, respective of their migratory vs. proliferative phenotype) when exposed to radio and/or chemotherapy [23, 27, 38], thus Γ_i and R_i will be different for each of the cell (sub)populations involved in the model. For more details we refer to Section 4 below.

3 Global existence of a weak solution

The local-in-time well-posedness of (2.1a)-(2.1e) with no-flux boundary conditions and appropriate initial conditions was proved in [43, Section 4] by extending the ideas of [28]. Here we prove the global existence of a weak solution of the following slightly simplified variant of (2.1a)-(2.1e), where the diffusion coefficient of the migrating cancer cells is uniformly positive and the switching rate γ is constant. More precisely, we consider (see the nondimensionalized system (4.5))

$$\begin{cases} \partial_t m = \nabla\cdot(D(m,q,v)\kappa\nabla m) - \nabla\cdot\left(\frac{\kappa v}{1+v} m\nabla v\right) + \lambda(y)q - \gamma m - r_m(t)m, \\ \partial_t q = \mu_q q\,(1-(m+q)-\eta_1 v) - \lambda(y)q + \gamma m - r_q(t)q, \\ \partial_t v = -\alpha m v - \beta q v + \mu_v v(1-v) - r_v(t)v, \\ \partial_t y = K_1(t)(1-y)v - K_{-1}(t)y, \\ \partial_t \kappa = -\delta\kappa + H(y(\cdot,t-\tau)), \end{cases} \tag{3.1}$$

with $x\in\Omega$ and $t>0$, where $\Omega\subset\mathbb{R}^n$ is a bounded domain with smooth boundary, $n\in\{1,2,3\}$. In addition, we impose no-flux boundary conditions (ν denotes the outer unit normal on $\partial\Omega$)

$$D(m,q,v)\kappa\,\partial_\nu m - \frac{\kappa v}{1+v} m\,\partial_\nu v = 0, \qquad x\in\partial\Omega,\ t>0, \tag{3.2}$$

and the initial conditions

$$\begin{aligned} & m(x,0)=m_0(x), \quad q(x,0)=q_0(x) \quad v(x,0)=v_0(x), \quad \kappa(x,0)=\kappa_0(x), \qquad x\in\Omega, \\ & y(x,t)=y_0(x,t), \qquad x\in\Omega,\ t\in[-\tau,0], \end{aligned} \tag{3.3}$$

where we assume that

$$m_0\in C^0(\bar\Omega), \quad q_0,v_0\in W^{1,2}(\Omega)\cap C^0(\bar\Omega), \quad \kappa_0\in W^{1,4}(\Omega), \quad y_0\in C^0([-\tau,0];W^{1,4}(\Omega)) \tag{3.4}$$

satisfy

$$m_0\ge 0, \quad q_0\ge 0, \quad v_0\ge 0, \quad \kappa_0>0 \quad \text{in } \bar\Omega \qquad \text{as well as} \quad 0\le y_0\le 1 \quad \text{in } \bar\Omega\times[-\tau,0]. \tag{3.5}$$

Furthermore, we assume that for any $A>0$ and $L>0$ there exist positive constants C_1 and C_2 such that

$$\begin{aligned} & D\in C^3([0,\infty)^3)\cap W^{2,\infty}([0,\infty)\times[0,A]\times[0,L]), \quad \lambda\in C^1([0,1]), \quad H\in C^3([0,1]), \\ & r_i := \Gamma_i R_i(d_r(\cdot)), K_j := k_j(d_c(\cdot)) \in C^1([0,\infty)), \quad i\in\{m,q,v\}, j\in\{1,-1\}, \\ & 0<C_2\le D(m,q,v)\le C_1 \quad \text{for all } (m,q,v)\in[0,\infty)\times[0,A]\times[0,L], \\ & 0<\lambda_2\le\lambda(y)\le\lambda_1, \quad 0\le H(y) \quad \text{for all } y\in[0,1], \\ & 0\le r_i(t)\le C_3, \quad 0<C_4\le K_j(t)\le C_3 \quad \text{for all } t\ge 0, i\in\{m,q,v\}, j\in\{1,-1\} \end{aligned} \tag{3.6}$$

with positive constants C_i, λ_i. Moreover, the parameters γ, μ_q, η_1, μ_v, $\alpha := \delta_v + \mu_v\eta_2$, $\beta := \delta_v\delta_q + \mu_v\eta_2$, $\delta := \delta_\kappa$, and τ are assumed to be positive.
The global existence will be proved for the following concept of weak solutions, where in view of the intended compactness properties we formally rewrite $\nabla m = 2\sqrt{1+m}\cdot\nabla\sqrt{1+m}$ (see [40]).

Definition 3.1 *Let $T\in(0,\infty)$. A weak solution to (3.1)-(3.3) consists of nonnegative functions*

$$\begin{aligned} & m\in L^1((0,T);L^2(\Omega)) \quad \text{with} \quad \sqrt{1+m}\in L^2((0,T);W^{1,2}(\Omega)) \quad \text{and} \quad \sqrt{m}\,\nabla v\in L^2(\Omega\times(0,T)), \\ & v\in L^\infty(\Omega\times(0,T))\cap L^2((0,T);W^{1,2}(\Omega)), \quad q,\kappa\in L^\infty(\Omega\times(0,T)), \quad y\in L^\infty(\Omega\times(-\tau,T)) \end{aligned}$$

which satisfy for all $\varphi \in C_0^\infty(\bar\Omega \times [0,T))$ *the equations*

$$-\int_0^T\int_\Omega m\partial_t\varphi - \int_\Omega m_0\varphi(\cdot,0) = -2\int_0^T\int_\Omega D(m,q,v)\kappa\sqrt{1+m}\nabla\sqrt{1+m}\cdot\nabla\varphi + \int_0^T\int_\Omega \frac{\kappa v}{1+v} m\nabla v\cdot\nabla\varphi + \int_0^T\int_\Omega (\lambda(y)q - \gamma m - r_m(t)m)\varphi, \tag{3.7}$$

$$-\int_0^T\int_\Omega q\partial_t\varphi - \int_\Omega q_0\varphi(\cdot,0) = \int_0^T\int_\Omega \Big\{\mu_q q\,(1-(m+q)-\eta_1 v) - \lambda(y)q + \gamma m - r_q(t)q\Big\}\varphi, \tag{3.8}$$

$$-\int_0^T\int_\Omega v\partial_t\varphi - \int_\Omega v_0\varphi(\cdot,0) = \int_0^T\int_\Omega \Big\{-\alpha m v - \beta q v + \mu_v v(1-v) - r_v(t)v\Big\}\varphi, \tag{3.9}$$

$$-\int_0^T\int_\Omega y\partial_t\varphi - \int_\Omega y_0\varphi(\cdot,0) = \int_0^T\int_\Omega \Big\{K_1(t)(1-y)v - K_{-1}(t)y\Big\}\varphi, \tag{3.10}$$

$$-\int_0^T\int_\Omega \kappa\partial_t\varphi - \int_\Omega \kappa_0\varphi(\cdot,0) = \int_0^T\int_\Omega \Big\{-\delta\kappa + H(y(\cdot,t-\tau))\Big\}\varphi. \tag{3.11}$$

(m,q,v,y,κ) *is a global weak solution to* (3.1)-(3.3)*, if it is a weak solution in* $\Omega\times(0,T)$ *for all* $T>0$.

Our main result is the existence of a global weak solution.

Theorem 3.2 *Let* $n \le 3$ *and* $\Omega \subset \mathbb{R}^n$ *be a bounded domain with smooth boundary and assume that* (3.4)-(3.6) *are fulfilled. Then there exists a global weak solution to* (3.1)-(3.3) *in the sense of Definition 3.1 satisfying*

$$m \in L^\infty((0,\infty),L^1(\Omega)), \quad q,v,\kappa \in L^\infty(\Omega\times(0,\infty)), \quad y \in L^\infty(\Omega\times(-\tau,\infty)).$$

This result remains true for a larger class of coefficient functions.

Remark 3.3 *Theorem 3.2 remains valid if the regularity assumptions in* (3.6) *are replaced by* $D \in C^1([0,\infty)^3)$*,* $\lambda, H \in C^1([0,1])$*,* $r_i, K_j \in C^1([0,\infty))$ *for* $i \in \{m,q,v\}$ *and* $j \in \{1,-1,\}$*. In order to prove this variant of the theorem, one has to use appropriate regularizations, which satisfy* (3.6)*, of these functions in the approximate problems given below. For the ease of presentation we give the proof only for the regularity assumptions in* (3.6) *and refer the reader to [39, (3.12)-(3.13)] for a related regularization. The assumption that* γ *is constant is only needed to prove Lemma 3.12.*

Our proof of Theorem 3.2 relies on the strategy of [40]. Namely, we construct an entropy-type functional for suitable regularizations of (3.1). This functional is quasi-dissipative in a certain sense and allows to deduce compactness properties which imply the existence of a global weak solution to the original problem. The main additional difficulty as compared to [40] and related macroscopic haptotaxis systems (see e.g., the references in the introduction of [40]) is the splitting into two cancer cell populations. Apart from the explicit dependence of v on m there is also an additional implicit feedback of m in the third equation of (3.1) through q, which in turn depends on m via the source term γm and satisfies an ODE without regularization by diffusion. This additional influence of m requires on the one hand more complicated estimates in order to control the haptotaxis term and is on the other hand the main reason for the uniform positivity assumption on the diffusion coefficient D in (3.6), which was not necessary in [40]. Moreover, in view of the absence of the logistic proliferation term in

the equation for m (which is now present in the equation for q), the entropy functional in Subsection 3.2 only provides an L^1-bound on $m_\varepsilon \ln m_\varepsilon$, instead of $c_\varepsilon^2 \ln c_\varepsilon$ in [40]. This leads to a slightly different argument for the compactness.
For $\varepsilon \in (0,1)$ we approximate (3.1)-(3.3) with the regularized problems

$$\begin{cases} \partial_t m_\varepsilon = \nabla \cdot (D(m_\varepsilon, q_\varepsilon, v_\varepsilon)\kappa_\varepsilon \nabla m_\varepsilon) - \nabla \cdot \left(\frac{\kappa_\varepsilon v_\varepsilon}{1+v_\varepsilon} m_\varepsilon \nabla v_\varepsilon\right) & \\ \qquad\qquad +\lambda(y_\varepsilon) q_\varepsilon - \gamma m_\varepsilon - r_m(t) m_\varepsilon - \varepsilon m_\varepsilon^\theta, & x \in \Omega,\, t>0, \\ \partial_t q_\varepsilon = \varepsilon \Delta q_\varepsilon + \mu_q q_\varepsilon \left(1 - (m_\varepsilon + q_\varepsilon) - \eta_1 v_\varepsilon\right) & \\ \qquad\qquad -\lambda(y_\varepsilon) q_\varepsilon + \gamma m_\varepsilon - r_q(t) q_\varepsilon, & x \in \Omega,\, t>0, \\ \partial_t v_\varepsilon = \varepsilon \Delta v_\varepsilon - \alpha m_\varepsilon v_\varepsilon - \beta q_\varepsilon v_\varepsilon + \mu_v v_\varepsilon (1 - v_\varepsilon) - r_v(t) v_\varepsilon, & x \in \Omega,\, t>0, \\ \partial_t y_\varepsilon = K_1(t)(1-y_\varepsilon) v_\varepsilon - K_{-1}(t) y_\varepsilon, & x \in \Omega,\, t>0, \\ \partial_t \kappa_\varepsilon = -\delta \kappa_\varepsilon + H(y_\varepsilon(\cdot, t-\tau)), & x \in \Omega,\, t>0, \\ \partial_\nu m_\varepsilon = \partial_\nu q_\varepsilon = \partial_\nu v_\varepsilon = 0, & x \in \partial\Omega,\, t>0, \\ m_\varepsilon(x,0) = m_{0\varepsilon}(x), \quad q_\varepsilon(x,0) = q_{0\varepsilon}(x), \quad v_\varepsilon(x,0) = v_{0\varepsilon}(x), & \\ \kappa_\varepsilon(x,0) = \kappa_{0\varepsilon}(x), \quad y_\varepsilon(x,t) = y_{0\varepsilon}(x,t), & x \in \Omega,\, t \in [-\tau, 0], \end{cases} \tag{3.12}$$

where $\theta > \max\{2, n\}$ is a fixed parameter and we choose families of functions $m_{0\varepsilon}$, $q_{0\varepsilon}$, $v_{0\varepsilon}$, $\kappa_{0\varepsilon}$, and $y_{0\varepsilon}$, $\varepsilon \in (0,1)$, satisfying

$$\begin{aligned} & m_{0\varepsilon}, q_{0\varepsilon}, v_{0\varepsilon}, \kappa_{0\varepsilon} \in C^3(\bar\Omega), \quad y_{0\varepsilon} \in C^3(\bar\Omega \times [-\tau, 0]), \quad \inf_{\varepsilon\in(0,1)} \inf_{x\in\Omega} \kappa_{0\varepsilon}(x) > 0, \\ & m_{0\varepsilon} > 0, \quad q_{0\varepsilon} > 0, \quad v_{0\varepsilon} > 0 \quad \text{in } \bar\Omega, \quad 0 < y_{0\varepsilon} < 1 \quad \text{in } \bar\Omega \times [-\tau, 0], \\ & \partial_\nu m_{0\varepsilon} = \partial_\nu q_{0\varepsilon} = \partial_\nu v_{0\varepsilon} = 0 \quad \text{on } \partial\Omega \end{aligned} \tag{3.13}$$

for all $\varepsilon \in (0,1)$ as well as

$$\begin{aligned} & m_{0\varepsilon} \to m_0 \quad \text{in } C^0(\bar\Omega), \quad q_{0\varepsilon} \to q_0 \quad \text{and} \quad v_{0\varepsilon} \to v_0 \quad \text{in } W^{1,2}(\Omega) \cap C^0(\bar\Omega), \\ & \kappa_{0\varepsilon} \to \kappa_0 \quad \text{in } W^{1,4}(\Omega), \quad y_{0\varepsilon} \to y_0 \quad \text{in } C^0([-\tau, 0]; W^{1,4}(\Omega)) \end{aligned} \tag{3.14}$$

as $\varepsilon \searrow 0$.
In the sequel we always assume that (3.4)-(3.6) as well as (3.13) and (3.14) are satisfied. The plan of our proof is as follows: In Section 3.1 we will prove the global existence for each of the approximate problems (3.12). Then we will construct an appropriate entropy-type functional for (3.12) in Section 3.2. This will allow us to deduce compactness properties and the existence of a global weak solution to (3.1) in Section 3.3.

3.1 Global existence for the approximate problems

We first prove the local existence of classical solutions to (3.12).

Lemma 3.4 *For any $\varepsilon \in (0,1)$ there exist $T_\varepsilon \in (0, \infty]$ and positive functions $m_\varepsilon, q_\varepsilon, v_\varepsilon, y_\varepsilon, \kappa_\varepsilon \in C^{2,1}(\bar\Omega \times [0, T_\varepsilon))$, which solve (3.12) in the classical sense in $\Omega \times (0, T_\varepsilon)$. If moreover $T_\varepsilon < \infty$ is fulfilled, then*

$$\limsup_{t \nearrow T_\varepsilon} \Big\{ \|m_\varepsilon(\cdot,t)\|_{C^{2+\beta}(\bar\Omega)} + \|q_\varepsilon(\cdot,t)\|_{C^{2+\beta}(\bar\Omega)} + \|v_\varepsilon(\cdot,t)\|_{C^{2+\beta}(\bar\Omega)}$$

$$+\|y_\varepsilon(\cdot,t)\|_{C^{2+\beta}(\bar\Omega)}+\|\kappa_\varepsilon(\cdot,t)\|_{C^{2+\beta}(\bar\Omega)}\Big\}=\infty\quad \textit{for all } \beta\in(0,1). \tag{3.15}$$

Proof. The proof is completely similar to the one of [40, Lemma 3.1] and relies on a fixed point argument in the space

$$X := \Big\{(m_\varepsilon,q_\varepsilon)\in (C^{\beta,\frac{\beta}{2}}(\bar\Omega\times[0,T]))^2 \,:\, m_\varepsilon,q_\varepsilon\ge 0,\ \|m_\varepsilon\|_{C^{\beta,\frac{\beta}{2}}(\bar\Omega\times[0,T])}+\|q_\varepsilon\|_{C^{\beta,\frac{\beta}{2}}(\bar\Omega\times[0,T])}\le \|m_{0\varepsilon}\|_{C^\beta(\bar\Omega)}+\|m_{0\varepsilon t}\|_{C^0(\bar\Omega)}+\|q_{0\varepsilon}\|_{C^\beta(\bar\Omega)}+\|q_{0\varepsilon t}\|_{C^0(\bar\Omega)}+1\Big\}.$$

for fixed $\varepsilon\in(0,1)$ and $\beta\in(0,1)$, where $m_{0\varepsilon t}$ and $q_{0\varepsilon t}$ are the right-hand sides of the first and second equation of (3.12), respectively, evaluated at $t=0$. □

In the following two lemmas we collect some elementary estimates which are uniform with respect to $\varepsilon\in(0,1)$.

Lemma 3.5 *For each $\varepsilon\in(0,1)$ we have the following estimates:*

$$0<q_\varepsilon(x,t)\le A:=\max\left\{\sup_{\varepsilon\in(0,1)}\|q_{0\varepsilon}\|_{L^\infty(\Omega)},1-\frac{\lambda_2}{\mu_q},\frac{\gamma}{\mu_q}\right\},\quad x\in\bar\Omega,\ t\in[0,T_\varepsilon), \tag{3.16}$$

$$0<v_\varepsilon(x,t)\le L:=\max\left\{\sup_{\varepsilon\in(0,1)}\|v_{0\varepsilon}\|_{L^\infty(\Omega)},1\right\},\quad x\in\bar\Omega,\ t\in[0,T_\varepsilon), \tag{3.17}$$

$$0<y_\varepsilon(x,t)\le 1,\quad x\in\bar\Omega,\ t\in[-\tau,T_\varepsilon), \tag{3.18}$$

$$0<\left\{\inf_{\varepsilon\in(0,1)}\inf_{x\in\Omega}\kappa_{0\varepsilon}(x)\right\}e^{-\delta t}\le\kappa_\varepsilon(x,t)\le P:=\max\left\{\sup_{\varepsilon\in(0,1)}\|\kappa_{0\varepsilon}\|_{L^\infty(\Omega)},\frac{1}{\delta}\|H\|_{L^\infty((0,1))}\right\} \tag{3.19}$$

$$\textit{and}\quad |\partial_t\kappa_\varepsilon(x,t)|\le\max\left\{\delta P,\|H\|_{L^\infty((0,1))}\right\}=\delta P,\quad x\in\bar\Omega,\ t\in[0,T_\varepsilon). \tag{3.20}$$

Proof. As all solution components of (3.12) are positive by Lemma 3.4, (3.16)-(3.19) are immediate consequences of comparison principles applied to the respective equations of (3.12), since (3.6), (3.13), and (3.14) are satisfied. Then (3.20) follows from the fifth equation in (3.12) in view of (3.19) and the nonnegativity of H. □

Lemma 3.6 *For any $\varepsilon\in(0,1)$ we have*

$$\int_\Omega m_\varepsilon(x,t)dx\le B:=\max\left\{\sup_{\varepsilon\in(0,1)}\int_\Omega m_{0\varepsilon},\frac{\lambda_1 A|\Omega|}{\gamma}\right\},\quad t\in(0,T_\varepsilon), \tag{3.21}$$

$$\varepsilon\int_t^{t+1}\int_\Omega m_\varepsilon^\theta(x,s)dxds\le B+\lambda_1A|\Omega|,\quad t\in(0,T_\varepsilon-1). \tag{3.22}$$

Proof. In view of (3.6), (3.16), and the positivity of m_ε, an integration of the first equation of (3.12) implies that

$$\frac{d}{dt}\int_\Omega m_\varepsilon\le\lambda_1A|\Omega|-\gamma\int_\Omega m_\varepsilon-\varepsilon\int_\Omega m_\varepsilon^\theta,\quad t\in(0,T_\varepsilon),$$

which implies (3.21) and then (3.22) after another integration. □

Based on the previous estimates, we can now prove the global existence for (3.12) just like in [40, Section 3.3]. For the sake of completeness, we give a short outline of the proof.

Lemma 3.7 *For each $\varepsilon \in (0,1)$ the solution to (3.12) exists globally in time and we have $T_\varepsilon = \infty$.*

Proof. We fix $\varepsilon \in (0,1)$ and $T > 0$ and set $\widehat{T_\varepsilon} := \min\{T, T_\varepsilon\}$. As $m_\varepsilon \in L^\theta(\Omega \times (0, \widehat{T_\varepsilon}))$ by (3.22), Lemma 3.5 implies that $f_\varepsilon := -\alpha m_\varepsilon v_\varepsilon - \beta q_\varepsilon v_\varepsilon + \mu_v v_\varepsilon(1 - v_\varepsilon) - r_v(t) v_\varepsilon$ is bounded in $L^\theta(\Omega \times (0, \widehat{T_\varepsilon}))$. Therefore, results on maximal Sobolev regularity (see [13]) applied to the third equation in (3.12) in conjunction with our choice $\theta > \max\{2, n\}$ imply that $W^{2,\theta}(\Omega) \hookrightarrow W^{1,\infty}(\Omega)$ and

$$\int_0^{\widehat{T_\varepsilon}} \|\nabla v_\varepsilon(\cdot,t)\|^2_{L^\infty(\Omega)} dt \leq C(T) \left(1 + \int_0^{\widehat{T_\varepsilon}} \|v_\varepsilon(\cdot,t)\|^\theta_{W^{2,\theta}(\Omega)} dt\right) \leq C_5(\varepsilon, T). \tag{3.23}$$

Next, we fix $A > 0$ and $L > 0$ as in Lemma 3.5 so that by (3.6) and (3.19) there exists $C_6(T) > 0$ such that $D(m_\varepsilon, q_\varepsilon, v_\varepsilon)\kappa_\varepsilon \geq C_6(T) > 0$ for $x \in \Omega$, $t \in (0, \widehat{T_\varepsilon})$. Hence, for fixed $p > 1$ we multiply the first equation in (3.12) by m_ε^{p-1} and obtain by dropping nonnegative terms and using integration by parts, Young's inequality, and Lemma 3.5

$$\begin{aligned}
\frac{1}{p}\frac{d}{dt}\int_\Omega m_\varepsilon^p &\leq -(p-1)C_6(T)\int_\Omega m_\varepsilon^{p-2}|\nabla m_\varepsilon|^2 + (p-1)\int_\Omega \frac{\kappa_\varepsilon v_\varepsilon}{1+v_\varepsilon} m_\varepsilon^{p-1}\nabla v_\varepsilon \cdot \nabla m_\varepsilon + \lambda_1 A \int_\Omega m_\varepsilon^{p-1} \\
&\leq \frac{(p-1)P^2L^2}{4C_6(T)}\|\nabla v_\varepsilon(\cdot,t)\|^2_{L^\infty(\Omega)}\int_\Omega m_\varepsilon^p + \lambda_1 A\left(|\Omega| + \int_\Omega m_\varepsilon^p\right), \quad t \in (0, \widehat{T_\varepsilon}).
\end{aligned}$$

Hence, in view of (3.23) an integration yields

$$\int_\Omega m_\varepsilon^p(\cdot,t) \leq C_7(\varepsilon, p, T), \qquad t \in (0, \widehat{T_\varepsilon}), \tag{3.24}$$

for some constant $C_7(\varepsilon, p, T) > 0$. As q_ε and v_ε are bounded, we deduce that $f_\varepsilon \in L^\infty((0, \widehat{T_\varepsilon}), L^p(\Omega))$ for any $p > 1$ is satisfied (f_ε is defined in the beginning of this proof) so that the properties of the Neumann heat semigroup applied to the third equation of (3.12) (see [16, Lemma 4.1]) show that

$$\|\nabla v_\varepsilon(\cdot,t)\|_{L^\infty(\Omega)} \leq C_8(\varepsilon, T), \quad t \in (0, \widehat{T_\varepsilon}).$$

Now this estimate together with (3.24) enables us to use parabolic Hölder and Schauder estimates to conclude that T_ε cannot be finite in view of (3.15) (see the proof of [40, Lemma 3.11] for details). □

3.2 An entropy-type functional

In this section we prove the following estimate which stems from an entropy-type functional and is the main step towards the existence of a global weak solution to (3.1).

Proposition 3.8 *Let $T > 0$. Then there exists a constant $C(T) > 0$ such that for any $\varepsilon \in (0,1)$ the solution to (3.12) fulfills*

$$\begin{aligned}
&\sup_{t\in(0,T)}\left\{\int_\Omega m_\varepsilon \ln m_\varepsilon + \int_\Omega \frac{\kappa_\varepsilon|\nabla v_\varepsilon|^2}{1+v_\varepsilon} + \int_\Omega |\nabla q_\varepsilon|^2 + \int_\Omega |\nabla y_\varepsilon|^2\right\} + \int_0^T\int_\Omega D(m_\varepsilon, q_\varepsilon, v_\varepsilon)\kappa_\varepsilon \frac{|\nabla m_\varepsilon|^2}{m_\varepsilon} \\
&+ \int_0^T\int_\Omega \kappa_\varepsilon m_\varepsilon \frac{|\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2} + \varepsilon\int_0^T\int_\Omega m_\varepsilon^\theta \ln(m_\varepsilon + 2) \leq C(T).
\end{aligned} \tag{3.25}$$

The proof of this estimate relies on the strategy established in [40, Section 4] and consists of proving the existence of an entropy-type functional by several integral estimates. The main difference here are additional estimates involving powers of ∇m_ε and ∇q_ε which arise due to the splitting of the cancer cell population. As a first step we estimate the time evolution of the first integral in (3.25) similar to [40, Lemma 4.3].

Lemma 3.9 *There exists $C > 0$ such that for any $\varepsilon \in (0, 1)$ and all $t > 0$ we have*

$$\begin{aligned}
&\frac{d}{dt}\int_\Omega m_\varepsilon \ln m_\varepsilon + \int_\Omega D(m_\varepsilon, q_\varepsilon, v_\varepsilon)\kappa_\varepsilon \frac{|\nabla m_\varepsilon|^2}{m_\varepsilon} + \frac{\varepsilon}{2}\int_\Omega m_\varepsilon^\theta \ln(m_\varepsilon + 2) \\
&\leq \int_\Omega \frac{\kappa_\varepsilon v_\varepsilon}{1 + v_\varepsilon}\nabla m_\varepsilon \cdot \nabla v_\varepsilon + C. \qquad (3.26)
\end{aligned}$$

Proof. We use the positivity of m_ε stated in Lemma 3.4 and the first equation in (3.12) to deduce by (3.6), (3.16), and (3.21) that

$$\begin{aligned}
\frac{d}{dt}\int_\Omega m_\varepsilon \ln m_\varepsilon &= \int_\Omega (\ln m_\varepsilon \partial_t m_\varepsilon + \partial_t m_\varepsilon) \\
&= -\int_\Omega D(m_\varepsilon, q_\varepsilon, v_\varepsilon)\kappa_\varepsilon \frac{|\nabla m_\varepsilon|^2}{m_\varepsilon} + \int_\Omega \frac{\kappa_\varepsilon v_\varepsilon}{1 + v_\varepsilon}\nabla m_\varepsilon \cdot \nabla v_\varepsilon + \int_\Omega \lambda(y_\varepsilon) q_\varepsilon \ln m_\varepsilon \\
&\quad -\int_\Omega \gamma m_\varepsilon \ln m_\varepsilon - \int_\Omega r_m(t) m_\varepsilon \ln m_\varepsilon - \varepsilon \int_\Omega m_\varepsilon^\theta \ln m_\varepsilon + \int_\Omega \lambda(y_\varepsilon) q_\varepsilon \\
&\quad -\int_\Omega \gamma m_\varepsilon - \int_\Omega r_m(t) m_\varepsilon - \varepsilon \int_\Omega m_\varepsilon^\theta \\
&\leq -\int_\Omega D(m_\varepsilon, q_\varepsilon, v_\varepsilon)\kappa_\varepsilon \frac{|\nabla m_\varepsilon|^2}{m_\varepsilon} + \int_\Omega \frac{\kappa_\varepsilon v_\varepsilon}{1 + v_\varepsilon}\nabla m_\varepsilon \cdot \nabla v_\varepsilon + \lambda_1 AB + (\gamma + C_3)\frac{|\Omega|}{e} \\
&\quad -\frac{\varepsilon}{2}\int_\Omega m_\varepsilon^\theta \ln(m_\varepsilon + 2) + c_5 + \lambda_1 A|\Omega| \qquad \text{for all } t > 0,
\end{aligned}$$

where in the latter estimate we have used

$$\int_\Omega \lambda(y_\varepsilon) q_\varepsilon \ln m_\varepsilon \leq \lambda_1 \int_{\{m_\varepsilon \geq 1\}} q_\varepsilon \ln m_\varepsilon \leq \lambda_1 A \int_{\{m_\varepsilon \geq 1\}} m_\varepsilon \leq \lambda_1 AB,$$

$\xi \ln \xi \geq -\frac{1}{e}$ for all $\xi > 0$ and the existence of $c_5 > 0$ such that $-\xi^\theta \ln \xi \leq -\frac{1}{2}\xi^\theta \ln(\xi + 2) + c_5$ for all $\xi > 0$ (see [40, Lemma 4.2]). This proves (3.26). □

Like in [40, Lemma 4.4], we are able to cancel the first term on the right-hand side of (3.26) in view of the following pointwise estimate. However, an additional term involving $|\nabla q_\varepsilon|^2$ is present here.

Lemma 3.10 *Let P be as defined in Lemma 3.5. Then we have for any $\varepsilon \in (0, 1)$*

$$\begin{aligned}
\partial_t \frac{\kappa_\varepsilon |\nabla v_\varepsilon|^2}{1 + v_\varepsilon} &\leq 2\varepsilon \frac{\kappa_\varepsilon}{1 + v_\varepsilon}\nabla v_\varepsilon \cdot \nabla \Delta v_\varepsilon - \varepsilon \frac{\kappa_\varepsilon}{(1 + v_\varepsilon)^2}|\nabla v_\varepsilon|^2 \Delta v_\varepsilon - 2\alpha \frac{\kappa_\varepsilon v_\varepsilon}{1 + v_\varepsilon}\nabla m_\varepsilon \cdot \nabla v_\varepsilon \\
&\quad + \frac{\beta^2 P}{2\mu_v}|\nabla q_\varepsilon|^2 - 2\alpha \kappa_\varepsilon m_\varepsilon \frac{|\nabla v_\varepsilon|^2}{(1 + v_\varepsilon)^2} + (2\mu_v + \delta) P \frac{|\nabla v_\varepsilon|^2}{1 + v_\varepsilon} \qquad (3.27)
\end{aligned}$$

for all $x \in \Omega$, $t > 0$.

Proof. As $v_\varepsilon \in C^\infty(\bar\Omega \times (0,\infty))$ by parabolic regularity theory (see [22]), we have

$$\partial_t \frac{\kappa_\varepsilon |\nabla v_\varepsilon|^2}{1+v_\varepsilon} = \frac{2\kappa_\varepsilon \nabla v_\varepsilon \cdot \nabla(\partial_t v_\varepsilon)}{1+v_\varepsilon} - \frac{\kappa_\varepsilon |\nabla v_\varepsilon|^2 \partial_t v_\varepsilon}{(1+v_\varepsilon)^2} + \frac{\partial_t \kappa_\varepsilon |\nabla v_\varepsilon|^2}{1+v_\varepsilon} =: I_1 - I_2 + I_3 \tag{3.28}$$

for $x \in \Omega$ and $t > 0$. Using the third equation in (3.12), Youngs's inequality, and (3.6), we obtain

$$\begin{aligned}
I_1 - I_2 \;&=\; \kappa_\varepsilon \Bigg\{ 2\varepsilon \frac{1}{1+v_\varepsilon} \nabla v_\varepsilon \cdot \nabla \Delta v_\varepsilon - 2\alpha \frac{m_\varepsilon |\nabla v_\varepsilon|^2}{1+v_\varepsilon} - 2\alpha \frac{v_\varepsilon}{1+v_\varepsilon} \nabla m_\varepsilon \cdot \nabla v_\varepsilon - 2\beta \frac{q_\varepsilon |\nabla v_\varepsilon|^2}{1+v_\varepsilon} \\
&\quad -2\beta \frac{v_\varepsilon}{1+v_\varepsilon} \nabla q_\varepsilon \cdot \nabla v_\varepsilon + 2\mu_v \frac{|\nabla v_\varepsilon|^2}{1+v_\varepsilon} - 4\mu_v \frac{v_\varepsilon |\nabla v_\varepsilon|^2}{1+v_\varepsilon} - 2r_v(t) \frac{|\nabla v_\varepsilon|^2}{1+v_\varepsilon} - \varepsilon \frac{|\nabla v_\varepsilon|^2 \Delta v_\varepsilon}{(1+v_\varepsilon)^2} \\
&\quad +\alpha \frac{m_\varepsilon v_\varepsilon |\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2} + \beta \frac{q_\varepsilon v_\varepsilon |\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2} - \mu_v \frac{v_\varepsilon |\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2} + \mu_v \frac{v_\varepsilon^2 |\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2} + r_v(t) \frac{v_\varepsilon |\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2} \Bigg\} \\
&\le\; 2\varepsilon \frac{\kappa_\varepsilon}{1+v_\varepsilon} \nabla v_\varepsilon \cdot \nabla \Delta v_\varepsilon - \varepsilon \frac{\kappa_\varepsilon}{(1+v_\varepsilon)^2} |\nabla v_\varepsilon|^2 \Delta v_\varepsilon - 2\alpha \frac{\kappa_\varepsilon v_\varepsilon}{1+v_\varepsilon} \nabla m_\varepsilon \cdot \nabla v_\varepsilon + \frac{\beta^2}{2\mu_v} \kappa_\varepsilon |\nabla q_\varepsilon|^2 \\
&\quad + \frac{\kappa_\varepsilon |\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2} \cdot \Big\{ -2\alpha m_\varepsilon (1+v_\varepsilon) - 2\beta q_\varepsilon (1+v_\varepsilon) + 2\mu_v v_\varepsilon^2 + 2\mu_v (1+v_\varepsilon) - 4\mu_v v_\varepsilon (1+v_\varepsilon) \\
&\quad -2r_v(t)(1+v_\varepsilon) + \alpha m_\varepsilon v_\varepsilon + \beta q_\varepsilon v_\varepsilon - \mu_v v_\varepsilon + \mu_v v_\varepsilon^2 + r_v(t) v_\varepsilon \Big\} \\
&=\; 2\varepsilon \frac{\kappa_\varepsilon}{1+v_\varepsilon} \nabla v_\varepsilon \cdot \nabla \Delta v_\varepsilon - \varepsilon \frac{\kappa_\varepsilon}{(1+v_\varepsilon)^2} |\nabla v_\varepsilon|^2 \Delta v_\varepsilon - 2\alpha \frac{\kappa_\varepsilon v_\varepsilon}{1+v_\varepsilon} \nabla m_\varepsilon \cdot \nabla v_\varepsilon + \frac{\beta^2}{2\mu_v} \kappa_\varepsilon |\nabla q_\varepsilon|^2 \\
&\quad + \frac{\kappa_\varepsilon |\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2} \cdot \Big\{ -2\alpha m_\varepsilon - \alpha m_\varepsilon v_\varepsilon - 2\beta q_\varepsilon - \beta q_\varepsilon v_\varepsilon + 2\mu_v - 3\mu_v v_\varepsilon - \mu_v v_\varepsilon^2 \\
&\quad -2r_v(t) - r_v(t) v_\varepsilon \Big\} \\
&\le\; 2\varepsilon \frac{\kappa_\varepsilon}{1+v_\varepsilon} \nabla v_\varepsilon \cdot \nabla \Delta v_\varepsilon - \varepsilon \frac{\kappa_\varepsilon}{(1+v_\varepsilon)^2} |\nabla v_\varepsilon|^2 \Delta v_\varepsilon - 2\alpha \frac{\kappa_\varepsilon v_\varepsilon}{1+v_\varepsilon} \nabla m_\varepsilon \cdot \nabla v_\varepsilon + \frac{\beta^2}{2\mu_v} \kappa_\varepsilon |\nabla q_\varepsilon|^2 \\
&\quad -2\alpha \kappa_\varepsilon m_\varepsilon \frac{|\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2} + 2\mu_v \frac{\kappa_\varepsilon |\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2}.
\end{aligned}$$

By inserting this estimate into (3.28) and using (3.19) and (3.20), we arrive at (3.27). □

When integrating (3.27), we can estimate the first two terms on the right-hand side exactly as in [40, Lemma 4.5]. Since the proof of the latter contains a mistake concerning the boundary term when integration by parts is used, we give a correct version here.

Lemma 3.11 *For any $T > 0$ there is $\tilde C(T) > 0$ such that for each $\varepsilon \in (0,1)$ we have*

$$\begin{aligned}
&2\varepsilon \int_\Omega \frac{\kappa_\varepsilon}{1+v_\varepsilon} \nabla v_\varepsilon \cdot \nabla \Delta v_\varepsilon - \varepsilon \int_\Omega \frac{\kappa_\varepsilon}{(1+v_\varepsilon)^2} |\nabla v_\varepsilon|^2 \Delta v_\varepsilon \\
&\le -\frac{3}{2}\varepsilon \int_\Omega \kappa_\varepsilon (1+v_\varepsilon) \Big| D^2 \ln(1+v_\varepsilon) \Big|^2 - 2\varepsilon \int_\Omega \frac{1}{1+v_\varepsilon} \nabla \kappa_\varepsilon \cdot (D^2 v_\varepsilon \cdot \nabla v_\varepsilon) \\
&\qquad + \varepsilon \int_\Omega \frac{1}{(1+v_\varepsilon)^2} |\nabla v_\varepsilon|^2 \nabla \kappa_\varepsilon \cdot \nabla v_\varepsilon + \varepsilon \tilde C(T) \int_\Omega \frac{|\nabla v_\varepsilon|^2}{1+v_\varepsilon} \qquad \textit{for all } t \in (0,T).
\end{aligned} \tag{3.29}$$

Proof. Using that $\partial_\nu v_\varepsilon = 0$ on $\partial\Omega$ implies $\partial_\nu|\nabla v_\varepsilon|^2 \le c_\Omega |\nabla v_\varepsilon|^2$ on $\partial\Omega$ with some $c_\Omega > 0$ depending only on the curvatures of Ω (see e.g. [31, Lemma 4.2]), we may integrate by parts and have (with $\partial_i := \partial_{x_i}$)

$$
\begin{aligned}
&2\int_\Omega \frac{\kappa_\varepsilon}{1+v_\varepsilon}\nabla v_\varepsilon \cdot \nabla\Delta v_\varepsilon = 2\sum_{i,j=1}^n \int_\Omega \frac{\kappa_\varepsilon}{1+v_\varepsilon}\partial_j v_\varepsilon \partial_{iij} v_\varepsilon \\
&\le -2\sum_{i,j=1}^n \int_\Omega \frac{\kappa_\varepsilon}{1+v_\varepsilon}(\partial_{ij}v_\varepsilon)^2 + 2\sum_{i,j=1}^n \int_\Omega \frac{\kappa_\varepsilon}{(1+v_\varepsilon)^2}\partial_i v_\varepsilon \partial_j v_\varepsilon \partial_{ij} v_\varepsilon - 2\sum_{i,j=1}^n \int_\Omega \frac{\partial_i \kappa_\varepsilon}{1+v_\varepsilon}\partial_j v_\varepsilon \partial_{ij} v_\varepsilon \\
&\quad + c_\Omega \int_{\partial\Omega} \frac{\kappa_\varepsilon}{1+v_\varepsilon}|\nabla v_\varepsilon|^2\, d\sigma
\end{aligned}
$$

as well as

$$
\begin{aligned}
&-\int_\Omega \frac{\kappa_\varepsilon}{(1+v_\varepsilon)^2}|\nabla v_\varepsilon|^2 \Delta v_\varepsilon = -\sum_{i,j=1}^n \int_\Omega \frac{\kappa_\varepsilon}{(1+v_\varepsilon)^2}(\partial_j v_\varepsilon)^2 \partial_{ii} v_\varepsilon \\
&= 2\sum_{i,j=1}^n \int_\Omega \frac{\kappa_\varepsilon}{(1+v_\varepsilon)^2}\partial_i v_\varepsilon \partial_j v_\varepsilon \partial_{ij} v_\varepsilon - 2\sum_{i,j=1}^n \int_\Omega \frac{\kappa_\varepsilon}{(1+v_\varepsilon)^3}(\partial_i v_\varepsilon)^2(\partial_j v_\varepsilon)^2 + \sum_{i,j=1}^n \int_\Omega \frac{\partial_i \kappa_\varepsilon}{(1+v_\varepsilon)^2}\partial_i v_\varepsilon (\partial_j v_\varepsilon)^2
\end{aligned}
$$

for all $t > 0$. Adding both estimates implies

$$
\begin{aligned}
&2\int_\Omega \frac{\kappa_\varepsilon}{1+v_\varepsilon}\nabla v_\varepsilon \cdot \nabla\Delta v_\varepsilon - \int_\Omega \frac{\kappa_\varepsilon}{(1+v_\varepsilon)^2}|\nabla v_\varepsilon|^2 \Delta v_\varepsilon \\
\le\ & -2\sum_{i,j=1}^n \int_\Omega \frac{\kappa_\varepsilon}{1+v_\varepsilon}\cdot \left|\partial_{ij} v_\varepsilon - \frac{\partial_i v_\varepsilon \partial_j v_\varepsilon}{1+v_\varepsilon}\right|^2 - 2\int_\Omega \frac{1}{1+v_\varepsilon}\nabla\kappa_\varepsilon \cdot (D^2 v_\varepsilon \cdot \nabla v_\varepsilon) \\
& + \int_\Omega \frac{1}{(1+v_\varepsilon)^2}|\nabla v_\varepsilon|^2 \nabla\kappa_\varepsilon \cdot \nabla v_\varepsilon + c_\Omega \int_{\partial\Omega}\frac{\kappa_\varepsilon}{1+v_\varepsilon}|\nabla v_\varepsilon|^2\, d\sigma \\
=\ & -2\int_\Omega \kappa_\varepsilon (1+v_\varepsilon)\left|D^2 \ln(1+v_\varepsilon)\right|^2 - 2\int_\Omega \frac{1}{1+v_\varepsilon}\nabla\kappa_\varepsilon \cdot (D^2 v_\varepsilon \cdot \nabla v_\varepsilon) \\
& + \int_\Omega \frac{1}{(1+v_\varepsilon)^2}|\nabla v_\varepsilon|^2 \nabla\kappa_\varepsilon \cdot \nabla v_\varepsilon + c_\Omega \int_{\partial\Omega}\frac{\kappa_\varepsilon}{1+v_\varepsilon}|\nabla v_\varepsilon|^2\, d\sigma
\end{aligned}
\tag{3.30}
$$

for all $t > 0$, where in the latter identity we use

$$
\partial_{ij}(\ln(1+v_\varepsilon)) = \frac{\partial_{ij} v_\varepsilon}{1+v_\varepsilon} - \frac{\partial_i v_\varepsilon \partial_j v_\varepsilon}{(1+v_\varepsilon)^2} = \frac{1}{1+v_\varepsilon}\left(\partial_{ij} v_\varepsilon - \frac{\partial_i v_\varepsilon \partial_j v_\varepsilon}{(1+v_\varepsilon)}\right). \tag{3.31}
$$

For estimating the boundary term in (3.30), we use an idea from [19]. Namely, we fix $r \in (0, \frac12)$, set $a := r + \frac12 \in (0,1)$, and use as in [19] the compact embedding of $W^{r+\frac12,2}(\Omega)$ into $L^2(\partial\Omega)$ (see [11, Proposition 4.22(ii) and Theorem 4.24(i)]) and the fractional Gagliardo-Nirenberg inequality (see [19, Lemma 2.5]). Upon a combination with (3.19) and Young's inequality, for any $\eta > 0$ there is $C_\eta > 0$ such that

$$
c_\Omega \int_{\partial\Omega} \frac{\kappa_\varepsilon}{1+v_\varepsilon}|\nabla v_\varepsilon|^2\, d\sigma \quad \le \quad C_5 \|\nabla v_\varepsilon\|^2_{W^{r+\frac12,2}(\Omega)}
$$

$$\begin{aligned} &\le C_6\left(\|\nabla|\nabla v_\varepsilon|\|_{L^2(\Omega)}^{2a}\|\nabla v_\varepsilon\|_{L^2(\Omega)}^{2(1-a)}+\|\nabla v_\varepsilon\|_{L^2(\Omega)}^2\right)\\ &\le \eta\|\nabla|\nabla v_\varepsilon|\|_{L^2(\Omega)}^2+C_\eta\|\nabla v_\varepsilon\|_{L^2(\Omega)}^2 \qquad \text{for all } t>0. \end{aligned} \tag{3.32}$$

In view of $\nabla|\nabla v_\varepsilon| = \frac{D^2 v_\varepsilon\cdot\nabla v_\varepsilon}{|\nabla v_\varepsilon|}$, (3.31), (3.17), and the inequality

$$\int_\Omega \frac{|\nabla\Psi|^4}{(1+\Psi)^3} \le (2+\sqrt{n})^2\int_\Omega (1+\Psi)\Big|D^2\ln(1+\Psi)\Big|^2, \tag{3.33}$$

which is valid for all $0\le\Psi\in C^2(\bar\Omega)$ with $\partial_\nu\Psi=0$ on $\partial\Omega$ (see [44, Lemma 3.3] for a proof), we further estimate

$$\begin{aligned} \int_\Omega |\nabla|\nabla v_\varepsilon||^2 &\le \int_\Omega \left|D^2 v_\varepsilon\right|^2\\ &\le \int_\Omega 2(1+v_\varepsilon)^2\left|D^2\ln(1+v_\varepsilon)\right|^2+\int_\Omega 2\frac{|\nabla v_\varepsilon|^4}{(1+v_\varepsilon)^2}\\ &\le 2(1+L)\left(\int_\Omega (1+v_\varepsilon)\left|D^2\ln(1+v_\varepsilon)\right|^2+\int_\Omega\frac{|\nabla v_\varepsilon|^4}{(1+v_\varepsilon)^3}\right)\\ &\le C_7\int_\Omega (1+v_\varepsilon)\left|D^2\ln(1+v_\varepsilon)\right|^2 \qquad \text{for all } t>0 \end{aligned} \tag{3.34}$$

with $C_7 := 2(1+L)(1+(2+\sqrt{n})^2)>0$.
As (3.19) implies the existence of $C_8(T)>0$ such that $\kappa_\varepsilon\ge C_8(T)$ in $\Omega\times(0,T)$, we insert (3.34) into (3.32), use (3.17) and choose $\eta := \frac{C_8(T)}{2C_7}>0$ to obtain

$$\begin{aligned} c_\Omega\int_{\partial\Omega}\frac{\kappa_\varepsilon}{1+v_\varepsilon}|\nabla v_\varepsilon|^2\,d\sigma &\le \eta C_7\int_\Omega (1+v_\varepsilon)\left|D^2\ln(1+v_\varepsilon)\right|^2+C_\eta\int_\Omega|\nabla v_\varepsilon|^2\\ &\le \frac{\eta C_7}{C_8(T)}\int_\Omega \kappa_\varepsilon(1+v_\varepsilon)\left|D^2\ln(1+v_\varepsilon)\right|^2+C_\eta(1+L)\int_\Omega\frac{|\nabla v_\varepsilon|^2}{1+v_\varepsilon}\\ &\le \frac12\int_\Omega \kappa_\varepsilon(1+v_\varepsilon)\left|D^2\ln(1+v_\varepsilon)\right|^2+C_\eta(1+L)\int_\Omega\frac{|\nabla v_\varepsilon|^2}{1+v_\varepsilon} \end{aligned}$$

for all $t\in(0,T)$. By inserting the latter estimate into (3.30), we obtain (3.29). □

Next we provide an appropriate estimate for the additional term $\int_\Omega|\nabla q_\varepsilon|^2$ coming from (3.27). This is the only place where we need the assumption that γ is constant.

Lemma 3.12 *There exists $C>0$ such that for each $\varepsilon\in(0,1)$ and all $t>0$ we have*

$$\frac{d}{dt}\int_\Omega|\nabla q_\varepsilon|^2 \le C\left\{\int_\Omega|\nabla q_\varepsilon|^2+\int_\Omega\frac{|\nabla m_\varepsilon|^2}{m_\varepsilon}+\int_\Omega\frac{|\nabla v_\varepsilon|^2}{1+v_\varepsilon}+\int_\Omega|\nabla y_\varepsilon|^2\right\}. \tag{3.35}$$

Proof. We have $q_\varepsilon\in C^\infty(\bar\Omega\times(0,T_\varepsilon))$ by parabolic regularity theory and $\partial_\nu|\nabla q_\varepsilon|^2\le c_\Omega|\nabla q_\varepsilon|^2$ on $\partial\Omega$ in view of $\partial_\nu q_\varepsilon=0$ on $\partial\Omega$ and the smoothness of $\partial\Omega$ (with c_Ω as defined in the proof of Lemma 3.11). Hence, the second equation of (3.12) and integration by parts in conjunction with Young's and Hölder's inequalities, (3.6), and Lemma 3.5 yield

$$\frac12\frac{d}{dt}\int_\Omega|\nabla q_\varepsilon|^2 = \int_\Omega\nabla q_\varepsilon\cdot\nabla(\partial_t q_\varepsilon)$$

$$
\begin{aligned}
&= \varepsilon \int_\Omega \nabla q_\varepsilon \cdot \nabla \Delta q_\varepsilon + \int_\Omega (\mu_q - \lambda(y_\varepsilon) - r_q(t))|\nabla q_\varepsilon|^2 - \int_\Omega \lambda'(y_\varepsilon) q_\varepsilon \nabla q_\varepsilon \cdot \nabla y_\varepsilon \\
&\quad -2\mu_q \int_\Omega q_\varepsilon |\nabla q_\varepsilon|^2 - \mu_q \int_\Omega m_\varepsilon |\nabla q_\varepsilon|^2 - \mu_q \int_\Omega q_\varepsilon \nabla q_\varepsilon \cdot \nabla m_\varepsilon - \mu_q \eta_1 \int_\Omega v_\varepsilon |\nabla q_\varepsilon|^2 \\
&\quad -\mu_q \eta_1 \int_\Omega q_\varepsilon \nabla q_\varepsilon \cdot \nabla v_\varepsilon + \int_\Omega \gamma \nabla q_\varepsilon \cdot \nabla m_\varepsilon \\
&\le -\varepsilon \int_\Omega \left|D^2 q_\varepsilon\right|^2 + \frac{\varepsilon}{2} \int_{\partial\Omega} \partial_\nu |\nabla q_\varepsilon|^2 d\sigma + \left(\mu_q - \lambda_2 + A^2 \|\lambda'\|^2_{L^\infty((0,1))}\right) \int_\Omega |\nabla q_\varepsilon|^2 \\
&\quad + \frac{1}{4} \int_\Omega |\nabla y_\varepsilon|^2 - 2\mu_q \int_\Omega q_\varepsilon |\nabla q_\varepsilon|^2 - \frac{3\mu_q}{4} \int_\Omega m_\varepsilon |\nabla q_\varepsilon|^2 + \mu_q A^2 \int_\Omega \frac{|\nabla m_\varepsilon|^2}{m_\varepsilon} \\
&\quad + 2\mu_q \int_\Omega q_\varepsilon |\nabla q_\varepsilon|^2 + \frac{\mu_q \eta_1^2 A}{8} \int_\Omega |\nabla v_\varepsilon|^2 + \frac{\mu_q}{4} \int_\Omega m_\varepsilon |\nabla q_\varepsilon|^2 + \frac{\gamma^2}{\mu_q} \int_\Omega \frac{|\nabla m_\varepsilon|^2}{m_\varepsilon} \\
&\le -\varepsilon \int_\Omega \left|D^2 q_\varepsilon\right|^2 + \frac{\varepsilon c_\Omega}{2} \int_{\partial\Omega} |\nabla q_\varepsilon|^2 d\sigma + \left(\mu_q - \lambda_2 + A^2 \|\lambda'\|^2_{L^\infty((0,1))}\right) \int_\Omega |\nabla q_\varepsilon|^2 \\
&\quad + \frac{1}{4} \int_\Omega |\nabla y_\varepsilon|^2 + \left(\mu_q A^2 + \frac{\gamma^2}{\mu_q}\right) \int_\Omega \frac{|\nabla m_\varepsilon|^2}{m_\varepsilon} + \frac{\mu_q \eta_1^2 A(1+L)}{8} \int_\Omega \frac{|\nabla v_\varepsilon|^2}{1+v_\varepsilon} \qquad (3.36)
\end{aligned}
$$

for all $t > 0$. Concerning the second term on the right-hand side, we fix $r \in (0, \frac{1}{2})$ and $a := r + \frac{1}{2} \in (0,1)$ and use the compact embedding of $W^{r+\frac{1}{2},2}(\Omega)$ into $L^2(\partial\Omega)$ and the fractional Gagliardo-Nirenberg inequality to estimate like in (3.32) and (3.34)

$$
\begin{aligned}
\frac{\varepsilon c_\Omega}{2} \int_{\partial\Omega} |\nabla q_\varepsilon|^2 d\sigma &\le \varepsilon C_5 \|\nabla q_\varepsilon\|^2_{W^{r+\frac{1}{2}}(\Omega)} \le \varepsilon C_6 \left(\|\nabla |\nabla q_\varepsilon|\|^{2a}_{L^2(\Omega)} \|\nabla q_\varepsilon\|^{2(1-a)}_{L^2(\Omega)} + \|\nabla q_\varepsilon\|^2_{L^2(\Omega)} \right) \\
&\le \varepsilon \|\nabla |\nabla q_\varepsilon|\|^2_{L^2(\Omega)} + \varepsilon C_7 \|\nabla q_\varepsilon\|^2_{L^2(\Omega)} \le \varepsilon \int_\Omega \left|D^2 q_\varepsilon\right|^2 + C_7 \int_\Omega |\nabla q_\varepsilon|^2
\end{aligned}
$$

in view of $\varepsilon \in (0,1)$. Inserting this into (3.36), we end up with (3.35). □

In a final preliminary step we estimate suitable terms involving ∇y_ε and $\nabla \kappa_\varepsilon$ like in [40, Lemmas 4.7-4.8].

Lemma 3.13 *There is $C > 0$ such that for any $\varepsilon \in (0,1)$ and all $t > 0$ we have*

$$
\frac{d}{dt} \int_\Omega |\nabla y_\varepsilon|^2 \le \int_\Omega |\nabla v_\varepsilon|^2 + C \int_\Omega |\nabla y_\varepsilon|^2 \quad \textit{and} \quad \frac{d}{dt} \int_\Omega |\nabla y_\varepsilon|^4 \le \int_\Omega |\nabla v_\varepsilon|^4 + C \int_\Omega |\nabla y_\varepsilon|^4
$$

$$
\textit{and} \quad \frac{d}{dt} \int_\Omega |\nabla \kappa_\varepsilon|^4 \le C \int_\Omega |\nabla y_\varepsilon(\cdot, t-\tau)|^4.
$$

Proof. In view of $v_\varepsilon \in C^\infty(\bar{\Omega} \times (0,\infty))$ and (3.13) we may use the fourth equation in (3.12), Young's inequality, (3.6), and Lemma 3.5 to obtain

$$
\begin{aligned}
\frac{1}{4} \frac{d}{dt} \int_\Omega |\nabla y_\varepsilon|^4 &= \int_\Omega |\nabla y_\varepsilon|^2 \nabla y_\varepsilon \cdot \nabla(\partial_t y_\varepsilon) \\
&= K_1(t) \int_\Omega (1 - y_\varepsilon) |\nabla y_\varepsilon|^2 \nabla y_\varepsilon \cdot \nabla v_\varepsilon - K_1(t) \int_\Omega v_\varepsilon |\nabla y_\varepsilon|^4 - K_{-1}(t) \int_\Omega |\nabla y_\varepsilon|^4
\end{aligned}
$$

$$\leq \frac{3}{4}C_3^{\frac{4}{3}}\int_\Omega |\nabla y_\varepsilon|^4 + \frac{1}{4}\int_\Omega |\nabla v_\varepsilon|^4 \tag{3.37}$$

as well as

$$\begin{aligned}
\frac{1}{4}\frac{d}{dt}\int_\Omega |\nabla\kappa_\varepsilon|^4 &= \int_\Omega |\nabla\kappa_\varepsilon|^2\nabla\kappa_\varepsilon\cdot\nabla(\partial_t\kappa_\varepsilon)\\
&= -\delta\int_\Omega |\nabla\kappa_\varepsilon|^4 + \int_\Omega H'(y(\cdot,t-\tau))|\nabla\kappa_\varepsilon|^2\nabla\kappa_\varepsilon\cdot\nabla y_\varepsilon(\cdot,t-\tau)\\
&\leq \frac{1}{4}\left(\frac{3}{4\delta}\right)^3\|H'\|^4_{L^\infty((0,1))}\int_\Omega |\nabla y_\varepsilon(\cdot,t-\tau)|^4.
\end{aligned}$$

The estimate concerning $\int_\Omega |\nabla y_\varepsilon|^2$ can be proved like in (3.37). □

Now we are in a position to prove Proposition 3.8, the main result of this section. The proof is similar to the one of [40, Lemma 4.1].

Proof of Proposition 3.8. We fix $T>0$ and $\varepsilon\in(0,1)$ (all constants C_i below do not depend on ε and their dependence on T is indicated). Then (3.19) implies the existence of $C_5(T)>0$ such that

$$\kappa_\varepsilon(x,t)\geq C_5(T)>0 \qquad \text{for all } x\in\Omega,\ t\in(0,T). \tag{3.38}$$

Hence, with $C_6(T):=\frac{(2+\sqrt{n})^2}{C_5(T)}>0$, we obtain from (3.17) and (3.33) that

$$\int_\Omega |\nabla v_\varepsilon|^4 \leq (1+L)^3\int_\Omega \frac{|\nabla v_\varepsilon|^4}{(1+v_\varepsilon)^3} \leq (1+L)^3C_6(T)\int_\Omega \kappa_\varepsilon(1+v_\varepsilon)\Big|D^2\ln(1+v_\varepsilon)\Big|^2 \tag{3.39}$$

for all $t\in(0,T)$. Hence, using (3.31), Young's inequality, (3.38), (3.39), and (3.17), we estimate the second and third term on the right-hand side of (3.29) according to

$$\begin{aligned}
&-2\varepsilon\int_\Omega \frac{1}{1+v_\varepsilon}\nabla\kappa_\varepsilon\cdot(D^2v_\varepsilon\cdot\nabla v_\varepsilon) + \varepsilon\int_\Omega \frac{1}{(1+v_\varepsilon)^2}|\nabla v_\varepsilon|^2\nabla\kappa_\varepsilon\cdot\nabla v_\varepsilon\\
= \;& -2\varepsilon\int_\Omega \nabla\kappa_\varepsilon\cdot(D^2\ln(1+v_\varepsilon)\cdot\nabla v_\varepsilon) - \varepsilon\int_\Omega \frac{1}{(1+v_\varepsilon)^2}|\nabla v_\varepsilon|^2\nabla\kappa_\varepsilon\cdot\nabla v_\varepsilon\\
\leq \;& \frac{\varepsilon}{4}\int_\Omega \kappa_\varepsilon(1+v_\varepsilon)\Big|D^2\ln(1+v_\varepsilon)\Big|^2 + 4\varepsilon\int_\Omega \frac{|\nabla\kappa_\varepsilon|^2|\nabla v_\varepsilon|^2}{\kappa_\varepsilon(1+v_\varepsilon)} + \frac{\varepsilon}{2C_6(T)}\int_\Omega \frac{|\nabla v_\varepsilon|^4}{(1+v_\varepsilon)^3}\\
&+\frac{27\varepsilon C_6^3(T)}{32}\int_\Omega (1+v_\varepsilon)|\nabla\kappa_\varepsilon|^4\\
\leq \;& \frac{\varepsilon}{4}\int_\Omega \kappa_\varepsilon(1+v_\varepsilon)\Big|D^2\ln(1+v_\varepsilon)\Big|^2 + \frac{3\varepsilon}{4C_6(T)}\int_\Omega \frac{|\nabla v_\varepsilon|^4}{(1+v_\varepsilon)^3} + 16\varepsilon C_6(T)\int_\Omega \frac{(1+v_\varepsilon)}{\kappa_\varepsilon^2}|\nabla\kappa_\varepsilon|^4\\
&+\frac{27\varepsilon C_6^3(T)(1+L)}{32}\int_\Omega |\nabla\kappa_\varepsilon|^4\\
\leq \;& \varepsilon\int_\Omega \kappa_\varepsilon(1+v_\varepsilon)\Big|D^2\ln(1+v_\varepsilon)\Big|^2 + \varepsilon\left(\frac{16C_6(T)(1+L)}{C_5^2(T)} + \frac{27C_6^3(T)(1+L)}{32}\right)\int_\Omega |\nabla\kappa_\varepsilon|^4
\end{aligned}$$

for all $t\in(0,T)$. Inserting the latter estimate and (3.29) into the integrated version of (3.27) and using (3.38), we have

$$\frac{d}{dt}\int_\Omega \frac{\kappa_\varepsilon|\nabla v_\varepsilon|^2}{1+v_\varepsilon} + 2\alpha\int_\Omega \kappa_\varepsilon m_\varepsilon\frac{|\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2} + \frac{\varepsilon}{2}\int_\Omega \kappa_\varepsilon(1+v_\varepsilon)\Big|D^2\ln(1+v_\varepsilon)\Big|^2$$

$$\leq \quad -2\alpha\int_\Omega \frac{\kappa_\varepsilon v_\varepsilon}{1+v_\varepsilon}\nabla m_\varepsilon\cdot\nabla v_\varepsilon + \frac{\beta^2 P}{2\mu_v}\int_\Omega |\nabla q_\varepsilon|^2 + C_7(T)\int_\Omega \frac{\kappa_\varepsilon|\nabla v_\varepsilon|^2}{1+v_\varepsilon} + \varepsilon C_7(T)\int_\Omega |\nabla\kappa_\varepsilon|^4$$

for all $t\in(0,T)$ with some $C_7(T)>0$. Multiplying this by $\frac{1}{2\alpha}$ and adding it to (3.26), we deduce the existence of $C_8>0$ such that

$$\begin{aligned}
&\frac{d}{dt}\left\{\int_\Omega m_\varepsilon\ln m_\varepsilon + \frac{1}{2\alpha}\int_\Omega \frac{\kappa_\varepsilon|\nabla v_\varepsilon|^2}{1+v_\varepsilon}\right\} + \int_\Omega D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon\frac{|\nabla m_\varepsilon|^2}{m_\varepsilon} + \int_\Omega \kappa_\varepsilon m_\varepsilon\frac{|\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2}\\
&+\frac{\varepsilon}{2}\int_\Omega m_\varepsilon^\theta\ln(m_\varepsilon+2) + \frac{\varepsilon}{4\alpha}\int_\Omega \kappa_\varepsilon(1+v_\varepsilon)\Big|D^2\ln(1+v_\varepsilon)\Big|^2\\
\leq\ & \frac{C_7(T)}{2\alpha}\int_\Omega \frac{\kappa_\varepsilon|\nabla v_\varepsilon|^2}{1+v_\varepsilon} + \frac{\beta^2 P}{4\alpha\mu_v}\int_\Omega|\nabla q_\varepsilon|^2 + \varepsilon\frac{C_7(T)}{2\alpha}\int_\Omega|\nabla\kappa_\varepsilon|^4 + C_8
\end{aligned}\tag{3.40}$$

for all $t\in(0,T)$. Next, let $C_2>0$ in (3.6) be fixed according to A and L defined in Lemma 3.5. Then (3.38) implies that $D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon\geq C_2C_5(T)$ in $\Omega\times(0,T)$. Denoting further the constant C from Lemma 3.12 by $C_9>0$ and setting $C_{10}(T):=\frac{C_2C_5(T)}{2C_9}>0$, we obtain from (3.40), Lemma 3.12, and (3.38) that

$$\begin{aligned}
&\frac{d}{dt}\left\{\int_\Omega m_\varepsilon\ln m_\varepsilon + \frac{1}{2\alpha}\int_\Omega\frac{\kappa_\varepsilon|\nabla v_\varepsilon|^2}{1+v_\varepsilon} + C_{10}(T)\int_\Omega|\nabla q_\varepsilon|^2\right\} + \frac{1}{2}\int_\Omega D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon\frac{|\nabla m_\varepsilon|^2}{m_\varepsilon}\\
&+\int_\Omega\kappa_\varepsilon m_\varepsilon\frac{|\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2} + \frac{\varepsilon}{2}\int_\Omega m_\varepsilon^\theta\ln(m_\varepsilon+2) + \frac{\varepsilon}{4\alpha}\int_\Omega\kappa_\varepsilon(1+v_\varepsilon)\Big|D^2\ln(1+v_\varepsilon)\Big|^2\\
\leq\ & C_{11}(T)\left(\int_\Omega\frac{\kappa_\varepsilon|\nabla v_\varepsilon|^2}{1+v_\varepsilon} + \int_\Omega|\nabla q_\varepsilon|^2 + \int_\Omega|\nabla y_\varepsilon|^2\right) + \varepsilon\frac{C_7(T)}{2\alpha}\int_\Omega|\nabla\kappa_\varepsilon|^4 + C_8
\end{aligned}\tag{3.41}$$

for all $t\in(0,T)$ with some $C_{11}(T)>0$. Next, we denote the constant C from Lemma 3.13 by $C_{12}>0$. In view of $|\nabla v_\varepsilon|^2\leq\frac{1+L}{C_5(T)}\frac{\kappa_\varepsilon|\nabla v_\varepsilon|^2}{1+v_\varepsilon}$ (due to (3.17) and (3.38)) and (3.39) we conclude from (3.41) and Lemma 3.13 with $C_{13}(T):=\frac{1}{4\alpha(1+L)^3C_6(T)}>0$ that

$$\begin{aligned}
&\frac{d}{dt}\Big\{\int_\Omega m_\varepsilon\ln m_\varepsilon + \frac{1}{2\alpha}\int_\Omega\frac{\kappa_\varepsilon|\nabla v_\varepsilon|^2}{1+v_\varepsilon} + C_{10}(T)\int_\Omega|\nabla q_\varepsilon|^2 + \int_\Omega|\nabla y_\varepsilon|^2 + \varepsilon\int_\Omega|\nabla\kappa_\varepsilon|^4\\
&+\varepsilon C_{13}(T)\int_\Omega|\nabla y_\varepsilon|^4\Big\} + \frac{1}{2}\int_\Omega D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon\frac{|\nabla m_\varepsilon|^2}{m_\varepsilon} + \int_\Omega\kappa_\varepsilon m_\varepsilon\frac{|\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2} + \frac{\varepsilon}{2}\int_\Omega m_\varepsilon^\theta\ln(m_\varepsilon+2)\\
\leq\ & C_{14}(T)\left(\int_\Omega\frac{\kappa_\varepsilon|\nabla v_\varepsilon|^2}{1+v_\varepsilon} + \int_\Omega|\nabla y_\varepsilon|^2\right) + C_{11}(T)\int_\Omega|\nabla q_\varepsilon|^2 + \varepsilon\frac{C_7(T)}{2\alpha}\int_\Omega|\nabla\kappa_\varepsilon|^4 + C_8\\
&+\varepsilon C_{12}\int_\Omega|\nabla y_\varepsilon(\cdot,t-\tau)|^4 + \varepsilon C_{12}C_{13}(T)\int_\Omega|\nabla y_\varepsilon|^4
\end{aligned}\tag{3.42}$$

for all $t\in(0,T)$ with some $C_{14}(T)>0$. Defining for $t\geq 0$ the nonnegative functions

$$\begin{aligned}
\mathcal{E}_\varepsilon(t) \ :=\ & \int_\Omega m_\varepsilon\ln m_\varepsilon + \frac{1}{2\alpha}\int_\Omega\frac{\kappa_\varepsilon|\nabla v_\varepsilon|^2}{1+v_\varepsilon} + C_{10}(T)\int_\Omega|\nabla q_\varepsilon|^2 + \int_\Omega|\nabla y_\varepsilon|^2 + \varepsilon\int_\Omega|\nabla\kappa_\varepsilon|^4\\
&+\varepsilon C_{13}(T)\int_\Omega|\nabla y_\varepsilon|^4 + \frac{|\Omega|}{e},
\end{aligned}$$

$$\begin{aligned}
\mathcal{D}_\varepsilon(t) &:= \frac{1}{2}\int_\Omega D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon\frac{|\nabla m_\varepsilon|^2}{m_\varepsilon}+\int_\Omega \kappa_\varepsilon m_\varepsilon\frac{|\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2}+\frac{\varepsilon}{2}\int_\Omega m_\varepsilon^\theta\ln(m_\varepsilon+2),\\
h_\varepsilon(t) &:= \int_\Omega |\nabla y_\varepsilon(\cdot,t)|^4, \qquad \text{with}\quad \varepsilon h_\varepsilon(t-\tau)\le \frac{1}{C_{13}(T)}\mathcal{E}_\varepsilon((t-\tau)_+)+\sup_{s\in[-\tau,0]}\int_\Omega|\nabla y_{0\varepsilon}(\cdot,s)|^4,
\end{aligned}$$

we deduce from (3.42) that there is $C_{15}(T)>0$ such that

$$\frac{d}{dt}\mathcal{E}_\varepsilon(t)+\mathcal{D}_\varepsilon(t)\le C_{15}(T)\left(\mathcal{E}_\varepsilon(t)+\varepsilon h_\varepsilon(t-\tau)\right) \qquad \text{for all } t\in(0,T).$$

As this corresponds to [40, (4.31)] and $\sup_{\varepsilon\in(0,1)}\mathcal{E}_\varepsilon(0)$ is finite due to (3.14), we may proceed as in the proof of [40, Lemma 4.1] to obtain $C_{16}(T)>0$ with

$$\sup_{t\in(0,T)}\mathcal{E}_\varepsilon(t)\le C_{16}(T) \quad \text{and} \quad \int_0^T \mathcal{D}_\varepsilon(t)dt\le C_{16}(T),$$

which proves (3.25). □

3.3 Global weak solution to the original problem

From estimate (3.25), which we gained from the entropy-type functional $\mathcal{E}_\varepsilon$, we will derive appropriate compactness properties for the solutions of (3.12) which then will imply the convergence to a global weak solution of the original problem (3.1)-(3.3). Large parts of our proofs rely on the ideas from [40, Section 5]. We first collect properties of m_ε.

Lemma 3.14 *Let $T>0$ be arbitrary. Then there is a constant $C(T)>0$ such that for any $\varepsilon\in(0,1)$*

$$\int_0^T \|\sqrt{1+m_\varepsilon(\cdot,t)}\|^2_{W^{1,2}(\Omega)}dt\le C(T) \tag{3.43}$$

is fulfilled. Moreover, $(\sqrt{1+m_\varepsilon})_{\varepsilon\in(0,1)}$ is strongly precompact in $L^2((0,T);L^p(\Omega))$ for any $p\in(1,6)$ and $(m_\varepsilon)_{\varepsilon\in(0,1)}$ is strongly precompact in $L^1((0,T);L^2(\Omega))$.

Proof. In view of (3.38) and (3.6) with $C_2=C_2(A,L)$ according to A,L from Lemma 3.5, we have

$$D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon\ge C_2C_5(T) \qquad \text{for all } x\in\Omega,\ t\in(0,T). \tag{3.44}$$

Hence, we obtain from (3.21) and Proposition 3.8 that

$$\begin{aligned}
\int_0^T\|\sqrt{1+m_\varepsilon}\|^2_{W^{1,2}(\Omega)} &= \int_0^T\int_\Omega(1+m_\varepsilon)+\frac{1}{4}\int_0^T\int_\Omega\frac{|\nabla m_\varepsilon|^2}{1+m_\varepsilon}\\
&\le T(|\Omega|+B)+\frac{1}{4C_2C_5(T)}\int_0^T\int_\Omega D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon\frac{|\nabla m_\varepsilon|^2}{m_\varepsilon}\le C_6(T)
\end{aligned}$$

for all $t\in(0,T)$ with some $C_6(T)>0$, which proves (3.43). Next let $k\in\mathbb{N}$ be such that $k>\frac{n+2}{2}$. We claim that

$$\int_0^T \|\partial_t\sqrt{1+m_\varepsilon(\cdot,t)}\|_{(W_0^{k,2}(\Omega))^*}dt\le C_7(T) \tag{3.45}$$

with some $C_7(T) > 0$. To this end, we fix $t \in (0,T)$ and $\Psi \in C_0^\infty(\Omega)$ and deduce from the first equation in (3.12) by using integration by parts, Young's inequality, (3.6), Lemma 3.5, and Lemma 3.6 that

$$\begin{aligned}
& 2\int_0^T \int_\Omega \partial_t \sqrt{1+m_\varepsilon}\Psi = \int_0^T \int_\Omega \partial_t m_\varepsilon \frac{\Psi}{\sqrt{1+m_\varepsilon}} \\
= & \frac{1}{2}\int_0^T \int_\Omega \frac{D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon}{(1+m_\varepsilon)^{\frac{3}{2}}}|\nabla m_\varepsilon|^2\Psi - \int_0^T \int_\Omega \frac{D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon}{(1+m_\varepsilon)^{\frac{1}{2}}}\nabla m_\varepsilon \cdot \nabla\Psi \\
& -\frac{1}{2}\int_0^T \int_\Omega \frac{\kappa_\varepsilon v_\varepsilon m_\varepsilon}{(1+v_\varepsilon)(1+m_\varepsilon)^{\frac{3}{2}}}\nabla m_\varepsilon \cdot \nabla v_\varepsilon \Psi + \int_0^T \int_\Omega \frac{\kappa_\varepsilon v_\varepsilon m_\varepsilon}{(1+v_\varepsilon)(1+m_\varepsilon)^{\frac{1}{2}}}\nabla v_\varepsilon \cdot \nabla\Psi \\
& + \int_0^T \int_\Omega \left(\lambda(y_\varepsilon)q_\varepsilon - \gamma m_\varepsilon - r_m(t)m_\varepsilon - \varepsilon m_\varepsilon^\theta\right)\frac{\Psi}{\sqrt{1+m_\varepsilon}} \\
\leq & \frac{1}{2}\|\Psi\|_{L^\infty(\Omega)} \int_0^T \int_\Omega D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon \frac{|\nabla m_\varepsilon|^2}{m_\varepsilon} \\
& + \|\nabla\Psi\|_{L^\infty(\Omega)} \left\{\frac{T|\Omega|C_1 P}{4} + \int_0^T \int_\Omega D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon \frac{|\nabla m_\varepsilon|^2}{m_\varepsilon}\right\} \\
& + \|\Psi\|_{L^\infty(\Omega)} \left\{\frac{1}{C_2}\int_0^T \int_\Omega D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon \frac{|\nabla m_\varepsilon|^2}{m_\varepsilon} + \frac{L^2}{16}\int_0^T \int_\Omega \kappa_\varepsilon m_\varepsilon \frac{|\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2}\right\} \\
& + \|\nabla\Psi\|_{L^\infty(\Omega)} \left\{\frac{T|\Omega|PL^2}{4} + \int_0^T \int_\Omega \kappa_\varepsilon m_\varepsilon \frac{|\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2}\right\} \\
& + \|\Psi\|_{L^\infty(\Omega)} \left\{T|\Omega|\lambda_1 A + T(\gamma + C_3)B + (T+1)(B + \lambda_1 A|\Omega|)\right\} \\
\leq & C_8(T)\|\Psi\|_{W^{1,\infty}(\Omega)}
\end{aligned} \tag{3.46}$$

in view of Proposition 3.8. Since $W_0^{k,2}(\Omega)$ is continuously embedded into $W^{1,\infty}(\Omega)$ due to $k > \frac{n+2}{2}$, there is some $C_9 > 0$ such that

$$\int_0^T \|\partial_t \sqrt{1+m_\varepsilon(\cdot,t)}\|_{(W_0^{k,2}(\Omega))^*} dt = \int_0^T \sup_{\Psi \in C_0^\infty(\Omega), \|\Psi\|_{W_0^{k,2}(\Omega)} \leq 1} \int_\Omega \partial_t \sqrt{1+m_\varepsilon(\cdot,t)}\Psi \leq C_9 C_8(T),$$

which proves (3.45). Now let $p \in (1,6)$ be arbitrary. Then in view of $n \leq 3$ and $k > \frac{n+2}{2}$ the embedding $W^{1,2}(\Omega) \hookrightarrow L^p(\Omega)$ is compact and $L^p(\Omega)$ is continuously embedded into the Hilbert space $(W_0^{k,2}(\Omega))^*$. As (3.43) and (3.45) imply that $(\sqrt{1+m_\varepsilon})_{\varepsilon\in(0,1)}$ is bounded in $L^2((0,T);W^{1,2}(\Omega))$ and $(\partial_t\sqrt{1+m_\varepsilon})_{\varepsilon\in(0,1)}$ is bounded in $L^1((0,T);(W_0^{k,2}(\Omega))^*)$, the strong precompactness of $(\sqrt{1+m_\varepsilon})_{\varepsilon\in(0,1)}$ in $L^2((0,T);L^p(\Omega))$ is a consequence of the Aubin-Lions Lemma (see e.g. Theorem 2.3 and Remark 2.1 in Chapter II of [42]). In particular, the case $p=4$ along with $m_\varepsilon \geq 0$ implies the strong precompactness of $(m_\varepsilon)_{\varepsilon\in(0,1)}$ in $L^1((0,T);L^2(\Omega))$. □

Next, we prove appropriate compactness properties for the other solution components.

Lemma 3.15 *Let $T > 0$ be arbitrary. Then there is a constant $C(T) > 0$ such that for any $\varepsilon \in (0,1)$*

$$\sup_{t\in(0,T)} \left\{\int_\Omega |\nabla q_\varepsilon(\cdot,t)|^2 + \int_\Omega |\nabla v_\varepsilon(\cdot,t)|^2 + \int_\Omega |\nabla y_\varepsilon(\cdot,t)|^2 + \int_\Omega |\nabla \kappa_\varepsilon(\cdot,t)|^2\right\} \leq C(T) \tag{3.47}$$

is satisfied. Moreover, $(q_\varepsilon)_{\varepsilon\in(0,1)}$*,* $(v_\varepsilon)_{\varepsilon\in(0,1)}$*,* $(y_\varepsilon)_{\varepsilon\in(0,1)}$*, and* $(\kappa_\varepsilon)_{\varepsilon\in(0,1)}$ *are strongly precompact in* $L^2(\Omega\times(0,T))$*.*

Proof. The estimates concerning ∇q_ε, ∇v_ε, and ∇y_ε claimed in (3.47) are immediate consequences of Proposition 3.8 and $|\nabla v_\varepsilon|^2 \le \frac{1+L}{C_5(T)}\frac{\kappa_\varepsilon|\nabla v_\varepsilon|^2}{1+v_\varepsilon}$ (by (3.17) and (3.38)). The estimate concerning $\nabla\kappa_\varepsilon$ then follows from the estimate on ∇y_ε, (3.14), and

$$\frac{1}{2}\frac{d}{dt}\int_\Omega |\nabla\kappa_\varepsilon|^2 \le \frac{1}{4\delta}\|H'\|^2_{L^\infty((0,1))}\int_\Omega |\nabla y_\varepsilon(\cdot,t-\tau)|^2 \qquad \text{for all } t>0,$$

which can be proved like in Lemma 3.13. Furthermore, (3.6), (3.12), and Lemma 3.5 imply the existence of $C_6>0$ such that

$$\sup_{t\in(0,\infty)}\left\{\|\partial_t y_\varepsilon\|_{L^\infty(\Omega)} + \|\partial_t\kappa_\varepsilon\|_{L^\infty(\Omega)}\right\} \le C_6. \tag{3.48}$$

When combined with (3.21) and (3.47), they further yield (in a way similar to (3.46))

$$\int_0^T \|\partial_t q_\varepsilon(\cdot,t)\|_{(W_0^{k,2}(\Omega))^*}dt + \int_0^T \|\partial_t v_\varepsilon(\cdot,t)\|_{(W_0^{k,2}(\Omega))^*}dt \le C_7(T) \tag{3.49}$$

with some $C_7(T)>0$. Hence, the claimed strong precompactness of the solution components in $L^2((0,T);L^2(\Omega))$ is a consequence of (3.47)-(3.49), Lemma 3.5, and the Aubin-Lions Lemma (like in the end of the proof of Lemma 3.14). □

Finally, we are in a position to prove the existence of a global weak solution to the original problem (3.1)-(3.3) like in the proof of [40, Theorem 1.1].

Proof of Theorem 3.2. First of all, by Lemmas 3.5, 3.6, 3.14, and 3.15 there exist nonnegative functions m, q, v, y, and κ having the regularity properties stated in Definition 3.1 and claimed in Theorem 3.2 such that along a suitable sequence $\varepsilon=\varepsilon_j\searrow 0$ as $j\to\infty$ we have for any $T>0$

$$\begin{aligned}
&l_\varepsilon \to l \qquad \text{strongly in } L^2(\Omega\times(0,T)) \text{ and a.e. in } \Omega\times(0,\infty), \quad \text{for } l\in\{\sqrt{1+m},q,v,y,\kappa\},\\
&m_\varepsilon \to m \qquad \text{strongly in } L^1((0,T);L^2(\Omega)) \text{ and a.e. in } \Omega\times(0,\infty),\\
&\nabla\sqrt{1+m_\varepsilon} \rightharpoonup \nabla\sqrt{1+m} \quad \text{and} \quad \nabla v_\varepsilon \rightharpoonup \nabla v \qquad \text{weakly in } L^2(\Omega\times(0,T)),\\
&\sqrt{m_\varepsilon}\,\nabla v_\varepsilon \rightharpoonup \sqrt{m}\,\nabla v \qquad \text{weakly in } L^2(\Omega\times(0,T)).
\end{aligned} \tag{3.50}$$

Here we deduce the last convergence from $\sqrt{m_\varepsilon}\to\sqrt{m}$ strongly in $L^2(\Omega\times(0,T))$ (and a.e.) and $\nabla v_\varepsilon \rightharpoonup \nabla v$ weakly in $L^2(\Omega\times(0,T))$, as Proposition 3.8, (3.17), and (3.38) imply that

$$\int_0^T\int_\Omega m_\varepsilon|\nabla v_\varepsilon|^2 \le \frac{(1+L)^2}{C_5(T)}\int_0^T\int_\Omega \kappa_\varepsilon m_\varepsilon\frac{|\nabla v_\varepsilon|^2}{(1+v_\varepsilon)^2} \le C_6(T)$$

for all $\varepsilon\in(0,1)$ with some $C_6(T)>0$. For fixed $T>0$ and $\varphi\in C_0^\infty(\bar\Omega\times[0,T))$ we obtain from the first equation in (3.12) that

$$-\int_0^T\int_\Omega m_\varepsilon\partial_t\varphi - \int_\Omega m_{0\varepsilon}\varphi(\cdot,0) = -2\int_0^T\int_\Omega D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon\sqrt{1+m_\varepsilon}\nabla\sqrt{1+m_\varepsilon}\cdot\nabla\varphi$$

$$+\int_0^T\int_\Omega \frac{\kappa_\varepsilon v_\varepsilon}{1+v_\varepsilon}\sqrt{m_\varepsilon}\sqrt{m_\varepsilon}\,\nabla v_\varepsilon\cdot\nabla\varphi+\int_0^T\int_\Omega(\lambda(y_\varepsilon)q_\varepsilon-\gamma m_\varepsilon-r_m(t)m_\varepsilon)\varphi-\varepsilon\int_0^T\int_\Omega m_\varepsilon^\theta\varphi \tag{3.51}$$

for all $\varepsilon\in(0,1)$. Passing to the limit $\varepsilon=\varepsilon_j\searrow 0$, we deduce from (3.50), (3.6), and (3.14) that each of the terms in (3.51) except the last one converges to the respective term of (3.7). Here we use that [40, Lemma 5.10] along with $0\le D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon\le C_1P$ and $0\le\frac{\kappa_\varepsilon v_\varepsilon}{1+v_\varepsilon}\le PL$ (see (3.6) and Lemma 3.5) imply that $D(m_\varepsilon,q_\varepsilon,v_\varepsilon)\kappa_\varepsilon\sqrt{1+m_\varepsilon}\to D(m,q,v)\kappa\sqrt{1+m}$ and $\frac{\kappa_\varepsilon v_\varepsilon}{1+v_\varepsilon}\sqrt{m_\varepsilon}\to\frac{\kappa v}{1+v}\sqrt{m}$ strongly in $L^2(\Omega\times(0,T))$.
Concerning the last term in (3.51), we denote the constant $C(T)$ from Proposition 3.8 by $C_7(T)$. Then for given $\eta>0$ we choose $S>0$ such that $\frac{C_7(T)}{\ln(S+2)}\le\frac{\eta}{2}$ and obtain from Proposition 3.8 that

$$\begin{aligned}\varepsilon\int_0^T\int_\Omega m_\varepsilon^\theta &= \varepsilon\int_0^T\int_\Omega\chi_{\{m_\varepsilon\le S\}}m_\varepsilon^\theta+\varepsilon\int_0^T\int_\Omega\chi_{\{m_\varepsilon>S\}}m_\varepsilon^\theta\\ &\le \varepsilon T|\Omega|S^\theta+\frac{\varepsilon}{\ln(S+2)}\int_0^T\int_\Omega m_\varepsilon^\theta\ln(m_\varepsilon+2)\le\frac{\eta}{2}+\frac{\eta}{2}\end{aligned}$$

for all $\varepsilon\in(0,\varepsilon_0)$ such that $\varepsilon_0T|\Omega|S^\theta\le\frac{\eta}{2}$. This implies that the last term in (3.51) converges to zero as $\varepsilon\searrow 0$. Similarly, (3.8)-(3.11) can be verified by using (3.50), (3.6), (3.14), and (3.47). □

4 Numerical simulations

In this section we perform numerical simulations of the system (2.1a)-(2.1e) for $n=2$ and $\Omega=(0,1)^2$. All simulations are performed with MATLAB and the cell-centered unstructured triangular mesh generation is implemented via the DistMesh MATLAB function package [33]. Space discretization is done via the Finite Volume Method (see e.g., [7, 1]) and the time discretization is implemented via an explicit one-step Euler method.
In our simulations we use for the terms and coefficients in (2.1a)-(2.1e) the following definitions:

$$\begin{aligned}\phi(\kappa,m,q,v)&:=D_c\kappa\frac{1+\frac{mq}{K_c^2}+\frac{mv}{K_cK_v}+\frac{qv}{K_cK_v}}{1+\frac{m}{K_c}(\frac{q}{K_c}+\frac{v}{K_v})}, & \psi(\kappa,v)&:=\frac{D_H\kappa v}{K_v+v},\\ \lambda(y)&:=\lambda_0(R_0+y), & \gamma(y)&:=\frac{\gamma_0}{R_0+y},\\ H(y(\cdot,t-\tau))&:=My(t-\tau).\end{aligned} \tag{4.1}$$

Thereby, we assume that the diffusion is enhanced by cell-cell and cell-tissue interactions and restrained by the interactions between moving cells and immotile components (proliferating cells and normal tissue). As in [28, 40], the diffusion is also supposed to be favorized by the cell contractivity. The haptotactic sensitivity is (moderately) aided by the interaction between moving cells and tissue and proportional to the cell's ability to contract and change its shape. In the switching rates λ and γ the constant R_0 denotes (as mentioned in Section 2) the total amount of relevant integrins on a cell's surface: we assume that all cells have the same (average) amount. Furthermore, we assume that a lower concentration of bound integrins inhibits the mesenchymal motion and hence, due to the "go-or-grow"hypothesis, causes a moving cell to switch to the proliferative regime. On the other hand,

increased receptor binding promotes contractivity and mesenchymal motion. Thus, the switching rates γ and λ are decreasing and increasing functions, respectively.
The effects of chemotherapy are described by way of dependence of the integrin binding/detachment rates on the chemotherapeutic dose d_c:

$$\begin{aligned} k_1(d_c) &:= \hat{k}_1 - b_d d_c, \\ k_{-1}(d_c) &:= \hat{k}_{-1} + u_d d_c, \end{aligned} \tag{4.2}$$

where $d_c(t) := \sum_{i=1}^{\hat{l}} \hat{d}_c(\hat{t}_i)\eta_\epsilon(t - \hat{t}_i)$, $\eta_\epsilon \in C_0^\infty((-\epsilon, \epsilon))$ satisfies $\eta_\varepsilon(0) = 1$ and $0 \le \eta_\varepsilon \le 1$, with ϵ being very small, $\hat{d}_c$ is the administered dose and $\hat{t}_i$ $(i = 1, \dots, \hat{l})$ are the times when the chemotherapy is applied. As we are not concerned here with the issue of an optimal treatment schedule, we will assume for simplicity a uniform dose distribution, i.e., $\hat{d}_c(\hat{t}_i) = \hat{d}_c =$ constant for all $i = 1, \dots, \hat{l}$, where $\hat{l}$ denotes the number of chemotherapy fractions. The values of the constants $\hat{k}_1, \hat{k}_{-1}, b_d, u_d$ are specified in Table 1. The same applies for all constants used in this model.
The radiotherapy is described by the following terms:

$$\begin{aligned} R_j(d_r) &:= \sum_{i=1}^{l} (1 - S_j(\alpha_j, \beta_j, d_r))\eta_\epsilon(t - t_i), \qquad t_i \in \text{radiotherapy} \\ S_j(\alpha_j, \beta_j, d_r) &:= \exp(-l(\alpha_j \hat{d}_r + \beta_j \hat{d}_r^2)) = \exp(-\alpha_j d_r(1 + \hat{d}_r/(\alpha_j/\beta_j))), \end{aligned} \tag{4.3}$$

where t is the current time, $j \in \{m, q, v\}$ represents the type of irradiated cells, d_r is the total dose and $\hat{d}_r$ is the dose per fraction. ″radiotherapy‶denotes the set of times t_i at which ionizing radiation is applied. The function $S_j(\alpha_j, \beta_j, d_r)$ denotes the survival fraction of the population of type j after application of radiotherapy, hence we adopted the linear quadratic (LQ) model [8, 10], which in spite of its shortcomings [21] is still the standard choice in radiation treatments (see e.g., [35]). The parameter α_j represents lethal lesions produced by a single radiation track (they are linearly related to the dose: $\alpha_j d_r$, cell kill per Gy), while β_j characterizes lethal lesions produced by two radiation tracks (quadratically related to the dose: $\beta_j d_r^2$, cell kill per Gy^2). The relevant parameter in the LQ model is actually the radiation sensitivity α_j/β_j , which correlates to the cell cycle length: late responding tissues with a slow cell cycle have a small α_j/β_j ratio, while it is large for early responding, highly aggressive cancers [37].

4.1 Nondimensionalization

For convenience of notation and computations we nondimensionalize the system (2.1a)-(2.1e) and introduce the following rescaling:

$$\begin{aligned} \tilde{m} &:= \frac{m}{K_c}, & \tilde{q} &:= \frac{q}{K_c}, & \tilde{v} &:= \frac{v}{K_v}, & \tilde{y} &:= \frac{y}{R_0}, \\ \tilde{t} &:= \frac{t}{T}, & \tilde{x} &:= \frac{x}{L}, & \tilde{\vartheta} &:= \frac{t}{\chi T}, \end{aligned} \tag{4.4}$$

where T and L denote the reference time and length scale, respectively, ϑ is the time variable corresponding to the much faster subcellular dynamics, and $\chi \in (0, 1)$ is a scaling constant. Using the rescaling (4.4) we obtain the following system in dimensionless form (we omit the tildes to simplify the notation):

$$\begin{cases} \partial_t m = \nabla \cdot (\phi(\kappa, m, q, v)\nabla m) - \nabla \cdot (\psi(\kappa, v) m \nabla v) + \lambda(y) q - \gamma(y) m - \Gamma_m R_m(d_r) m \\ \partial_t q = \mu_q q \left(1 - (m+q) - \eta_1 v\right) - \lambda(y) q + \gamma(y) m - \Gamma_q R_q(d_r) q \\ \partial_t v = -\delta_v (m + \delta_q q) v + \mu_v v \left(1 - \eta_2 (m+q) - v\right) - \Gamma_v R_v(d_r) v \\ \partial_\vartheta y = k_1(d_c)(1-y)v - k_{-1}(d_c) y \\ \partial_\vartheta \kappa = -\delta_\kappa \kappa + H(y(\cdot, t-\tau)) \end{cases} \tag{4.5}$$

where the rescaled motility functions and transition rates are given by:

$$\begin{aligned} \phi(\kappa, m, q, v) &= D_c \kappa \frac{1 + mq + mv + qv}{1 + m(q+v)}, & \psi(\kappa, v) &= \frac{D_H \kappa v}{1+v}, \\ \lambda(y) &= \lambda_0 (1+y), & \gamma(y) &= \frac{\gamma_0}{1+y}. \end{aligned} \tag{4.6}$$

4.2 Implementation

We approximate the solution to (4.5) by piecewise constant functions on each triangle Ω_i (with tessellation $\bigcup_{i\in I} \Omega_i = \Omega$, I being an index set). Specifically, the time marching is done by the one-step Euler method to advance the ODE solutions $S^{(k)} := (q^{(k)}, v^{(k)}, y^{(k)}, \kappa^{(k)}) \to S^{(k+1)}$ from the time level $k \in \mathbb{N}_0$ to $k+1$. Although this method is only of first order in time, we employ the operator splitting for separating the diffusion (with source terms) and the advection terms in order to advance the piecewise constant PDE solution $m^{(k)} \to m^{(k+1)}$. Thus, the scheme's overall accuracy is of first order in space and time as well. The operator splitting consists of two steps:
Step 1: $m^{(k)} \to m^{(*)}$ solving the advection problem $\partial_t m = -\nabla \cdot (\psi(\kappa, v) m \nabla v)$ for one time step $\triangle t$, using $m^{(k)}$ as the initial value. We use a monotone, E-flux scheme, such as the Godunov method (see e.g., [1, 25]), which is given by the following:

$$m_i^{(*)} = m_i^{(k)} - \frac{\triangle t}{|\Omega_i|} \left(\sum_{j \in A(i)} |\partial \Omega_{ij}| E_{\overrightarrow{n_{ij}}}(m_i^{(k)}, m_j^{(k)}) \right),$$

where
$m_i^{(k)} = \frac{1}{|\Omega_i|} \int_{\Omega_i} m^{(k)}$ is the average value of the piecewise constant solution $m^{(k)}$ over the triangle Ω_i (with tessellation $\bigcup_{i\in I} \Omega_i = \Omega$, I being an index set) at the time level k,
$A(i)$ is an index set of the neighboring triangles of Ω_i,
$\partial\Omega_{ij}$ is the boundary edge between triangles Ω_i and Ω_j,
$E_{\overrightarrow{n_{ij}}}(m_i^{(k)}, m_j^{(k)})$ is the Godunov flux from Ω_i to Ω_j, $\overrightarrow{n_{ij}}$ is the outward unit normal, pointing out of Ω_i and into Ω_j. The Godunov flux is given by:

$$E_{\overrightarrow{n_{ij}}}(m_i^{(k)}, m_j^{(k)}) = \begin{cases} \min\limits_{u \in [m_i^{(k)}, m_j^{(k)}]} f(u) n_x + g(u) n_y, & \text{if } m_i^{(k)} \le m_j^{(k)} \\ \max\limits_{u \in [m_j^{(k)}, m_i^{(k)}]} f(u) n_x + g(u) n_y, & \text{otherwise.} \end{cases}$$

Here, n_x, n_y denote the x and y components of the unit normal $\overrightarrow{n_{ij}}$. The functions f and g are given by:

$$f(u) = u \cdot \psi(\kappa_i^{(k)}, v_i^{(k)}) \partial_x v^{(k)}|_{\partial\Omega_{ij}}$$
$$g(u) = u \cdot \psi(\kappa_i^{(k)}, v_i^{(k)}) \partial_y v^{(k)}|_{\partial\Omega_{ij}},$$

where

$$\partial_x v^{(k)}|_{\partial\Omega_{ij}} = \frac{v_j^{(k)} - v_i^{(k)}}{|x_j - x_i|},$$
$$\partial_y v^{(k)}|_{\partial\Omega_{ij}} = \frac{v_j^{(k)} - v_i^{(k)}}{|y_j - y_i|},$$
$$\psi(\kappa_i^{(k)}, v_i^{(k)})|_{\partial\Omega_{ij}} = \frac{1}{2}\left(\psi(\kappa_i^{(k)}, v_i^{(k)}) + \psi(\kappa_j^{(k)}, v_j^{(k)})\right),$$

with (x_i, y_i) being cell center coordinates on the triangle Ω_i, $v_i^{(k)}$ and $\kappa_i^{(k)}$ are cell averages at the time level k defined similarly as above.
Step 2: $m^{(*)} \to m^{(k+1)}$ solving the reaction-diffusion problem $\partial_t m = \nabla \cdot (\phi(\kappa, m, q, v)\nabla m) + \lambda(y)q - \gamma(y)m - \Gamma_m R_m(d_r)m$ for one time step $\triangle t$, using $m^{(*)}$ as the initial value. The scheme is given by the following:

$$m_i^{(k+1)} = m_i^{(*)} - \frac{\triangle t}{|\Omega_i|}\left(\sum_{j\in A(i)} |\partial\Omega_{ij}| D_{\overrightarrow{n_{ij}}}(m_i^{(*)}, m_j^{(*)})\right) + \triangle t P_i^{(*)},$$

where

$$D_{\overrightarrow{n_{ij}}}(m_i^{(*)}, m_j^{(*)}) = \phi(\kappa_i^{(k)}, m_i^{(*)}, q_i^{(k)}, v_i^{(k)})\left(\partial_x m^{(*)} n_x + \partial_y m^{(*)} n_y\right)|_{\partial\Omega_{ij}}$$
$$P_i^{(*)} = \lambda(y_i^{(k)})q_i^{(k)} - \gamma(y_i^{(k)})m_i^{(*)} - \Gamma_m R_m(d_r^{(k)})m_i^{(*)}.$$

Here, the spatial derivatives and the function ϕ at the boundary edge are approximated similarly as above. The average values $y_i^{(k)}$, $q_i^{(k)}$ at the time level k are defined similarly as above and $d_r^{(k)}$ is the irradiation dose at time level k.
We use the one-step explicit Euler method to obtain the solutions $q_i^{(k+1)}$ and $v_i^{(k+1)}$:

$$\begin{aligned}
q_i^{(k+1)} &= q_i^{(k)} + \triangle t\mu_q q_i^{(k)}(1 - (m_i^{(k)} + q_i^{(k)}) - \eta_1 v_i^{(k)}) \\
&\quad - \triangle t\lambda(y_i^{(k)})q_i^{(k)} + \triangle t\gamma(y_i^{(k)})m_i^{(k)} - \triangle t\Gamma_q R_q(d_r^{(k)})q_i^{(k)} \\
v_i^{(k+1)} &= v_i^{(k)} - \triangle t\delta_v(m_i^{(k)} + \delta_q q_i^{(k)})v_i^{(k)} + \triangle t\mu_v v_i^{(k)}(1 - \eta_2(m_i^{(k)} + q_i^{(k)}) - v_i^{(k)}) \\
&\quad - \triangle t\Gamma_v R_v(d_r^{(k)})v_i^{(k)}
\end{aligned}$$

The numerical solution $y_i^{(k+1)}$ at the time level $k+1$ is obtained by the following consecutive application of the one-step implicit Euler method:

$$y_i^{(k+\chi(j+1))} = \frac{y_i^{(k+\chi j)} + \overline{\triangle t}k_1(d_c^{(k)})v_i^{(k)}}{1 + \overline{\triangle t}k_1(d_c^{(k)})v_i^{(k)} + \overline{\triangle t}k_{-1}(d_c^{(k)})}$$

where $j = 0, 1, ..., \frac{1}{\chi} - 1$, $\overline{\triangle t} = \frac{\triangle t}{\chi}$ is the time step for subcellular dynamics, $d_c^{(k)}$ and $y_i^{(k+\chi(j+1))}$ are the drug doses and the solution, respectively, at the time level $k + \chi(j + 1)$, with $\chi \in (0, 1)$ being the time scaling constant. That is, for one single event in one time step $\triangle t$ on the macroscopic level, there are $1/\chi$ events taking place on the microscopic level. This reflects the assertion of subcellular dynamics being much faster.

Similarly, the numerical solution $\kappa_i^{(k+1)}$ is obtained by the following implicit Euler method:

$$\kappa_i^{(k+\chi(j+1))} = \frac{\kappa_i^{(k+\chi j)} + H(y_i^{(k+\chi(j+1)-\frac{\tau}{\triangle t})})}{1 + \overline{\triangle t}\delta_\kappa},$$

for $j = 0, 1, ..., \frac{1}{\chi} - 1$. Thus, the numerical scheme is completely defined.

4.3 Parameter assessment

Before performing numerical simulations, we first assess the model parameters. In the following we consider a rectangular domain $\Omega = (0, 1)^2$, the time step for the microscopic level $\overline{\triangle t} = 0.1$, and the scaling constant $\chi = 0.01$, along with the delay $\tau = 6$. The parameters used for our simulations are given in the following table:

Parameter	Range	Source	Parameter	Range	Source
$\hat{k}_1 = 1$	fixed	[17]	$\delta_v = 0.1$	0.5-10	[2]
$\hat{k}_{-1} = 0.5$	fixed	[17]	$\delta_q = 0.5$	0-50	[9]
$b_d = 0.1$	fixed	estimated	$u_d = 0.1$	fixed	estimated
$\delta_\kappa = 2$	fixed	[28]	$M = 2$	fixed	[28]
$\mu_v = 0.02$	$5 \cdot 10^{-3}$—$2 \cdot 10^{-1}$	estimated	$\eta_2 = 2.72$	1—5	[28]
$\Gamma_v = 0.0315$	0.03—0.045	[29]	$\frac{\alpha_v}{\beta_v} = 0.1Gy$	0.1—1	[29]
$\mu_q = 0.5$	0.5—2	[2]	$\eta_1 = 1.75$	1.5—3	[29]
$\lambda_0 = 0.2$	fixed	[29]	$\gamma_0 = 0.3$	fixed	[29]
$\Gamma_q = 0.5$	fixed	[29]	$\frac{\alpha_q}{\beta_q} = 10Gy$	fixed	[29]
$D_c = 10^{-3}$	10^{-5}—10^{-3}	[2]	$D_H = 1$	10^{-2}—1	[2]
$\Gamma_m = 0.08$	fixed	[29]	$\frac{\alpha_m}{\beta_m} = 8Gy$	fixed	[29]
$T = 0.6 \cdot 10^6 s$	fixed	[2]	$L = \sqrt{10}cm$	fixed	[2]

Table 1: Parameters used in the model.

We assume a hyperfractionated radiotherapy with a daily dose of 2Gy, i.e. $\hat{d}_r = 2$. The dose of chemotherapeutic drug is taken such that the integrin binding rate is reduced by half, while the unbinding rate is increased twofold, i.e. $\hat{d}_c = 5$.

4.4 Initial conditions

We simulate the initial condition v_0 of the ECM density with the help of uniformly distributed random numbers on the interval $(0, 1)$:

$$v_0(x, y) \sim \mathcal{U}(0, 1), \quad (x, y) \in \Omega.$$

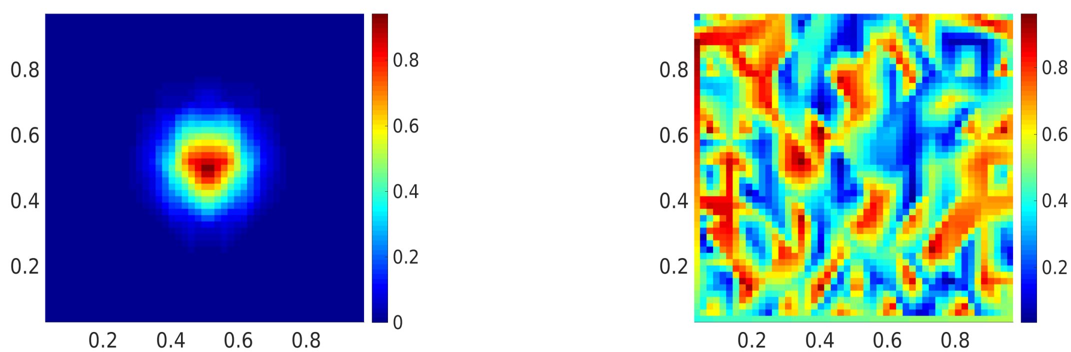
We assume that the initial density of the migrating cancer cells m_0 constitute 70% of the total initial cancer cell density $c_0 := m_0 + q_0$. The function c_0 is given by the following:

$$c_0(x, y) = \exp\left(-\frac{(x-0.5)^2 + (y-0.5)^2)}{2\epsilon^2}\right), \quad (x, y) \in \Omega,$$

where we took $\epsilon = 0.08$. This shape of the initial (overall) cancer cell density corresponds to a very localized tumor situated in the center of the simulation domain. Since $c_0 > 0$ in Ω, we take the initial condition y_0 of the concentration of bound integrins on an individual cancer cell to be proportional to the density v_0 of normal tissue. Furthermore, we assume the initial condition κ_0 of the contractivity function to be proportional to v_0 as well. Thus, y_0 and κ_0 are given by the following:

$$y_0 = \xi_1 v_0, \qquad \kappa_0 = \xi_2 v_0,$$

where $\xi_1, \xi_2 \in (0, 1)$. In our simulations we used $\xi_1 = 0.5$ and $\xi_2 = 0.4$. The plots of c_0 and v_0 are shown in Figure 1.



(a) Initial total cancer cell density c_0

(b) Initial density of normal tissue v_0

Fig. 1: Initial conditions for tumor cells and normal tissue

4.5 Results

In this section we present the simulation results obtained by applying the numerical method described in the previous subsection. The treatment schedules are as follows:

- **Strategy 0**: No therapy. Simulation of the evolution of (2.1a)-(2.1e) for 9 weeks.
- **Strategy 1**: 3 weeks of neoadjuvant chemotherapy, followed by 6 weeks of concurrent chemo- and radiotherapy.
- **Strategy 2**: 3 weeks of no therapy, followed by 6 weeks of radiotherapy.

All strategies, except strategy 0, are started 1 week after the diagnosis time $t = 0$ (we assumed one week is needed for the therapy planning). Chemo- and radiotherapy are applied during weekdays with

breaks during weekends. These allow the healthy tissue to recover from irradiation therapy, however they also have a similar effect (at an even higher degree) on the neoplastic tissue.
Fig. 2 shows that the tissue is mainly degraded around the original tumor site, as expected. Furthermore, the invasion into the surrounding tissue is clearly visible, whereby the cancer cells with migrating phenotype are able to surpass the regions with lower ECM density. While the migrating cells are able to spread into ECM-dense regions, the proliferating ones remain concentrated around the initial tumor bed where the ECM is sparse.

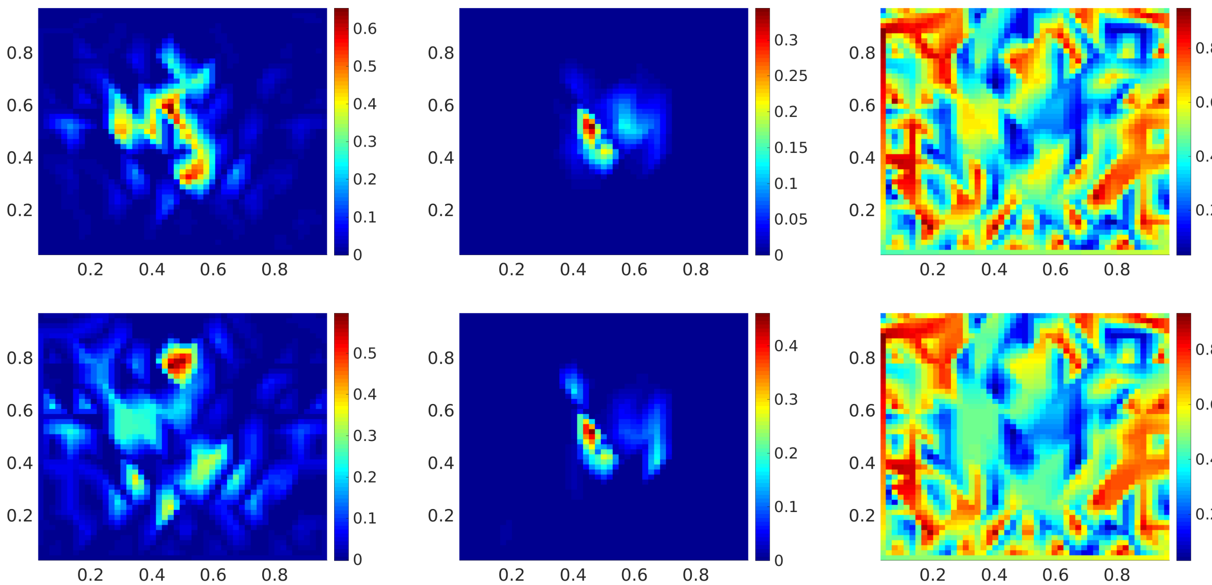


Fig. 2: Strategy 0 (no therapy). Densities of the moving cells (left column), the proliferating cells (middle column), and the normal tissue (right column) at 4 weeks (top row) and 10 weeks (bottom row) after diagnosis.

The effect of combining chemo- and radiotherapy (strategy 1, Fig. 3) compared with irradiation only (strategy 2, Fig. 4) can be seen in Fig. 5 (densities with strategy 2 minus strategy 1). We can observe that combination of integrin binding inhibition with radiotherapy yields a better outcome on the periphery of the tumor, since fewer cancer cells invaded the surrounding tissue. Moreover, the ECM is degraded to a lesser extent on the periphery as well. Also, due to strategy 2 there is a larger pocket of proliferating cancer cells, visible in the bottom middle plot of Fig. 5. Therefore, the combination of such chemo- and radiotherapy seems to be helpful especially in inhibiting the cancer spread. On the other hand, also notice that it results in higher cancer cell density around the original tumor site, with an enhanced degradation of the peritumoral tissue. This tumor localization can, however, be beneficial for follow-up therapies and suggests a possible reduction of the combined chemo- and radiotherapy duration and a concentration instead at the end of the therapy on the cell kill, when it is easier to deplete the proliferating (hence therapy respondent and rather immotile) cells.

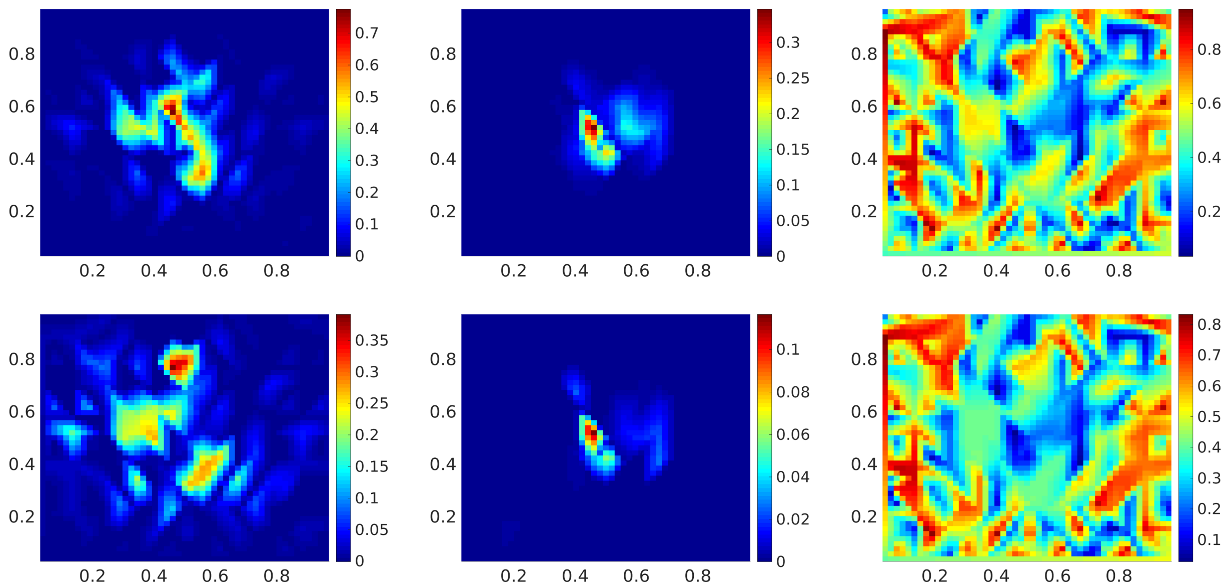


Fig. 3: Strategy 1. Densities of the moving cells (left column), the proliferating cells (middle column), and the normal tissue (right column) at 4 weeks (i.e., at the end of the neoadjuvant chemotherapy, top row) and 10 weeks (i.e., at the end of all therapy, bottom row).

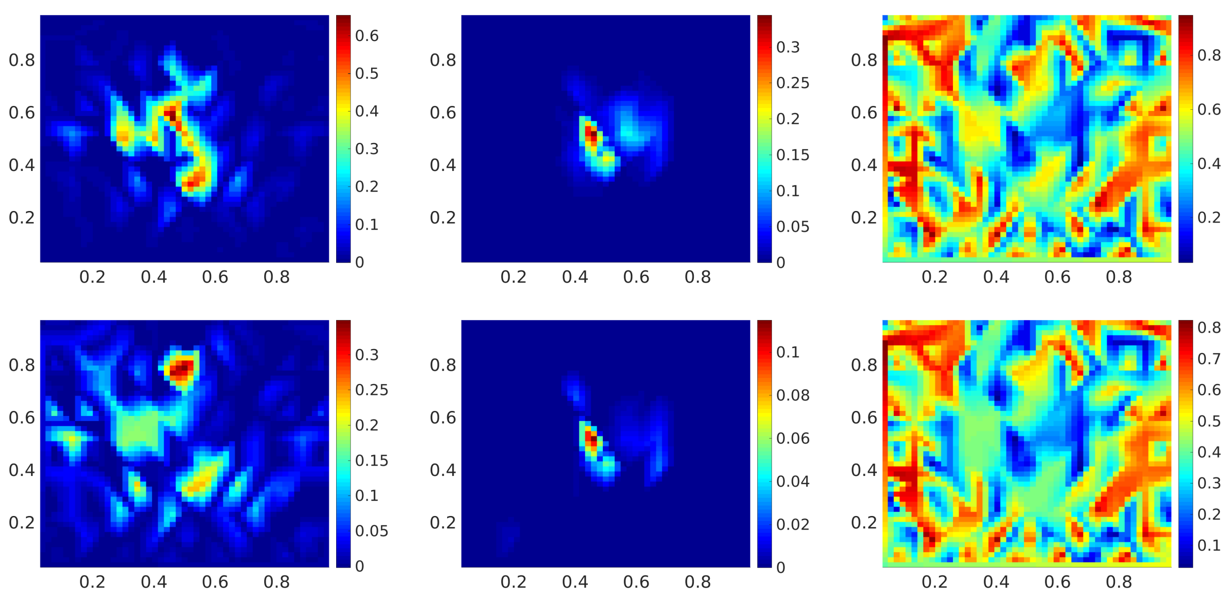


Fig. 4: Strategy 2. Densities of the moving cells (left column), the proliferating cells (middle column), and the normal tissue (right column) at 4 weeks (i.e., after no therapy, top row) and 10 weeks (i.e., at the end of radiotherapy, bottom row).

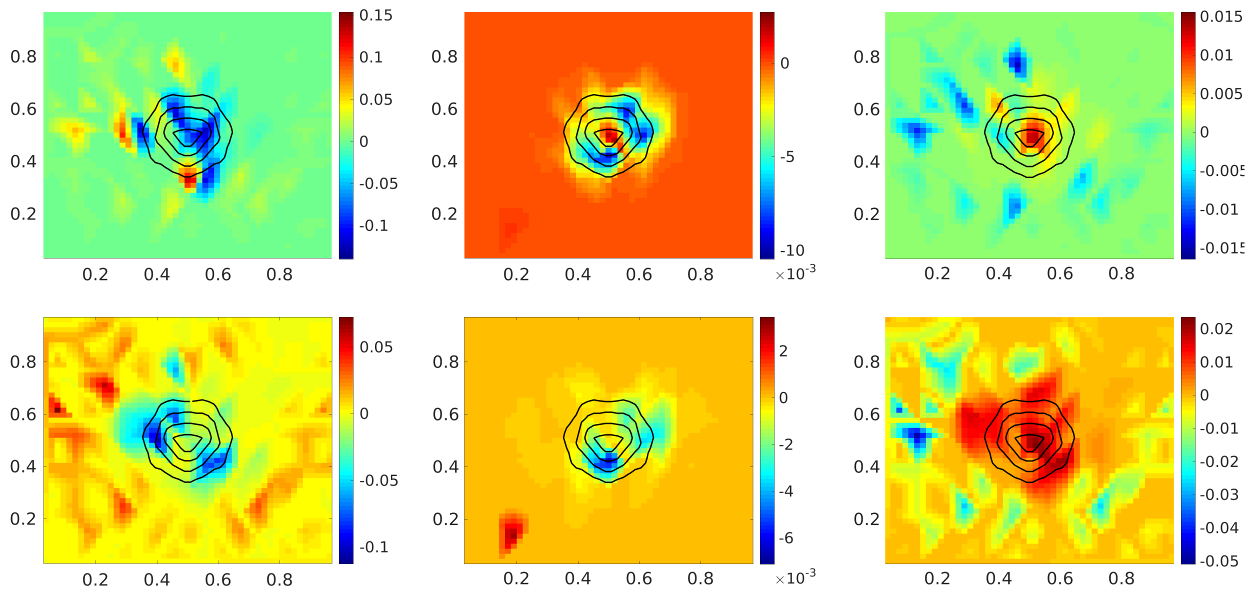


Fig. 5: Difference between strategy 2 and strategy 1. Shown are differences in the densities of moving cells (left column), proliferating cells (middle column), and normal tissue (right column), respectively, each of them under strategy 2 minus the same densities under strategy 1, at 4 weeks (top row) and 10 weeks (bottom row). Contour lines indicate initial total cancer cell densities above 0.2.

To assess the effect of the contractivity function –which we associate with the ability of cells to change their shape and to adapt their motion according to the local structure of the surrounding ECM[1], see also [28]– we plot in Figure 6 its values computed under each of the therapy strategies, along with the corresponding differences, both in the middle of the 9th therapy week and at the end of it, when tissue recovering takes place. We also show in Figure 7 differences between the densities of the two tumor cell subpopulations and of the normal tissue in the cases with ($\kappa = \kappa(y)$) and without contractivity ($\kappa \equiv$ constant) under strategy 1[2] (bottom row), also looking at the differences between the two therapy strategies in the absence of contractivity (top row).
When contractivity is ignored we observe a similar behavior of the cancer cell and normal tissue densities under both therapy strategies (Figure 7, top row). However, the difference between the two strategies is much smaller than in the case with contractivity (compare top row of Figure 7 with bottom row of Figure 5). Furthermore, Figure 6 shows that during therapy (top row) the contractivity is reduced under strategy 1, while during the weekend breaks (bottom row) there are only small differences between the two therapy strategies. This behavior is mainly due to the inhibition of integrin binding by the chemotherapy. In the presence of contractivity more migrating cells are under way in the peritumoral region; integrin inhibition will reduce contractivity and whence their density (Fig. 7, bottom row, left). The higher contractivity seems to be beneficial for proliferating

[1]These effects are actually controled by the subcellular dynamics exerting (or not) a direct influence on the motility of the cells via diffusion and taxis coefficients

[2]The contractivity function depends on the integrin binding and the latter is supposed to be impaired by the chemotherapy only involved in strategy 1.

cells almost exclusively at the original tumor site, while at distant sites the reduced (or even absent) contractivity will induce the migrating cells to stop and proliferate (see Fig. 7, bottom row, middle).

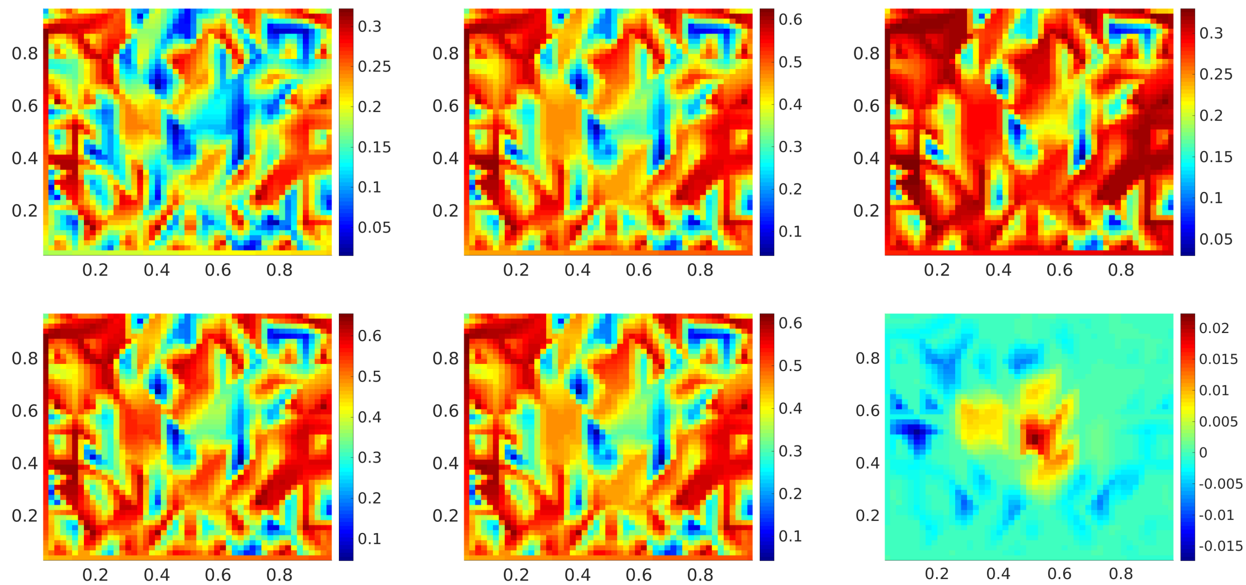


Fig. 6: Contractivity function under strategy 1 (left column), strategy 2 (middle column) and the difference between the two strategies, i.e. contractivity under strategy 2 - contractivity under strategy 1 (right column), in the middle (top row) and at the end (bottom row) of the nineth therapy week .

5 Discussion

In this work we considered a multiscale model for tumor invasion through the tissue network, which takes into account the tumor heterogeneity w.r.t. migration and proliferation phenotypes and its influence on the outcome of some therapy approaches. The latter involve chemotherapy (aiming at inhibiting the binding of receptors on the cell surface to their insoluble ligands in the ECM) and radiotherapy, with the purpose of depleting the neoplastic tissue. We proved the global existence of weak solutions to the coupled PDE-ODE system by constructing an appropriate entropy functional. To the best of our knowledge, this is the first global existence result for a haptotaxis equation which contains nonlinear diffusion and taxis coefficients and is coupled with two macroscopic ODEs. The problem of (global) boundedness and uniqueness of solutions remains open. This also applies to the situation with degenerate diffusion or even to the nondegenerate case where, however, the solution-dependent diffusion coefficient does not satisfy the uniform positivity assumption required in Section 3. While some results about PDE-ODE systems with degenerate diffusion have recently become available for pure macroscopic models of tumor invasion with haptotaxis [41, 45, 46], by our knowledge there are no corresponding references for multiscale models with or without splitting into two or more subpopulations. These issues are still to be investigated.
The numerical simulations in Section 4 show that the model predicts -under biologically reasonable

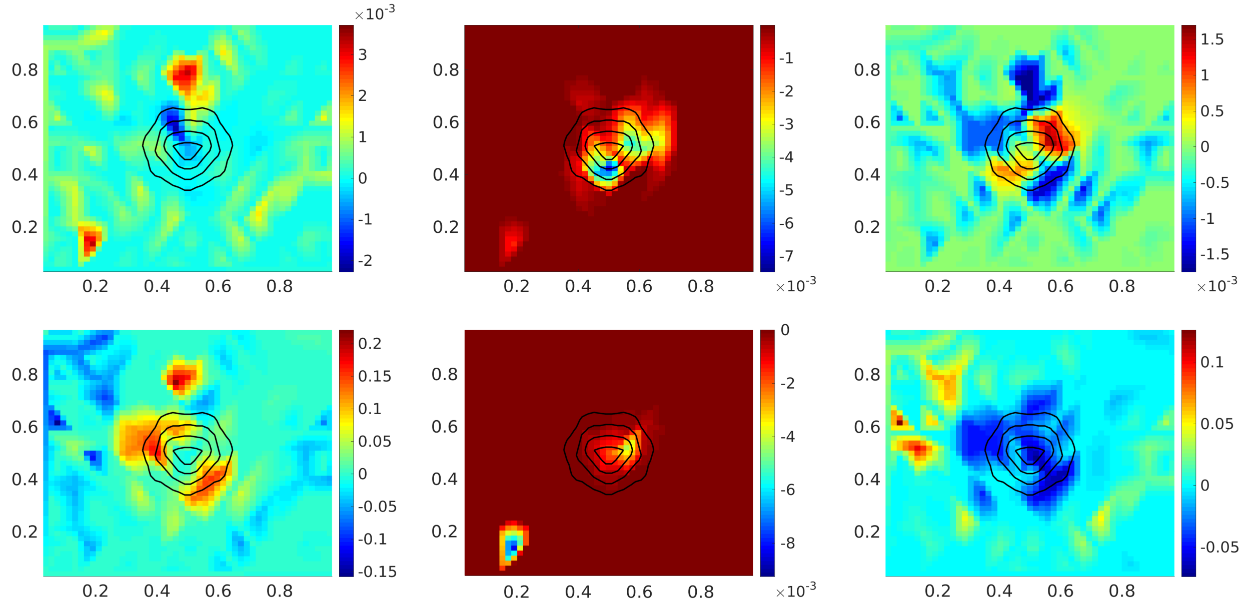


Fig. 7: Top row: difference between strategy 2 and strategy 1 in the absence of contractivity. Bottom row: difference between the cases with and without contractivity, both under strategy 1. Shown are the densities of moving cells (left column), proliferating cells (middle column), and normal tissue (right column), all at 10 weeks. Contour lines indicate initial total cancer cell densities above 0.2

parameter choices- the expected behavior: irregular patterns of tumor spread with new foci due not only to the migrating cells, but also to the proliferating ones, as consequence of the dynamic switch between the two subpopulations; the more localized and close-to-tumor development of the proliferating cells, along with the corresponding degradation of the host tissue. Concerning the two therapy strategies, the neo-adjuvant chemotherapy followed by concurrent chemo- and radiotherapy seems to be more effective than radiotherapy alone. This also applies to chemotherapy alone (results not shown), as the latter is not directly aimed at cell kill. These findings are in accordance with clinical experience [36, 34]. The multiscality of our model makes it particularly adequate to investigate the effects of a chemical agent impairing the receptor binding ability on the overall response of the tumor, thereby also opening the way to enhance the prediction of the neoplastic lesion extent into the tissue.

Acknowledgment

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