Multiscale Modeling
of
Glioma Invasion

Anne Dietrich

**TECHNISCHE UNIVERSITÄT
KAISERSLAUTERN**

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Acknowledgment

Abstract

Gliomas are one of the most common types of primary brain tumors. Among those, high grade astrocytomas - so-called glioblastoma multiforme - are the most aggressive type of cancer originating in the brain, leaving patients a median survival time of 15 to 20 months after diagnosis. The invasive behavior of the tumor leads to considerable difficulties regarding the localization of all tumor cells, and thus impedes successful therapy. Here, mathematical models can help to enhance the assessment of the tumor's extent.

In this thesis, we set up a multiscale model for the evolution of a glioblastoma. Starting on the microscopic level, we model subcellular binding processes and velocity dynamics of single cancer cells. From the resulting mesoscopic equation, we derive a macroscopic equation via scaling methods. Combining this equation with macroscopic descriptions of the tumor environment, a nonlinear PDE-ODE-system is obtained. We consider several variations of the derived model, amongst others introducing a new model for therapy by gliadel wafers, a treatment approach indicated i.a. for recurrent glioblastoma.

We prove global existence of a weak solution to a version of the developed PDE-ODE-system, containing degenerate diffusion and flux limitation in the taxis terms of the tumor equation. The nonnegativity and boundedness of all components of the solution by their biological carrying capacities is shown.

Finally, 2D-simulations are performed, illustrating the influence of different parts of the model on tumor evolution. The effects of treatment by gliadel wafers are compared to the therapy outcomes of classical chemotherapy in different settings.

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Chapter 1

Introduction

In 2020, cancer was the second most frequent cause of death in Germany [67]. While nowadays some types of cancer, like prostate cancer or melanoma, have good chances of healing, there are other types with very poor prognosis. After diagnosis of a glioblastoma multiforme, the most aggressive type of cancer originating in the brain, patients have median survival time of 15 to 20 months [28]. The aggressive spread and invasive behavior of the tumor cells combined with the necessity not to destroy essential vital functions during surgery causes the impossibility of a complete removal of the tumor. The usual therapy consists of surgical resection combined with chemotherapy and/or radiation. It is agreed that during surgical resection, the largest part of the tumor should be removed. Still, there are different concepts on how much brain volume should be resected to maximize survival time while preserving important functions [40]. The expression 'gross total resection' is often used in this context, originally being defined as complete removal of tumor mass. Having an understanding of the infiltrative behavior of gliomas, it is clear that a complete removal is barely possible. Meanwhile, it is spoken of gross total resection if at least 90-97% of the tumor are removed [33]. The concept of supramaximal resection was used in more recent studies [33, 43, 87]. Supramaximal resection means that also the large part of non-contrast-enhancing tumor components is removed. The difficulty lies in the identification of those tumor parts.
Even by supramaximal resection, not all tumor cells can be surgically removed due to their infiltrative behavior. Such single invasive cells are neither visible in MRI nor cognizable by the surgeon during resection, and are hence not accounted for in therapy planning. Mathematical simulations could give guidance where non-contrast-enhancing as well as invasive tumor cells can be expected, such that appropriate therapy is possible.

State of the art

Most models for glioma invasion are based on a macroscopic ansatz. An early approach to this kind of modeling was done by Murray [53] in 1989. The ansatz by Murray has been further developed in a variety of papers by the introduction of taxis terms, taking into account extracellular signaling, e.g. [31, 35]. Originally supposing a constant diffusion coefficient, the model was slightly precised by differing between white and grey matter [72]. Later on, patient specific data

were included by usage of a diffusion tensor, including the individual anisotropy of the brain, e.g. [9, 39]. Switches between subpopulations have been modeled, respecting the go-or-grow-dichotomy, which means the switch of glioma cells between proliferating and migrating status, see e.g. [65, 85]. Different models for the interplay between tumor and its environment have been developed, e.g. [3, 48], modeling hypoxia and angiogenesis.

The major drawback in this kind of modeling lies in the neglection of subcellular processes. Those are only respected in a heuristic way. A different approach was done in [8] for general multicellular systems. Starting from a microscopic kinetic description including cell velocity and so-called activity variables describing the biological microscopic state of a cell, macroscopic models are deduced by scaling methods. In [13, 14, 15, 20, 21, 22, 32, 42], from this kind of equations macroscopic systems for tumor spread are deduced by limit procedures, the resulting equations containing information on brain tissue anisotropy and subcellular dynamics.

In the present work, we build up on the latter approach. The resulting model is a nonlinear PDE-ODE-system containing flux limitation in the diffusion and taxis terms and degenerate diffusion. To the best of my knowledge, analysis for a similar model has not been performed yet.

Outline

The thesis is structured as follows:

- **Chapter 2 (Modeling):** Starting on the scale of single cells, we model binding to the extracellular matrix and velocity dynamics in dependence on spatial gradients of acidity, tissue, and tumor cell densities. The corresponding mesoscopic equation contains transport terms with respect to these activity and velocity variables. Unlike previous models, the velocity dynamics here allows for changes in both speed and direction. Beyond a more precise modeling of regions of decreased motility due to high tumor density, this ansatz allows to include the concept of the go-or-grow dichotomy without switching between different subspecies. A closed system of moment equations is deduced. From this system, a macroscopic PDE with degenerate flux limited diffusion, chemo- and haptotaxis is derived by scaling methods. Combining this PDE with equations for acidity, tissue density and vascularization, a nonlinear PDE-ODE-system with flux-limitation and degenerate diffusion is obtained.

  Beside the main model, we present some further modeling approaches, including changes in the taxis terms of the endothelial cell equation, therapy approaches and switches between the subspecies of migrating and proliferating cells.

- **Chapter 3 (Analysis):** We prove global existence of a weak solution to the model introduced in chapter 2, making a simplification in the flux limitation of the diffusion term. The main difficulty of the existence proof lies in the degeneracy of the diffusion and the strong nonlinear coupling of the PDE-ODE-system, including flux limitation in the taxis terms.

  We show how the proof for existence of a weak solution of the main model can be adapted to get a global bounded weak solution also for some of the model variations introduced in chapter 2.

- **Chapter 4 (Simulations):** In this chapter we show 2D simulations of the models from chapter 2. The code for the main model was implemented by Niklas Kolbe and Nikolaos Sfakianakis [18]. In the scope of this thesis, the code was adapted in order to obtain simulations also for the model's variations. We show the influence of the flux limitation by comparing simulations for tumor spread with and without flux limitation. The angiogenic behavior of endothelial cells is illustrated, comparing the different modeling approaches for taxis of endothelial cells introduced in chapter 2. We contrast a classical go-or-grow-model, where cells are divided into subspecies, with the main model, where we included the go-or-grow-dichotomy via the cell speed from microscale dynamics. Finally, different therapy approaches are simulated and compared.

Chapter 2

Modeling

The spread of a tumor is triggered by several factors. In [29], six hallmarks leading to neoplastic disease are presented. We want to focus on two of these hallmarks: angiogenesis and invasion.

Angiogenesis describes the growth of blood vessels into the tumor as a consequence of overexpression of proangiogenic factors like vascular endothelial growth factor. The formed vasculature sustains the tumor with nutrients and oxygen and enables it to dispose of waste products like carbon dioxide [29].

A common feature of all glioblastoma subtypes is the aggressive invasive behavior. Thereby, the invasion can be performed by individual cells as well as collectively and follows preexisting structures like white matter tracts [77]. For the invasion of glioma cells, often triggered by chemotactic signals [63], frequent changes in cell-ECM-interactions play a major role [24].

The presented model and its variations aim to cover both the effects of angiogenesis and invasion.

In this chapter, multiscale models for anisotropic spread of glioblastoma and possible therapies are introduced. The chapter is structured as follows:

In section 2.1, a model describing the microscopic and mesoscopic dynamics of glioma cells and the macroscopic evolution of the tumor environment is introduced. From the micro-meso-description of tumor cells, a closed system of moment equations is derived. Using scaling methods, the system of moment equations is reduced to a single macroscopic equation, which - in combination with the macroscopic equations for the tumor environment - describes the development and spread of the neoplasm.

In sections 2.2 and 2.3, variations of the model developed in 2.1 are presented. While in section 2.2 different forms of taxis for vascularization are considered, in section 2.3 the focus lies on a more detailed description of the go-or-grow dichotomy.

Finally, in section 2.4 models for different kinds of treatment are set up.

2.1 A multiscale model for glioma spread

This section was first published in *Multiscale modeling of glioma invasion: from receptor binding to flux-limited macroscopic PDEs* in 2022.[1] The model devel-

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oped in this section considers the following aspects:

- migration of cancer cells due to pH gradients, tissue gradients and population pressure, incorporating the effects of tissue alignment,

- binding of cancer cells to tissue fibers,

- influence of acidic environment on tumor evolution,

- vascularization.

The presented multiscale modeling approach follows the ideas of several previous papers [13, 14, 15, 21, 20, 22, 32]. Involving signed gradients of tactic signals, the microscopic description of velocity dynamics is related to that in [15], but differs by a non-constant cell speed. Beneath other effects, this approach enables the incorporation of the influence of population density on cell motility. The performed upscaling is related but differs in several aspects from earlier limiting procedures and leads to a macroscopic PDE-ODE system featuring for glioma cell density degenerate self-diffusion and multiple taxis, all of which are flux-limited.

2.1.1 Microscopic scale

Dynamics of the receptor binding state y

Let y and R denote the cell surface concentration of receptors bound to ECM and the total surface concentration of receptors able to bind to ECM, respectively. For simplicity, we assume R to be constant. The surface concentration of free receptors for a cell in binding state y is then given by $R-y$ with $y \in Y := [0, R]$. Let k^+ denote the attachment rate of a free receptor to adjacent tissue fibers, and let k^- denote the corresponding detachment rate. Then the process of binding and unbinding in dependence on the macroscopic tissue density $Q(t, x)$ is described by

$$(R - y) + Q \underset{k^-}{\overset{k^+}{\rightleftarrows}} y.$$
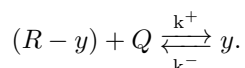
The corresponding ODE obtained by mass action kinetics is

$$\dot{y} = k^+(R - y)Q - k^- y =: G(y, Q). \tag{2.1}$$

Dynamics of cell velocity v

The migration of cancer cells is affected by different gradients. Decreasing pH has a repelling effect, whereas the cells are attracted by gradients of tissue density [56]. The lower the surface concentration of bound tissue receptors of a cell, the more sensitive it reacts towards tissue gradients. We further assume that cancer cells try to avoid regions of high cell densities. Under these assumptions, the preferred direction of a cell can be modeled by a weighted sum of the gradients $-\nabla_x h$, $\nabla_x Q$ and $-\nabla_x M$, where M represents the macroscopic

tumor cell density. For constants $\rho_1, \rho_2 \in (0,1)$ fulfilling $\rho_1 + \rho_2 < 1$, we choose

$$b = (1 - \rho_1 - \rho_2) \frac{-\nabla h}{\sqrt{\left(\frac{K_h}{\xi}\right)^2 + |\nabla h|^2}} + \rho_1 \frac{R - y}{R} \frac{\nabla Q}{\sqrt{\left(\frac{K_Q}{\xi}\right)^2 + |\nabla Q|^2}}$$
$$+ \rho_2 \frac{-\nabla M}{\sqrt{\left(\frac{K_M}{\xi}\right)^2 + |\nabla M|^2}}.$$

ξ is a constant to be selected in correspondence to appropriate time and length scales. We will adress this issue in subsection 2.1.4.

Typically, glioma cells migrate along tissue fibers, following the white matter tracts [24]. Diffusion tensor imaging (DTI) provides a means to assess (with the aid of the water diffusion tensor $\mathbb{D}_W$) the anisotropic brain structure down to the level of voxels with edges of 1-2mm. The joint effect of fiber tract orientation and the preferred direction relating to gradients leads to a change in velocity orientation of the form

$$\mathbb{D}_W \cdot b = \sum_{i=1}^n \alpha_i \omega_i \omega_i^T b = \sum_{i=1}^n \alpha_i \omega_i \langle \omega_i, b \rangle,$$

where ω_i are normed eigenvectors of $\mathbb{D}_W$ with corresponding eigenvalues α_i. The acceleration is then given by

$$g(t,x) = a_1 \frac{K_M - M}{K_M} \mathbb{D}_W b, \; a_1 > 0,$$

where the factor $\frac{K_M - M}{K_M}$ is due to limited motility in crowded regions.

A cell which is not exposed to external signal gradients will probably slow down its migrational process. We model deceleration by $-a_2 v$, $a_2 > 0$. Altogether we obtain the following equation for velocity dynamics:

$$\frac{\partial v}{\partial t} = g(t,x) - a_2 v =: S(v, y, h, Q, M). \tag{2.2}$$

We see that $g(t,x)$ is bounded:

$$|g(t,x)| = |a_1 \frac{K_M - M}{K_M} \mathbb{D}_W b| = a_1 \frac{K_M - M}{K_M} |\sum_{i=1}^n \alpha_i \omega_i \langle \omega_i, b \rangle| \leq a_1 \alpha_{max}$$

(the boundedness of M by its carrying capacity K_M will be shown in lemma 3.1.7). Starting with speed $s := |v| \leq s_{max} := \frac{a_1}{a_2} \alpha_{max}$ and assuming the water diffusion tensor $\mathbb{D}_W$ to be constant in time, the speed s_{max} cannot be exceeded. In case of a water diffusion tensor which varies in time and space, α_{max} and hence also s_{max} depend on t and x and we have $s = |v| \leq \bar{s}_{max} := \max_{0 \leq t \leq T, x \in \bar{\Omega}} s_{max}(t,x)$.

2.1.2 Mesoscopic scale

We consider the cell density function

$$p(t, x, v, y) : [0, T] \times \mathbb{R}^N \times V \times Y \to \mathbb{R}_0^+, \quad V \subset \mathbb{R}^N, Y \subset \mathbb{R}_0^+,$$

depending on time t, position x, velocity v and activity variable y. The velocity variable $v = s\theta$ contains information on speed $s \in [0, s_{max}]$ and direction $\theta \in \mathbb{S}^{N-1}$ of a cell. The scalar variable y denotes the surface concentration of cell receptors bound to tissue. The macroscopic tumor cell density is obtained by integration over velocity and activity variables:

$$M(t, x) = \int_Y \int_V p(t, x, v, y) \, \mathrm{d}v \, \mathrm{d}y.$$

Then the dynamics of p can be described by way of a kinetic transport equation of the form

$$\frac{\partial p}{\partial t} + \nabla_x \cdot (vp) + \frac{\partial}{\partial y}(G(y, Q)p) + \nabla_v \cdot (S(v, y, h, Q, M)p) = \beta(p), \qquad (2.3)$$

where the right hand side $\beta(p)$ accounts for source terms to be addressed below. In difference to previous models [12, 13, 14, 15, 21, 20, 22, 30, 32, 55] in the kinetic theory of active particles framework [7], velocity reorientations are not described by way of a turning operator on the right hand side, but by the modeling of the velocity dynamics via $S(v, y, h, Q, M)$.

The proliferative activity of cancer cells depends on their actual binding state. Without connection to the surrounding tissue, cells cannot perform mitosis and even die through anoikis [25, 46]. On the other hand, too many bounds also inhibit cell division.

We will factorize the proliferation rate into a part β_1, which is independent of y, and a part β_2, which depends on y and for which we choose $\beta_2 = \frac{y(R-y)}{R^2}$. Therewith, the proliferation is nearly turned off when there are too few or too many receptors bound to tissue. The y-independent part of the proliferation rate is modeled due to the assumption of glioma cells not being able to proliferate and migrate at the same time, also known as go-or-grow-dichotomy [27, 84]. Unlike previous models [13, 22, 32, 36, 70, 85], where the tumor cells are split into mutually exclusive migrating and proliferating subpopulations, the mentioned dichotomous behavior is taken into account here by relating the y-independent part of the proliferation rate to cell speed in a decreasing manner. A more detailed modeling of the go-or-grow phenomenon with a splitting of the glioma population into subpopulations as in [13, 22, 32, 36, 70, 85] is presented in section 2.3. As the adaptation of speed to the surrounding environment happens fast compared with the time needed for proliferation, we approximate the velocity by the quasi-steady state v^* of its dynamics. The corresponding speed is denoted by $s^* = |v^*|$. Taking into account also the detrimental influences of a highly acidic environment as well as of population pressure by surrounding cancer cells, we propose for the y-independent part of the proliferation rate

$$\beta_1(h, M, s^*) = \mu_M \frac{s_{max} - s^*}{s_{max}} \left(1 - \frac{M}{K_M}\right) \frac{K_h}{K_h + h},$$

with μ_M, K_h being constants, the latter representing a threshold acidity level beyond which the cancer cells cannot advance through the cell cycle leading to mitosis [75, 78]. After proliferation, the binding state of the daughter cells might differ from the original state. We assume that the receptor binding states of daughter cells are distributed symmetrically around the quasi-steady state

y^* of the binding dynamics (2.1). Since the binding dynamics is a very fast process compared to the time needed for proliferation, it is nearby to assume that the receptor binding states of the daughter cells do not depend on the original activity states of the mother cells. Hence, we are led to choosing

$$\beta(y, p, h, M, s^*) = \beta_1(h, M, s^*) \int_Y \beta_2(y')\chi(t, x, y)p(t, x, v, y') \, \mathrm{d}y',$$

where χ is a probability kernel representing the likelihood of cells to receive a receptor binding regime y after division. As such, it holds $\int_Y \chi(t, x, y) \, \mathrm{d}y = 1$ and further, due to our assumption of symmetry around y^*, $\int_Y (y - y^*)\chi(t, x, y) \, \mathrm{d}y = 0$.

2.1.3 Macroscopic scale

Tissue

The acidity produced by the tumor cells by upregulated glycolysis degrades the surrounding tissue [38]. Assuming that the latter is regenerated in a logistic way, we take

$$\dot{Q}(t) = \mu_Q Q(1 - \frac{Q}{K_Q}) - \delta_Q \frac{h}{K_h + h}Q \tag{2.4}$$

with μ_Q, δ_Q constants. For the initial condition we choose

$$Q(0) = K_Q \left(1 - \sqrt{\frac{tr(\mathbb{D}_W)}{3d_{ref}}}\right), \tag{2.5}$$

where the constant d_{ref} is the maximum value (taken over all positions x) any of the entries of $\mathbb{D}_W$ can reach (corresponding to the diagonal entries of $\mathbb{D}_W$ for no surrounding tissue).

Acidity

The dynamics of acidity concentration h in the tumor microenvironment is modeled by

$$\partial_t h = D_h \Delta h + \mu_h \frac{M}{K_M + M} \left(1 - \frac{h}{K_h}\right)_+ - \delta_h he, \tag{2.6}$$

where the second term on the right hand side describes proton production by tumor cells, which is limited by the acidity threshold K_h, whereas the third term describes uptake by blood vessels, which are represented by the density e of endothelial cells. Later on, we will show that for $0 \leq h(0, x) \leq K_h$, K_h is never exceeded, so there is no need to take the positive part in the second term on the right hand side.

Vascularization

The tumor itself stimulates growth of blood vessels by producing certain growth factors. The latter are increasingly expressed under hypoxic conditions, which

is typically occuring at sites with high tumor cell density [19]. Our model for endothelial growth builds upon the one presented in [10], where vascularization of a tumor is described by endothelial cells following tumor angiogenic factor. Since we do not want to inflate the model with yet another space-time dependent variable explicitly accounting for the concentration of such growth factor, we propose instead a chemotactic bias of endothelial cells towards regions with lower pH and choose for their evolution

$$\partial_t e = D_e \Delta e - \varsigma_e \nabla \cdot \left(e \left(1 - \frac{e}{K_e} \right) \nabla h \right) + G_e(h, M) e \left(1 - \frac{e}{K_e} \right). \qquad (2.7)$$

The growth term $G_e(h, M)$ should be increasing w.r.t. h and M, and could be assigned, e.g., the form $G_e(h, M) = \mu_e \frac{hM}{K_h K_M + hM}$. Moreover, we assume that the tactic sensitivity decreases with the amount of available vasculature. Variational approaches to model the tactic behavior of endothelial cells without introducing a further equation for endothelial growth factors are discussed in section 2.2.

2.1.4   Non-dimensionalization

Before deducing a macroscopic model, we non-dimensionalize equations (2.3)-(2.7). To this aim, we define

$$\hat{t} = \frac{t}{\tau}, \; \hat{x} = \frac{x}{\xi}, \; \hat{y} = \frac{y}{R}, \; \hat{v} = \frac{v}{s_{max}}, \; \hat{p} = \frac{R s_{max}}{K_M} p, \; \hat{Q} = \frac{Q}{K_Q}, \; \hat{h} = \frac{h}{K_h}, \; \hat{e} = \frac{e}{K_e},$$
$$\hat{M} = \iint \hat{p} \, d\hat{v} \, d\hat{y}, \; \hat{V} = [0, 1] \times \mathbb{S}^{N-1}, \; \hat{Y} = [0, 1].$$

Note, that

$$\hat{M} = \int_{\hat{Y}} \int_{\hat{V}} \hat{p} \, d\hat{v} \, d\hat{y} = \int_0^1 \int_{\mathbb{S}^{N-1}} \int_0^1 \hat{p} \, d\hat{s} \, d\theta \, d\hat{y} = \int_Y \int_V \frac{R s_{max}}{K_M} p \frac{1}{R s_{max}} \, dv \, dy$$
$$= \frac{M}{K_M}.$$

Applying the above transformations on (2.3) and multiplying the outcome by $\frac{R \tau s_{max}}{K_M}$, we arrive at

$$\partial_{\hat{t}} \hat{p} + \frac{\tau s_{max}}{\xi} \nabla_{\hat{x}} \cdot (\hat{v}\hat{p}) + k^- \tau \frac{\partial}{\partial \hat{y}} \left(\hat{G}(\hat{y}, \hat{Q})\hat{p} \right) + a_2 \tau \nabla_{\hat{v}} \cdot \left(\hat{S}(\hat{v}, \hat{y}, \hat{h}, \hat{Q}, \hat{M})\hat{p} \right)$$
$$= \mu_M \tau \hat{\beta}(\hat{y}, \hat{p}, \hat{h}, \hat{M}, \hat{s}^*), \qquad (2.8)$$

where

$$\hat{G}(\hat{y}, \hat{Q}) = \hat{\kappa}(1 - \hat{y})\hat{Q} - \hat{y}, \quad \text{with } \hat{\kappa} = \frac{K_Q k^+}{k^-},$$

$$\hat{S}(\hat{v}, \hat{y}, \hat{h}, \hat{Q}, \hat{M}) = \frac{a_1}{a_2 s_{max}}(1 - \hat{M})\mathbb{D}_W \hat{b}(\hat{y}, \hat{h}, \hat{Q}, \hat{M}) - \hat{v},$$

$$\hat{b}(\hat{y}, \hat{h}, \hat{Q}, \hat{M}) = (1 - \rho_1 - \rho_2)\frac{-\nabla \hat{h}}{\sqrt{1 + |\nabla \hat{h}|^2}} + \rho_1(1 - \hat{y})\frac{\nabla \hat{Q}}{\sqrt{1 + |\nabla \hat{Q}|^2}}$$

$$+ \rho_2 \frac{-\nabla \hat{M}}{\sqrt{1 + |\nabla \hat{M}|^2}},$$

$$\hat{\beta}(\hat{y}, \hat{p}, \hat{h}, \hat{M}, \hat{s}^*) = (1 - \hat{M})\hat{\eta}(\hat{h}, \hat{s}^*)\int_{\hat{y}} \hat{y}'(1 - \hat{y}')\hat{\chi}(\hat{y})\hat{p}(\hat{y}')\,\mathrm{d}\hat{y}',$$

$$\hat{\eta}(\hat{h}, \hat{s}^*) = \frac{1 - \hat{s}^*}{1 + \hat{h}}, \quad \hat{s}^* = \frac{s^*}{s_{max}}, \quad \hat{\chi}(\hat{y}) = R\chi(\hat{y}R).$$

Note, that it still holds $\int_{\hat{Y}} \hat{\chi}(\hat{y})\,\mathrm{d}\hat{y} = \int_{\hat{Y}} R\chi(\hat{y}R)\,\mathrm{d}\hat{y} = \int_Y R\chi(y)\frac{1}{R}\,\mathrm{d}y = 1$.
Equation (2.4) is rescaled as

$$\partial_{\hat{t}}\hat{Q} = \hat{\mu}_Q \hat{Q}(1 - \hat{Q}) - \hat{\delta}_Q \frac{\hat{h}}{1 + \hat{h}}\hat{Q}, \qquad (2.9)$$

with $\hat{\mu}_Q = \tau\mu_Q$ and $\hat{\delta}_Q = \tau\delta_Q$ and the initial condition becoming

$$\hat{Q}(0) = 1 - \sqrt{\frac{tr(\mathbb{D}_W(\hat{x}))}{3d_{ref}}}.$$

From (2.6), we obtain

$$\partial_{\hat{t}}\hat{h} = \hat{D}_h \Delta\hat{h} + \hat{\mu}_h(1 - \hat{h})\frac{\hat{M}}{1 + \hat{M}} - \hat{\delta}_h \hat{h}\hat{e}, \qquad (2.10)$$

where $\hat{D}_h = \frac{D_h \tau}{\xi^2}$, $\hat{\mu}_h = \frac{\mu_h \tau}{K_h}$, $\hat{\delta}_h = \delta_h K_e \tau$.
Finally, we obtain from (2.7)

$$\partial_{\hat{t}}\hat{e} = \hat{D}_e \Delta\hat{e} - \hat{\varsigma}_e \nabla \cdot \left(\hat{e}(1 - \hat{e})\nabla\hat{h}\right) + \hat{G}_e(\hat{h}, \hat{M})\hat{e}(1 - \hat{e}), \qquad (2.11)$$

where $\hat{D}_e = \frac{D_e \tau}{\xi^2}$, $\hat{\varsigma}_e = \frac{\varsigma_e K_h \tau}{\xi^2}$, $\hat{G}_e(\hat{h}, \hat{M}) = \hat{\mu}_e \frac{\hat{h}\hat{M}}{1 + \hat{h}\hat{M}}$, $\hat{\mu}_e = \mu_e \tau$.
In the following, we will drop the hat symbol from all variables for simplicity of writing.
We are still free to choose the scaling variables τ and ξ. What is a suitable choice of these variables depends on the processes of interest and the time and length scales upon which they are happening. We choose $\tau = \frac{1}{\mu_M}$, which means that one time unit corresponds to the (average) proliferation time of glioma cells. For the length scale, we choose the distance which can maximally be covered by a cell in one time unit, hence $\xi = \tau \cdot s_{max} = \frac{s_{max}}{\mu_M}$. Thus, we obtain the following

non-dimensionalized system:

$$\partial_t p + \nabla_x \cdot (vp) + \frac{k^-}{\mu_M}\partial_y(G(y,Q)p) + \frac{a_2}{\mu_M}\nabla_v \cdot (S(v,y,h,Q,M)p)$$
$$= \beta(y,p,h,M,s^*), \tag{2.12a}$$

$$\partial_t Q = \mu_Q Q(1-Q) - \delta_Q \frac{h}{1+h}Q, \tag{2.12b}$$

$$\partial_t h = D_h \Delta h + \mu_h(1-h)\frac{M}{1+M} - \delta_h he, \tag{2.12c}$$

$$\partial_t e = D_e \Delta e - \varsigma_e \nabla \cdot (e(1-e)\nabla h) + G_e(h,M)e(1-e), \tag{2.12d}$$
with

$$G(y) = \kappa(1-y)Q - y, \tag{2.12e}$$

$$S(v,y,h,Q,M) = \frac{a_1}{a_2 s_{max}}(1-M)\mathbb{D}_W b - v, \tag{2.12f}$$

$$b(y,h,Q,M) = (1-\rho_1-\rho_2)\frac{-\nabla h}{\sqrt{1+|\nabla h|^2}} + \rho_1(1-y)\frac{\nabla Q}{\sqrt{1+|\nabla Q|^2}}$$
$$+ \rho_2 \frac{-\nabla M}{\sqrt{1+|\nabla M|^2}}, \tag{2.12g}$$

$$\beta(y,p,h,M,s^*) = (1-M)\eta(h,s^*)\int_Y y'(1-y')\chi(y)p(y')\,\mathrm{d}y', \tag{2.12h}$$

$$\eta(h,s^*) = \frac{1-s^*}{1+h} \tag{2.12i}$$

$$G_e(h,M) = \mu_e \frac{hM}{1+hM}. \tag{2.12j}$$

The kinetic equation (2.12a) is still characterizing mesoscopic dynamics of cancer cells, as p depends on time, position, velocity, and the activity variable (cell surface density of receptors bound to tissue fibers). Thus, the attempt to solve system (2.12) numerically has to face the high dimensionality of the phase space $\mathbb{R}^N \times V \times Y$, which is quite inconvenient. Therefore, in the next subsection we aim at deducing a macroscopic counterpart of (2.12a), to be coupled with the rest of equations in (2.12).

2.1.5 Derivation of a fully macroscopic system

Assumptions and notations

We make the following simplifying assumptions, which will be needed in the process of obtaining a closed system by integrating w.r.t. y and v:

$$\int_V \int_Y (v-v^*)(y-y^*)p\,\mathrm{d}y\,\mathrm{d}v \approx 0, \quad \int_V \int_Y (y-y^*)^2 p\,\mathrm{d}y\,\mathrm{d}v \approx 0,$$
$$\int_V \int_Y (v_i-v_i^*)(v-v^*)p\,\mathrm{d}y\,\mathrm{d}v \approx 0, \quad \nabla_x \cdot \int_V \int_Y (v_i-v_i^*)(v-v^*)p\,\mathrm{d}y\,\mathrm{d}v \approx 0,$$

where v_i is the i-th component of the vector v, and $y^* = \frac{\kappa Q}{1+\kappa Q}$ and $v^* = (1-M)\frac{a_1}{a_2 s_{max}}\mathbb{D}_W b$ are the quasi-stationary states of the correspondingly non-dimension-

alized microscopic dynamics (2.1) and (2.2). Thus, we assume that some of the second order moments for the tumor cell distribution w.r.t. deviations of v and y from their steady states are negligible, which is reasonable, since the microscopic dynamics of receptor binding and velocity innovations happen very fast in comparison to the (mesoscopic) behavior of cell groups sharing the same regimes of activity and kinetic variables. The second order moment of v is not required to nullify, but only its divergence.

Subsequently we use the following notations:

$$M(t,x) := \int_V \int_Y p \, \mathrm{d}y \, \mathrm{d}v, \qquad M^y(t,x) := \int_V \int_Y yp \, \mathrm{d}y \, \mathrm{d}v,$$

$$M_i^v(t,x) := \int_V \int_Y v_i p \, \mathrm{d}y \, \mathrm{d}v, \qquad M^v(t,x) := \int_V \int_Y vp \, \mathrm{d}y \, \mathrm{d}v = (M_i^v)_{i=1}^N.$$

Boundary conditions

Due to the performed non-dimensionalization, the domains Y and V are given by

$$Y = (0,1) \text{ and } V = B_1(0) \subset \mathbb{R}^3.$$

We assume p to be compactly supported in the $V \times Y$ space.

Remark 2.1.1. Equation (2.12a) is of transport type with respect to y and v. Hence, boundary conditions w.r.t. these variables must be prescribed only at the inflow boundary of Y and V.

- Inflow boundary of Y: The dynamics of y is given by $\dot{y} = \frac{k^-}{\mu_M} G(y,Q) = \frac{k^-}{\mu_M}(\kappa(1-y)Q - y)$. A binding state $y \in \partial Y$ is part of the inflow boundary, if $G(y,Q) \cdot \nu < 0$, where ν is the outward normal vector on the boundary. On $\partial Y = \{0,1\}$, it holds

$$G(0) \cdot \nu(0) = \kappa Q \cdot (-1) < 0 \quad \text{and} \quad G(1) \cdot \nu(1) = -1 \cdot 1 < 0.$$

  Hence, the inflow boundary of Y coincides with ∂Y. Thus, boundary conditions can be prescribed on the whole of ∂Y.

- Inflow boundary of V: The dynamics of v is determined by $\dot{v} = \frac{a_2}{\mu_M} S(v) = \frac{a_2}{\mu_M}\left(\frac{a_1}{a_2 s_{max}}(1-M)\mathbb{D}_W b - v\right)$, where $|b| < 1$. Now let $v \in \partial B_1(0)$, so $|v| = 1$. The corresponding outward normal vector is then given by $\nu = v$, and we obtain

$$S(v) \cdot \nu = \left\langle \frac{a_1}{a_2 s_{max}}(1-M)\mathbb{D}_W b, v \right\rangle - \langle v, v \rangle$$

$$= \frac{a_1}{a_2 s_{max}}(1-M)\left\langle \sum_{i=1}^3 \alpha_i \omega_i \langle \omega_i, b\rangle, v \right\rangle - |v|^2$$

$$\leq \frac{a_1}{a_2 s_{max}}(1-M)\left|\sum_{i=1}^3 \alpha_i \omega_i \langle \omega_i, b\rangle\right| - 1$$

$$\leq \frac{a_1}{a_2 s_{max}}\alpha_{max} \underbrace{|b|}_{<1} - 1$$

$$< \frac{a_1}{a_2 s_{max}}\frac{a_2}{a_1}s_{max} - 1 = 0,$$

where we used boundedness of M by its carrying capacity, which is shown later on in the analysis section. Hence, V only has an inflow boundary, therefore boundary conditions can be prescribed on the whole of ∂V.

Equations for the moments

For simplicity of writing, temporarily all dependencies of the coefficient functions on the macroscopic density functions h, Q, e and M are dropped. We integrate (2.12a) with respect to y and v:

$$\partial_t M + \nabla_x \cdot M^v + \frac{k^-}{\mu_M} \int_V \int_Y \partial_y (G(y)p) \, \mathrm{d}y \, \mathrm{d}v + \frac{a_2}{\mu_M} \int_V \int_Y \nabla_v \cdot (S(v,y)p) \, \mathrm{d}y \, \mathrm{d}v$$
$$= \int_V \int_Y \beta(y,p) \, \mathrm{d}y \, \mathrm{d}v.$$

The third and fourth term on the left hand side are zero due to the chosen boundary conditions. For the integral on the right hand side we find

$$\int_V \int_Y \beta(y,p) \, \mathrm{d}y \, \mathrm{d}v = \int_V \int_Y (1-M)\eta(s^*) \int_Y y'(1-y')\chi(y)p(y') \, \mathrm{d}y' \, \mathrm{d}y \, \mathrm{d}v$$
$$= (1-M)\eta(s^*) \underbrace{\int_Y \chi(y) \, \mathrm{d}y}_{=1} \underbrace{\int_V \int_Y y'(1-y')p(y') \, \mathrm{d}y' \, \mathrm{d}v}_{(A)},$$

from which by

$$(A) = \int_V \int_Y y(1-y)p(y) \, \mathrm{d}y \, \mathrm{d}v = \int_V \int_Y yp(y) \, \mathrm{d}y \, \mathrm{d}v - \int_V \int_Y y^2 p(y) \, \mathrm{d}y \, \mathrm{d}v$$
$$= M^y - \underbrace{\int_V \int_Y (y-y^*)^2 p(y) \, \mathrm{d}y \, \mathrm{d}v}_{\approx 0} - \int_V \int_Y 2y^* y p(y) \, \mathrm{d}y \, \mathrm{d}v$$
$$+ \int_V \int_Y (y^*)^2 p(y) \, \mathrm{d}y \, \mathrm{d}v$$
$$= M^y - 2y^* M^y + (y^*)^2 M$$

we conclude

$$\int_V \int_Y \beta(y,p) \, \mathrm{d}y \, \mathrm{d}v = (1-M)\eta(s^*)\left(M^y - 2y^* M^y + (y^*)^2 M\right).$$

Hence, we obtain the macroscopic equation

$$\partial_t M + \nabla_x \cdot M^v = \eta(s^*)(1-M)\left(M^y - 2y^* M^y + (y^*)^2 M\right). \qquad (2.13)$$

To obtain a closed system we need further equations for the moments M^y and M^v. To this aim, we multiply (2.12a) by y and again integrate with respect to y und v:

$$\partial_t M^y + \nabla_x \cdot \int_Y \int_V vyp \, \mathrm{d}y \, \mathrm{d}v + \frac{k^-}{\mu_M} \int_V \int_Y y\partial_y (G(y)p) \, \mathrm{d}y \, \mathrm{d}v$$
$$+ \frac{a_2}{\mu_M} \int_V \int_Y y\nabla_v \cdot (S(v,y)p) \, \mathrm{d}y \, \mathrm{d}v \qquad (2.14)$$
$$= \int_V \int_Y y\beta(y,p) \, \mathrm{d}y \, \mathrm{d}v.$$

Again, the fourth term is zero due to the chosen boundary conditions. The third term on the left hand side can be computed by partial integration:

$$
\begin{aligned}
\frac{k^-}{\mu_M} \int_V \int_Y y \partial_y (G(y)p) \, \mathrm{d}y \, \mathrm{d}v &= -\frac{k^-}{\mu_M} \int_V \int_Y G(y)p \, \mathrm{d}y \, \mathrm{d}v \\
&= -\frac{k^-}{\mu_M} \int_V \int_Y (\kappa Q(1-y) - y)p \, \mathrm{d}y \, \mathrm{d}v \\
&= \frac{k^-}{\mu_M}(\kappa Q + 1)M^y - \frac{k^- \kappa}{\mu_M} QM.
\end{aligned}
$$

For the remaining terms we find

$$
\begin{aligned}
\nabla_x \cdot \int_V \int_Y vyp \, \mathrm{d}y \, \mathrm{d}v &= \nabla_x \cdot \int_V \int_Y (v - v^*)(y - y^*)p \, \mathrm{d}y \, \mathrm{d}v \\
&\quad + \nabla_x \cdot \int_V \int_Y (vy^* + v^*y)p \, \mathrm{d}y \, \mathrm{d}v - \nabla_x \cdot \int_V \int_Y y^*v^*p \, \mathrm{d}y \, \mathrm{d}v \\
&= \nabla_x \cdot (y^* M^v + v^* M^y - y^* v^* M),
\end{aligned}
$$

$$
\begin{aligned}
\int_V \int_Y y\beta(y,p) \, \mathrm{d}y \, \mathrm{d}v &= \eta(s^*)(1-M) \int_V \int_Y y\chi(y) \, \mathrm{d}y \int_Y y'(1-y')p(y') \, \mathrm{d}y' \, \mathrm{d}v \\
&= \eta(s^*)(1-M)y^*(M^y - 2y^* M^y + (y^*)^2 M),
\end{aligned}
$$

where we used the symmetry of χ around y^*:

$$
\int_Y y\chi(y) \, \mathrm{d}y = \underbrace{\int_Y (y - y^*)\chi(y) \, \mathrm{d}y}_{=0} + y^* \underbrace{\int_Y \chi(y) \, \mathrm{d}y}_{=1} = y^*.
$$

Putting the above terms together, we find from (2.14)

$$
\begin{aligned}
\partial_t M^y &+ \nabla_x \cdot (y^* M^v + v^* M^y - y^* v^* M) + \frac{k^-}{\mu_M}((\kappa Q + 1)M^y - \kappa QM) \\
&= \eta(s^*)(1-M)y^*(M^y - 2y^* M^y + (y^*)^2 M).
\end{aligned}
\tag{2.15}
$$

To find an equation for M^v, we repeat the computations from above, now multiplying (2.12a) by v_i instead of y. Integration w.r.t. v yields

$$
\begin{aligned}
\partial_t M_i^v &+ \int_V \int_Y v_i \nabla_x \cdot (vp) \, \mathrm{d}y \, \mathrm{d}v + \frac{a_2}{\mu_M} \int_V \int_Y v_i \nabla_v \cdot (S(v,y)p) \, \mathrm{d}y \, \mathrm{d}v \\
&= \int_V \int_Y v_i \beta(y,p) \, \mathrm{d}y \, \mathrm{d}v.
\end{aligned}
$$

We compute the terms separately:

$$
\begin{aligned}
\int_V \int_Y v_i \nabla_x \cdot (vp) \, \mathrm{d}y \, \mathrm{d}v &= \nabla_x \cdot \int_V \int_Y v_i vp \, \mathrm{d}y \, \mathrm{d}v \\
&= \nabla_x \cdot \underbrace{\int_V \int_Y (v_i - v_i^*)(v - v^*)p \, \mathrm{d}y \, \mathrm{d}v}_{\approx 0} \\
&\quad + \nabla_x \cdot \int_V \int_Y (v_i v^* + v_i^* v - v_i^* v^*)p \, \mathrm{d}y \, \mathrm{d}v \\
&= \nabla_x \cdot (v^* M_i^v + v_i^* M^v - v_i^* v^* M),
\end{aligned}
$$

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and

$$\int_V \int_Y v_i \nabla_v \cdot (S(v,y)p) \, \mathrm{d}y \, \mathrm{d}v$$

$$= \int_Y \left[\int_V v_i \partial_{v_i}(S_i(v,y)p) \, \mathrm{d}v + \sum_{j=1, j\neq i}^{n} \int_V v_i \partial_{v_j}(S_j(v,y)p) \, \mathrm{d}v \right] \mathrm{d}y$$

$$= \int_Y \int_{V\backslash V_i} \int_{V_i} v_i \partial_{v_i}(S_i(v,y)p) \, \mathrm{d}v_i \, \mathrm{d}\tilde{v}_i \, \mathrm{d}y$$

$$+ \sum_{j=1, j\neq i}^{n} \int_Y \int_{V\backslash V_j} v_i \int_{V_j} \partial_{v_j}(S_j(v,y)p) \, \mathrm{d}v_j \, \mathrm{d}\tilde{v}_j \, \mathrm{d}y$$

$$= \int_Y \int_{V\backslash V_i} \left(v_i \underbrace{S_i(v,y)p|_{\partial V_i}}_{=0} - \int_{V_i} S_i(v,y)p \, \mathrm{d}v_i \right) \mathrm{d}\tilde{v}_i \, \mathrm{d}y$$

$$+ \sum_{j=1, j\neq i}^{n} \int_Y \int_{V\backslash V_j} v_i \underbrace{S_j(v,y)p|_{\partial V_j}}_{=0} \mathrm{d}\tilde{v}_j \, \mathrm{d}y$$

$$= -\int_Y \int_V S_i(v,y)p \, \mathrm{d}v \, \mathrm{d}y$$

$$= -\int_Y \int_V (g_i^{(1)}p + yg_i^{(2)}p - v_i p) \, \mathrm{d}v \, \mathrm{d}y$$

$$= -g_i^{(1)}M - g_i^{(2)}M^y + M_i^v,$$

where we used the notation $v = (v_i, \tilde{v}_i) \in V_i \times V_{\neq i} = V$ along with (recall (2.12f))

$$S(v,y) = g(y) - v = g^{(1)} + yg^{(2)} - v,$$

$$g^{(1)} = \frac{a_1}{a_2 s_{max}}(1-M)\mathbb{D}_W \left((1-\rho_1-\rho_2)\frac{-\nabla h}{\sqrt{1+|\nabla h|^2}} + \rho_1 \frac{\nabla Q}{\sqrt{1+|\nabla Q|^2}} \right.$$

$$\left. +\rho_2 \frac{-\nabla M}{\sqrt{1+|\nabla M|^2}} \right),$$

$$g^{(2)} = -\frac{a_1}{a_2 s_{max}}\rho_1 y(1-M)\mathbb{D}_W \frac{\nabla Q}{\sqrt{1+|\nabla Q|^2}}.$$

Eventually,

$$\int_V \int_Y v_i \beta(y,p) \, \mathrm{d}y \, \mathrm{d}v$$

$$= \eta(s^*)(1-M) \int_V \int_Y v_i \int_Y \chi(y)y'(1-y')p(y') \, \mathrm{d}y' \, \mathrm{d}y \, \mathrm{d}v$$

$$= \eta(s^*)(1-M) \underbrace{\int_Y \chi(y) \, \mathrm{d}y}_{=1} \int_V \int_Y v_i y'(1-y')p(y') \, \mathrm{d}y' \, \mathrm{d}v$$

$$= \eta(s^*)(1-M) \left(\int_V \int_Y (v_i - v_i^*)(y-y^2)p(y) \, \mathrm{d}y \, \mathrm{d}v \right.$$

$$+ v_i^* \int_V \int_Y (y - y^2) p(y) \, \mathrm{d}y \, \mathrm{d}v \Big)$$

$$= \eta(s^*)(1 - M) \left(\int_V \int_Y (v_i - v_i^*)(y - y^*) p(y) \, \mathrm{d}y \, \mathrm{d}v \right.$$

$$+ y^* \int_V \int_Y (v_i - v_i^*) p(y) \, \mathrm{d}y \, \mathrm{d}v$$

$$- \int_V \int_Y (v_i - v_i^*)(y - y^*)^2 p(y) \, \mathrm{d}y \, \mathrm{d}v$$

$$- \int_V \int_Y (v_i - v_i^*)(2yy^* - (y^*)^2) p(y) \, \mathrm{d}y \, \mathrm{d}v$$

$$+ \int_V \int_Y v_i^* y p(y) \, \mathrm{d}y \, \mathrm{d}v - \int_V \int_Y v_i^* (y - y^*)^2 p(y) \, \mathrm{d}y \, \mathrm{d}v$$

$$\left. - \int_V \int_Y v_i^* (2yy^* - (y^*)^2) p(y) \, \mathrm{d}y \, \mathrm{d}v \right)$$

$$= \eta(s^*)(1 - M) \left(y^* M_i^v - y^* v_i^* M \right.$$

$$\left. - \int_V \int_Y v_i (2yy^* - (y^*)^2) p(y) \, \mathrm{d}y \, \mathrm{d}v + v_i^* M^y \right)$$

$$= \eta(s^*)(1 - M) \left(y^* M_i^v - y^* v_i^* M - 2y^* v_i^* M^y - 2(y^*)^2 M_i^v \right.$$

$$\left. + 2(y^*)^2 v_i^* M + (y^*)^2 M_i^v + v_i^* M^y \right)$$

$$= \eta(s^*)(1 - M) \left((2(y^*)^2 v_i^* - y^* v_i^*) M + (v_i^* - 2y^* v_i^*) M^y \right.$$

$$\left. + (y^* - (y^*)^2) M_i^v \right).$$

Hence, summarizing the terms calculated above, we find

$$\partial_t M_i^v + \nabla_x \cdot (v^* M_i^v + v_i^* M^v - v_i^* v^* M) + \frac{a_2}{\mu_M} \left(M_i^v - g_i^{(1)} M - g_i^{(2)} M^y \right)$$

$$= \eta(s^*)(1 - M) \left((2(y^*)^2 v_i^* - y^* v_i^*) M + (v_i^* - 2y^* v_i^*) M^y + (y^* - (y^*)^2) M_i^v \right).$$

(2.16)

for $i = 1, 2, ..., N$. Summarizing (2.13),(2.15) and (2.16), we obtain a closed macroscopic system:

$$\partial_t M + \nabla_x \cdot M^v = \eta(s^*)(1 - M) \left(M^y - 2y^* M^y + (y^*)^2 M \right), \qquad (2.17\text{a})$$

$$\partial_t M^y + \nabla_x \cdot (y^* M^v + v^* M^y - y^* v^* M) + \frac{k^-}{\mu_M} \left((\kappa Q + 1) M^y - \kappa Q M \right) \qquad (2.17\text{b})$$

$$= \eta(s^*)(1 - M) y^* (M^y - 2y^* M^y + (y^*)^2 M),$$

$$\partial_t M_i^v + \nabla_x \cdot (v^* M_i^v + v_i^* M^v - v_i^* v^* M) + \frac{a_2}{\mu_M} \left(M_i^v - g_i^{(1)} M - g_i^{(2)} M^y \right)$$

$$= \eta(s^*)(1 - M) \left((2(y^*)^2 v_i^* - y^* v_i^*) M + (v_i^* - 2y^* v_i^*) M^y + (y^* - (y^*)^2) M_i^v \right).$$

(2.17c)

Upscaling

The aim of this section is to derive a single macroscopic equation for M from system (2.17a) - (2.17c) by scaling methods. For this, we take a closer look at the involved parameters. In literature, the following values can be found:

- $\mu_M \sim 10^{-4} \frac{1}{min}$ [68]

- $k^- \sim 6 \frac{1}{min}$ [21]

- $\kappa \sim 1$ [21]

For a_2 no reliable data could be found. We assume, that $a_2 \sim 10 \frac{1}{min}$. This value corresponds to the ability of a cell reaching near to its maximal speed in approximately $10s$ (which seems reasonable but is, however, only a guess). We set $\epsilon = 10^{-5}$ and find

$$\frac{\mu_M}{a_2} \approx 10^{-5} = \epsilon$$

and

$$\frac{\mu_M}{k^-} \approx 10^{-5} = \epsilon.$$

Applying these estimates to the equations (2.17a)-(2.17c) deduced above, we find

$$\partial_t M + \nabla_x \cdot M^v = \eta(s^*)(1 - M)\left(M^y - 2y^* M^y + (y^*)^2 M\right), \qquad (2.18a)$$

$$\epsilon \partial_t M^y + \epsilon \nabla_x \cdot (y^* M^v + v^* M^y - y^* v^* M) + (\kappa Q + 1)M^y - \kappa Q M$$
$$= \epsilon \eta(s^*)(1 - M)(M^y - 2y^* M^y + (y^*)^2 M), \qquad (2.18b)$$

$$\epsilon \partial_t M_i^v + \epsilon \nabla_x \cdot (v^* M_i^v + v_i^* M^v - v_i^* v^* M) + M_i^v - g_i^{(1)} M - g_i^{(2)} M^y$$
$$= \epsilon \eta(s^*)(1 - M)\left((2(y^*)^2 v_i^* - y^* v_i^*)M + (v_i^* - 2y^* v_i^*)M^y \qquad (2.18c)\right.$$
$$\left. + (y^* - (y^*)^2)M_i^v\right).$$

Remark 2.1.2. The presented method for scaling differs from the one applied in e.g. [20, 32]. Instead of directly prescribing scalings of t and x by some small parameter ϵ, we stick to the more parameter focused method applied in [8], considering the (in our case biologically) prescribed orders of the model parameters after non-dimensionalization with time and length scale of interest. The result corresponds in the given case with a hyperbolic scaling. Compared to directly setting $x \to \epsilon x$, $t \to \epsilon t$, the approach has the advantage, that - assuming the availability of reliable data on the parameter orders - we directly obtain the correct scaling for the non-derivative terms of the model corresponding to the chosen time and length scale.

We consider Hilbert expansions

$$M = M_0 + \epsilon M_1 + ...,$$
$$M^v = M_0^v + \epsilon M_1^v + ...,$$
$$M^y = M_0^y + \epsilon M_1^y + ...$$

Plugging this into (2.18a)-(2.18c), sorting by orders of ϵ and considering only the leading order terms, we deduce from equation (2.18b)

$$(\kappa Q + 1)M_0^y = \kappa Q M_0 \quad \Rightarrow \quad M_0^y = \frac{\kappa Q}{\kappa Q + 1}M_0 = y^* M_0. \qquad (2.19)$$

Equation (2.18c) yields

$$M_{0_i}^v - g_i^{(1)} M_0 - g_i^{(2)} M_0^y = 0,$$

where $g_i^{(1)} = g_i^{(1)}(M_0)$. Plugging in (2.19) we find

$$M_{0_i}^v = (g_i^{(1)} + y^* g_i^{(2)})M_0 = g_i(y^*)M_0 \qquad (2.20)$$

Collecting leading order terms in (2.18a) and using (2.19) and (2.20), we find

$$\partial_t M_0 + \nabla_x \cdot (g(y^*)M_0) = G_M(h, s^*, y^*)M_0(1 - M_0), \qquad (2.21)$$

where

$$g(y^*) = \frac{a_1}{a_2 s_{max}}(1 - M_0)\mathbb{D}_W b(y^*),$$

$$b(y^*) = (1 - \rho_1 - \rho_2)\frac{-\nabla h}{\sqrt{1 + |\nabla h|^2}} + \rho_1(1 - y^*)\frac{\nabla Q}{\sqrt{1 + |\nabla Q|^2}} + \rho_2\frac{-\nabla M_0}{\sqrt{1 + |\nabla M_0|^2}},$$

$$G_M(h, s^*, y^*) = \eta(h, s^*)\left(y^* - (y^*)^2\right) = \frac{(1 - s^*)(y^* - (y^*)^2)}{1 + h}.$$

This is a genuinely macroscopic reaction-diffusion-taxis PDE for the leading term M_0 in the Hilbert expansion of the macroscopic glioma density M, thus it is supposed to approximate the tumor density dynamics for $\epsilon \to 0$.[2] The rest of the equations in system (2.12) were already macroscopic.

So far, we considered the space variable $x \in \mathbb{R}^N$, however, we should actually deal with a bounded region in which glioma cells, normal tissue, acidity and endothelial cells are evolving. Let $\Omega \subset \mathbb{R}^N$ be such a bounded domain with sufficiently smooth boundary. By the non-dimensionalization, the domain on which (2.24) holds is $\tilde{\Omega} = \frac{\mu_M}{s_{max}}\Omega$, with outer unit normal vector $\nu(x)$ at $x \in \partial\Omega$. Assuming no normal mass flux across the boundary gives the mesoscopic no flux condition

$$0 = \int_V \int_Y vp(t, x, v, y) \cdot \nu(x)\,\mathrm{d}y\,\mathrm{d}v = M_0^v(t, x) \cdot \nu(x) = g(y^*)M_0(t, x) \cdot \nu(x),$$
$$\text{for all } x \in \partial\tilde{\Omega}, \ t > 0,$$
$$(2.22)$$

cf. [61]. The other PDEs in (2.24) were introduced in subsection 2.1.3 directly on a macroscopic level, thus we can simply impose no-flux conditions:

$$D_h \nabla h \cdot \nu = 0 \quad \text{on } \partial\tilde{\Omega}, \ t > 0, \qquad (2.23a)$$

$$(D_e \nabla e - \varsigma_e e(1 - e)\nabla h) \cdot \nu = 0 \quad \text{on } \partial\tilde{\Omega}, \ t > 0. \qquad (2.23b)$$

The subsequently summarized system (2.24) with boundary conditions (2.22) and (2.23) has to be supplemented with adequate initial conditions. These can be the tumor cell distribution observed at diagnosis, an estimate of the macroscopic volume fraction of the tissue as proposed in (2.5), some (estimated) acidity distribution at diagnosis and a given distribution of endothelial cell density. For convenience of notation we will subsequently write M instead of M_0, and Ω instead of $\tilde{\Omega}$. We summarize the full macroscopic system characterizing glioma dynamics under the influence of tissue, acidity, and vasculature:

---

[2]This is just a formal deduction; a rigorous study of convergence is not performed in the scope of this thesis.

Model 2.1: The basic model

$$\partial_t M + \nabla_x \cdot (g(h, Q, M, y^*)M) = G_M(h, s^*, y^*)(1 - M)M, \qquad \text{(2.24a)}$$

$$\partial_t Q = \mu_Q Q(1 - Q) - \delta_Q \frac{h}{1 + h} Q, \qquad \text{(2.24b)}$$

$$\partial_t h = D_h \Delta h + \mu_h (1 - h) \frac{M}{1 + M} - \delta_h h e, \qquad \text{(2.24c)}$$

$$\partial_t e = D_e \Delta e - \varsigma_e \nabla_x \cdot (e(1 - e)\nabla_x h) + G_e(h, M)e(1 - e) \qquad \text{(2.24d)}$$

in $\mathbb{R}^+ \times \Omega$ (in $\mathbb{R}^+ \times \bar{\Omega}$ for equation (2.24b)), with

$$g(h, Q, M, y^*) = \frac{a_1}{a_2 s_{max}}(1 - M)\mathbb{D}_W b(h, Q, M, y^*), \qquad \text{(2.25a)}$$

$$b(h, Q, M, y^*) = (1 - \rho_1 - \rho_2)\frac{-\nabla h}{\sqrt{1 + |\nabla h|^2}} + \rho_1(1 - y^*)\frac{\nabla Q}{\sqrt{1 + |\nabla Q|^2}}$$
$$+ \rho_2 \frac{-\nabla M}{\sqrt{1 + |\nabla M|^2}}, \qquad \text{(2.25b)}$$

$$G_M(h, s^*, y^*) = \frac{(1 - s^*)(y^* - (y^*)^2)}{1 + h}, \qquad \text{(2.25c)}$$

$$G_e(h, M) = \mu_e \frac{hM}{1 + hM}, \qquad \text{(2.25d)}$$

$$s^* = |g(h, Q, M, y^*)|, \qquad \text{(2.25e)}$$

$$y^* = \frac{\kappa Q}{1 + \kappa Q}, \qquad \text{(2.25f)}$$

boundary conditions

$$Mg(h, Q, M, y^*) \cdot \nu = 0 \quad \text{on } \partial\Omega, \, t > 0, \qquad \text{(2.26a)}$$
$$D_h \nabla h \cdot \nu = 0 \quad \text{on } \partial\Omega, \, t > 0, \qquad \text{(2.26b)}$$
$$(D_e \nabla e - \varsigma_e e(1 - e)\nabla h) \cdot \nu = 0 \quad \text{on } \partial\Omega, \, t > 0, \qquad \text{(2.26c)}$$

and nonnegative initial data

$$M(0, x) = M_0(x), \, h(0, x) = h_0(x), \, e(0, x) = e_0(x) \quad \text{for } x \in \Omega, \quad \text{(2.27a)}$$
$$Q(0, x) = Q_0(x) \qquad\qquad\qquad\qquad\qquad \text{for } x \in \bar{\Omega}, \quad \text{(2.27b)}$$

bounded by their carrying capacities, i.e.

$$0 \le M_0(x), Q_0(x), h_0(x), e_0(x) \le 1.$$

The system features self-diffusion, repellent pH-taxis, and haptotaxis, all of which involve limited fluxes. The diffusivity, taxis sensitivity functions and even the proliferation rate depend on the solution components, directly or via the steady state y^* of receptor binding dynamics. Thus, although macroscopic, they still carry information from the lowermost (subcellular) level modeled here.

2.2 Endothelial cells following $\nabla M/\nabla(hM)$

In section 2.1, we modeled the spread of endothelial cells by pH-taxis. As was already mentioned there, blood vessels actually do not spread into acidic regions but into regions of high concentrations of vascular endothelial growth factor (VEGF). Since VEGF is mainly produced by cancer cells in contact with an acidic environment, there is a correlation between pH and VEGF concentration. In section 2.1, we did not set up a separate equation for production and diffusion of VEGF in order to avoid inflating the model with a further equation. Instead, we assumed that VEGF and protons diffuse in a similar way. Being a product of cancer cells in contact with acidity, while the latter is also produced by cancer cells, we simply replaced VEGF concentration in the taxis term by pH, leading to

$$\partial_t e = D_e \Delta e - \varsigma_e \nabla_x \cdot (e(1-e)\nabla_x h) + G_e(h,M)e(1-e),$$

$$G_e(h,M) = \mu_e \frac{hM}{K_h K_M + hM}.$$

Assuming instead that VEGF concentration is dominated by production rather than diffusion, it makes more sense to approximate VEGF by hM, which is proportional to the production rate of VEGF. Note, that this approach means to neglect diffusivity of VEGF. A third possible approach could be to drop h and assume, that VEGF concentration is proportional to the density of cancer cells.

We shortly introduce the changes in the modeling of endothelial cells for the two approaches suggested above. Later on, we show in simulations how the choice of the taxis term affects the resulting vascularization of the tumor.

2.2.1 Modeling

Substantially, we stick to the model introduced in section 2.1. Changes are made in equation (2.7): We choose now

$$\partial_t e = D_e \Delta e - \varsigma_e \nabla \left(e\left(1 - \frac{e}{K_e}\right) \nabla f^{(i)}\right) + G_e(h,M)e\left(1 - \frac{e}{K_e}\right), \quad (2.28)$$

$$G_e(h,M) = \mu_e \frac{hM}{K_h K_M + hM},$$

replacing the pH-tactic term ∇h by $\nabla f^{(i)}$, $i = 1, 2$. We set

$$f^{(1)}(M) = M \text{ and } f^{(2)}(h,M) = hM.$$

Finally, we have to non-dimensionalize equation (2.28). Proceeding in the same way as was done in section 2.1.4, now with $\hat{\varsigma}_e^{(1)} = \frac{\varsigma_e K_M \tau}{\xi^2}$ and $\hat{\varsigma}_e^{(2)} = \frac{\varsigma_e K_h K_M \tau}{\xi^2}$, we find (dropping the hats)

$$\partial_t e = D_e \Delta e - \varsigma_e^{(i)} \nabla \cdot \left(e(1-e)\nabla f^{(i)}(h,M)\right) + G_e(h,M)e(1-e),$$
$$(2.29)$$

$$G_e(h,M) = \mu_e \frac{hM}{1 + hM}. \tag{2.30}$$

For $i = 1$ or $i = 2$, the complete macroscopic system is given by

Model 2.2: Endothelials following $\nabla M/\nabla(hM)$

$$\partial_t M + \nabla_x \cdot (g(h, Q, M, y^*)M) = G_M(h, s^*, y^*)(1 - M)M, \tag{2.31a}$$

$$\partial_t Q = \mu_Q Q(1 - Q) - \delta_Q \frac{h}{1 + h} Q, \tag{2.31b}$$

$$\partial_t h = D_h \Delta h + \mu_h (1 - h) \frac{M}{1 + M} - \delta_h he, \tag{2.31c}$$

$$\partial_t e = D_e \Delta e - \varsigma_e^{(i)} \nabla \cdot \left(e(1 - e) \nabla f^{(i)}(h, M) \right) + G_e(h, M)e(1 - e) \tag{2.31d}$$

in $\mathbb{R}^+ \times \Omega$ (in $\mathbb{R}^+ \times \bar{\Omega}$ for equation (2.31b)), with

$$g(h, Q, M, y^*) = \frac{a_1}{a_2 s_{max}}(1 - M_0)\mathbb{D}_W b(h, Q, M, y^*), \tag{2.32a}$$

$$b(h, Q, M, y^*) = (1 - \rho_1 - \rho_2)\frac{-\nabla h}{\sqrt{1 + |\nabla h|^2}} + \rho_1(1 - y^*)\frac{\nabla Q}{\sqrt{1 + |\nabla Q|^2}}$$
$$+ \rho_2 \frac{-\nabla M}{\sqrt{1 + |\nabla M|^2}}, \tag{2.32b}$$

$$G_M(h, s^*, y^*) = \frac{(1 - s^*)(y^* - (y^*)^2)}{1 + h}, \tag{2.32c}$$

$$f^{(i)}(M) = \begin{cases} M, & \text{if } i = 1, \\ hM, & \text{if } i = 2, \end{cases} \tag{2.32d}$$

$$G_e(h, M) = \mu_e \frac{hM}{1 + hM}, \tag{2.32e}$$

$$s^* = |g(h, Q, M, y^*)|, \tag{2.32f}$$

$$y^* = \frac{\kappa Q}{1 + \kappa Q}, \tag{2.32g}$$

boundary conditions

$$Mg(h, Q, M, y^*) \cdot \nu = 0 \quad \text{on } \partial\Omega, \, t > 0, \tag{2.33a}$$

$$D_h \nabla h \cdot \nu = 0 \quad \text{on } \partial\Omega, \, t > 0, \tag{2.33b}$$

$$(D_e \nabla e - \varsigma_e^{(i)} e(1 - e)\nabla f^{(i)}(h, M)) \cdot \nu = 0 \quad \text{on } \partial\Omega, \, t > 0, \tag{2.33c}$$

and nonnegative initial data

$$M(0, x) = M_0(x), \, h(0, x) = h_0(x), \, e(0, x) = e_0(x) \quad \text{for } x \in \Omega, \tag{2.34a}$$

$$Q(0, x) = Q_0(x) \qquad\qquad\qquad \text{for } x \in \bar{\Omega}, \tag{2.34b}$$

bounded by their carrying capacities, i.e.

$$0 \le M_0(x), Q_0(x), h_0(x), e_0(x) \le 1.$$

2.3 The go-or-grow hypothesis

In the models in sections 2.1 and 2.2, we integrated the assumption that proliferating cells do not migrate (the so called go-or-grow dichotomy) by a speed dependent proliferation rate. We want to compare this ansatz with a more classical modeling approach for the go-or-grow phenomenon. In [32, 69, 70, 85], the population of cancer cells is divided into two subpopulations: migrating and proliferating cells. While in many works the modeling is performed directly on the macroscopic level, as was done for example in [69, 85], there also exist models connecting different scales [36, 70] as well as works deriving macroscopic models from the micro-mesolevel [32]. We choose the latter approach, modifying the micro-meso-model set up in section 2.1 and again performing an upscaling. In simulations in chapter 4, the resulting macroscopic system will be compared with the basic model 2.1 based on the speed dependent proliferation rate.

2.3.1 Modeling

The population of cancer cells is divided into a population of migrating cancer cells $m(t, x, y, v)$ and a population of proliferating cancer cells $p(t, x, y)$. Equation (2.3) has to be split into two equations, where for the equation for p the transport terms and for the equation for m the proliferation term are dropped. Both equations are complemented by transition terms w_{mp}, w_{pm} between the two populations:

$$\frac{\partial m}{\partial t} + \nabla_x \cdot (vm) + \frac{\partial}{\partial y}(G(y, Q)m) + \nabla_v \cdot (S(v, y, h, Q, C)m)$$
$$= w_{pm}(m, p) - w_{mp}(m, p), \tag{2.35}$$

$$\frac{\partial p}{\partial t} + \frac{\partial}{\partial y}(G(y, Q)p) = \beta(p, m) + \int_V w_{mp}(m, p)\, \mathrm{d}v - \int_V w_{pm}(m, p)\, \mathrm{d}v. \tag{2.36}$$

In the following, $M(t, x) = \int_V \int_Y m \, \mathrm{d}y \, \mathrm{d}v$ and $P(t, x) = \int_Y p \, \mathrm{d}y$ will denote the total concentrations of migrating and proliferating cells. By $C(t, x) = M(t, x) + P(t, x)$ we denote the total concentration of all cancer cells.

Dynamics of the binding state

The dynamics of the binding state is chosen as in subsection 2.1.1, so

$$G(y, Q) = k^+(R - y)Q - k^- y. \tag{2.37}$$

Dynamics of cell velocity

Corresponding to the modeling in subsection 2.1, the dynamics of cell velocity is modeled by

$$S(v, y, h, Q, C) = g(y, h, Q, C) - a_2 v, \tag{2.38}$$

where

$$g(y, h, Q, C) = a_1 \frac{K_C - C}{K_C} \mathbb{D}_W b,$$

$$b(y, h, Q, C) = (1 - \rho_1 - \rho_2) \frac{-\nabla h}{\sqrt{\left(\frac{K_h}{\xi}\right)^2 + |\nabla h|^2}} + \rho_1 \frac{R - y}{R} \frac{\nabla Q}{\sqrt{\left(\frac{K_Q}{\xi}\right)^2 + |\nabla Q|^2}}$$

$$+ \rho_2 \frac{-\nabla C}{\sqrt{\left(\frac{K_C}{\xi}\right)^2 + |\nabla C|^2}}.$$

Transition terms

We assume that the decision to switch between migrating and proliferating phenotype depends on the signal strength a cell receives. The stronger the received signal the more cells switch from proliferation to migration in order to follow the received signal. In case of low signal, more cells stop migration and start to proliferate. We choose the following switch terms:

$$w_{mp}(m, p) = \alpha_1 (a_1^2 \alpha_{max}^2 - |g|^2) m,$$

$$w_{pm}(m, p) = \alpha_2 |g|^2 p \delta \left(\frac{|v|}{s_{max}}\right).$$

Recall $|g| \leq a_1 \alpha_{max}$, hence for a maximal signal $|g|$ we obtain $w_{mp}(m, p) = 0$, meaning that no cells switch from migrational to proliferative regime. After transition of a cell from proliferative to migrational stage, the cell starts with speed 0 before accelerating into the direction of the received signal. Hence, we choose the factor $\delta \left(\frac{|v|}{s_{max}}\right)$ in w_{pm}, such that the distribution of velocities after a switch from proliferation to migration is concentrated in $v = 0$.

Proliferation

Proliferation is modeled similarly as in subsection 2.1.2. The main difference lies in dropping the speed dependent term $\frac{s_{max} - s^*}{s_{max}}$ and replacing in the logistic growth term $\frac{M}{K_M}$ by $\frac{C}{K_C}$, where K_C is the carrying capacity for cancer cells (which should have the same value as K_M in section 2.1). We choose

$$\beta(p, m) = \beta_1(h, C) \int_Y \beta_2(y') \chi(t, x, y) p(t, x, y') \, dy',$$

where

$$\beta_1(h, C) = \mu_P \left(1 - \frac{C}{K_C}\right) \frac{K_h}{K_h + h} \quad \text{and} \quad \beta_2(y) = \frac{y(R - y)}{R^2}.$$

Tissue

The modeling of tissue density is identical to that in section 2.1.3, so

$$\dot{Q}(t) = \mu_Q Q (1 - \frac{Q}{K_Q}) - \delta_Q \frac{h}{K_h + h} Q. \tag{2.39}$$

Again, the initial condition is chosen as

$$Q(0) = K_Q \left(1 - \sqrt{\frac{tr(\mathbb{D}_W)}{3d_{ref}}} \right).$$

Acidity

The concentration h of protons in the tumor environment is modeled similarly to section 2.1.3:

$$\partial_t h = D_h \Delta h + \mu_h \frac{P}{K_C + P} \left(1 - \frac{h}{K_h} \right) - \delta_h h e. \qquad (2.40)$$

Here, we replaced $\frac{M}{K_M + M}$ by $\frac{P}{K_C + P}$ to take into account, that predominantly proliferating cancer cells produce an acidic environment as a result of the proliferation cycle.

Vascularization

Finally, also the equation describing vascularization can be mainly retained:

$$\partial_t e = D_e \Delta e - \varsigma_e \nabla \left(e \left(1 - \frac{e}{K_e} \right) \nabla h \right) + G_e(h, P) e \left(1 - \frac{e}{K_e} \right). \qquad (2.41)$$

The growth term $G_e(h, P)$ should be increasing w.r.t. h and P, and is here chosen as $G_e(h, P) = \mu_e \frac{hP}{K_h K_C + hP}$.

2.3.2 Non-dimensionalization

Analogously to section 2.1.4, we non-dimensionalize equations (2.35)-(2.41). To this aim, we define

$$\hat{t} = \frac{t}{\tau}, \ \hat{x} = \frac{x}{\xi}, \ \hat{y} = \frac{y}{R}, \ \hat{v} = \frac{v}{s_{max}}, \ \hat{p} = \frac{R}{K_C} p, \ \hat{m} = \frac{R s_{max}}{K_C} m, \ \hat{Q} = \frac{Q}{K_Q},$$

$$\hat{h} = \frac{h}{K_h}, \ \hat{e} = \frac{e}{K_e}, \ \hat{M} = \int_{\hat{V}} \int_{\hat{Y}} \hat{m} \, d\hat{v} \, d\hat{y}, \ \hat{P} = \int_{\hat{Y}} \hat{p} \, d\hat{y}, \ \hat{C} = \hat{M} + \hat{P}.$$

Note, that

$$\hat{M} = \int_{\hat{V}} \int_{\hat{Y}} \hat{m} \, d\hat{v} \, d\hat{y} = \int_{V} \int_{Y} \frac{R s_{max}}{K_C} m \cdot \frac{1}{R s_{max}} \, dv \, dy = \frac{M}{K_C},$$

$$\hat{P} = \int_{\hat{Y}} \hat{p} \, d\hat{y} = \int_{Y} \frac{R}{K_C} p \cdot \frac{1}{R} \, dy = \frac{P}{K_C},$$

$$\hat{C} = \hat{M} + \hat{P} = \frac{M}{K_C} + \frac{P}{K_C} = \frac{C}{K_C}.$$

Multiplying equation (2.35) by $\frac{R \tau s_{max}}{K_C}$ and equation (2.36) by $\frac{R\tau}{K_C}$ and applying the above transformations, we obtain

$$\partial_{\hat{t}} \hat{m} + \frac{\tau s_{max}}{\xi} \nabla_x \cdot (\hat{v} \hat{m}) + k^- \tau \partial_{\hat{y}} \left(\hat{G}(\hat{y}) \hat{m} \right) + a_2 \tau \nabla_{\hat{v}} \cdot \left(\hat{S}(\hat{v}, \hat{y}, \hat{h}, \hat{Q}, \hat{C}) \hat{m} \right)$$
$$= \mu_P \tau \hat{w}_{pm}(\hat{m}, \hat{p}) - \mu_P \tau \hat{w}_{mp}(\hat{m}, \hat{p})$$

$$(2.42)$$

and

$$\partial_{\hat{t}}\hat{p} + k^{-}\tau\partial_{\hat{y}}\left(\hat{G}(\hat{y})\hat{p}\right) = \mu_P\tau\hat{\beta}(\hat{p}) + \mu_P\tau\int_{\hat{V}}\hat{w}_{mp}(\hat{m},\hat{p})\,\mathrm{d}\hat{v}$$
$$- \mu_P\tau\int_{\hat{V}}\hat{w}_{pm}(\hat{m},\hat{p})\,\mathrm{d}\hat{v}, \tag{2.43}$$

where

$$\hat{G}(\hat{y},\hat{Q}) = \hat{k}(1-\hat{y})\hat{Q} - \hat{y}, \quad \hat{k} = \frac{K_Q k^{+}}{k^{-}},$$

$$\hat{S}(\hat{v},\hat{y},\hat{h},\hat{Q},\hat{C}) = \hat{g} - \hat{v},$$

$$\hat{g}(\hat{y},\hat{h},\hat{Q},\hat{C}) = \frac{(1-\hat{C})}{\alpha_{max}}\mathbb{D}_W\hat{b},$$

$$\hat{b}(\hat{y},\hat{h},\hat{Q},\hat{C}) = (1-\rho_1-\rho_2)\frac{-\nabla\hat{h}}{\sqrt{1+|\nabla\hat{h}|^2}} + \rho_1(1-\hat{y})\frac{\nabla\hat{Q}}{\sqrt{1+|\nabla\hat{Q}|^2}}$$

$$+ \rho_2\frac{-\nabla\hat{C}}{\sqrt{1+|\nabla\hat{C}|^2}}$$

$$\hat{\beta}(\hat{y},\hat{p},\hat{h},\hat{C}) = (1-\hat{C})\hat{\eta}(\hat{h})\int_{\hat{Y}}\hat{y}'(1-\hat{y}')\hat{\chi}(\hat{y})\hat{p}(\hat{y}')\,\mathrm{d}\hat{y}',$$

$$\hat{\eta}(\hat{h}) = \frac{1}{1+\hat{h}}, \quad \hat{\chi}(\hat{y}) = R\chi(\hat{y}R),$$

$$\hat{w}_{mp}(\hat{m},\hat{p}) = \hat{\alpha}_1(1-|\hat{g}|^2)\hat{m}, \quad \hat{w}_{pm}(\hat{m},\hat{p}) = \hat{\alpha}_2|\hat{g}|^2\delta(|\hat{v}|)\hat{p},$$

$$\hat{\alpha}_1 = \frac{\alpha_1 a_1^2\alpha_{max}^2}{\mu_P}, \quad \hat{\alpha}_2 = \frac{\alpha_2 a_1^2\alpha_{max}^2}{\mu_P}.$$

Note, that it still holds $\int_{\hat{Y}}\hat{\chi}(\hat{y})\,\mathrm{d}\hat{y} = \int_{\hat{Y}}R\chi(\hat{y}R)\,\mathrm{d}\hat{y} = \int_Y R\chi(y)\frac{1}{R}\,\mathrm{d}y = 1$.
With $\hat{\mu}_Q = \tau\mu_Q$ and $\hat{\delta}_Q = \tau\delta_Q$, equation (2.39) is rescaled as

$$\partial_{\hat{t}}\hat{Q} = \hat{\mu}_Q\hat{Q}(1-\hat{Q}) - \hat{\delta}_Q\frac{\hat{h}}{1+\hat{h}}\hat{Q} \quad \text{with i.c.} \quad \hat{Q}(0) = 1 - \sqrt{\frac{tr(\mathbb{D}_W)}{3d_{ref}}}. \tag{2.44}$$

From (2.40), we obtain

$$\partial_{\hat{t}}\hat{h} = \hat{D}_h\Delta\hat{h} + \hat{\mu}_h(1-\hat{h})\frac{\hat{P}}{1+\hat{P}} - \hat{\delta}_h\hat{h}\hat{e}, \tag{2.45}$$

where $\hat{D}_h = \frac{D_h\tau}{\xi^2}$, $\hat{\mu}_h = \tau\frac{\mu_h}{K_h}$, $\hat{\delta}_h = \tau\delta_h K_e$.
Finally, we obtain from equation (2.41)

$$\partial_{\hat{t}}\hat{e} = \hat{D}_e\Delta\hat{e} - \hat{\varsigma}_e\nabla\cdot\left(\hat{e}(1-\hat{e})\nabla\hat{h}\right) + \hat{G}_e(\hat{h},\hat{P})\hat{e}(1-\hat{e}), \tag{2.46}$$

where $\hat{D}_e = \frac{D_e\tau}{\xi^2}$, $\hat{\varsigma}_e = \frac{\varsigma_e K_h\tau}{\xi^2}$, $\hat{G}_e(\hat{h},\hat{P}) = \hat{\mu}_e\frac{\hat{h}\hat{P}}{1+\hat{h}\hat{P}}$, $\hat{\mu}_e = \mu_e\tau$.
Choosing $\tau = \frac{1}{\mu_P}$ and $\xi = \frac{s_{max}}{\mu_P}$ and dropping the hats, we find the non-

dimensionalized system

$$\partial_t m + \nabla_x \cdot (vm) + \frac{k^-}{\mu_P} \partial_y(G(y,Q)m) + \frac{a_2}{\mu_P} \nabla_v \cdot (S(v,y,h,Q,C)m)$$
$$= w_{pm}(y,m,p,h,Q,C) - w_{mp}(y,v,m,p,h,Q,C), \tag{2.47a}$$

$$\partial_t p + \frac{k^-}{\mu_P} \partial_y(G(y,Q)p) = \beta(y,p,h,C) + \int_V w_{mp}(y,v,m,p,h,Q,C)\,\mathrm{d}v$$
$$- \int_V w_{pm}(y,m,p,h,Q,C)\,\mathrm{d}v, \tag{2.47b}$$

$$\partial_t Q = \mu_Q Q(1-Q) - \delta_Q \frac{h}{1+h}Q, \tag{2.47c}$$

$$\partial_t h = D_h \Delta h + \mu_h(1-h)\frac{P}{1+P} - \delta_h he, \tag{2.47d}$$

$$\partial_t e = D_e \Delta e - \varsigma_e \nabla \cdot (e(1-e)\nabla h) + G_e(h,P)e(1-e), \tag{2.47e}$$

with

$$G(y,Q) = \kappa(1-y)Q - y, \tag{2.47f}$$

$$S(v,y,h,Q,C) = \frac{a_1}{a_2 s_{max}}(1-C)\mathbb{D}_W b(y,h,Q,C) - v, \tag{2.47g}$$

$$b(y,h,Q,C) = (1-\rho_1-\rho_2)\frac{-\nabla h}{\sqrt{1+|\nabla h|^2}} + \rho_1(1-y)\frac{\nabla Q}{\sqrt{1+|\nabla Q|^2}}$$
$$+ \rho_2 \frac{-\nabla C}{\sqrt{1+|\nabla C|^2}}, \tag{2.47h}$$

$$\beta(y,p,h,C) = (1-C)\eta(h)\int_Y y'(1-y')\chi(y)p(y')\,\mathrm{d}y', \quad \eta(h) = \frac{1}{1+h}, \tag{2.47i}$$

$$w_{mp}(y,v,m,p,h,Q,C) = \alpha_1(1-|g|^2)m, \tag{2.47j}$$

$$w_{pm}(y,m,p,h,Q,C) = \alpha_2|g|^2\delta(|v|)p, \tag{2.47k}$$

$$G_e(h,P) = \mu_e \frac{hP}{1+hP}. \tag{2.47l}$$

2.3.3 Derivation of a fully macroscopic system

Assumptions and notations

In analogy to subsection 2.1.5 we make the following simplifying assumptions:

$$\int_V \int_Y (v-v^*)(y-y^*)m\,\mathrm{d}y\,\mathrm{d}v \approx 0, \quad \int_V \int_Y (y-y^*)^2 p\,\mathrm{d}y\,\mathrm{d}v \approx 0,$$

$$\int_V \int_Y (y-y^*)^2 m\,\mathrm{d}y\,\mathrm{d}v \approx 0, \quad \int_V \int_Y (v_i-v_i^*)(v-v^*)m\,\mathrm{d}y\,\mathrm{d}v \approx 0,$$

$$\nabla_x \cdot \int_V \int_Y (v_i-v_i^*)(v-v^*)m\,\mathrm{d}y\,\mathrm{d}v \approx 0,$$

where again v_i is the i-th component of the vector v, and $y^* = \frac{\kappa Q}{1+\kappa Q}$ and $v^* = (1-C)\frac{a_1}{a_2 s_{max}}\mathbb{D}_W b$ are the quasi-stationary states of (2.37) and (2.38).

We will use the following notations:

$$M(t,x) := \int_V \int_Y m \, dy \, dv, \qquad M^y(t,x) := \int_V \int_Y ym \, dy \, dv,$$

$$M_i^v(t,x) := \int_V \int_Y v_i m \, dy \, dv, \qquad M^v(t,x) := \int_V \int_Y vm \, dy \, dv = (M_i^v)_{i=1}^n,$$

$$P(t,x) := \int_V \int_Y p \, dy \, dv, \qquad P^y(t,x) := \int_V \int_Y yp \, dy \, dv.$$

Boundary conditions

Due to the performed non-dimensionalization, the domains Y and V are given by

$$Y = (0,1) \text{ and } V = B_1(0) \subset \mathbb{R}^3.$$

We assume m and p to be compactly supported in the $V \times Y$ space and in the Y space, respectively.

Remark 2.3.1. Again, equations (2.47a) and (2.47b) are of transport type with respect to y and v (y, respectively). Hence, boundary conditions can only be prescribed at the inflow boundary of Y and V (Y). We proceed analogously to the foregoing section:

- Inflow boundary of Y: The dynamics of y is described by $\dot{y} = \frac{k^-}{\mu_P} G(y,Q) = \frac{k^-}{\mu_P}(\kappa(1-y)Q - y)$. A binding state $y \in \partial Y$ is part of the inflow boundary, if $G(y) \cdot \nu < 0$, where ν is the outward normal vector on the boundary. On $\partial Y = \{0,1\}$ it holds

$$G(0) \cdot \nu(0) = \kappa Q \cdot (-1) < 0 \text{ and } G(1) \cdot \nu(1) = -1 \cdot 1 < 0.$$

  Hence, the inflow boundary of Y coincides with ∂Y. Thus, boundary conditions can be prescribed on the whole of ∂Y.

- Inflow boundary of V: The dynamics of v is determined by $\dot{v} = \frac{a_2}{\mu_P} S(v) = \frac{k^-}{\mu_P}\left(\frac{a_1}{a_2 s_{max}}(1-C)\mathbb{D}_W b - v\right)$, where $|b| < 1$. Now let $v \in \partial B_1(0)$, so $|v| = 1$. The corresponding outward normal vector is then given by $\nu = v$, and we obtain

$$S(v) \cdot \nu = \left\langle \frac{a_1}{a_2 s_{max}}(1-C)\mathbb{D}_W b, v \right\rangle - \langle v, v \rangle$$

$$= \frac{a_1}{a_2 s_{max}}(1-C)\left\langle \sum_{i=1}^3 \alpha_i \omega_i \langle \omega_i, b \rangle, v \right\rangle - |v|^2$$

$$\leq \frac{a_1}{a_2 s_{max}}(1-C)\left| \sum_{i=1}^3 \alpha_i \omega_i \langle \omega_i, b \rangle \right| - 1$$

$$\leq \frac{a_1}{a_2 s_{max}}\alpha_{max} \underbrace{|b|}_{<1} - 1$$

$$< \frac{a_1}{a_2 s_{max}} \frac{a_2}{a_1} s_{max} - 1 = 0.$$

  The used boundedness of C by its carrying capacity is shown later on in the analysis section. Hence, V only has an inflow boundary, therefore boundary conditions can be prescribed on the whole of ∂V.

Equations for the moments

To derive a macroscopic system we proceed as in subsection 2.1.5. For simplicity of writing, in the following computations the dependencies of the coefficient functions on the macroscopic density functions h, Q, P, M and e are dropped. First, we integrate (2.47a) with respect to y and v:

$$\partial_t M + \nabla_x \cdot M^v + \frac{k^-}{\mu_P} \int_V \int_Y \partial_y(G(y)m) \, \mathrm{d}y \, \mathrm{d}v + \frac{a_2}{\mu_P} \int_V \int_Y \nabla_v \cdot (S(v,y)m) \, \mathrm{d}y \, \mathrm{d}v$$
$$= \int_V \int_Y w_{pm} \, \mathrm{d}y \, \mathrm{d}v - \int_V \int_Y w_{mp} \, \mathrm{d}y \, \mathrm{d}v.$$

The third and fourth term on the left hand side are zero due to the chosen boundary conditions. Setting again $g = g^{(1)} + yg^{(2)}$, we find for the integrals on the right hand side

$$\frac{1}{\alpha_2} \int_V \int_Y w_{pm} \, \mathrm{d}y \, \mathrm{d}v = \int_V \int_Y \delta(|v|)|g|^2 p \, \mathrm{d}y \, \mathrm{d}v$$
$$= \int_V \delta(|v|) \, \mathrm{d}v \int_Y |g|^2 p \, \mathrm{d}y$$
$$= \int_Y |g^{(1)} + yg^{(2)}|^2 p \, \mathrm{d}y$$
$$= \int_Y |g^{(1)}|^2 p + y^2 |g^{(2)}|^2 p + 2y\langle g^{(1)}, g^{(2)}\rangle p \, \mathrm{d}y$$
$$= |g^{(1)}|^2 P + 2\langle g^{(1)}, g^{(2)}\rangle P^y + |g^{(2)}|^2(-(y^*)^2 P + 2y^* P^y)$$

and

$$\frac{1}{\alpha_1} \int_V \int_Y w_{mp} \, \mathrm{d}y \, \mathrm{d}v$$
$$= \int_V \int_Y (1 - |g^{(1)} + yg^{(2)}|^2)m \, \mathrm{d}y \, \mathrm{d}v$$
$$= \int_V \int_Y (1 - |g^{(1)}|^2)m - y^2|g^{(2)}|^2 m - 2y\langle g^{(1)}, g^{(2)}\rangle m \, \mathrm{d}y \, \mathrm{d}v$$
$$= (1 - |g^{(1)}|^2)M - \int_V \int_Y (y - y^*)^2|g^{(2)}|^2 m \, \mathrm{d}y \, \mathrm{d}v$$
$$+ \int_V \int_Y (y^*)^2|g^{(2)}|^2 m \, \mathrm{d}y \, \mathrm{d}v - 2y^* \int_V \int_Y y|g^{(2)}|^2 m \, \mathrm{d}y \, \mathrm{d}v - 2\langle g^{(1)}, g^{(2)}\rangle M^y$$
$$= (1 - |g^{(1)}|^2)M + (y^*)^2|g^{(2)}|^2 M - 2y^*|g^{(2)}|^2 M^y - 2\langle g^{(1)}, g^{(2)}\rangle M^y.$$

Hence, we obtain the macroscopic equation

$$\partial_t M + \nabla_x \cdot M^v$$
$$= \alpha_2 \left(|g^{(1)}|^2 P + 2\langle g^{(1)}, g^{(2)}\rangle P^y + |g^{(2)}|^2(-(y^*)^2 P + 2y^* P^y) \right)$$
$$- \alpha_1 \left((1 - |g^{(1)}|^2)M + (y^*)^2|g^{(2)}|^2 M - 2y^*|g^{(2)}|^2 M^y - 2\langle g^{(1)}, g^{(2)}\rangle M^y \right).$$
$$\tag{2.48}$$

We repeat the procedure for (2.47b), now integrating only with respect to y:

$$\partial_t P + \frac{k^-}{\mu_P} \int_Y \partial_y(G(y)p) \, \mathrm{d}y = \int_Y \beta(y,p) \, \mathrm{d}y + \int_V \int_Y w_{mp} \, \mathrm{d}y \, \mathrm{d}v - \int_V \int_Y w_{pm} \, \mathrm{d}y \, \mathrm{d}v.$$

Again, the second integral on the left hand side is zero due to boundary conditions. Analogously to the computation in section 2.1.5, for the first term on the right hand side we obtain

$$
\int_Y \beta(y,p)\,\mathrm{d}y = \frac{1-C}{1+h}\int_Y \chi(y)\,\mathrm{d}y \int_V \int_Y y'(1-y')p(y')\,\mathrm{d}y'
$$
$$
= \frac{1-C}{1+h}(P^y - 2y^* P^y + (y^*)^2 P).
$$

The second and third term on the right hand side were derived above, so we find

$$
\partial_t P = \frac{1-C}{1+h}\left(P^y - 2y^* P^y + (y^*)^2 P\right)
$$
$$
+ \alpha_1 \left((1-|g^{(1)}|^2)M + (y^*)^2|g^{(2)}|^2 M - 2y^*|g^{(2)}|^2 M^y - 2\langle g^{(1)}, g^{(2)}\rangle M^y\right)
$$
$$
- \alpha_2 \left(|g^{(1)}|^2 P + 2\langle g^{(1)}, g^{(2)}\rangle P^y + |g^{(2)}|^2(-(y^*)^2 P + 2y^* P^y)\right).
$$
(2.49)

For a closed system, we further need equations for the moments M^y, P^y and M^v. To this aim, we multiply (2.47a) by y and again integrate with respect to y and v:

$$
\partial_t M^y + \nabla_x \cdot \int_Y \int_V vym\,\mathrm{d}y\,\mathrm{d}v + \frac{k^-}{\mu_P}\int_V \int_Y y\partial_y(G(y)m)\,\mathrm{d}y\,\mathrm{d}v
$$
$$
+ \frac{a_2}{\mu_P}\int_V \int_Y y\nabla_v \cdot (S(v,y)m)\,\mathrm{d}y\,\mathrm{d}v
$$
$$
= \int_V \int_Y yw_{pm}\,\mathrm{d}y\,\mathrm{d}v - \int_V \int_Y yw_{mp}\,\mathrm{d}y\,\mathrm{d}v.
$$

Again, the fourth term is zero due to the chosen boundary conditions. For the second and third integral on the left hand side, we obtain as in section 2.1.5

$$
\nabla_x \cdot \int_V \int_Y vym\,\mathrm{d}y\,\mathrm{d}v = \nabla_x \cdot (y^* M^v + v^* M^y - y^* v^* M)
$$

and

$$
\int_V \int_Y y\frac{\partial}{\partial y}(G(y)m)\,\mathrm{d}y\,\mathrm{d}v = (\kappa Q + 1)M^y - \kappa Q M.
$$

For the terms on the right hand side we find

$$
\frac{1}{\alpha_2}\int_V \int_Y yw_{pm}\,\mathrm{d}y\,\mathrm{d}v = \int_Y y|g|^2 p\,\mathrm{d}y \int_V \delta(|v|)\,\mathrm{d}v
$$
$$
= \left(-2\langle g^{(1)}, g^{(2)}\rangle(y^*)^2 - 2|g^{(2)}|^2(y^*)^3\right)P
$$
$$
+ \left(|g^{(1)}|^2 + 4\langle g^{(1)}, g^{(2)}\rangle y^* + 3|g^{(2)}|^2(y^*)^2\right)P^y
$$

and

$$
\frac{1}{\alpha_1}\int_V \int_Y yw_{mp}\,\mathrm{d}y\,\mathrm{d}v = \int_V \int_Y y(1-|g|^2)m\,\mathrm{d}y\,\mathrm{d}v
$$
$$
= \left(2\langle g^{(1)}, g^{(2)}\rangle(y^*)^2 + 2|g^{(2)}|^2(y^*)^3\right)M
$$
$$
+ \left(1 - |g^{(1)}|^2 - 4\langle g^{(1)}, g^{(2)}\rangle y^* - 3|g^{(2)}|^2(y^*)^2\right)M^y.
$$

Altogether, we find

$$
\begin{aligned}
\partial_t M^y + &\nabla_x \cdot (y^* M^v + v^* M^y - y^* v^* M) + \frac{k^-}{\mu_P} \left((\kappa Q + 1) M^y - \kappa Q M \right) \\
&= \alpha_2 \left(\left(-2 \langle g^{(1)}, g^{(2)} \rangle (y^*)^2 - 2 |g^{(2)}|^2 (y^*)^3 \right) P \right. \\
&\qquad \left. + \left(|g^{(1)}|^2 + 4 \langle g^{(1)}, g^{(2)} \rangle y^* + 3 |g^{(2)}|^2 (y^*)^2 \right) P^y \right) \\
&\quad - \alpha_1 \left(\left(2 \langle g^{(1)}, g^{(2)} \rangle (y^*)^2 + 2 |g^{(2)}|^2 (y^*)^3 \right) M \right. \\
&\qquad \left. + \left(1 - |g^{(1)}|^2 - 4 \langle g^{(1)}, g^{(2)} \rangle y^* - 3 |g^{(2)}|^2 (y^*)^2 \right) M^y \right).
\end{aligned} \tag{2.50}
$$

To find an equation for P^y we multiply (2.47b) by y and integrate with respect to y:

$$
\begin{aligned}
\partial_t P^y + &\frac{k^-}{\mu_P} \int_V \int_Y y \frac{\partial}{\partial y} (G(y) p) \,\mathrm{d}y \,\mathrm{d}v \\
&= \int_V \int_Y y \beta(y, p) \,\mathrm{d}y \,\mathrm{d}v + \int_V \int_Y y w_{mp} \,\mathrm{d}y \,\mathrm{d}v - \int_V \int_Y y w_{pm} \,\mathrm{d}y \,\mathrm{d}v.
\end{aligned}
$$

The second term on the left hand side is given by

$$
\int_Y y \frac{\partial}{\partial y} (G(y) p) \,\mathrm{d}y = (\kappa Q + 1) P^y - \kappa Q P.
$$

For the first term on the right hand side we find

$$
\begin{aligned}
\int_Y y \beta(p, y, C) \,\mathrm{d}y &= \frac{1 - C}{1 + h} \int_Y y \chi(y) \,\mathrm{d}y \int_Y y'(1 - y') p(y') \,\mathrm{d}y' \\
&= \frac{1 - C}{1 + h} y^* (P^y - 2 y^* P^y + (y^*)^2 P).
\end{aligned}
$$

The second and third term on the right hand side were already computed above. Altogether, we find

$$
\begin{aligned}
\partial_t P^y + &\frac{k^-}{\mu_P} \left((\kappa Q + 1) P^y - \kappa Q P \right) \\
&= \frac{1 - C}{1 + h} y^* (P^y - 2 y^* P^y + (y^*)^2 P) \\
&\quad + \alpha_1 \left(\left(2 \langle g^{(1)}, g^{(2)} \rangle (y^*)^2 + 2 |g^{(2)}|^2 (y^*)^3 \right) M \right. \\
&\qquad \left. + \left(1 - |g^{(1)}|^2 - 4 \langle g^{(1)}, g^{(2)} \rangle y^* - 3 |g^{(2)}|^2 (y^*)^2 \right) M^y \right) \\
&\quad - \alpha_2 \left(\left(-2 \langle g^{(1)}, g^{(2)} \rangle (y^*)^2 - 2 |g^{(2)}|^2 (y^*)^3 \right) P \right. \\
&\qquad \left. + \left(|g^{(1)}|^2 + 4 \langle g^{(1)}, g^{(2)} \rangle y^* + 3 |g^{(2)}|^2 (y^*)^2 \right) P^y \right).
\end{aligned} \tag{2.51}
$$

To find an equation for M^v, we repeat the computations from above, now

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multiplying (2.47a) by v_i instead of y. Integration w.r.t. v yields

$$\partial_t M_i^v + \int_V \int_Y v_i \nabla_x \cdot (vm) \, \mathrm{d}y \, \mathrm{d}v + \frac{k^-}{\mu_P} \int_V \int_Y v_i \frac{\partial}{\partial y}(G(y)m) \, \mathrm{d}y \, \mathrm{d}v$$

$$+ \frac{a_2}{\mu_P} \int_V \int_Y v_i \nabla_v \cdot (S(v,y)m) \, \mathrm{d}y \, \mathrm{d}v$$

$$= \int_V \int_Y v_i w_{pm} \, \mathrm{d}y \, \mathrm{d}v - \int_V \int_Y v_i w_{mp} \, \mathrm{d}y \, \mathrm{d}v.$$

The third term on the right hand side is again zero due to boundary conditions. The other terms are computed as follows:

$$\int_V \int_Y v_i \nabla_x \cdot (vm) \, \mathrm{d}y \, \mathrm{d}v = \nabla_x \cdot \int_V \int_Y v_i vm \, \mathrm{d}y \, \mathrm{d}v$$

$$= \nabla_x \cdot \int_V \int_Y (v_i - v_i^*)(v - v^*)m \, \mathrm{d}y \, \mathrm{d}v$$

$$+ \nabla_x \cdot \int_V \int_Y (v_i v^* + v_i^* v - v_i^* v^*)m \, \mathrm{d}y \, \mathrm{d}v$$

$$= \nabla_x \cdot (v^* M_i^v + v_i^* M^v - v_i^* v^* M),$$

$$\int_V \int_Y v_i \nabla_v \cdot (S(v,y)m) \, \mathrm{d}y \, \mathrm{d}v$$

$$= \int_Y \left[\int_V v_i \partial_{v_i}(S_i(v,y)m) \, \mathrm{d}v + \sum_{j=1, j \neq i}^n \int_V v_i \partial_{v_j}(S_j(v,y)m) \, \mathrm{d}v \right] \mathrm{d}y$$

$$= \int_Y \int_{V \setminus V_i} \int_{V_i} v_i \partial_{v_i}(S_i(v,y)m) \, \mathrm{d}v_i \, \mathrm{d}\tilde{v}_i \, \mathrm{d}y$$

$$+ \sum_{j=1, j \neq i}^n \int_Y \int_{V \setminus V_j} v_i \int_{V_j} \partial_{v_j}(S_j(v,y)m) \, \mathrm{d}v_j \, \mathrm{d}\tilde{v}_j \, \mathrm{d}y$$

$$= \int_Y \int_{V \setminus V_i} \left(v_i \underbrace{S_i(v,y)m|_{\partial V_i}}_{=0} - \int_{V_i} S_i(v,y)m \, \mathrm{d}v_i \right) \mathrm{d}\tilde{v}_i \, \mathrm{d}y$$

$$+ \sum_{j=1, j \neq i}^n \int_Y \int_{V \setminus V_j} v_i \underbrace{S_j(v,y)m|_{\partial V_j}}_{=0} \, \mathrm{d}\tilde{v}_j \, \mathrm{d}y$$

$$= - \int_Y \int_V S_i(v,y)m \, \mathrm{d}v \, \mathrm{d}y = - \int_Y \int_V (g_i^{(1)}m + y g_i^{(2)}m - v_i m) \, \mathrm{d}v \, \mathrm{d}y$$

$$= -g_i^{(1)} M - g_i^{(2)} M^y + M_i^v,$$

$$\frac{1}{\alpha_2} \int_V \int_Y v_i w_{pm} \, \mathrm{d}y \, \mathrm{d}v = \int_V v_i \delta(v) \, \mathrm{d}v \int_Y |g|^2 p \, \mathrm{d}y = 0,$$

$$\frac{1}{\alpha_1} \int_V \int_Y v_i w_{mp} \, dy \, dv$$

$$= \int_V \int_Y v_i (1 - |g^{(1)} + y g^{(2)}|^2) m \, dy \, dv$$

$$= \int_V \int_Y v_i m \, dy \, dv - \int_V \int_Y |g^{(1)}|^2 v_i m \, dy \, dv - 2 \int_V \int_Y v_i y \langle g^{(1)}, g^{(2)} \rangle m \, dy \, dv$$

$$\quad - \int_V \int_Y v_i y^2 |g^{(2)}|^2 m \, dy \, dv$$

$$= M_i^v - |g^{(1)}|^2 M_i^v - 2 \langle g^{(1)}, g^{(2)} \rangle \left(\int_V \int_Y (v_i - v_i^*)(y - y^*) m \, dy \, dv \right.$$

$$\quad \left. + \int_V \int_Y (v_i y^* + v_i^* y) m \, dy \, dv - \int_V \int_Y v_i^* y^* m \, dy \, dv \right)$$

$$\quad - |g^{(2)}|^2 \left(\int_V \int_Y v_i (y - y^*)^2 m \, dy \, dv + \int_V \int_Y 2 y^* y v_i m \, dy \, dv \right.$$

$$\quad \left. - \int_V \int_Y (y^*)^2 v_i m \, dy \, dv \right)$$

$$= (1 - |g^{(1)}|^2) M_i^v - 2 \langle g^{(1)}, g^{(2)} \rangle \left(y^* M_i^v + v_i^* M^y - y^* v_i^* M \right)$$

$$\quad - |g^{(2)}|^2 \left(2 y^* \int_V \int_Y (v_i - v_i^*)(y - y^*) m \, dy \, dv \right.$$

$$\quad \left. + 2 y^* \int_V \int_Y (v_i^* y + v_i y^*) m \, dy \, dv - 2 y^* \int_V \int_Y y^* v_i^* m \, dy \, dv - (y^*)^2 M_i^v \right)$$

$$= \left(1 - |g^{(1)}|^2 - 2 \langle g^{(1)}, g^{(2)} \rangle y^* - |g^{(2)}|^2 (y^*)^2 \right) M_i^v$$

$$\quad + \left(-2 \langle g^{(1)}, g^{(2)} \rangle v_i^* - 2 |g^{(2)}|^2 y^* v_i^* \right) M^y$$

$$\quad + \left(2 \langle g^{(1)}, g^{(2)} \rangle v_i^* y^* + 2 |g^{(2)}|^2 (y^*)^2 v_i^* \right) M.$$

Hence, we find the equation

$$\partial_t M_i^v + \nabla_x \cdot (v^* M_i^v + v_i^* M^v - v_i^* v^* M) + \frac{a_2}{\mu_P} \left(M_i^v - g_i^{(1)} M - g_i^{(2)} M^y \right)$$

$$= -\alpha_1 \left(1 - |g^{(1)}|^2 - 2 \langle g^{(1)}, g^{(2)} \rangle y^* - |g^{(2)}|^2 (y^*)^2 \right) M_i^v$$

$$\quad - \alpha_1 \left(-2 \langle g^{(1)}, g^{(2)} \rangle v_i^* - 2 |g^{(2)}|^2 y^* v_i^* \right) M^y$$

$$\quad - \alpha_1 \left(2 \langle g^{(1)}, g^{(2)} \rangle v_i^* y^* + 2 |g^{(2)}|^2 (y^*)^2 v_i^* \right) M.$$

$$(2.52)$$

for $i = 1, 2, \ldots$. Together, (2.48) - (2.52) form a closed macroscopic system.

Upscaling

In this section we derive single macroscopic equations for M and P from system (2.48) - (2.52) by scaling methods. We proceed analogously to subsection 2.1.5. Additionally to the parameter values presented there, we need estimates on α_1, α_2. Since no specific data are available, we simply assume that the decision to switch between migrating and proliferating state is made about once during

the time of a cell cycle. Hence, due to the chosen non-dimensionalization we find $\alpha_1, \alpha_2 \sim 1$. Applying the parameter estimates of section 2.1.5 to the equations (2.48) - (2.52), we find

$$\partial_t M + \nabla_x \cdot M^v = - \left(-|g^{(1)}|^2 + (y^*)^2 |g^{(2)}|^2 \right) (\alpha_2 P + \alpha_1 M)$$
$$+ \left(2\langle g^{(1)}, g^{(2)} \rangle + 2y^* |g^{(2)}|^2 \right) (\alpha_2 P^y + \alpha_1 M^y) - \alpha_1 M,$$

$$(2.53)$$

$$\partial_t P = \frac{1-C}{1+h} \left((1-2y^*) P^y + (y^*)^2 P \right) + \left(-|g^{(1)}|^2 + (y^*)^2 |g^{(2)}|^2 \right) (\alpha_2 P + \alpha_1 M)$$
$$- \left(2\langle g^{(1)}, g^{(2)} \rangle + 2y^* |g^{(2)}|^2 \right) (\alpha_2 P^y + \alpha_1 M^y) + \alpha_1 M,$$

$$(2.54)$$

$$\epsilon \partial_t M^y + \epsilon \nabla_x \cdot (y^* M^v + v^* M^y - y^* v^* M) + ((\kappa Q + 1) M^y - \kappa Q M)$$
$$= - \epsilon \left(2\langle g^{(1)}, g^{(2)} \rangle (y^*)^2 + 2|g^{(2)}|^2 (y^*)^3 \right) (\alpha_1 M + \alpha_2 P)$$
$$+ \epsilon \left(|g^{(1)}|^2 + 4\langle g^{(1)}, g^{(2)} \rangle y^* + 3|g^{(2)}|^2 (y^*)^2 \right) (\alpha_1 M^y + \alpha_2 P^y) - \epsilon \alpha_1 M^y,$$

$$(2.55)$$

$$\epsilon \partial_t P^y + ((\kappa Q + 1) P^y - \kappa Q P)$$
$$= \epsilon \frac{1-C}{1+h} y^* (P^y - 2y^* P^y + (y^*)^2 P)$$
$$+ \epsilon \left(2\langle g^{(1)}, g^{(2)} \rangle (y^*)^2 + 2|g^{(2)}|^2 (y^*)^3 \right) (\alpha_1 M + \alpha_2 P)$$
$$- \epsilon \left(|g^{(1)}|^2 + 4\langle g^{(1)}, g^{(2)} \rangle y^* + 3|g^{(2)}|^2 (y^*)^2 \right) (\alpha_1 M^y + \alpha_2 P^y) + \epsilon \alpha_1 M^y,$$

$$(2.56)$$

$$\epsilon \partial_t M_i^v + \epsilon \nabla_x \cdot (v^* M_i^v + v_i^* M^v - v_i^* v^* M) + \left(M_i^v - g_i^{(1)} M - g_i^{(2)} M^y \right)$$
$$= - \epsilon \left(1 - |g^{(1)}|^2 - 2\langle g^{(1)}, g^{(2)} \rangle y^* - |g^{(2)}|^2 (y^*)^2 \right) \alpha_1 M_i^v$$
$$+ \epsilon \left(2\langle g^{(1)}, g^{(2)} \rangle v_i^* + 2|g^{(2)}|^2 y^* v_i^* \right) \alpha_1 M^y$$
$$+ \epsilon \left(-2\langle g^{(1)}, g^{(2)} \rangle y^* v_i^* - 2|g^{(2)}|^2 (y^*)^2 v_i^* \right) \alpha_1 M.$$

$$(2.57)$$

Again, we consider Hilbert expansions

$$M = M_0 + \epsilon M_1 + ...,$$
$$P = P_0 + \epsilon P_1 + ...,$$
$$M^y = M_0^y + \epsilon M_1^y + ...,$$
$$P^y = P_0^y + \epsilon P_1^y + ...,$$
$$M^v = M_0^v + \epsilon M_1^v + ...,$$

plug this into (2.53)-(2.57) and sort by orders of ϵ. From equations (2.55) and (2.56) we deduce by collecting leading order terms

$$(\kappa Q + 1) M_0^y = \kappa Q M_0 \quad \Rightarrow \quad M_0^y = \frac{\kappa Q}{\kappa Q + 1} M_0 = y^* M_0 \qquad (2.58)$$

and

$$(\kappa Q + 1)P_0^y = \kappa Q P_0 \quad \Rightarrow \quad P_0^y = \frac{\kappa Q}{\kappa Q + 1} P_0 = y^* P_0. \qquad (2.59)$$

Equation (2.57) yields

$$M_{0_i}^v - g_i^{(1)} M_0 - g_i^{(2)} M_0^y = 0,$$

where $g_i^{(j)} = g_i^{(j)}(M_0)$, $j = 1, 2$. Plugging in (2.58) we find

$$M_{0_i}^v = (g_i^{(1)} + y^* g_i^{(2)})M_0 = g_i(y^*)M_0. \qquad (2.60)$$

Collecting zero order terms in (2.53) and using (2.58) and (2.60), we find

$$\partial_t M_0 + \nabla_x \cdot (g(y^*)M_0) = |g(y^*)|^2 (\alpha_1 M_0 + \alpha_2 P_0) - \alpha_1 M_0, \qquad (2.61)$$

where

$$g(y^*) = \frac{a_1}{a_2 s_{max}}(1 - C_0)\mathbb{D}_W b(y^*),$$

$$b(y^*) = (1 - \rho_1 - \rho_2)\frac{-\nabla h}{\sqrt{1 + |\nabla h|^2}} + \rho_1(1 - y^*)\frac{\nabla Q}{\sqrt{1 + |\nabla Q|^2}} + \rho_2 \frac{-\nabla C_0}{\sqrt{1 + |\nabla C_0|^2}},$$

$$C_0 = M_0 + P_0.$$

Analogously, we collect zero order terms in (2.54) and, using (2.59), we find

$$\partial_t P_0 = G_P(h, y^*)(1 - C_0)P_0 - |g(y^*)|^2 (\alpha_2 P_0 + \alpha_1 M_0) + \alpha_1 M_0, \qquad (2.62)$$

$$\text{with} \quad G_P(h, y^*) = \frac{y^* - (y^*)^2}{1 + h}.$$

Choosing boundary conditions in correspondence to subsection 2.1.5, and dropping the indices in M_0 and P_0, we summarize the full macroscopic system:

Model 2.3: Go-or-grow

$$\partial_t M + \nabla_x \cdot (g(h, Q, M, P, y^*)M)$$
$$= |g(h, Q, M, P, y^*)|^2 (\alpha_1 M + \alpha_2 P) - \alpha_1 M \qquad \text{in } \mathbb{R}^+ \times \Omega, \quad (2.63a)$$

$$\partial_t P = G_P(h, y^*)(1 - M - P)P$$
$$- |g(h, Q, M, P, y^*)|^2 (\alpha_1 M + \alpha_2 P) + \alpha_1 M \qquad \text{in } \mathbb{R}^+ \times \Omega, \quad (2.63b)$$

$$\partial_t Q = \mu_Q Q(1 - Q) - \delta_Q \frac{h}{1 + h}Q \qquad \text{in } \mathbb{R}^+ \times \bar{\Omega}, \quad (2.63c)$$

$$\partial_t h = D_h \Delta h + \mu_h(1 - h)\frac{P}{1 + P} - \delta_h h e \qquad \text{in } \mathbb{R}^+ \times \Omega, \quad (2.63d)$$

$$\partial_t e = D_e \Delta e - \varsigma_e \nabla_x \cdot (e(1 - e)\nabla_x h)$$
$$+ G_e(h, P)e(1 - e) \qquad \text{in } \mathbb{R}^+ \times \Omega, \quad (2.63e)$$

---

with

$$g(h, Q, M, P, y^*) = \frac{a_1}{a_2 s_{max}}(1 - M - P)\mathbb{D}_W b(h, Q, M, P, y^*), \qquad (2.64\text{a})$$

$$b(h, Q, M, P, y^*) = (1 - \rho_1 - \rho_2)\frac{-\nabla h}{\sqrt{1 + |\nabla h|^2}} + \rho_1(1 - y^*)\frac{\nabla Q}{\sqrt{1 + |\nabla Q|^2}}$$
$$+ \rho_2 \frac{-\nabla(M + P)}{\sqrt{1 + |\nabla(M + P)|^2}},$$
$$\qquad (2.64\text{b})$$

$$G_P(h, y^*) = \frac{y^* - (y^*)^2}{1 + h}, \qquad (2.64\text{c})$$

$$G_e(h, P) = \mu_e \frac{hP}{1 + hP}, \qquad (2.64\text{d})$$

$$y^* = \frac{\kappa Q}{1 + \kappa Q}, \qquad (2.64\text{e})$$

boundary conditions

$$g(h, Q, M, P, y^*)M \cdot \nu = 0 \quad \text{on } \partial\Omega,\, t > 0, \qquad (2.65\text{a})$$
$$\nabla h \cdot \nu = 0 \quad \text{on } \partial\Omega,\, t > 0, \qquad (2.65\text{b})$$
$$(D_e \nabla e - \varsigma_e e(1 - e\nabla h)) \cdot \nu = 0 \quad \text{on } \partial\Omega,\, t > 0, \qquad (2.65\text{c})$$

and nonnegative initial data

$$M(0, x) = M_0(x),\ P(0, x) = P_0(x),$$
$$h(0, x) = h_0(x),\ e(0, x) = e_0(x) \qquad \text{for } x \in \Omega, \qquad (2.66\text{a})$$
$$Q(0, x) = Q_0(x) \qquad\qquad\qquad \text{for } x \in \bar{\Omega}, \qquad (2.66\text{b})$$

bounded by their carrying capacities, i.e.

$$0 \le M_0(x), P_0(x), M_0(x) + P_0(x), Q_0(x), h_0(x), e_0(x) \le 1.$$

2.4 Therapy approaches

There are several possible therapy approaches to slow down the spread of a glioma. The most common one is a combination of surgical resection with radiation and/or classical chemotherapy. There already exists a variety of models for radiation and chemotherapy, see for example [32, 49, 64]. Therefore, we want to focus on a different therapy approach. Gliadel Wafers are a locally acting form of chemotherapy for which only few mathematical models exist [5, 23].

We will start this section by introducing a model for therapy by gliadel wafers, which refines and expands the model presented by Fleming et al in [23]. From the mesoscopic modeling we will derive a macroscopic system based on the one obtained in section 2.1, now containing therapy terms and a reaction diffusion equation for the chemotherapeutic agent.
A simple modeling approach for classical chemotherapy is shortly introduced, so that in the simulations in chapter 4 we can compare the effects of gliadel

wafers with classical chemotherapy.

2.4.1 Gliadel wafers

Gliadel wafers are biodegradable polymers containing the chemotherapeutic agent carmustine. Placed around the cavity after surgical resection of the tumor, the carmustine bound in the polymer matrix starts to solute after a short time and diffuses into the surrounding tissue and cavity [23]. The advantage when compared to classical chemotherapy lies in the local action of the agent and circumvention of the need to cross the blood brain barrier [2]. For patients with recurrent glioblastoma, it is indicated as additional therapy to surgical resection [1, 2].

Modeling

Let C be the concentration of soluted carmustine. Then the diffusion process was described by Fleming et al [23] as

$$C_t = D\Delta C - \delta_C C.$$

Here, D is a diffusion constant and δ_C is the decay rate of carmustine. There are two major drawbacks of this model: First, the model contains no source term describing the release of carmustine from the wafers. Second, the model neglects the brain structure. Therefore, we change the model by adding a source term $r(C)$, which is specified later on, and by replacing the diffusion constant D by a multiple $D_C\mathbb{D}_W$ of the water diffusion tensor.
Furthermore, in the model by Fleming et al the decay rate δ_C is assumed to be a constant. Since we explicitly model angiogenesis, we can include the information about vascularization into the decay term, modeling removal of the drug by the blood stream as well as chemical decay. Taking all these into account, we make the following ansatz for the description of carmustine concentration dynamics:

$$C_t = D_C\nabla \cdot (\mathbb{D}_W\nabla C) - \delta_C(e)C + r(C). \tag{2.67}$$

The decay and source terms are chosen as follows:

- **Modeling of the decay rate $\delta_\mathbf{C}(\mathbf{e})$** : In the model for drug decay we want to take into account two effects: first, the removal of drug from the brain via the blood stream across the blood-brain-barrier, and second, chemical decay. This leads to the following expression:

$$\delta_C(e) = k_{bbb}e + k_d.$$

- **Modeling of the source term $\mathbf{r}(\mathbf{C})$** : For the source term we have to model dissolution of the drug from the gliadel wafer. According to [23], the ratio of dissoluted carmustine and carmustine in total is given by

$$\frac{C_{\text{dissoluted}}}{C_{\text{total}}} = 4\sqrt{\frac{D_{\text{eff}}t}{\pi L^2}}, \text{ as long as } \frac{C_{\text{dissoluted}}}{C_{\text{total}}} \leq 0.6,$$

where D_{eff} is the effective diffusion coefficient of carmustine in the polymer matrix of the wafer and L is the half-thickness of the polymer disc. In the
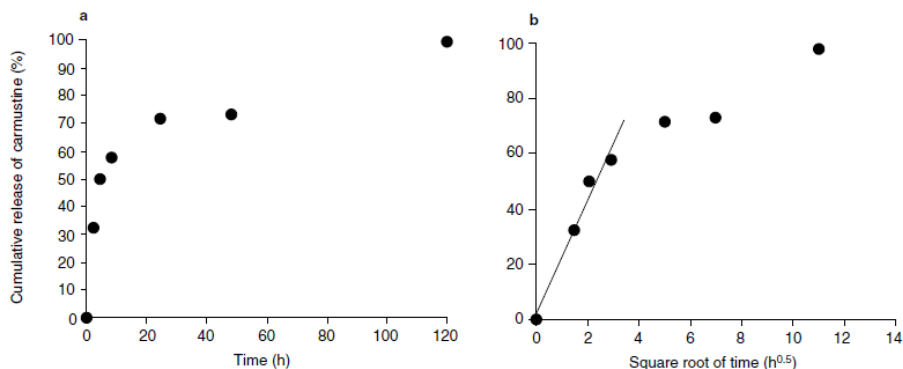
Figure 2.1: In vivo release kinetics of carmustine from GLIADEL® wafers in normal rat brains. (a) Cumulative amount of carmustine (% of total loaded) released as a function of implantation time. (b) Cumulative amount of carmustine (% of total loaded) released as a function of the square root of time; the solid line is a linear fit to the data points (figure and description from [23] with permission from Springer Nature, original data from [17] with permission from Elsevier).

paper of Fleming and Saltzman it remains unclear, what happens after dissolution of 60% of carmustine. An exponential growth, abruptly stopping when the polymer is completely soluted, is proclaimed, this assumption being based on only three data points. Beside the assumption of exponential growth, the measured curve has to be interpreted carefully. The data, which are illustrated in figure 2.1 by [23], were produced by Dang et al in [17]. They measured the concentration of dissolved carmustine dispersed in the brain, not the concentration of dissolved carmustine in the wafer itself (which is the concentration of interest). As was already mentioned in [17], the square-root-like behavior suggests a diffusive process. Therefore, it stands to reason that about 60% of the contained carmustine can be interpreted as more or less freely diffusive substance. The remaining carmustine $C_{\text{remaining}}$ is released from the wafer as the polymer matrix degrades [17, 23, 58]. The degradation of the polymer matrix is an autocatalytic process [58]. Assuming that the wafer is homogenous and thus the release of catalytic enzymes and carmustine during degradation of the wafer are proportional, we obtain

$$r(C) = aC_{\text{remaining}}C. \qquad (2.68)$$

Let $C_{\text{total}}(x)$ be the amount of carmustine contained (in bound or dissoluted form) in the wafer at position x at $t = 0$. It is important to note that in general $C_{\text{remaining}}(t,x) \neq C_{\text{total}}(x) - C(t,x)$ due to the diffusivity of C. Instead, we have to introduce an additional equation for the remaining concentration of carmustine. The remaining concentration is bound in the wafer's polymer matrix and does not diffuse. Hence, we obtain the ODE

$$\partial_t C_{\text{remaining}} = -aC_{\text{remaining}}C,$$

which can be solved explicitly by

$$C_{\text{remaining}}(t,x) = C_{\text{remaining}}(0,x)e^{-a\int_0^t C(s,x)\,\mathrm{d}s} = \frac{2}{5}C_{\text{total}}(x)e^{-a\int_0^t C(s,x)\,\mathrm{d}s}.$$

Hence, we find

$$\partial_t C = D_C\nabla\cdot(\mathbb{D}_W\nabla C) - \delta_C(e)C + \frac{2a}{5}CC_{\text{total}}(x)e^{-a\int_0^t C(s,x)\,\mathrm{d}s},$$
(2.69)

$$C(0,x) = \frac{3}{5}C_{\text{total}}(x).$$
(2.70)

Let Ω_W denote the domain, where the wafer is placed. Then it is nearby to set

$$C_{\text{total}}(x) = \tilde{C}_{\text{total}}\cdot\mathbb{1}_{\Omega_W}.$$
(2.71)

It can be assumed that the wafers boundary is not completely sharp. Hence, we smoothen $C_{\text{total}}(x)$ from above and replace (2.71) by

$$C_{\text{total}}(x) = \tilde{C}_{\text{total}}\cdot\mathbb{1}_{\Omega_W}*j(x),$$
(2.72)

where

$$j(x) = \frac{c}{q^N}\exp\left(-\frac{1}{1-\left|\frac{x}{q}\right|^2}\right).$$

The smaller the choice of $0 < q < 1$, the sharper the boundary is. The constant c has to satisfy $\int_{[-q,q]^N} j(x)\,\mathrm{d}x = 1$.

Finally, it remains to model the influence of carmustine on the cancer cell population and the surrounding tissue.
The simplest way to model chemotherapeutic effects is saturated decay with some decay rate δ_M for tumor degradation and a decay rate δ_{QC} for tissue degradation, respectively, leading to reaction terms of the form $-\delta_M\frac{C}{K_C+C}M$ in the M-equation and $-\delta_{QC}\frac{C}{K_C+C}Q$ in the Q-equation. As carmustine kills cells in a specific phase of the cell cycle, it exclusively effects proliferating cells [45]. Starting the modeling on the mesoscopic scale, we can refine the degradation term for tumor cells by taking into account this dependence of drug efficiency on the proliferative activity. This kind of dependence was modeled for example by [49], where tumor cells were divided into proliferating and migrating (hence non-proliferating) subpopulations. In the current model we do not define tumor subpopulations but still assume that the efficiency of the drug depends on proliferative activity, which in turn depends on the migrational speed of the cells (see section 2.1.2). Hence, in the above reaction term for the M-equation we choose δ_M not to be a constant but to depend on cell speed s. Same as in subsection 2.1.2, we simplify by using the quasi-steady state s^* instead of s. We choose

$$\delta_M(s^*) = \sigma\frac{s_{max}-s^*}{s_{max}}.$$

Furthermore, we incorporate the fact that high cell concentrations impede proliferation, by adding the factor $\left(1-\frac{M}{K_M}\right)$. On the mesoscopic level, this leads

to the reaction term $-\delta_M(s^*)\left(1 - \frac{M}{K_M}\right)\frac{C}{K_C+C}p$ in the mesoscopic equation for p, hence

$$\frac{\partial p}{\partial t} + \nabla_x \cdot (vp) + \frac{\partial}{\partial y}(G(y,Q)p) + \nabla_v \cdot (S(v,y,h,Q,M)p)$$
$$= \beta(y,p,h,M,s^*) - \delta_M(s^*)\left(1 - \frac{M}{K_M}\right)\frac{C}{K_C+C}p, \tag{2.73}$$

where all coefficient functions are chosen as in section 2.1.

Non-dimensionalization and Scaling

We non-dimensionalize equations (2.69), (2.4) complemented by the above reaction term for Q, and (2.73) analogously to subsection 2.1.4, further choosing $K_C = \max_{x \in \bar{\Omega}} C_{\text{total}}(x)$, $\hat{a} = \frac{aK_C}{\mu_M}$, $\hat{C}_{\text{total}} = \frac{C_{\text{total}}}{K_C}$, $\hat{C} = \frac{C}{K_C}$, $\hat{D}_C = \frac{\mu_M}{s_{max}^2}D_C$, $\hat{k}_{bbb} = \frac{k_{bbb}K_e}{\mu_M}$, $\hat{k}_d = \frac{k_d}{\mu_M}$, $\hat{\sigma} = \frac{\sigma}{\mu_M}$, $\hat{\mu}_Q = \frac{\mu_Q}{\mu_M}$, $\hat{\delta}_Q = \frac{\delta_Q}{\mu_M}$, $\hat{\delta}_{QC} = \frac{\delta_{QC}}{\mu_M}$, and - dropping the hats - obtain

$$\partial_t C = D_C \nabla \cdot (\mathbb{D}_W \nabla C) - (k_{bbb}e + k_d)C + \frac{2a}{5}C_{\text{total}}(x)Ce^{-a\int_0^t C(s,x)\,\mathrm{d}s}, \tag{2.74}$$

$$\partial_t Q = \mu_Q Q(1-Q) - \delta_Q \frac{h}{1+h}Q - \delta_{QC}\frac{C}{1+C}Q \tag{2.75}$$

and

$$\partial_t p + \nabla_x \cdot (vp) + \frac{k^-}{\mu_M}\partial_y(G(y,Q)p) + \frac{a_2}{\mu_M}\nabla_v \cdot (S(v,y,h,Q,M)p)$$
$$= \beta(y,p,h,M,s^*) - \sigma(1-s^*)\frac{C}{1+C}p(1-M).$$

Assuming σ to be of order 1, we repeat the procedure from subsection 2.1.5. Computing moment equations and sorting terms by order of ϵ in the same way, we obtain the macroscopic equation

$$\partial_t M + \nabla_x \cdot (g(h,Q,M,y^*)M)$$
$$= G_M(h,s^*,y^*)M(1-M) - \delta_M(s^*)\frac{C}{1+C}M(1-M), \tag{2.76}$$

where now

$$\delta_M(s^*) = \sigma(1-s^*). \tag{2.77}$$

The model (2.74)-(2.77) is completed by (2.24c),(2.24d),(2.25), (2.26) as well as zero-flux boundary conditions

$$D_C \mathbb{D}_W \nabla C \cdot \nu = 0 \ \text{ on } \partial\Omega, \ t > 0 \tag{2.78}$$

for C, and initial data to be specified later (cf. remark 3.2.6).
We summarize the macroscopic model:

Model 2.4: Therapy by gliadel wafers

$$\partial_t M + \nabla_x \cdot (g(h, Q, M, y^*)M)$$
$$= G_M(h, s^*, y^*)(1 - M)M - \delta_M(s^*)\frac{C}{1 + C}M(1 - M), \tag{2.79a}$$

$$\partial_t Q = \mu_Q Q(1 - Q) - \delta_Q \frac{h}{1 + h}Q - \delta_{QC}\frac{C}{1 + C}Q, \tag{2.79b}$$

$$\partial_t h = D_h \Delta h + \mu_h(1 - h)\frac{M}{1 + M} - \delta_h he, \tag{2.79c}$$

$$\partial_t e = D_e \Delta e - \varsigma_e \nabla_x \cdot (e(1 - e)\nabla_x h) + G_e(h, M)e(1 - e), \tag{2.79d}$$

$$\partial_t C = D_C \nabla \cdot (\mathbb{D}_W \nabla C) - (k_{bbb}e + k_d)C + \frac{2a}{5}C_{\text{total}}(x)Ce^{-a\int_0^t C(s,x)\,\mathrm{d}s} \tag{2.79e}$$

in $\mathbb{R}^+ \times \Omega$ (in $\mathbb{R}^+ \times \bar{\Omega}$ for equation (2.79b)), with

$$g(h, Q, M, y^*) = \frac{a_1}{a_2 s_{max}}(1 - M)\mathbb{D}_W b(h, Q, M, y^*), \tag{2.80a}$$

$$b(h, Q, M, y^*) = (1 - \rho_1 - \rho_2)\frac{-\nabla h}{\sqrt{1 + |\nabla h|^2}} + \rho_1(1 - y^*)\frac{\nabla Q}{\sqrt{1 + |\nabla Q|^2}}$$
$$+ \rho_2 \frac{-\nabla M}{\sqrt{1 + |\nabla M|^2}}, \tag{2.80b}$$

$$G_M(h, s^*, y^*) = \frac{(1 - s^*)(y^* - (y^*)^2)}{1 + h}, \tag{2.80c}$$

$$\delta_M(s^*) = \sigma(1 - s^*), \tag{2.80d}$$

$$G_e(h, M) = \mu_e \frac{hM}{1 + hM}, \tag{2.80e}$$

$$s^* = |g(h, Q, M, y^*)|, \tag{2.80f}$$

$$y^* = \frac{\kappa Q}{1 + \kappa Q}, \tag{2.80g}$$

boundary conditions

$$g(h, Q, M, y^*)M \cdot \nu = 0 \quad \text{on } \partial\Omega, t > 0, \tag{2.81a}$$
$$D_h \nabla h \cdot \nu = 0 \quad \text{on } \partial\Omega, t > 0, \tag{2.81b}$$
$$(D_e \nabla e - \varsigma_e e(1 - e)\nabla h) \cdot \nu = 0 \quad \text{on } \partial\Omega, t > 0, \tag{2.81c}$$
$$D_C \mathbb{D}_W \nabla C \cdot \nu = 0 \quad \text{on } \partial\Omega, t > 0, \tag{2.81d}$$

and nonnegative initial data

$$M(0, x) = M_0(x), \; h(0, x) = h_0(x),$$
$$e(0, x) = e_0(x), \; C(0, x) = \frac{3}{5}C_{\text{total}}(x) \qquad \text{for } x \in \Omega, \tag{2.82a}$$
$$Q(0, x) = Q_0(x) \qquad \text{for } x \in \bar{\Omega}, \tag{2.82b}$$

bounded by their carrying capacities, i.e.

$$0 \leq M_0(x), Q_0(x), h_0(x), e_0(x) \leq 1.$$

2.4.2 Classical chemotherapy

Surgery with subsequent radiation and/or chemotherapy with temozolomide is the standard treatment of glioblastoma [51]. There are different concepts for chemotherapy planning. Patients treated with so called maximum tolerated dose are given high doses of chemotherapeutic agent followed by some drug-free interval for regeneration before the next high-level dose is administered. In metronomic chemotherapy, a low dose of chemotherapeutic agent is administered frequently without drug-free breaks. In the standard scheme for chemotherapy, recommended i.e. by the University Medical Center Munich, a metronomic chemotherapy with daily doses of temozolomide is administered for about six weeks, followed by six cycles of maximum tolerated dose (one cycle consisting of five consecutive days of high daily doses followed by a break of 23 days) [66]. Still, the best way to dose chemotherapy is yet unclear. There are several studies analyzing the effects of different dosing schemes beyond standard therapy. Beside studies about the effect of metronomic chemotherapy (e.g. [34, 37, 60, 71]) with different results regarding prolongation of life time, also further schemes are analyzed (e.g. one week of daily doses and one week of break in turn [26, 73]).

For modeling, up to some parameter values there is no difference between these schemes. Although metronomic chemotherapy is also called continuous chemotherapy, there are of course still time intervals between the administration of drug, even though smaller than in the case of maximum tolerated dose treatment. The difference between the schemes lies in the time interval between administration of drugs and the given dose. Hence, it is sufficient to set up one model. We will show simulation results for both maximum tolerated dose and metronomic scheme in chapter 4.

Modeling

The chemotherapeutic agent is transported to the brain by blood vessels. Assuming that it can be further transported by diffusion outside the blood vessels, we make the following ansatz:

$$\frac{\partial C}{\partial t} = D_C \nabla \cdot (\mathbb{D}_W \nabla C) + s(t)e - d_C C.$$

Here, $s(t)$ describes the administration of the drug and d_C denotes its decay. Drug is administered at fixed times $t_1 < t_2 < ... < t_n$. Assuming an oral administration, according to the absorption curves measured in [6] we model the dose given at time t_i by

$$s_i(t) = \begin{cases} d_i e^{-\frac{\sigma_i}{b_i^2 - (t_i - t)^2}} & \text{for } |t_i - t| < b_i, \\ 0 \text{ otherwise,} \end{cases}$$

where b_i is the time span in which the brain obtains new drug during a single administration (for example this could be the time needed for absorption of the

drug substance from a temozolomide tablet), and σ_i is chosen such that

$$\int_{-b_i+t_i}^{b_i+t_i} e^{-\frac{\sigma_i}{b_i^2-(t_i-t)^2}} = 1.$$

Then the source term s is given by

$$s(t) = \frac{1}{K_e} \sum_{i=1}^{n} s_i(t).$$

Compared to metronomic therapy, the administered doses d_i and the differences between the t_i are larger for therapy with maximum tolerated dose.

The effect of chemotherapy on the tumor and the surrounding tissue is modeled as in section 2.4.1, with possibly different decay rates σ, δ_{QC} due to the different chemotherapeutic agents, leading on the macroscopic level to the reaction rates $-\delta_M(s^*)\frac{C}{K_C+C}M$ with $\delta_M(s^*) = \sigma(1-s^*)$ for the M-equation and $-\delta_{QC}\frac{C}{K_C+C}Q$ for the Q-equation.

Non-dimensionalization and scaling

Choosing $\hat{d}_C = \frac{d_C}{\mu_M}$, $\hat{d}_i = \frac{d_i}{\mu_M K_C}$, $\hat{b}_i = b_i\mu_M$, $\hat{\sigma}_i = \sigma_i\mu_M^2$, $\hat{t}_i = t_i\mu_M$ additionally to the notations for non-dimensionalization in subsection 2.4.1, we obtain in complete analogy to subsection 2.4.1 the following macroscopic system via scaling methods:

Model 2.5: Classical chemotherapy

$$\partial_t M + \nabla_x \cdot (g(h, Q, M, y^*)M)$$
$$= G_M(h, s^*, y^*)(1 - M)M - \delta_M(s^*)\frac{C}{1+C}M(1 - M), \tag{2.83a}$$

$$\partial_t Q = \mu_Q Q(1 - Q) - \delta_Q \frac{h}{1+h}Q - \delta_{QC}\frac{C}{1+C}Q, \tag{2.83b}$$

$$\partial_t h = D_h \Delta h + \mu_h(1 - h)\frac{M}{1+M} - \delta_h he, \tag{2.83c}$$

$$\partial_t e = D_e \Delta e - \varsigma_e \nabla_x \cdot (e(1 - e)\nabla_x h) + G_e(h, M)e(1 - e), \tag{2.83d}$$

$$\partial_t C = D_C \nabla(\mathbb{D}_W \nabla C) + s(t)e - d_C C \tag{2.83e}$$

in $\mathbb{R}^+ \times \Omega$ (in $\mathbb{R}^+ \times \bar{\Omega}$ for equation (2.83b)), with

$$g(h, Q, M, y^*) = \frac{a_1}{a_2 s_{max}}(1 - M)\mathbb{D}_W b(h, Q, M, y^*), \tag{2.84a}$$

$$b(h, Q, M, y^*) = (1 - \rho_1 - \rho_2)\frac{-\nabla h}{\sqrt{1+|\nabla h|^2}} + \rho_1(1 - y^*)\frac{\nabla Q}{\sqrt{1+|\nabla Q|^2}}$$
$$+ \rho_2 \frac{-\nabla M}{\sqrt{1+|\nabla M|^2}}, \tag{2.84b}$$

$$G_M(h, s^*, y^*) = \frac{(1 - s^*)(y^* - (y^*)^2)}{1 + h}, \tag{2.84c}$$

$$\delta_M(s^*) = \sigma(1 - s^*), \tag{2.84d}$$

$$G_e(h, M) = \mu_e \frac{hM}{1 + hM}, \tag{2.84e}$$

$$s(t) = \sum_{i=1}^{n} s_i(t), \; s_i(t) = \begin{cases} d_i e^{-\frac{\sigma_i}{b_i^2 - (t_i - t)^2}} & \text{for } |t_i - t| < b_i, \\ 0 \text{ otherwise,} \end{cases} \tag{2.84f}$$

$$s^* = |g(h, Q, M, y^*)|, \tag{2.84g}$$

$$y^* = \frac{\kappa Q}{1 + \kappa Q}, \tag{2.84h}$$

boundary conditions

$$g(h, Q, M, y^*)M \cdot \nu = 0 \quad \text{on } \partial\Omega, \, t > 0, \tag{2.85a}$$

$$D_h \nabla h \cdot \nu = 0 \quad \text{on } \partial\Omega, \, t > 0, \tag{2.85b}$$

$$(D_e \nabla e - \varsigma_e e(1 - e)\nabla h) \cdot \nu = 0 \quad \text{on } \partial\Omega, \, t > 0, \tag{2.85c}$$

$$D_C \mathbb{D}_W \nabla C \cdot \nu = 0 \quad \text{on } \partial\Omega, \, t > 0, \tag{2.85d}$$

and nonnegative initial data

$$\begin{aligned} M(0, x) = M_0(x), \; h(0, x) = h_0(x), \\ e(0, x) = e_0(x), \; C(0, x) = 0 \end{aligned} \qquad \text{for } x \in \Omega, \tag{2.86a}$$

$$Q(0, x) = Q_0(x) \qquad \text{for } x \in \bar{\Omega}, \tag{2.86b}$$

bounded by their carrying capacities, i.e.

$$0 \leq M_0(x), Q_0(x), h_0(x), e_0(x) \leq 1.$$

Chapter 3

Analysis

In this chapter, the models developed in chapter 2 are analyzed regarding the existence of weak solutions. In section 3.1, existence of a global weak solution to a simplified version of the basic model developed in section 2.1 is proven. In section 3.2, this proof is adapted to the model variations presented in sections 2.2 and 2.4.

3.1 Analysis of the basic model

In this section we consider a simplified version of model 2.1 developed in section 2.1. Dropping the flux limitation in the diffusion term of M, we obtain a PDE-ODE system with strongly degenerate diffusion, hapto- and chemotaxis and flux saturation in the taxis terms. The main challenge lies in the degeneracy of the diffusion term, leading to the common regularity problems. In [80, 81, 82, 85, 86], existence of solutions to degenerate diffusion-haptotaxis-systems have been analyzed. Similar to these works, we approximate the problem by a regularized version, additionally decoupling the system in order to handle the flux saturation. By this approximation we obtain nonnegativity and boundedness of the solution by its carrying capacity. The boundedness of the gradient is obtained by splitting the domain into a (time-dependent) part where no degeneracy occurs and a part of degeneracy, proving that the gradient equals zero on the latter domain.

Remark 3.1.1. The problems arising in the original model from flux saturation in the diffusion term of M as well as a possible approach for solving them are addressed in the end of this section (cf. subsection 3.1.5).

We consider the following system:

> ## Model 3.1: Simplified basic model
>
> $$\partial_t Q = \mu_Q Q(1-Q) - \delta_Q \frac{h}{1+h} Q, \tag{3.1a}$$
>
> $$\partial_t h = D_h \Delta h + \mu_h (1-h) \frac{M}{1+M} - \delta_h h e, \tag{3.1b}$$
>
> $$\partial_t e = D_e \Delta e - \varsigma_e \nabla \cdot (e(1-e)\nabla h) + G_e(h, M)e(1-e), \tag{3.1c}$$
>
> $$\partial_t M + \nabla_x \cdot (g(h, Q, M, y^*)M) = G_M(h, s^*, y^*)(1-M)M \tag{3.1d}$$
>
> in $\mathbb{R}^+ \times \Omega$ (in $\mathbb{R}^+ \times \bar{\Omega}$ for equation (3.1a)), where
>
> $$g(h, Q, M, y^*) = \frac{a_1}{a_2 s_{max}} (1-M) \mathbb{D}_W b(h, Q, M, y^*), \tag{3.2a}$$
>
> $$b(h, Q, M, y^*) = (1-\rho_1) \frac{-\nabla h}{\sqrt{1+|\nabla h|^2}} + \rho_1(1-y^*) \frac{\nabla Q}{\sqrt{1+|\nabla Q|^2}} - \rho_2 \nabla M, \tag{3.2b}$$
>
> $$G_M(h, s^*, y^*) = \frac{(1-s^*)(y^* - (y^*)^2)}{1+h}, \tag{3.2c}$$
>
> $$G_e(h, M) = \mu_e \frac{hM}{1+hM}, \tag{3.2d}$$
>
> $$s^* = \left| \frac{a_1}{a_2 s_{max}} (1-M) \mathbb{D}_W \left((1-\rho_1) \frac{-\nabla h}{\sqrt{1+|\nabla h|^2}} \right. \right. $$
> $$\left. \left. + \rho_1(1-y^*) \frac{\nabla Q}{\sqrt{1+|\nabla Q|^2}} \right) \right|, \tag{3.2e}$$
>
> $$y^* = \frac{\kappa Q}{\kappa Q + 1}, \tag{3.2f}$$
>
> with zero flux boundary conditions
>
> $$(g(h, Q, M, y^*)M) \cdot \nu = 0 \qquad \text{on } \partial\Omega, \; t > 0, \tag{3.3a}$$
>
> $$D_h \nabla h \cdot \nu = 0 \qquad \text{on } \partial\Omega, \; t > 0, \tag{3.3b}$$
>
> $$(D_e \nabla e - \varsigma_e e(1-e)\nabla h) \cdot \nu = 0 \qquad \text{on } \partial\Omega, \; t > 0, \tag{3.3c}$$
>
> and initial data
>
> $$Q(0, x) = Q_0(x) \in C^1(\bar{\Omega}) \cap W^{2,2}(\Omega), \quad h(0, x) = h_0(x) \in W^{1,4}(\Omega),$$
> $$e(0, x) = e_0(x) \in W^{1,4}(\Omega), \quad M(0, x) = M_0(x) \in W^{1,4}(\Omega) \tag{3.4}$$
>
> with $Q_0(x), h_0(x), e_0(x), M_0(x) \in [0, 1]$ for all $x \in \Omega$, and $\nabla Q_0(x) \cdot \nu = 0$ for all $x \in \partial\Omega$, where Ω is a sufficiently smooth bounded domain of $\mathbb{R}^N$ with $N \leq 3$.

Remark 3.1.2. The flux limitation in the original basic model ensured boundedness of s^* by 1. Dropping the flux limitation for the diffusion term, this boundedness is lost. To ensure that the proliferation term G_M is still nonnega-

tive, we simplify s^* by dropping ∇M, hence choosing (3.2e). The proliferation term G_M is the only term affected by this simplification.

Remark 3.1.3. Adapting the initial condition, we could also choose $N > 3$. In this case, for the subsequent proofs to work we have to set $h_0, e_0, M_0 \in W^{1,N+1}(\Omega)$. Since the case $N > 3$ is from a biological point of view not of interest, we stick to $N \leq 3$ for simplicity of writing.

The aim of this section is to prove the existence of a global weak solution to model 3.1:

Theorem 3.1.4. *There exists a global weak solution to system (3.1)-(3.4) in the sense of definition 3.1.5 given below.*

Definition 3.1.5. We call $(Q, h, e, M) : \mathbb{R}_0^+ \times \bar{\Omega} \to [0,1]^4$ a global weak solution to system (3.1)-(3.4), if for all $T \in (0, \infty)$ it holds

$$Q, h \in \mathcal{L}^\infty(0, T; W^{1,2}(\Omega)), \ e, M \in \mathcal{L}^\infty([0, T) \times \Omega) \cap \mathcal{L}^2(0, T; W^{1,2}(\Omega))$$

and

$$-\int_0^T \int_\Omega \phi_t Q \, dx \, dt - \int_\Omega \phi(0, \cdot) Q_0 \, dx \tag{3.5a}$$
$$= \int_0^T \int_\Omega \phi \left(\mu_Q Q(1 - Q) - \delta_Q \frac{h}{1 + h} Q \right) dx \, dt,$$

$$-\int_0^T \int_\Omega \phi_t h \, dx \, dt - \int_\Omega \phi(0, \cdot) h_0 \, dx$$
$$= -\int_0^T \int_\Omega D_h \nabla \phi \cdot \nabla h \, dx \, dt \tag{3.5b}$$
$$+ \int_0^T \int_\Omega \phi \left(\mu_h (1 - h) \frac{M}{1 + M} - \delta_h h e \right) dx \, dt,$$

$$-\int_0^T \int_\Omega \phi_t e \, dx \, dt - \int_\Omega \phi(0, \cdot) e_0 \, dx$$
$$= -\int_0^T \int_\Omega D_e \nabla \phi \cdot \nabla e \, dx \, dt + \int_0^T \int_\Omega \varsigma_e e(1 - e) \nabla \phi \cdot \nabla h \, dx \, dt \tag{3.5c}$$
$$+ \int_0^T \int_\Omega \phi \, G_e(h, M) e(1 - e) \, dx \, dt,$$

$$-\int_0^T \int_\Omega \phi_t M \, dx \, dt - \int_\Omega \phi(0, \cdot) M_0 \, dx$$
$$= \int_0^T \int_\Omega M \nabla \phi \cdot g(h, Q, M, y^*) \, dx \, dt \tag{3.5d}$$
$$+ \int_0^T \int_\Omega \phi \, G_M(h, s^*, y^*) M(1 - M) \, dx \, dt$$

for all $\phi \in C_0^\infty([0, T) \times \Omega)$.

Remark 3.1.6. For the remaining chapter, we will assume that $\mathbb{D}_W(x)$ is positive definite for all $x \in \bar{\Omega}$, and sufficiently smooth. The minimum and maximum eigenvalues of $\mathbb{D}_W(x)$ on $\bar{\Omega}$ are denoted by α_{min} and α_{max}.

The outline of the proof is as follows:

We start by regularizing and decoupling system (3.1) iteratively. For the decoupled system a priori estimates are derived. Next, using theory by Amann [4], we show that there exists a unique classical solution to the decoupled system. Finally, we prove that the constructed sequence of solutions to the decoupled system converges to a weak solution of the original system.

3.1.1 Decoupled and regularized system

We start our existence proof by decoupling and regularizing system (3.1). The decoupling is not complete; basically, we decouple the ODE from the rest of the PDE system and temporarily eliminate the dependency of M on ∇h. The equation for the cancer cells is regularized by an additional diffusion term. Further, we regularize the initial data for Q.

Let Q_1, h_1, e_1, M_1 be some functions in $(C^\infty((0,\infty)\times\bar{\Omega})\cap C([0,\infty)\times\bar{\Omega}))^4$ fulfilling the initial condition (3.4). Let $(Q_0^{(k)})_k$ be a sequence of functions in $C^\infty(\bar{\Omega})$, fulfilling $Q_0^{(k)}(x) \in [0,1]$ for all $x \in \Omega$ and $\nabla Q_0^{(k)}(x) \cdot \nu(x) = 0$ for all $x \in \partial\Omega$, such that $Q_0^{(k)} \to Q_0$ in $C^1(\bar{\Omega})\cap W^{2,2}(\Omega)$. Let $(\epsilon_k)_{k\in\mathbb{N}}$ be a monotone decreasing null sequence with $\epsilon_k \neq 0$ for all k. Then for $k = 2, 3, ...$ we define the following decoupled and regularized system:

$$\partial_t Q_k = \mu_Q Q_k (1 - Q_k) - \delta_Q \frac{h_{k-1}}{1 + h_{k-1}} Q_k, \tag{3.6a}$$

$$\partial_t h_k = D_h \Delta h_k + \mu_h (1 - h_k)\frac{M_k}{1 + M_k} - \delta_h h_k e_k, \tag{3.6b}$$

$$\partial_t e_k = D_e \Delta e_k - \varsigma_e \nabla \cdot (e_k(1 - e_k)\nabla h_k) + G_e(h_k, M_k)e_k(1 - e_k), \tag{3.6c}$$

$$\partial_t M_k + \nabla \cdot (g_k M_k) - \epsilon_k \Delta M_k = G_M(h_{k-1}, s_k^*, y_k^*)M_k(1 - M_k) \tag{3.6d}$$

in $\mathbb{R}^+ \times \Omega$ (in $\mathbb{R}^+ \times \bar{\Omega}$ for equation (3.6a)), where

$$g_k = \frac{a_1}{a_2 s_{max}}(1 - M_k)\mathbb{D}_W b_k, \tag{3.7a}$$

$$b_k = (1 - \rho_1)\frac{-\nabla h_{k-1}}{\sqrt{1 + |\nabla h_{k-1}|^2}} + \rho_1(1 - y_k^*)\frac{\nabla Q_k}{\sqrt{1 + |\nabla Q_k|^2}} - \rho_2 \nabla M_k, \tag{3.7b}$$

$$y_k^* = \frac{\kappa Q_k}{\kappa Q_k + 1}, \tag{3.7c}$$

$$s_k^* = \left| \frac{a_1}{a_2 s_{max}} M_k(1 - M_k)\mathbb{D}_W \left((1 - \rho_1)\frac{-\nabla h_{k-1}}{\sqrt{1 + |\nabla h_{k-1}|^2}} \right.\right.$$
$$\left.\left. + \rho_1(1 - y_k^*)\frac{\nabla Q_k}{\sqrt{1 + |\nabla Q_k|^2}} \right) \right|, \tag{3.7d}$$

with corresponding boundary conditions

$$(g_k M_k - \epsilon_k \nabla M_k) \cdot \nu = 0 \qquad \text{on } \partial\Omega, t > 0, \tag{3.8a}$$

$$D_h \nabla h_k \cdot \nu = 0 \qquad \text{on } \partial\Omega, t > 0, \tag{3.8b}$$

$$(D_e \nabla e_k - \varsigma_e e_k(1 - e_k)\nabla h_k) \cdot \nu = 0 \qquad \text{on } \partial\Omega, t > 0, \tag{3.8c}$$

and fulfilling the initial data in (3.4), but with regularized data for Q_k:

$$Q_k(0,x) = Q_0^{(k)}(x) \in C^\infty(\bar{\Omega}), \quad h_k(0,x) = h_0(x) \in W^{1,4}(\Omega),$$
$$e_k(0,x) = e_0(x) \in W^{1,4}(\Omega), \quad M_k(0,x) = M_0(x) \in W^{1,4}(\Omega) \tag{3.9}$$

with $Q_0^{(k)}(x), h_0(x), e_0(x), M_0(x) \in [0,1]$ for all $x \in \Omega$, and $\nabla Q_0^{(k)}(x) \cdot \nu = 0$ for all $x \in \partial\Omega$.

3.1.2 A priori estimates

In this subsection we want to find a priori estimates on the solutions of the decoupled system.

Lemma 3.1.7. *Let $T > 0$ and*

$$(Q_{k-1}, h_{k-1}, e_{k-1}, M_{k-1}) \in (C^\infty((0,T) \times \bar{\Omega}) \cap C([0,T] \times \bar{\Omega}))^4$$

and let

$$(Q_k, h_k, e_k, M_k) \in (C^\infty((0,T) \times \bar{\Omega}) \cap C([0,T] \times \bar{\Omega}))^4$$

be a corresponding solution to system (3.6)-(3.9). Then there exist constants $c_Q(T), c_h(T), c_e(T), c_M(T), c_{QQ}(T), c_{hh}(T)$, depending on time and initial data only, such that the following implication holds: If $Q_{k-1}, h_{k-1}, e_{k-1}, M_{k-1}$ fulfill

$$0 \le Q_{k-1}, h_{k-1}, e_{k-1}, M_{k-1} \le 1,$$
$$\|\nabla Q_{k-1}\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^4(\Omega))} \le c_Q(T), \quad \|\nabla h_{k-1}\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^4(\Omega))} \le c_h(T),$$
$$\|\nabla e_{k-1}\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \le c_e(T), \quad \|\nabla M_{k-1}\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \le c_M(T),$$
$$\|\Delta Q_{k-1}\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^2(\Omega))} \le c_{QQ}(T), \quad \|\Delta h_{k-1}\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \le c_{hh}(T),$$

then it holds

$$0 \le Q_k, h_k, e_k, M_k \le 1,$$
$$\|\nabla Q_k\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^4(\Omega))} \le c_Q(T), \quad \|\nabla h_k\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^4(\Omega))} \le c_h(T),$$
$$\|\nabla e_k\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \le c_e(T), \quad \|\nabla M_k\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \le c_M(T),$$
$$\|\Delta Q_k\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^2(\Omega))} \le c_{QQ}(T), \quad \|\Delta h_k\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \le c_{hh}(T).$$

Proof.

- **$0 \le \mathbf{Q_k} \le 1$.** Consider equation (3.6a):

$$\partial_t Q_k = \mu_Q Q_k(1 - Q_k) - \delta_Q \frac{h_{k-1}}{1 + h_{k-1}} Q_k.$$

  As by assumption h_{k-1} is nonnegative, $Q_k = 1$ is a supersolution. Furthermore, $Q_k = 0$ is obviously a subsolution. Hence,

$$0 \le Q_k \le 1.$$

- **$0 \leq M_k \leq 1$**. Consider equation (3.6d):

$$\partial_t M_k + \frac{a_1}{a_2 s_{max}} \nabla \cdot (M_k(1 - M_k) \mathbb{D}_W b_k) - \epsilon_k \Delta M_k$$
$$= G_M(h_{k-1}, s_k^*, y_k^*) M_k(1 - M_k).$$

We want to prove $0 \leq M_k \leq 1$. To this aim, we check the assumptions of theorem A.1.6. Denoting the system coefficients a_i, b_i, g from that theorem temporarily by $\tilde{a}_i, \tilde{b}_i, \tilde{g}$ to avoid confusion with the constants a_1, a_2 and the functions b_k, g from our model, we find

$$a_{ij} = \frac{a_1 \rho_2}{a_2 s_{max}} u(1 - u)(\mathbb{D}_W)_{ij} + \epsilon_k I_{ij} \text{ for } i, j = 1, ..., N,$$

$$\tilde{a}_i = \frac{a_1(1 - \rho_1)}{a_2 s_{max}} \frac{1 - u}{\sqrt{1 + \|\nabla h_{k-1}\|^2}} (\mathbb{D}_W \nabla h_{k-1})_i$$
$$- \frac{a_1 \rho_1}{a_2 s_{max}} (1 - y_k^*) \frac{1 - u}{\sqrt{1 + \|\nabla Q_k\|^2}} (\mathbb{D}_W \nabla Q_k)_i \text{ for } i = 1, ..., N,$$

$$a_0 = -y_k^*(1 - y_k^*) \frac{1 - s_k^*}{1 + h_{k-1}} (1 - u),$$

$$\tilde{b}_i = 0 \text{ for } i = 1, ..., N,$$

$$f = 0,$$

$$\tilde{g} = 0.$$

Let $D_0 := (-\frac{1}{2}, \frac{3}{2})$. Then all coefficients of $\mathcal{A}$ and $\mathcal{B}$ in (A.1) are C^∞-smooth w.r.t. x, t and u. Further note, that the set $D \subset D_0$ in (A.2) is nonempty: For example, $\frac{a_1 \rho_2}{a_2 s_{max}} u(1 - u) \mathbb{D}_W + \epsilon_k I$ is positive definite for $u = 0$. Choosing $p = 4$, the condition $\frac{N}{p} < 1 < (1 + \frac{1}{p}) \wedge (2 - \frac{N}{p})$ is fulfilled with $N \leq 3$.

Choosing D_0 as above, we find that the first condition of theorem A.1.6 is fulfilled. The assumptions on f and $\tilde{g}$ are trivially fulfilled. Then due to $u(0, x) = M_0(x) \geq 0$, we conclude $M_k(t, x) = u(t, x) \geq 0$.

To show $M_k(t, x) \leq 1$, we first note that with $u = 1 - M_k$ equation (3.6d) is equivalent to

$$\partial_t u + \frac{a_1}{a_2 s_{max}} \nabla \cdot (u(1 - u) \mathbb{D}_W c_k) - \epsilon_k \Delta u = -G_M(h_{k-1}, s_k^*, y_k^*) u(1 - u)$$

with $c_k = (1 - \rho_1) \frac{\nabla h_{k-1}}{\sqrt{1 + |\nabla h_{k-1}|^2}} + \rho_1(1 - y_k^*) \frac{-\nabla Q_k}{\sqrt{1 + |\nabla Q_k|^2}} - \rho_2 \nabla u$.

Hence, the application of theorem A.1.6 works as described above (the only difference lies in the signs of $\tilde{a}_i$ and a_0), and due to $u(0, x) = 1 - M_0(x) \geq 0$, we conclude $1 - M_k(t, x) = u(t, x) \geq 0$, so $M_k(t, x) \leq 1$.

- **$\|\nabla \mathbf{Q_k}\|_{\mathcal{L}^\infty(\mathbf{0}, \mathbf{T}; \mathcal{L}^4(\mathbf{\Omega}))} \leq \mathbf{c_Q(T)}$**. To find a bound on ∇Q_k, we differentiate equation (3.6a) with respect to x:

$$\frac{\partial}{\partial t}(\nabla Q_k) = \mu_Q(1 - 2Q_k) \nabla Q_k - \delta_Q \frac{h_{k-1}}{1 + h_{k-1}} \nabla Q_k - \delta_Q \frac{\nabla h_{k-1}}{(1 + h_{k-1})^2} Q_k.$$

Multiplication with $|\nabla Q_k|^2 \nabla Q_k$ and integration over Ω yields

$$\frac{1}{4}\frac{\partial}{\partial t}\left(\int_\Omega |\nabla Q_k|^4 \,\mathrm{d}x\right) = \mu_Q \int_\Omega (1-2Q_k)|\nabla Q_k|^4 \,\mathrm{d}x$$
$$- \delta_Q \int_\Omega \frac{h_{k-1}}{1+h_{k-1}}|\nabla Q_k|^4 \,\mathrm{d}x$$
$$- \delta_Q \int_\Omega \frac{Q_k|\nabla Q_k|^2}{(1+h_{k-1})^2}\nabla h_{k-1} \cdot \nabla Q_k \,\mathrm{d}x.$$

Using $0 \le Q_k, h_{k-1} \le 1$ we conclude

$$\left|\frac{\partial}{\partial t}\left(\|\nabla Q_k\|^4_{\mathcal{L}^4(\Omega)}\right)\right| \le 4(\mu_Q + \delta_Q)\|\nabla Q_k\|^4_{\mathcal{L}^4(\Omega)}$$
$$+ 4\delta_Q\|\nabla h_{k-1}\|_{\mathcal{L}^4(\Omega)}\|\nabla Q_k\|^3_{\mathcal{L}^4(\Omega)}$$
$$\le 4(\mu_Q + \delta_Q)\|\nabla Q_k\|^4_{\mathcal{L}^4(\Omega)}$$
$$+ 4\delta_Q c_h(T)(1 + \|\nabla Q_k\|^4_{\mathcal{L}^4(\Omega)}).$$

Then

$$\left|\frac{\partial}{\partial t}\left(\|\nabla Q_k\|^4_{\mathcal{L}^4(\Omega)}\right)\right| \le \left(4(\mu_Q + \delta_Q) + 4\delta_Q c_h(T)\right)\|\nabla Q_k\|^4_{\mathcal{L}^4(\Omega)}$$
$$+ 4\delta_Q c_h(T),$$

and we conclude by Gronwall's inequality

$$\|\nabla Q_k(t,\cdot)\|^4_{\mathcal{L}^4(\Omega)} \le \|\nabla Q_k(0,\cdot)\|^4_{\mathcal{L}^4(\Omega)}e^{(4(\mu_Q+\delta_Q)+4\delta_Q c_h(T))t}$$
$$+ \int_0^t 4\delta_Q c_h(T)e^{(4(\mu_Q+\delta_Q)+4\delta_Q c_h(T))(t-s)} \,\mathrm{d}s$$
$$\le \|\nabla Q_0^{(k)}\|^4_{\mathcal{L}^4(\Omega)}e^{(4(\mu_Q+\delta_Q)+4\delta_Q c_h(T))T}$$
$$+ 4\delta_Q c_h(T)Te^{(4(\mu_Q+\delta_Q)+4\delta_Q c_h(T))T}$$
$$\le c_Q^4(T)$$

for all $t \in (0,T)$ and some constant c_Q independent of k. Hence,

$$\|\nabla Q_k\|_{\mathcal{L}^\infty(0,T;\mathcal{L}^4(\Omega))} \le c_Q(T).$$

- **$0 \le e_k \le 1$.** Consider equation (3.6c):

$$\partial_t e_k = D_e \Delta e_k - \varsigma_e \nabla \cdot (e_k(1-e_k)\nabla h_k) + G_e(h_k, M_k)e_k(1-e_k).$$

To apply theorem A.1.1, we need the equation in non-divergence form:

$$\partial_t e_k = D_e \Delta e_k - \varsigma_e(1-2e_k)\nabla h_k \cdot \nabla e_k + e_k(1-e_k)\left(-\varsigma_e \Delta h_k + G_e(h_k, M_k)\right).$$

Then, due to the C^∞-smoothness of e_k, h_k and M_k, the assumptions of theorem A.1.1 are fulfilled with

$$a_{ij}(t,x) = D_e, \quad a_i(t,x) = \varsigma_e(1-2e_k)\partial_{x_i}h_k$$

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and

$$a(t,x) = -(1 - e_k)\left(-\varsigma_e \Delta h_k + G_e(h_k, M_k)\right)$$
$$= -(1 - e_k)\left(-\varsigma_e \Delta h_k + \mu_e \frac{h_k M_k}{1 + h_k M_k}\right).$$

Hence, we obtain $0 \le e_k$. To show $e_k \le 1$, we set $u = 1 - e_k$, leading to

$$\partial_t u - D_e \Delta u + \varsigma_e(1 - 2e_k)\nabla h_k \cdot \nabla u + e_k u\left(-\varsigma_e \Delta h_k + G_e(h_k, M_k)\right) = 0.$$

Furthermore, for initial data $e_0 \le 1$ we find $u_0 \ge 0$ and the boundary condition for u is given by $\nabla u \cdot \nu = \nabla(1 - e_k) \cdot \nu = 0$ on $\partial\Omega$. Hence, we can again apply theorem A.1.1 to obtain $0 \le u = 1 - e_k$, thus $e_k \le 1$.

- **$0 \le \mathbf{h_k} \le 1$.** Consider equation (3.6b):

$$\partial_t h_k = D_h \Delta h_k + \mu_h(1 - h_k)\frac{M_k}{1 + M_k} - \delta_h h_k e_k.$$

By applying theorem A.1.1, we directly obtain $h_k \ge 0$. $h_k \le 1$ is obtained analogously to $e_k \le 1$: With $u = 1 - h_k$, we find

$$\partial_t u - D_h \Delta u + \mu_h u \frac{M_k}{1 + M_k} + \delta_h e_k u = \delta_h e_k \ge 0.$$

Hence, we can again apply theorem A.1.1 to obtain $0 \le u = 1 - h_k$, thus $h_k \le 1$.

- **$\|\nabla \mathbf{h_k}\|_{\mathcal{L}^\infty((\mathbf{0},\mathbf{T});\mathcal{L}^4(\mathbf{\Omega}))} \le \mathbf{c_h(T)}$.** Consider once more equation (3.6b):

$$\partial_t h_k = D_h \Delta h_k + \mu_h(1 - h_k)\frac{M_k}{1 + M_k} - \delta_h h_k e_k.$$

We want to prove the claimed boundedness of $\|\nabla h_k\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^4)}$ independently of k. For shortness, we set

$$f_k(t,x) = \mu_h(1 - h_k)\frac{M_k}{1 + M_k} - \delta_h h_k e_k.$$

Note that for given functions h_k, e_k and M_k we can interpret f_k as a function of t and x rather than a function of h_k, e_k and M_k. Using the Neumann heat semigroup, we find

$$h_k(t,x) = e^{tD_h\Delta}h_0(x) + \int_0^t e^{(t-s)D_h\Delta}f_k(s,x)\,\mathrm{d}s.$$

Using theorem A.1.10 and the boundedness of f_k, we conclude

$$\|\nabla h_k(t, \cdot)\|_{\mathcal{L}^4(\Omega)}$$

$$\leq \|\nabla \left(e^{tD_h\Delta}h_0(\cdot)\right)\|_{\mathcal{L}^4(\Omega)} + \int_0^t \|\nabla \left(e^{(t-s)D_h\Delta}f_k(s, \cdot)\right)\|_{\mathcal{L}^4(\Omega)} \, \mathrm{d}s$$

$$\leq C_1 e^{-\lambda_1 D_h t}\|\nabla h_0\|_{\mathcal{L}^4(\Omega)}$$

$$+ C_2 \int_0^t (1 + (D_h(t-s))^{-\frac{1}{2}})e^{-\lambda_1(t-s)D_h}\|f_k(s, \cdot)\|_{\mathcal{L}^4(\Omega)} \, \mathrm{d}s$$

$$\leq C_1\|\nabla h_0\|_{\mathcal{L}^4(\Omega)} + C_3 \int_0^t (1 + (D_h(t-s))^{-\frac{1}{2}})e^{-\lambda_1(t-s)D_h} \, \mathrm{d}s$$

$$\leq C_1\|\nabla h_0\|_{\mathcal{L}^4(\Omega)} + C_4(T)$$

$$=: c_h(T),$$

$\lambda_1 > 0$ being the first nonzero eigenvalue of $-\Delta$ under Neumann boundary conditions. Hence,

$$\|\nabla h_k\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^4(\Omega))} \leq c_h(T).$$

- $\|\nabla \mathbf{e_k}\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \leq \mathbf{c_e(T)}$. Now consider again equation (3.6c):

$$\partial_t e_k = D_e\Delta e_k - \varsigma_e\nabla \cdot (e_k(1 - e_k)\nabla h_k) + G_e(h_k, M_k)e_k(1 - e_k).$$

We will use the results obtained so far to prove boundedness of $\|\nabla e_k\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))}$. To this aim, we multiply equation (3.6c) by e_k and integrate over Ω:

$$\frac{1}{2}\partial_t \int_\Omega e_k^2 \, \mathrm{d}x + D_e \int_\Omega |\nabla e_k|^2 \, \mathrm{d}x = \varsigma_e \int_\Omega e_k(1 - e_k)\nabla h_k\nabla e_k \, \mathrm{d}x$$

$$+ \int_\Omega G_e(h_k, M_k)e_k^2(1 - e_k) \, \mathrm{d}x$$

$$\Leftrightarrow \frac{1}{2}\partial_t\|e_k\|_{\mathcal{L}^2(\Omega)}^2 + D_e\|\nabla e_k\|_{\mathcal{L}^2(\Omega)}^2 = \varsigma_e \int_\Omega e_k(1 - e_k)\nabla h_k\nabla e_k \, \mathrm{d}x$$

$$+ \mu_e \int_\Omega \frac{h_k M_k}{1 + h_k M_k}e_k^2(1 - e_k) \, \mathrm{d}x.$$

Next, we integrate with respect to time:

$$\frac{1}{2}\|e_k(\cdot, T)\|_{\mathcal{L}^2(\Omega)}^2 + D_e\|\nabla e_k\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))}^2$$

$$= \frac{1}{2}\|e_k(\cdot, 0)\|_{\mathcal{L}^2(\Omega)}^2 + \varsigma_e \int_0^T \int_\Omega e_k(1 - e_k)\nabla h_k\nabla e_k \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \mu_e \int_0^T \int_\Omega \frac{h_k M_k}{1 + h_k M_k}e_k^2(1 - e_k) \, \mathrm{d}x \, \mathrm{d}t.$$

Young´s inequality yields

$$\frac{1}{2}\|e_k(\cdot,T)\|^2_{\mathcal{L}^2(\Omega)} + D_e\|\nabla e_k\|^2_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))}$$

$$\leq \frac{1}{2}\|e_k(\cdot,0)\|^2_{\mathcal{L}^2(\Omega)}$$

$$+ \varsigma_e\left(\frac{\epsilon}{2}\|\nabla e_k\|^2_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} + \frac{1}{2\epsilon}\|\nabla h_k\|^2_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))}\right) + T|\Omega|\mu_e$$

for arbitrary $\epsilon > 0$. It follows

$$\left(D_e - \frac{\epsilon}{2}\varsigma_e\right)\|\nabla e_k\|^2_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \leq \frac{1}{2}\|e_0\|^2_{\mathcal{L}^2(\Omega)} + \varsigma_e\frac{1}{2\epsilon}\|\nabla h_k\|^2_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))}$$
$$+ T|\Omega|\mu_e.$$

For ϵ small enough, it holds $D_e - \frac{\epsilon}{2}\varsigma_e > 0$, so we can divide by this coefficient to obtain

$$\|\nabla e_k\|^2_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))}$$
$$\leq \left(D_e - \frac{\epsilon}{2}\varsigma_e\right)^{-1}\left(\frac{1}{2}\|e_0\|^2_{\mathcal{L}^2(\Omega)} + \varsigma_e\frac{1}{2\epsilon}\|\nabla h_k\|^2_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} + T|\Omega|\mu_e\right).$$

As $\|\nabla h_k\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^4(\Omega))}$ is bounded independently of k, so is $\|\nabla h_k\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))}$. Hence, $\|\nabla e_k\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \leq c_e(T)$, where $c_e(T)$ is a constant independent of k.

- $\|\nabla \mathbf{M_k}\|_{\mathcal{L}^2((\mathbf{0},\mathbf{T});\mathcal{L}^2(\mathbf{\Omega}))} \leq \mathbf{c_M(T)}$. Consider once more equation (3.6d):

$$\partial_t M_k + \frac{a_1}{a_2 s_{max}}\nabla\cdot(M_k(1-M_k)\mathbb{D}_W b_k) - \epsilon_k\Delta M_k$$
$$= G_M(h_{k-1}, s_k^*, y_k^*)M_k(1-M_k).$$

We have to prove boundedness of the gradient of M_k independently of k. To find a bound independently of ϵ_k, the methods used above cannot be applied here. Instead, let $0 < \delta < \frac{1}{2}$ and define the function

$$f_\delta(M) := \begin{cases} \ln\left(\frac{\delta}{1-\delta}\right) & \text{for } M = 0, \\ f_\delta^{(1)} & \text{for } 0 < M \leq \delta, \\ \ln\left(\frac{M}{1-M}\right) & \text{for } \delta < M < 1-\delta, \\ f_\delta^{(2)} & \text{for } 1-\delta \leq M < 1, \\ \ln\left(\frac{1-\delta}{\delta}\right) & \text{for } M = 1, \end{cases}$$

where

$$f_\delta^{(1)} : (0,\delta] \to \left[\ln\left(\frac{\delta}{1-\delta}\right) - 1, \ln\left(\frac{\delta}{1-\delta}\right)\right] \quad \text{and}$$

$$f_\delta^{(2)} : [1-\delta,1) \to \left[\ln\left(\frac{1-\delta}{\delta}\right), \ln\left(\frac{1-\delta}{\delta}\right) + 1\right]$$

are chosen such that f_δ is sufficiently smooth and satisfies

$$|f_\delta'(M)| \leq \frac{2}{\delta(1-\delta)} \quad \text{and} \quad f_\delta'(M) \geq -1.$$
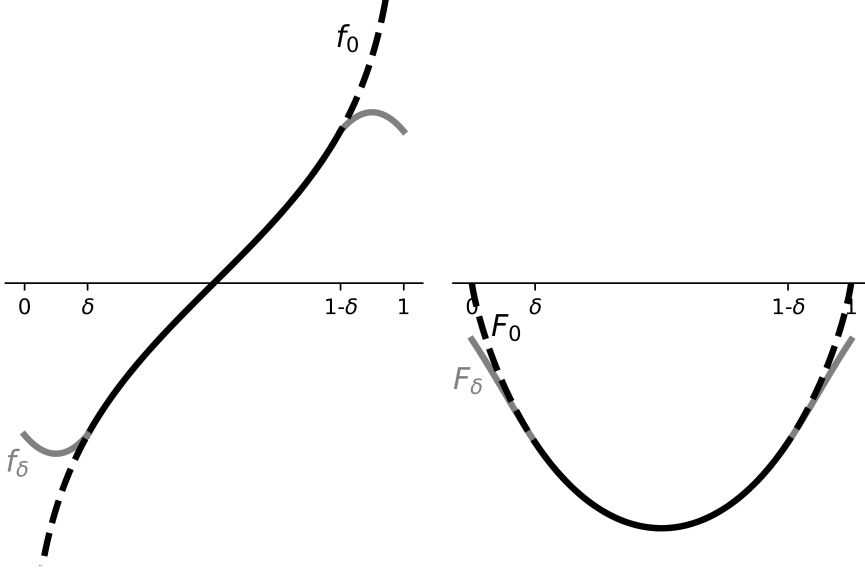
Figure 3.1: Illustration of the functions $f_\delta, f_0, F_\delta, F_0$.

We further define

$$f_0(M) := \ln\left(\frac{M}{1-M}\right) \ \text{ for } \ 0 < M < 1.$$

For an illustration of f_δ and f_0 see figure 3.1. We multiply equation (3.6d) by $f_\delta(M_k)$ and integrate over Ω:

$$\int_\Omega f_\delta(M_k)\partial_t M_k \, \mathrm{d}x + \frac{a_1}{a_2 s_{max}} \int_\Omega f_\delta(M_k)\nabla \cdot (M_k(1-M_k)\mathbb{D}_W b_k) \, \mathrm{d}x$$
$$- \int_\Omega \epsilon_k f_\delta(M_k)\Delta M_k \, \mathrm{d}x$$
$$= \int_\Omega f_\delta(M_k)G_M(h_{k-1}, s_k^*, y_k^*)M_k(1-M_k) \, \mathrm{d}x.$$

For the first term on the left hand side, we find

$$\int_\Omega f_\delta(M_k)\partial_t M_k \, \mathrm{d}x = \int_\Omega \partial_t F_\delta(M_k) \, \mathrm{d}x = \partial_t \int_\Omega F_\delta(M_k) \, \mathrm{d}x,$$

where $F_\delta' = f_\delta$, hence

$$F_\delta(M) = \begin{cases} (1-M)\ln(1-M) + M\ln(M) & \text{for } \delta < M < 1-\delta, \\ \text{smooth and bounded} & \text{otherwise.} \end{cases}$$

F_δ and its limit function F_0, defined later on in this proof, are illustrated in figure 3.1.

Now for each time $t \in (0, T)$, we define a domain where $\delta < M_k < 1 - \delta$:

$$\Omega_\delta^t := \{x \in \Omega : \delta < M_k(t, x) < 1 - \delta\}.$$

The idea is now, to split the integral into an integral over Ω_δ^t and an integral over $\Omega \backslash \Omega_\delta^t$, and to show that the latter converges to zero for $\delta \to 0$:

$$\partial_t \int_\Omega F_\delta(M_k)\,\mathrm{d}x + \frac{a_1}{a_2 s_{max}} \int_{\Omega_\delta^t} f_\delta(M_k) \nabla \cdot (M_k(1-M_k)\mathbb{D}_W b_k)\,\mathrm{d}x$$

$$+ \frac{a_1}{a_2 s_{max}} \int_{\Omega \backslash \Omega_\delta^t} f_\delta(M_k) \nabla \cdot (M_k(1-M_k)\mathbb{D}_W b_k)\,\mathrm{d}x$$

$$- \epsilon_k \int_\Omega f_\delta(M_k) \Delta M_k\,\mathrm{d}x$$

$$= \int_{\Omega_\delta^t} f_\delta(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1-M_k)\,\mathrm{d}x$$

$$+ \int_{\Omega \backslash \Omega_\delta^t} f_\delta(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1-M_k)\,\mathrm{d}x.$$

Partial integration yields

$$\partial_t \int_\Omega F_\delta(M_k)\,\mathrm{d}x - \frac{a_1}{a_2 s_{max}} \int_{\Omega_\delta^t} \nabla M_k \mathbb{D}_W b_k\,\mathrm{d}x + \epsilon_k \int_\Omega f_\delta'(M_k)|\nabla M_k|^2\,\mathrm{d}x$$

$$- \frac{a_1}{a_2 s_{max}} \int_{\Omega \backslash \Omega_\delta^t} M_k(1-M_k)(f_\delta(M_k))' \nabla M_k \cdot \mathbb{D}_W b_k\,\mathrm{d}x$$

$$= \int_{\Omega_\delta^t} f_\delta(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1-M_k)\,\mathrm{d}x$$

$$+ \int_{\Omega \backslash \Omega_\delta^t} f_\delta(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1-M_k)\,\mathrm{d}x.$$

where we used

$$\nabla f_\delta(M_k) = (f_\delta(M_k))' \nabla M_k, \quad (f_\delta(M_k))' = \frac{1}{M_k(1-M_k)} \text{ on } \Omega_\delta^t.$$

Note that the boundary terms on $\partial \Omega_\delta^t \backslash \partial \Omega$ of the second and fourth term, arising from partial integration, cancel each other. Integrating w.r.t. time on the interval $(\gamma, T - \gamma)$ for $\gamma \in (0, \frac{T}{2})$, we obtain

$$\int_\Omega F_\delta(M_k(T-\gamma, \cdot))\,\mathrm{d}x - \int_\Omega F_\delta(M_k(\gamma, \cdot))\,\mathrm{d}x$$

$$- \frac{a_1}{a_2 s_{max}} \int_\gamma^{T-\gamma} \int_{\Omega_\delta^t} \nabla M_k \mathbb{D}_W b_k\,\mathrm{d}x\,\mathrm{d}t$$

$$- \frac{a_1}{a_2 s_{max}} \int_\gamma^{T-\gamma} \int_{\Omega \backslash \Omega_\delta^t} M_k(1-M_k)(f_\delta(M_k))' \nabla M_k \cdot \mathbb{D}_W b_k\,\mathrm{d}x\,\mathrm{d}t$$

$$+ \epsilon_k \int_\gamma^{T-\gamma} \int_\Omega f_\delta'(M_k)|\nabla M_k|^2\,\mathrm{d}x\,\mathrm{d}t$$

$$= \int_\gamma^{T-\gamma} \int_{\Omega_\delta^t} f_\delta(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1-M_k)\,\mathrm{d}x\,\mathrm{d}t$$

$$+ \int_\gamma^{T-\gamma} \int_{\Omega \backslash \Omega_\delta^t} f_\delta(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1-M_k)\,\mathrm{d}x\,\mathrm{d}t.$$

$$(3.10)$$

Now, we aim to take the limit of this equation for $\delta \to 0$. As M_k, h_{k-1} and Q_k are C^∞, it holds

$$\lim_{\delta \to 0} \int_\gamma^{T-\gamma} \int_{\Omega_\delta^t} \nabla M_k \mathbb{D}_W b_k \,\mathrm{d}x \,\mathrm{d}t = \int_\gamma^{T-\gamma} \int_{\Omega_0^t} \nabla M_k \mathbb{D}_W b_k \,\mathrm{d}x \,\mathrm{d}t$$

as well as

$$\lim_{\delta \to 0} \int_\gamma^{T-\gamma} \int_{\Omega_\delta^t} f_\delta(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1 - M_k) \,\mathrm{d}x \,\mathrm{d}t$$
$$= \int_\gamma^{T-\gamma} \int_{\Omega_0^t} f_0(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1 - M_k) \,\mathrm{d}x \,\mathrm{d}t.$$

For the latter, we used the uniform continuity of $f_\delta(M_k)M_k(1-M_k)$ (note that $\ln\left(\frac{M}{1-M}\right) M(1-M)$ converges to 0 for both $M \to 0$ and $M \to 1$). Defining

$$F_0(M) = \begin{cases} (1 - M)\ln(1 - M) + M \ln(M) & \text{for } 0 < M < 1, \\ 0 & \text{otherwise,} \end{cases}$$

we find that $F_\delta \to F_0$ uniformly as $\delta \to 0$, hence

$$\lim_{\delta \to 0} \int_\Omega F_\delta(M_k(T - \gamma, \cdot)) \,\mathrm{d}x = \int_\Omega F_0(M_k(T - \gamma, \cdot)) \,\mathrm{d}x$$

and

$$\lim_{\delta \to 0} \int_\Omega F_\delta(M_k(\gamma, \cdot)) \,\mathrm{d}x = \int_\Omega F_0(M_k(\gamma, \cdot)) \,\mathrm{d}x.$$

The remaining task for taking the limit is now to show that the integral terms over $\Omega \backslash \Omega_\delta^t$ vanish. First, we consider the integral

$$\int_\gamma^{T-\gamma} \int_{\Omega \backslash \Omega_\delta^t} M_k(1 - M_k)(f_\delta(M_k))' \nabla M_k \cdot \mathbb{D}_W b_k \,\mathrm{d}x \,\mathrm{d}t.$$

Splitting b_k into its three components with M_k, h_{k-1} and Q_k, we have to compute three integrals. Using $|f_\delta'(M_k)| \leq \frac{2}{\delta(1-\delta)}$, we make the following

estimate, where we drop constants for simplicity:

$$\left| \int_\gamma^{T-\gamma} \int_{\Omega\setminus\Omega_\delta^t} M_k(1-M_k)(f_\delta(M_k))'\nabla M_k \cdot \mathbb{D}_W \nabla M_k \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$\leq \int_\gamma^{T-\gamma} \int_{\Omega\setminus\Omega_\delta^t} M_k(1-M_k) \left| (f_\delta(M_k))' \right| \alpha_{max} \left| \nabla M_k \right|^2 \, \mathrm{d}x \, \mathrm{d}t$$

$$\leq \int_\gamma^{T-\gamma} \int_{\Omega\setminus\Omega_\delta^t} M_k(1-M_k)\frac{2\alpha_{max}}{\delta(1-\delta)} \left| \nabla M_k \right|^2 \, \mathrm{d}x \, \mathrm{d}t$$

$$= \int_\gamma^{T-\gamma} \int_{\Omega\setminus\Omega_0^t} M_k(1-M_k)\frac{2\alpha_{max}}{\delta(1-\delta)} \left| \nabla M_k \right|^2 \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \int_\gamma^{T-\gamma} \int_{\Omega_0^t\setminus\Omega_\delta^t} M_k(1-M_k)\frac{2\alpha_{max}}{\delta(1-\delta)} \left| \nabla M_k \right|^2 \, \mathrm{d}x \, \mathrm{d}t$$

$$\leq \int_\gamma^{T-\gamma} \int_{\Omega\setminus\Omega_0^t} \frac{2\alpha_{max}}{\delta(1-\delta)} M_k(1-M_k) \left| \nabla M_k \right|^2 \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \int_\gamma^{T-\gamma} \int_{\Omega_0^t\setminus\Omega_\delta^t} \frac{2\alpha_{max}}{1-\delta} \left| \nabla M_k \right|^2 \, \mathrm{d}x \, \mathrm{d}t,$$

where we used

$$M_k(1-M_k) \leq \delta \quad \text{on} \quad \Omega_0^t\setminus\Omega_\delta^t = \{x \in \Omega : M_k(t,x) \in (0,\delta] \cup [1-\delta, 1)\}.$$

Since M_k is a C^∞-function, ∇M_k is bounded on $(\gamma, T-\gamma) \times \bar{\Omega}$ (though at this point of our computations the bound may depend on k, of course). As further $\Omega_\delta^t \to \Omega_0^t$ for $\delta \to 0$, the second term vanishes in the limit. Now $\Omega\setminus\Omega_0^t$ is the set where $M_k = 0$ or $M_k = 1$. Hence,

$$\int_\gamma^{T-\gamma} \int_{\Omega\setminus\Omega_0^t} \frac{2\alpha_{max}}{\delta(1-\delta)} M_k(1-M_k) \left| \nabla M_k \right|^2 \, \mathrm{d}x \, \mathrm{d}t = 0.$$

The computations for the other components of b_k work analogously, so we finally obtain

$$\lim_{\delta\to 0} \int_\gamma^{T-\gamma} \int_{\Omega\setminus\Omega_\delta^t} M_k(1-M_k)(f_\delta(M_k))'\nabla M_k \cdot \mathbb{D}_W b_k \, \mathrm{d}x \, \mathrm{d}t = 0.$$

Now consider the integral

$$\int_\gamma^{T-\gamma} \int_{\Omega\setminus\Omega_\delta^t} f_\delta(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1-M_k) \, \mathrm{d}x \, \mathrm{d}t.$$

For shortness, we will drop the factor $G_M(h_{k-1}, s_k^*, y_k^*)$ - it is sufficiently smooth and bounded. Again, we split the integral:

$$\int_\gamma^{T-\gamma} \int_{\Omega\setminus\Omega_\delta^t} f_\delta(M_k) M_k(1-M_k) \, \mathrm{d}x \, \mathrm{d}t$$

$$= \int_\gamma^{T-\gamma} \int_{\Omega\setminus\Omega_0^t} f_\delta(M_k) M_k(1-M_k) \, \mathrm{d}x \, \mathrm{d}t + \int_\gamma^{T-\gamma} \int_{\Omega_0^t\setminus\Omega_\delta^t} f_\delta(M_k) M_k(1-M_k) \, \mathrm{d}x \, \mathrm{d}t.$$

On the domain of the first integral it holds either $M_k = 0$ or $M_k = 1$. Hence, we find

$$\int_\gamma^{T-\gamma} \int_{\Omega \setminus \Omega_0^t} f_\delta(M_k) M_k (1 - M_k) \, \mathrm{d}x \, \mathrm{d}t = 0 \ \text{ for all } \delta > 0,$$

and thus

$$\lim_{\delta \to 0} \int_\gamma^{T-\gamma} \int_{\Omega \setminus \Omega_0^t} f_\delta(M_k) M_k (1 - M_k) \, \mathrm{d}x \, \mathrm{d}t = 0.$$

On the domain $\Omega_0^t \setminus \Omega_\delta^t$ of the second integral, it holds either $0 < M_k \le \delta$ or $1 - \delta \le M_k < 1$. Splitting the integral again, we find

$$\left| \int_\gamma^{T-\gamma} \int_{\Omega_0^t \setminus \Omega_\delta^t} f_\delta(M_k) M_k (1 - M_k) \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$\le \left| \int_\gamma^{T-\gamma} \int_{\Omega_0^t \setminus \Omega_\delta^t, M_k \le \delta} f_\delta^{(1)}(M_k) M_k (1 - M_k) \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$+ \left| \int_\gamma^{T-\gamma} \int_{\Omega_0^t \setminus \Omega_\delta^t, M_k \ge 1-\delta} f_\delta^{(2)}(M_k) M_k (1 - M_k) \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$\le \int_\gamma^{T-\gamma} \int_{\Omega_0^t \setminus \Omega_\delta^t, M_k \le \delta} \left| \ln\left(\frac{\delta}{1-\delta} \right) - 1 \right| M_k (1 - M_k) \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \int_\gamma^{T-\gamma} \int_{\Omega_0^t \setminus \Omega_\delta^t, M_k \ge 1-\delta} \left| \ln\left(\frac{1-\delta}{\delta} \right) + 1 \right| M_k (1 - M_k) \, \mathrm{d}x \, \mathrm{d}t$$

$$\le \int_\gamma^{T-\gamma} \int_{\Omega_0^t \setminus \Omega_\delta^t, M_k \le \delta} \left(-\ln(\delta) + \ln(1-\delta) + 1 \right) \delta \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \int_\gamma^{T-\gamma} \int_{\Omega_0^t \setminus \Omega_\delta^t, M_k \ge 1-\delta} \left(-\ln(\delta) + \ln(1-\delta) + 1 \right) \delta \, \mathrm{d}x \, \mathrm{d}t$$

$$= \int_\gamma^{T-\gamma} \int_{\Omega_0^t \setminus \Omega_\delta^t} \left(-\delta \ln(\delta) + \delta \ln(1-\delta) + \delta \right) \, \mathrm{d}x \, \mathrm{d}t.$$

This integral is bounded independently of δ. Furthermore, the integrand converges to 0 as $\delta \to 0$. Hence,

$$\lim_{\delta \to 0} \int_\gamma^{T-\gamma} \int_{\Omega_0^t \setminus \Omega_\delta^t} f_\delta(M_k) M_k (1 - M_k) \, \mathrm{d}x \, \mathrm{d}t = 0$$

and also

$$\lim_{\delta \to 0} \left| \int_\gamma^{T-\gamma} \int_{\Omega \setminus \Omega_\delta^t} f_\delta(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k (1 - M_k) \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$= \lim_{\delta \to 0} \left| \int_\gamma^{T-\gamma} \int_{\Omega_0^t \setminus \Omega_\delta^t} f_\delta(M_k) \underbrace{G_M(h_{k-1}, s_k^*, y_k^*)}_{\geq 0 \text{ and bounded by } 1} M_k (1 - M_k) \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$\leq \lim_{\delta \to 0} \left| \int_\gamma^{T-\gamma} \int_{\Omega_0^t \setminus \Omega_\delta^t} f_\delta(M_k) M_k (1 - M_k) \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$= 0.$$

This leaves

$$\lim_{\delta \to 0} \epsilon_k \int_\gamma^{T-\gamma} \int_\Omega f_\delta'(M_k) |\nabla M_k|^2 \, \mathrm{d}x \, \mathrm{d}t$$

$$= \int_\gamma^{T-\gamma} \int_{\Omega_0^t} f_0(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k (1 - M_k) \, \mathrm{d}x \, \mathrm{d}t$$

$$- \int_\Omega F_0(M_k(\cdot, T - \gamma)) \, \mathrm{d}x + \int_\Omega F_0(M_k(\cdot, \gamma)) \, \mathrm{d}x$$

$$+ \frac{a_1}{a_2 s_{max}} \int_\gamma^{T-\gamma} \int_{\Omega_0^t} \nabla M_k \mathbb{D}_W b_k \, \mathrm{d}x \, \mathrm{d}t.$$

Hence, the limit exists, and we can make the following estimate:

$$\int_\gamma^{T-\gamma} \int_\Omega f_\delta'(M_k) |\nabla M_k|^2 \, \mathrm{d}x \, \mathrm{d}t$$

$$= \int_\gamma^{T-\gamma} \int_{\Omega \setminus \Omega_\delta^t} f_\delta'(M_k) |\nabla M_k|^2 \, \mathrm{d}x \, \mathrm{d}t + \int_\gamma^{T-\gamma} \int_{\Omega_\delta^t} f_\delta'(M_k) |\nabla M_k|^2 \, \mathrm{d}x \, \mathrm{d}t$$

$$\geq - \int_\gamma^{T-\gamma} \int_{\Omega \setminus \Omega_\delta^t} |\nabla M_k|^2 \, \mathrm{d}x \, \mathrm{d}t,$$

where we used the nonnegativity of f_δ' on Ω_δ^t as well as $f_\delta' \geq -1$ on $\Omega \setminus \Omega_\delta^t$. Now we split the remaining term:

$$- \int_\gamma^{T-\gamma} \int_{\Omega \setminus \Omega_\delta^t} |\nabla M_k|^2 \, \mathrm{d}x \, \mathrm{d}t$$

$$= - \int_\gamma^{T-\gamma} \int_{\Omega \setminus \Omega_0^t} |\nabla M_k|^2 \, \mathrm{d}x \, \mathrm{d}t - \int_\gamma^{T-\gamma} \int_{\Omega_0^t \setminus \Omega_\delta^t} |\nabla M_k|^2 \, \mathrm{d}x \, \mathrm{d}t.$$

Since $\Omega \setminus \Omega_0^t$ is the set where $M_k = 0$ or $M_k = 1$, on the interior of this set it holds $\nabla M_k = 0$. Since the boundary of $\Omega \setminus \Omega_0^t$ is a nullset, this implies $\int_{\Omega \setminus \Omega_0^t} |\nabla M_k|^2 \, \mathrm{d}x = 0$ for all $t > 0$. The second term converges to zero for $\delta \to 0$ since ∇M_k is bounded. Hence, we find

$$\lim_{\delta \to 0} \epsilon_k \int_\gamma^{T-\gamma} \int_\Omega f_\delta'(M_k) |\nabla M_k|^2 \, \mathrm{d}x \, \mathrm{d}t \geq 0.$$

Altogether, this leads to the inequality

$$\int_\Omega F_0(M_k(\cdot, T-\gamma))\,\mathrm{d}x - \int_\Omega F_0(M_k(\cdot,\gamma))\,\mathrm{d}x$$

$$- \frac{a_1}{a_2 s_{max}} \int_\gamma^{T-\gamma} \int_{\Omega_0^t} \nabla M_k \mathbb{D}_W b_k \,\mathrm{d}x\,\mathrm{d}t$$

$$\leq \int_\gamma^{T-\gamma} \int_{\Omega_0^t} f_0(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1-M_k)\,\mathrm{d}x\,\mathrm{d}t.$$

Now for $\gamma \to 0$, we find

$$\int_\Omega F_0(M_k(\cdot, T))\,\mathrm{d}x - \int_\Omega F_0(M_k(\cdot, 0))\,\mathrm{d}x - \frac{a_1}{a_2 s_{max}} \int_0^T \int_{\Omega_0^t} \nabla M_k \mathbb{D}_W b_k \,\mathrm{d}x\,\mathrm{d}t$$

$$\leq \int_0^T \int_{\Omega_0^t} f_0(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1-M_k)\,\mathrm{d}x\,\mathrm{d}t.$$

From this inequality, we now aim to find an estimate on $\|\nabla M_k\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))}$. Since $\nabla M_k = 0$ on $\Omega \setminus \Omega_0^t$ except a nullset, it holds $\int_{\Omega \setminus \Omega_0^t} \nabla M_k \mathbb{D}_W b_k \,\mathrm{d}x = 0$ for all $t > 0$. Further, since M_k, h_{k-1}, s_k^* and y_k^* are bounded independently of k, there is a constant $c > 0$ such that

$$\frac{a_2 s_{max}}{a_1 \rho_2} \left(\int_0^T \int_{\Omega_0^t} f_0(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1-M_k)\,\mathrm{d}x\,\mathrm{d}t \right.$$

$$\left. - \int_\Omega F_0(M_k(\cdot, T))\,\mathrm{d}x + \int_\Omega F_0(M_k(\cdot, 0))\,\mathrm{d}x \right) \qquad (3.11)$$

$$\leq c(T).$$

Hence, we find

$$\int_0^T \int_\Omega \nabla M_k \, \mathbb{D}_W \nabla M_k \,\mathrm{d}x\,\mathrm{d}t$$

$$= \int_0^T \int_{\Omega_0^t} \nabla M_k \, \mathbb{D}_W \nabla M_k \,\mathrm{d}x\,\mathrm{d}t$$

$$\leq c(T) - \frac{1-\rho_1}{\rho_2} \int_0^T \int_{\Omega_0^t} \frac{\nabla M_k \, \mathbb{D}_W \nabla h_{k-1}}{\sqrt{1+|\nabla h_{k-1}|^2}} \,\mathrm{d}x\,\mathrm{d}t \qquad (3.12)$$

$$+ \int_0^T \int_{\Omega_0^t} \frac{\rho_1(1-y_k^*)}{\rho_2} \frac{\nabla M_k \, \mathbb{D}_W \nabla Q_k}{\sqrt{1+|\nabla Q_k|^2}} \,\mathrm{d}x\,\mathrm{d}t,$$

from which we conclude

$$\int_0^T \int_\Omega \alpha_{min} |\nabla M_k|^2 \, \mathrm{d}x \, \mathrm{d}t$$

$$\leq c(T) + \frac{1 - \rho_1}{\rho_2} \int_0^T \int_{\Omega_0^t} \frac{\alpha_{max} |\nabla M_k| |\nabla h_{k-1}|}{\sqrt{1 + |\nabla h_{k-1}|^2}} \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \int_0^T \int_{\Omega_0^t} \frac{\rho_1 (1 - y_k^*)}{\rho_2} \frac{\alpha_{max} |\nabla M_k| |\nabla Q_k|}{\sqrt{1 + |\nabla Q_k|^2}} \, \mathrm{d}x \, \mathrm{d}t$$

$$\leq c(T) + \frac{1 - \rho_1}{\rho_2} \int_0^T \int_\Omega \frac{\alpha_{max} |\nabla M_k| |\nabla h_{k-1}|}{\sqrt{1 + |\nabla h_{k-1}|^2}} \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \int_0^T \int_\Omega \frac{\rho_1 (1 - y_k^*)}{\rho_2} \frac{\alpha_{max} |\nabla M_k| |\nabla Q_k|}{\sqrt{1 + |\nabla Q_k|^2}} \, \mathrm{d}x \, \mathrm{d}t$$

$$\leq c(T) + \frac{1 - \rho_1}{\rho_2} \int_0^T \int_\Omega \alpha_{max} |\nabla M_k| \, \mathrm{d}x \, \mathrm{d}t + \frac{\rho_1}{\rho_2} \int_0^T \int_\Omega \alpha_{max} |\nabla M_k| \, \mathrm{d}x \, \mathrm{d}t$$

$$= c(T) + \frac{1}{\rho_2} \int_0^T \int_\Omega \alpha_{max} |\nabla M_k| \, \mathrm{d}x \, \mathrm{d}t$$

$$\leq c(T) + \frac{\alpha_{max}}{\rho_2} \frac{\epsilon}{2} \|\nabla M_k\|^2_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} + \frac{\alpha_{max}}{\rho_2} \frac{1}{2\epsilon} T |\Omega|.$$

It follows

$$\left(\alpha_{min} - \frac{\alpha_{max}}{\rho_2} \frac{\epsilon}{2} \right) \|\nabla M_k\|^2_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \leq c(T) + \frac{\alpha_{max}}{\rho_2} \frac{1}{2\epsilon} T |\Omega|$$

and hence

$$\|\nabla M_k\|^2_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \leq \frac{1}{\alpha_{min} - \frac{\alpha_{max}}{\rho_2} \frac{\epsilon}{2}} \left(c(T) + \frac{\alpha_{max}}{\rho_2} \frac{1}{2\epsilon} T |\Omega| \right) =: c_M^2(T),$$

$$(3.13)$$

where we choose ϵ small enough, such that $\alpha_{min} - \frac{\alpha_{max}}{\rho_2} \frac{\epsilon}{2} > 0$.

- $\|\Delta h_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \leq c_{hh}(T)$. Consider once more equation (3.6b). Multiplication of (3.6b) by Δh_k and integration yields

$$\int_0^T \int_\Omega \partial_t h_k \, \Delta h_k \, \mathrm{d}x \, \mathrm{d}t = D_h \int_0^T \int_\Omega (\Delta h_k)^2 \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \int_0^T \int_\Omega \left(\mu_h (1 - h_k) \frac{M_k}{1 + M_k} - \delta_h h_k e_k \right) \Delta h_k \, \mathrm{d}x \, \mathrm{d}t.$$

Setting $f_k := \mu_h (1 - h_k) \frac{M_k}{1 + M_k} - \delta_h h_k e_k$ and using partial integration, we find

$$-\frac{1}{2} \int_0^T \int_\Omega \partial_t \left(|\nabla h_k| \right)^2 \, \mathrm{d}x \, \mathrm{d}t = D_h \int_0^T \int_\Omega (\Delta h_k)^2 \, \mathrm{d}x \, \mathrm{d}t - \int_0^T \int_\Omega \nabla f_k \nabla h_k \, \mathrm{d}x \, \mathrm{d}t,$$

which implies

$$D_h \|\Delta h_k\|^2_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} = -\frac{1}{2}\|\nabla h_k(T,\cdot)\|^2_{\mathcal{L}^2(\Omega)} + \frac{1}{2}\|\nabla h_k(0,\cdot)\|^2_{\mathcal{L}^2(\Omega)}$$
$$+ \int_0^T \int_\Omega \nabla f_k \nabla h_k \,\mathrm{d}x\,\mathrm{d}t.$$

(3.14)

The first two terms on the right hand side are bounded by $|\Omega|^{\frac{1}{2}} c_h^2(T)$ due to $\|\nabla h_k\|_{\mathcal{L}^\infty(0,T;\mathcal{L}^4(\Omega))} \le c_h(T)$. For the third term on the right hand side, we find

$$\left| \int_0^T \int_\Omega \nabla f_k \nabla h_k \,\mathrm{d}x\,\mathrm{d}t \right|$$
$$\le \left| \int_0^T \int_\Omega \frac{\partial f_k}{\partial e_k} \nabla e_k \nabla h_k \,\mathrm{d}x\,\mathrm{d}t \right| + \left| \int_0^T \int_\Omega \frac{\partial f_k}{\partial h_k} \nabla h_k \nabla h_k \,\mathrm{d}x\,\mathrm{d}t \right|$$
$$+ \left| \int_0^T \int_\Omega \frac{\partial f_k}{\partial M_k} \nabla M_k \nabla h_k \,\mathrm{d}x\,\mathrm{d}t \right|$$
$$= \left| \int_0^T \int_\Omega -\delta_h h_k \nabla e_k \nabla h_k \,\mathrm{d}x\,\mathrm{d}t \right|$$
$$+ \left| \int_0^T \int_\Omega \left(-\mu_h \frac{M_k}{1+M_k} - \delta_h e_k \right) |\nabla h_k|^2 \,\mathrm{d}x\,\mathrm{d}t \right|$$
$$+ \left| \int_0^T \int_\Omega \mu_h \frac{1-h_k}{(1+M_k)^2} \nabla M_k \nabla h_k \,\mathrm{d}x\,\mathrm{d}t \right|$$
$$\le \delta_h \|\nabla e_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \|\nabla h_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} + (\mu_h + \delta_h)\|\nabla h_k\|^2_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}$$
$$+ \mu_h \|\nabla M_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \|\nabla h_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}$$
$$\le \delta_h c_e(T) T^{\frac{1}{2}} |\Omega|^{\frac{1}{4}} c_h(T) + (\mu_h+\delta_h)T|\Omega|^{\frac{1}{2}} c_h^2(T) + \mu_h c_M(T)T^{\frac{1}{2}}|\Omega|^{\frac{1}{4}} c_h(T).$$

Hence, equation (3.14) implies

$$\|\Delta h_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \le c_{hh}(T)$$

for some constant $c_{hh}(T)$, which is independent of k.

- $\|\Delta \mathbf{Q_k}(\mathbf{t},\cdot)\|_{\mathcal{L}^\infty(\mathbf{0,T};\mathcal{L}^2(\mathbf{\Omega}))} \le \mathbf{c_{QQ}(T)}$. Finally, consider equation (3.6a) again. Apply Δ to (3.6a):

$$\partial_t(\Delta Q_k) = -2\mu_Q |\nabla Q_k|^2 + \mu_Q(1-2Q_k)\Delta Q_k - \delta_Q \frac{h_{k-1}}{1+h_{k-1}}\Delta Q_k$$
$$- 2\delta_Q \frac{\nabla h_{k-1}\nabla Q_k}{(1+h_{k-1})^2} - \delta_Q \frac{Q_k}{(1+h_{k-1})^2}\Delta h_{k-1}$$
$$+ 2\delta_Q \frac{Q_k}{(1+h_{k-1})^3}|\nabla h_{k-1}|^2.$$

Multiplication with ΔQ_k and integration w.r.t. x yields

$$
\frac{1}{2} \int_\Omega \partial_t (\Delta Q_k)^2 \, \mathrm{d}x
$$

$$
= -2\mu_Q \int_\Omega |\nabla Q_k|^2 \Delta Q_k \, \mathrm{d}x + \mu_Q \int_\Omega (1 - 2Q_k)(\Delta Q_k)^2 \, \mathrm{d}x
$$

$$
- \delta_Q \int_\Omega \frac{h_{k-1}}{1 + h_{k-1}} (\Delta Q_k)^2 \, \mathrm{d}x - 2\delta_Q \int_\Omega \frac{\nabla h_{k-1} \nabla Q_k}{(1 + h_{k-1})^2} \Delta Q_k \, \mathrm{d}x
$$

$$
- \delta_Q \int_\Omega \frac{Q_k}{(1 + h_{k-1})^2} \Delta h_{k-1} \Delta Q_k \, \mathrm{d}x
$$

$$
+ 2\delta_Q \int_\Omega \frac{Q_k}{(1 + h_{k-1})^3} |\nabla h_{k-1}|^2 \Delta Q_k \, \mathrm{d}x.
$$

Using $Q_k, h_{k-1} \in [0, 1]$, this implies

$$
\left| \frac{\partial}{\partial t} \, \|\Delta Q_k\|_{\mathcal{L}^2(\Omega)}^2 \right|
$$

$$
\leq 4\mu_Q \|\nabla Q_k\|_{\mathcal{L}^4(\Omega)}^2 \|\Delta Q_k\|_{\mathcal{L}^2(\Omega)} + 2(\mu_Q + \delta_Q)\|\Delta Q_k\|_{\mathcal{L}^2(\Omega)}^2
$$

$$
+ 4\delta_Q \|\nabla h_{k-1}\|_{\mathcal{L}^4(\Omega)} \|\nabla Q_k\|_{\mathcal{L}^4(\Omega)} \|\Delta Q_k\|_{\mathcal{L}^2(\Omega)}
$$

$$
+ 2\delta_Q \|\Delta h_{k-1}\|_{\mathcal{L}^2(\Omega)} \|\Delta Q_k\|_{\mathcal{L}^2(\Omega)} + 4\delta_Q \|\nabla h_{k-1}\|_{\mathcal{L}^4(\Omega)}^2 \|\Delta Q_k\|_{\mathcal{L}^2(\Omega)}
$$

$$
\leq 2(\mu_Q + \delta_Q)\|\Delta Q_k\|_{\mathcal{L}^2(\Omega)}^2 + 2\delta_Q \|\Delta h_{k-1}\|_{\mathcal{L}^2(\Omega)} \|\Delta Q_k\|_{\mathcal{L}^2(\Omega)}
$$

$$
+ 4 \left(\mu_Q \|\nabla Q_k\|_{\mathcal{L}^4(\Omega)}^2 + \delta_Q \|\nabla h_{k-1}\|_{\mathcal{L}^4(\Omega)} \|\nabla Q_k\|_{\mathcal{L}^4(\Omega)} \right.
$$

$$
\left. + \delta_Q \|\nabla h_{k-1}\|_{\mathcal{L}^4(\Omega)}^2 \right) \|\Delta Q_k\|_{\mathcal{L}^2(\Omega)}
$$

$$
\leq 2(\mu_Q + \delta_Q)\|\Delta Q_k\|_{\mathcal{L}^2(\Omega)}^2 + 2\delta_Q \|\Delta h_{k-1}\|_{\mathcal{L}^2(\Omega)} (\|\Delta Q_k\|_{\mathcal{L}^2(\Omega)}^2 + 1)
$$

$$
+ 4 \left(\mu_Q c_Q^2(T) + \delta_Q c_h(T) c_Q(T) + \delta_Q c_h^2(T) \right) (\|\Delta Q_k\|_{\mathcal{L}^2(\Omega)}^2 + 1)
$$

$$
= (C_1(T) + C_2 \|\Delta h_{k-1}\|_{\mathcal{L}^2(\Omega)})\|\Delta Q_k\|_{\mathcal{L}^2(\Omega)}^2 + C_3 \|\Delta h_{k-1}\|_{\mathcal{L}^2(\Omega)} + C_4(T),
$$

where we used

$$
\|\Delta Q_k\|_{\mathcal{L}^2(\Omega)} \leq \|\Delta Q_k\|_{\mathcal{L}^2(\Omega)}^2 + 1.
$$

Applying Gronwall´s inequality yields

$$
\|\Delta Q_k(T, \cdot)\|_{\mathcal{L}^2(\Omega)}^2
$$

$$
\leq \|\Delta Q_0^{(k)}\|_{\mathcal{L}^2(\Omega)}^2 e^{\int_0^T (C_1(T) + C_2 \|\Delta h_{k-1}\|_{\mathcal{L}^2(\Omega)}) \, \mathrm{d}s}
$$

$$
+ \int_0^T (C_3 \|\Delta h_{k-1}\|_{\mathcal{L}^2(\Omega)} + C_4(T)) e^{\int_s^T (C_1(T) + C_2 \|\Delta h_{k-1}\|_{\mathcal{L}^2(\Omega)}) \, \mathrm{d}\tau} \, \mathrm{d}s
$$

$$
\leq \|\Delta Q_0^{(k)}\|_{\mathcal{L}^2(\Omega)}^2 e^{C_1(T)T + C_2 \|\Delta h_{k-1}\|_{\mathcal{L}^1(0, T; \mathcal{L}^2(\Omega))}}
$$

$$
+ \int_0^T (C_3 \|\Delta h_{k-1}\|_{\mathcal{L}^2(\Omega)} + C_4(T)) e^{C_1(T)T + C_2 \|\Delta h_{k-1}\|_{\mathcal{L}^1(0, T; \mathcal{L}^2(\Omega))}} \, \mathrm{d}s
$$

$$
\leq \|\Delta Q_0^{(k)}\|_{\mathcal{L}^2(\Omega)}^2 C_5(T) + \int_0^T (C_3 \|\Delta h_{k-1}\|_{\mathcal{L}^2(\Omega)} + C_4(T)) C_5(T) \, \mathrm{d}s
$$

$$
\leq \|\Delta Q_0^{(k)}\|_{\mathcal{L}^2(\Omega)}^2 C_5(T) + C_6(T)
$$

$$
\leq c_{QQ}^2(T)
$$

for some constant c_{QQ} independent of k. Hence,

$$\|\Delta Q_k(t,\cdot)\|_{\mathcal{L}^\infty(0,T;\mathcal{L}^2(\Omega))} \leq c_{QQ}(T).$$

$\square$

3.1.3 Existence of a solution to the decoupled system

Lemma 3.1.8. *Let $M_0, h_0, e_0 \in W^{1,4}(\Omega)$, $Q_0^{(k)} \in C^\infty(\bar{\Omega})$ with*

$$0 \leq M_0, h_0, e_0, Q_0^{(k)} \leq 1.$$

Let further

$$(Q_{k-1}, h_{k-1}, e_{k-1}, M_{k-1}) \in (C^\infty((0,\infty) \times \bar{\Omega}) \cap C([0,\infty) \times \bar{\Omega}))^4$$

fulfill the bounds from lemma 3.1.7. Then system (3.6)-(3.9) has a unique global solution

$$(Q_k, h_k, e_k, M_k) \in (C^\infty((0,\infty) \times \bar{\Omega}) \cap C([0,\infty) \times \bar{\Omega}))^4,$$

which fulfills again the bounds from lemma 3.1.7.

Proof. Global existence of Q_k is obtained from equation (3.6a) by applying standard theory for ODEs, using the boundedness of Q_k. The postulated smoothness properties can be deduced from remark A.1.9.
Now consider system (3.6b)-(3.6d). Using the notations of theorem A.1.2 with $u^k = \begin{pmatrix} h_k \\ e_k \\ M_k \end{pmatrix}$, the system coefficients are as follows:

- From equation (3.6b)

$$a_{ii}^{11} = D_h \ \text{ for } i = 1, ..., N$$
$$a_{ij}^{11} = 0 \ \text{ for } i \neq j,$$
$$a_{ij}^{12} = a_{ij}^{13} = 0 \ \text{ for } i, j = 1, ..., N,$$
$$a_i^{1r} = b_i^{1r} = 0 \ \text{ for } i = 1, ..., N, \ r = 1, 2, 3,$$
$$a_0^{12} = a_0^{13} = 0,$$
$$a_0^{11} = \delta_h u_2^k,$$
$$f_1 = \mu_h(1 - u_1^k)\frac{u_3^k}{1 + u_3^k},$$

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- From equation (3.6c)

$$a_{ii}^{22} = D_e \ \text{ for } i = 1, ..., N,$$

$$a_{ij}^{22} = 0 \ \text{ for } i \neq j,$$

$$a_{ii}^{21} = -\varsigma_e u_2^k (1 - u_2^k) \ \text{ for } i = 1, ..., N,$$

$$a_{ij}^{21} = 0 \ \text{ for } i \neq j,$$

$$a_{ij}^{23} = 0 \ \text{ for } i, j = 1, ..., N,$$

$$a_i^{2r} = b_i^{2r} = 0 \ \text{ for } i = 1, ..., N, \ r = 1, 2, 3,$$

$$a_0^{21} = a_0^{23} = 0,$$

$$a_0^{22} = -\mu_e \frac{u_1^k u_3^k}{1 + u_1^k u_3^k} (1 - u_2^k),$$

$$f_2 = 0,$$

- From equation (3.6d)

$$a_{ij}^{33} = \frac{a_1 \rho_2}{a_2 s_{max}} u_3^k (1 - u_3^k)(\mathbb{D}_W)_{ij} + \epsilon_k I_{ij} \ \text{ for } i, j = 1, ..., N,$$

$$a_{ij}^{31} = a_{ij}^{32} = 0 \ \text{ for } i, j = 1, ..., N,$$

$$a_i^{31} = a_i^{32} = 0 \ \text{ for } i = 1, ..., N,$$

$$b_i^{3r} = 0 \ \text{ for } i = 1, ..., N, \ r = 1, 2, 3,$$

$$a_i^{33} = \frac{a_1(1 - \rho_1)}{a_2 s_{max}} \frac{1 - u_3^k}{\sqrt{1 + \|\nabla u_1^{k-1}\|^2}} (\mathbb{D}_W \nabla u_1^{k-1})_i$$

$$- \frac{a_1 \rho_1}{a_2 s_{max}} (1 - y_k^*) \frac{1 - u_3^k}{\sqrt{1 + \|\nabla Q_k\|^2}} (\mathbb{D}_W \nabla Q_k)_i \ \text{ for } i = 1, ..., N,$$

$$a_0^{31} = a_0^{32} = 0,$$

$$a_0^{33} = -y_k^*(1 - y_k^*) \frac{1 - s_k^*}{1 + u_1^{k-1}} (1 - u_3^k),$$

$$f_3 = 0.$$

We check the assumptions of theorem A.1.2: Let $D_0 := (-\frac{1}{2}, \frac{3}{2})^3$. Then all coefficients of $\mathcal{A}$ and $\mathcal{B}$ are C^∞-smooth w.r.t. x, t and u. Further note, that the set $D \subset D_0$ is nonempty: For example consider

$$a_{ij}(0, 0, 0) = \begin{pmatrix} D_h I_{ij} & 0 & 0 \\ 0 & D_e I_{ij} & 0 \\ 0 & 0 & \epsilon_k I_{ij} \end{pmatrix},$$

where due to the positivity of D_h, D_e and ϵ_k we find that

$$\left(\sum_{i,j=1}^{N} a_{ij}^{kl}(0, 0, 0)\xi_i \xi_j \right)_{k,l=1}^{3}$$

is positive definite for all $\xi \in \mathbb{R}^N \backslash \{0\}$. Hence, $(0, 0, 0) \in D$. f is C^∞-smooth on $((\mathbb{R}_0^+ \times \bar{\Omega} \times D_0) \times \mathbb{R}^{3 \times N}, \mathbb{R}^3)$, hence also on $((\mathbb{R}_0^+ \times \bar{\Omega} \times D) \times \mathbb{R}^{3 \times N}, \mathbb{R}^3)$. Furthermore, f is independent of the gradient of u. Choosing $p = 4$, the condition

$\frac{N}{p} < 1 < (1 + \frac{1}{p}) \wedge (2 - \frac{N}{p})$ is fulfilled with $N \leq 3$. Since it further holds $g = 0$ and the initial data are all at least in $W^{1,4}(\Omega)$, by theorems A.1.2, A.1.3 and A.1.4 there exists a unique solution $u^k \in C^\infty((0, t^+) \times \bar{\Omega}, \mathbb{R}^3)$ for some $t^+ > 0$. Due to the positivity of ϵ_k, there is some $\delta > 0$ such that $(a_{ij}^{33})_{ij}$ is positive definite for $u_3^k \in (-\delta, 1 + \delta)$, hence by $0 \leq h_k, e_k, M_k \leq 1$, u^k is bounded away from ∂D. Then by theorem A.1.5 we find $t^+ = \infty$.

The bounds on Q_k, h_k, e_k and M_k are given by lemma 3.1.7. $\qquad \square$

Remark 3.1.9. In the proof of lemma 3.1.8 above, we needed $N \leq 3$ in order to fulfill the condition $\frac{N}{p} < 1 < (1 + \frac{1}{p}) \wedge (2 - \frac{N}{p})$ for $p = 4$. Choosing stronger assumptions on the initial data (i.e. $h_0, e_0, M_0 \in W^{1,N+1}(\Omega)$), the theorem works also for the (biologically irrelevant) case $N > 3$.

Starting with some arbitrary functions $Q_1, h_1, e_1, M_1 \in C^\infty((0, \infty) \times \bar{\Omega}) \cap C([0, \infty) \times \bar{\Omega})$, fulfilling the assumptions on $(Q_{k-1}, h_{k-1}, e_{k-1}, M_{k-1})$ from lemma 3.1.7, lemma 3.1.8 ensures the existence of an iteratively defined sequence of unique global solutions $(Q_k, h_k, e_k, M_k)_{k \geq 2}$ to system (3.6)-(3.9), fulfilling the bounds of lemma 3.1.7.

3.1.4 Existence of a global weak solution

Finally, we have to show that the constructed sequence of solutions to system (3.6)-(3.9) converges to a weak solution of the original system (3.1).

Lemma 3.1.10. *Let $(Q_k, h_k, e_k, M_k)_k$ be the sequence of global solutions to system (3.6)-(3.9) constructed in section 3.1.3. Then there exist*

$$M, h, e, Q : \mathbb{R}_0^+ \times \bar{\Omega} \to [0, 1],$$

such that for all $T > 0$ it holds

$$M, e \in \mathcal{L}^2(0, T; W^{1,2}(\Omega)), \qquad h, Q \in \mathcal{L}^\infty(0, T; W^{1,2}(\Omega)),$$

and there exists a subsequence $(Q_{k_n}, h_{k_n}, e_{k_n}, M_{k_n})_n$ such that

$$M_{k_n} \to M \ \ in \ \mathcal{L}^2(0, T; \mathcal{L}^2(\Omega)), \qquad h_{k_n} \to h \ \ in \ \mathcal{L}^\infty(0, T; \mathcal{L}^2(\Omega)),$$
$$e_{k_n} \to e \ \ in \ \mathcal{L}^2(0, T; \mathcal{L}^2(\Omega)), \qquad Q_{k_n} \to Q \ \ in \ \mathcal{L}^\infty(0, T; \mathcal{L}^2(\Omega)),$$

and

$$M_{k_n} \rightharpoonup M \ \ in \ \mathcal{L}^2(0, T; W^{1,2}(\Omega)), \qquad e_{k_n} \rightharpoonup e \ \ in \ \mathcal{L}^2(0, T; W^{1,2}(\Omega)),$$
$$h_{k_n} \rightharpoonup h \ \ in \ \mathcal{L}^2(0, T; W^{1,2}(\Omega)), \qquad h_{k_n} \overset{*}{\rightharpoonup} h \ \ in \ \mathcal{L}^\infty(0, T; W^{1,2}(\Omega)),$$
$$Q_{k_n} \rightharpoonup Q \ \ in \ \mathcal{L}^2(0, T; W^{1,2}(\Omega)), \qquad Q_{k_n} \overset{*}{\rightharpoonup} Q \ \ in \ \mathcal{L}^\infty(0, T; W^{1,2}(\Omega)).$$

Proof. For the proof of this lemma, we will use the theorem of Aubin-Lions (theorem A.1.11).

In theorem A.1.11, let $X = W^{1,2}(\Omega)$, $B = \mathcal{L}^2(\Omega)$, and $Y = W^{-1,2}(\Omega)$, and let $T > 0$. The boundedness of $(M_k)_k$ in $\mathcal{L}^2(0, T; W^{1,2}(\Omega))$ is given by lemma 3.1.7. To check the boundedness of $(\partial_t M_k)_k$ in $\mathcal{L}^2(0, T; W^{-1,2}(\Omega)) =$

$(\mathcal{L}^2(0, T; W_0^{1,2}(\Omega)))^*$, let $\phi \in \mathcal{L}^2(0, T; W_0^{1,2}(\Omega))$. We multiply (3.6d) by ϕ and integrate over $(0, T) \times \Omega$:

$$\left| \int_0^T \int_\Omega \partial_t M_k \cdot \phi \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$\leq \epsilon_k \left| \int_0^T \int_\Omega \nabla M_k \cdot \nabla \phi \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$+ \frac{a_1}{a_2 s_{max}} \cdot \left(\rho_2 \left| \int_0^T \int_\Omega (M_k(1 - M_k) \mathbb{D}_W \nabla M_k) \cdot \nabla \phi \, \mathrm{d}x \, \mathrm{d}t \right| \right.$$

$$+ (1 - \rho_1) \left| \int_0^T \int_\Omega \left(M_k(1 - M_k) \mathbb{D}_W \frac{\nabla h_{k-1}}{\sqrt{1 + |\nabla h_{k-1}|^2}} \right) \cdot \nabla \phi \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$\left. + \rho_1 \left| \int_0^T \int_\Omega \left((1 - y_k^*) M_k(1 - M_k) \mathbb{D}_W \frac{\nabla Q_k}{\sqrt{1 + |\nabla Q_k|^2}} \right) \cdot \nabla \phi \, \mathrm{d}x \, \mathrm{d}t \right| \right)$$

$$+ \left| \int_0^T \int_\Omega G_M(h_{k-1}, s_k^*, y_k^*) M_k(1 - M_k) \phi \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$\leq \epsilon_k \int_0^T \int_\Omega |\nabla M_k| |\nabla \phi| \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \frac{a_1}{a_2 s_{max}} \left(\rho_2 \int_0^T \int_\Omega \alpha_{max} M_k(1 - M_k) |\nabla M_k| |\nabla \phi| \, \mathrm{d}x \, \mathrm{d}t \right.$$

$$+ (1 - \rho_1) \int_0^T \int_\Omega \alpha_{max} M_k(1 - M_k) \left| \frac{\nabla h_{k-1}}{\sqrt{1 + |\nabla h_{k-1}|^2}} \right| |\nabla \phi| \, \mathrm{d}x \, \mathrm{d}t$$

$$\left. + \rho_1 \int_0^T \int_\Omega \alpha_{max}(1 - y_k^*) M_k(1 - M_k) \left| \frac{\nabla Q_k}{\sqrt{1 + |\nabla Q_k|^2}} \right| |\nabla \phi| \, \mathrm{d}x \, \mathrm{d}t \right)$$

$$+ \int_0^T \int_\Omega |G_M(h_{k-1}, s_k^*, y_k^*) M_k(1 - M_k)| |\phi| \, \mathrm{d}x \, \mathrm{d}t$$

$$\leq c \left(\int_0^T \int_\Omega |\nabla M_k| |\nabla \phi| \, \mathrm{d}x \, \mathrm{d}t + \int_0^T \int_\Omega \left| \frac{\nabla h_{k-1}}{\sqrt{1 + |\nabla h_{k-1}|^2}} \right| |\nabla \phi| \, \mathrm{d}x \, \mathrm{d}t \right.$$

$$\left. + \int_0^T \int_\Omega \left| \frac{\nabla Q_k}{\sqrt{1 + |\nabla Q_k|^2}} \right| |\nabla \phi| \, \mathrm{d}x \, \mathrm{d}t + \int_0^T \int_\Omega |\phi| \, \mathrm{d}x \, \mathrm{d}t \right)$$

$$\leq c \left(\|\nabla M_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} + \left\| \frac{\nabla h_{k-1}}{\sqrt{1 + |\nabla h_{k-1}|^2}} \right\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \right.$$

$$\left. + \left\| \frac{\nabla Q_k}{\sqrt{1 + |\nabla Q_k|^2}} \right\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \right) \|\nabla \phi\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} + c\|\phi\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}$$

$$\leq C(T) \|\phi\|_{\mathcal{L}^2(0,T;W^{1,2}(\Omega))}.$$

Hence, $(\partial_t M_k)_k$ is bounded in $\mathcal{L}^2(0, T; W^{-1,2}(\Omega))$ and by theorem A.1.11 there exists a subsequence $(M_{k_n})_n$ with $M_{k_n} \to M$ in $\mathcal{L}^2(0, T; \mathcal{L}^2(\Omega))$.
The boundedness of $(M_{k_n})_n$ in $\mathcal{L}^2(0, T; W^{1,2}(\Omega))$ implies the existence of a fur-

ther subsequence $(M_{k_{n_l}})_l$ with $M_{k_{n_l}} \rightharpoonup M$ in $\mathcal{L}^2(0, T; W^{1,2}(\Omega))$.

Next, we show convergence of a subsequence of $(h_k)_k$. To be precise, we should be looking for a subsequence of $(h_{k_{n_l}})_l$, $(k_{n_l})_l$ being the sequence from above, in order to find a convergent subsequence of both $(M_k)_k$ and $(h_k)_k$. For simplicity of writing, we drop the subindex n_l in the following. Choosing $X = W^{1,2}(\Omega)$, $B = \mathcal{L}^2(\Omega)$ and $Y = W^{-1,2}(\Omega)$, we have to check the boundedness of $(\partial_t h_k)_k$ in $\mathcal{L}^2(0, T; W^{-1,2}(\Omega)) = (\mathcal{L}^2(0, T; W_0^{1,2}(\Omega)))^*$ (the boundedness of $(h_k)_k$ in $\mathcal{L}^\infty(0, T; W^{1,2}(\Omega))$ is given by lemma 3.1.7). To this aim, let $\phi \in \mathcal{L}^2(0, T; W_0^{1,2}(\Omega))$. Multiplying (3.6b) by ϕ and integrating over Ω yields

$$
\left| \int_\Omega \partial_t h_k \cdot \phi \, \mathrm{d}x \right|
$$

$$
\leq D_h \left| \int_\Omega \Delta h_k \cdot \phi \, \mathrm{d}x \right| + \left| \int_\Omega \mu_h (1 - h_k) \frac{M_k}{1 + M_k} \phi \, \mathrm{d}x \right| + \left| \int_\Omega \delta_h h_k e_k \phi \, \mathrm{d}x \right|
$$

$$
\leq D_h \int_\Omega |\nabla h_k| |\nabla \phi| \, \mathrm{d}x + \mu_h \|\phi\|_{\mathcal{L}^1(\Omega)} + \delta_h \|\phi\|_{\mathcal{L}^1(\Omega)}
$$

$$
\leq D_h \|\nabla h_k\|_{\mathcal{L}^2(\Omega)} \|\nabla \phi\|_{\mathcal{L}^2(\Omega)} + (\mu_h + \delta_h) \|\phi\|_{\mathcal{L}^1(\Omega)}
$$

$$
\leq D_h c_h \|\nabla \phi\|_{\mathcal{L}^2(\Omega)} + (\mu_h + \delta_h) \|\phi\|_{\mathcal{L}^1(\Omega)}
$$

$$
\leq C \|\phi\|_{W^{1,2}(\Omega)}.
$$

Hence, $(\partial_t h_k)_k$ is bounded in $\mathcal{L}^2(0, T; W^{-1,2}(\Omega))$ and by theorem A.1.11 we conclude the existence of a subsequence $(h_{k_n})_n$ with $h_{k_n} \to h$ in $\mathcal{L}^\infty(0, T; \mathcal{L}^2(\Omega))$. By boundedness of $(h_{k_n})_n$ in $\mathcal{L}^\infty(0, T; W^{1,2}(\Omega))$, there exists a subsubsequence $(h_{k_{n_l}})_l$ with $h_{k_{n_l}} \rightharpoonup h$ in $\mathcal{L}^2(0, T; W^{1,2}(\Omega))$ and $h_{k_{n_l}} \overset{*}{\rightharpoonup} h$ in $\mathcal{L}^\infty(0, T; W^{1,2}(\Omega))$.

To show convergence of a subsequence of $(e_k)_k$, we repeat the procedure from above. Again, let $X = W^{1,2}(\Omega)$, $B = \mathcal{L}^2(\Omega)$ and $Y = W^{-1,2}(\Omega)$. The boundedness of $(e_k)_k$ in $\mathcal{L}^2(0, T; W^{1,2}(\Omega))$ is given by lemma 3.1.7. Let $\phi \in \mathcal{L}^2(0, T; W_0^{1,2}(\Omega))$. Multiplying (3.6c) by ϕ and integrating over $(0, T) \times \Omega$ yields

$$
\left| \int_0^T \int_\Omega \partial_t e_k \cdot \phi \, \mathrm{d}x \, \mathrm{d}t \right|
$$

$$
\leq \int_0^T \left(D_e \left| \int_\Omega \Delta e_k \cdot \phi \, \mathrm{d}x \right| + \varsigma_e \left| \int_\Omega \nabla \cdot (e_k (1 - e_k) \nabla h_k) \phi \, \mathrm{d}x \right| \right.
$$

$$
\left. + \left| \int_\Omega G_e(h_k, M_k) e_k (1 - e_k) \phi \, \mathrm{d}x \right| \right) \mathrm{d}t
$$

$$
\leq D_e \int_0^T \int_\Omega |\nabla e_k| |\nabla \phi| \, \mathrm{d}x \, \mathrm{d}t + \varsigma_e \int_0^T \int_\Omega |\nabla h_k| |\nabla \phi| \, \mathrm{d}x \, \mathrm{d}t + \mu_e \int_0^T \int_\Omega |\phi| \, \mathrm{d}x \, \mathrm{d}t
$$

$$\leq D_e \int_0^T \|\nabla e_k\|_{\mathcal{L}^2(\Omega)} \|\nabla \phi\|_{\mathcal{L}^2(\Omega)} \, \mathrm{d}t + \varsigma_e \int_0^T \|\nabla h_k\|_{\mathcal{L}^2(\Omega)} \|\nabla \phi\|_{\mathcal{L}^2(\Omega)} \, \mathrm{d}t$$

$$+ \mu_e \int_0^T \|\phi\|_{\mathcal{L}^1(\Omega)} \, \mathrm{d}t$$

$$\leq D_e \|\nabla e_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \|\nabla \phi\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}$$

$$+ \varsigma_e \|\nabla h_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \|\nabla \phi\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} + \mu_e \|\phi\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}$$

$$\leq C(T) \|\phi\|_{\mathcal{L}^2(0,T;W^{1,2}(\Omega))}.$$

Again, by theorem A.1.11 we conclude the existence of a subsequence $(e_{k_n})_n$ with $e_{k_n} \to e$ in $\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))$.
The boundedness of $(e_{k_n})_n$ in $\mathcal{L}^2(0,T;W^{1,2}(\Omega))$ implies the existence of a further subsequence $(e_{k_{n_l}})_l$ with $e_{k_{n_l}} \rightharpoonup e$ in $\mathcal{L}^2(0,T;W^{1,2}(\Omega))$.

Finally, we repeat the procedure for $(Q_k)_k$. Again, let $X = W^{1,2}(\Omega)$, $B = \mathcal{L}^2(\Omega)$ and $Y = W^{-1,2}(\Omega)$. The boundedness of $(Q_k)_k$ in $\mathcal{L}^\infty(0,T;W^{1,2}(\Omega))$ is given by lemma 3.1.7. Let $\phi \in \mathcal{L}^2(0,T;W_0^{1,2}(\Omega))$. By multiplying (3.6c) by ϕ and integrating over Ω, we obtain

$$\left| \int_\Omega \partial_t Q_k \cdot \phi \, \mathrm{d}x \right| \leq \mu_Q \left| \int_\Omega Q_k(1 - Q_k)\phi \, \mathrm{d}x \right| + \delta_Q \left| \int_\Omega \frac{h_{k-1}}{1 + h_{k-1}} Q_k \phi \, \mathrm{d}x \right|$$

$$\leq \mu_Q \|\phi\|_{\mathcal{L}^1(\Omega)} + \delta_Q \|\phi\|_{\mathcal{L}^1(\Omega)}$$

$$\leq C \|\phi\|_{W^{1,2}(\Omega)}.$$

Hence, $(\partial_t Q_k)_k$ is bounded in $\mathcal{L}^2(0,T;W^{-1,2}(\Omega))$ and by theorem A.1.11 we can conclude the existence of a subsequence $(Q_{k_n})_n$ with $Q_{k_n} \to Q$ in $\mathcal{L}^\infty(0,T;\mathcal{L}^2(\Omega))$. By boundedness of $(Q_{k_n})_n$ in $\mathcal{L}^\infty(0,T;W^{1,2}(\Omega))$, there exists a subsubsequence $(Q_{k_{n_l}})_l$ with $Q_{k_{n_l}} \rightharpoonup Q$ in $\mathcal{L}^2(0,T;W^{1,2}(\Omega))$ and $Q_{k_{n_l}} \stackrel{*}{\rightharpoonup} Q$ in $\mathcal{L}^\infty(0,T;W^{1,2}(\Omega))$.

To show $M(t,x), h(t,x), e(t,x), Q(t,x) \in [0,1]$ a.e., we note that

$$\|M_k\|_{\mathcal{L}^\infty((0,T)\times\Omega)}, \|h_k\|_{\mathcal{L}^\infty((0,T)\times\Omega)}, \|e_k\|_{\mathcal{L}^\infty((0,T)\times\Omega)}, \|Q_k\|_{\mathcal{L}^\infty((0,T)\times\Omega)} \leq 1$$

implies

$$M_{k_n} \stackrel{*}{\rightharpoonup} M, \ h_{k_n} \stackrel{*}{\rightharpoonup} h, \ e_{k_n} \stackrel{*}{\rightharpoonup} e, \ Q_{k_n} \stackrel{*}{\rightharpoonup} Q$$

in $\mathcal{L}^\infty((0,T)\times\Omega)$ for some subsequences, and it holds

$$\|M\|_{\mathcal{L}^\infty((0,T)\times\Omega)}, \|h\|_{\mathcal{L}^\infty((0,T)\times\Omega)}, \|e\|_{\mathcal{L}^\infty((0,T)\times\Omega)}, \|Q\|_{\mathcal{L}^\infty((0,T)\times\Omega)} \leq 1.$$

Since $0 \leq M_k, h_k, e_k, Q_k \leq 1$ implies $\|1 - M_k\|_{\mathcal{L}^\infty((0,T)\times\Omega)}, \|1 - h_k\|_{\mathcal{L}^\infty((0,T)\times\Omega)},$ $\|1 - e_k\|_{\mathcal{L}^\infty((0,T)\times\Omega)}, \|1 - Q_k\|_{\mathcal{L}^\infty((0,T)\times\Omega)} \leq 1$, we conclude as above $\|1 - M\|_{\mathcal{L}^\infty((0,T)\times\Omega)}, \|1-h\|_{\mathcal{L}^\infty((0,T)\times\Omega)}, \|1-e\|_{\mathcal{L}^\infty((0,T)\times\Omega)}, \|1-Q\|_{\mathcal{L}^\infty((0,T)\times\Omega)} \leq 1.$ Hence, $0 \leq M, h, e, Q \leq 1$ almost everywhere. $\qquad\square$

Next, we show that M, h, e, Q is indeed a weak solution to the given problem.

Theorem 3.1.11. *The limit functions M, h, e, Q constructed in the proof of lemma 3.1.10 are a global weak solution to (3.1)-(3.4) in the sense of definition 3.1.5.*

For the proof of this theorem, we will often use the following result:

Corollary 3.1.12. [1] *Let $m, n, N \in \mathbb{N}$, let $E \subset \mathbb{R}^N$ be a bounded domain, and let $D \subset \mathbb{R}^m$ be closed. Let further $p \in [1, \infty]$, $r \in [1, \infty)$ and let $f : D \to \mathbb{R}^n$ be bounded in $\mathcal{L}^\infty(D)$ and continuous. If a sequence of $\mathcal{L}^p$-functions $(a_k)_k$ with $a_k : \mathbb{R}^N \to D$ converges strongly to some a in $\mathcal{L}^p(E)$, then $f(a_{k_l}) \to f(a)$ in $\mathcal{L}^r(E)$ for some subsequence $(a_{k_l})_l$.*

Proof. Strong convergence of $(a_k)_k$ in measure implies convergence of a subsequence almost everywhere. Together with continuity of f, this implies almost everywhere convergence of a subsequence of $f(a_k)$ to $f(a)$. Using the dominated convergence theorem, we find a converging subsequence $f(a_{k_l}) \to f(a)$ in $\mathcal{L}^r(\Omega)$. $\square$

Proof of theorem 3.1.11. Let $T > 0$ and $\phi \in C_0^\infty([0, T) \times \Omega)$. First, consider equation (3.6a). It holds

$$
-\int_0^T \int_\Omega \phi_t Q_k \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0, \cdot) Q_0^{(k)} \, \mathrm{d}x
$$
$$
= \int_0^T \int_\Omega \phi \left(\mu_Q Q_k (1 - Q_k) - \delta_Q \frac{h_{k-1}}{1 + h_{k-1}} Q_k \right) \mathrm{d}x \, \mathrm{d}t.
\tag{3.15}
$$

As $Q_k \to Q$ in $\mathcal{L}^\infty(0, T; \mathcal{L}^2(\Omega))$ (or at least, this holds for a subsequence of Q_k) and $\phi_t \in C_0^\infty([0, T) \times \Omega)$, we find

$$
\left| \int_0^T \int_\Omega \phi_t (Q - Q_k) \, \mathrm{d}x \, \mathrm{d}t \right| \leq c \int_0^T \int_\Omega |Q - Q_k| \, \mathrm{d}x \, \mathrm{d}t \to 0.
\tag{3.16}
$$

By $Q_0^{(k)} \to Q_0$ in $W^{2,2}(\Omega)$, we further obtain

$$
\left| \int_\Omega \phi(0, \cdot)(Q_0 - Q_0^{(k)}) \right| \to 0
\tag{3.17}
$$

By boundedness and continuity of $f(Q_k, h_{k-1}) := \mu_Q Q_k (1 - Q_k) - \delta_Q \frac{h_{k-1}}{1 + h_{k-1}} Q_k$ (remember, that $0 \leq h_{k-1}, Q_k \leq 1$) and the strong convergence of (subsequences of) $(Q_k)_k$ and $(h_k)_k$, we conclude by corollary 3.1.12 $f(Q_k, h_{k-1}) \to f(Q, h)$ in $\mathcal{L}^1(0, T; \mathcal{L}^1(\Omega))$. Hence, it holds

$$
\left| \int_0^T \int_\Omega \phi \left(\mu_Q Q_k (1 - Q_k) - \delta_Q \frac{h_{k-1}}{1 + h_{k-1}} Q_k - \mu_Q Q(1 - Q) + \delta_Q \frac{h}{1 + h} Q \right) \mathrm{d}x \, \mathrm{d}t \right|
$$
$$
\leq \|\phi\|_{C([0,T] \times \bar{\Omega})} \int_0^T \int_\Omega |f(Q_k, h_{k-1}) - f(Q, h)| \, \mathrm{d}x \, \mathrm{d}t
$$
$$
\to 0.
\tag{3.18}
$$

Combining (3.15)-(3.18) yields

$$
-\int_0^T \int_\Omega \phi_t Q \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0, \cdot) Q_0 \, \mathrm{d}x = \int_0^T \int_\Omega \phi \left(\mu_Q Q(1 - Q) - \delta_Q \frac{h}{1 + h} Q \right) \mathrm{d}x \, \mathrm{d}t.
$$

---

[1] The result should be well known; since no suitable source could be found, we give the statement together with the corresponding proof.

Next, consider equation (3.6b). It holds

$$-\int_0^T \int_\Omega \phi_t h_k \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0, \cdot) \, h_0 \, \mathrm{d}x$$

$$= -\int_0^T \int_\Omega D_h \nabla\phi \cdot \nabla h_k \, \mathrm{d}x \, \mathrm{d}t + \int_0^T \int_\Omega \phi \left(\mu_h (1 - h_k) \frac{M_k}{1 + M_k} - \delta_h h_k e_k \right) \mathrm{d}x \, \mathrm{d}t.$$

$$(3.19)$$

As we did for equation (3.16), we find

$$\left| \int_0^T \int_\Omega \phi_t (h - h_k) \, \mathrm{d}x \, \mathrm{d}t \right| \leq c \int_0^T \int_\Omega |h - h_k| \, \mathrm{d}x \, \mathrm{d}t \to 0. \qquad (3.20)$$

It further holds

$$\int_0^T \int_\Omega D_h \nabla\phi (\nabla h - \nabla h_k) \, \mathrm{d}x \, \mathrm{d}t \to 0, \qquad (3.21)$$

since $\nabla\phi \in \mathcal{L}^2(0, T; \mathcal{L}^2(\Omega))$ and $(\nabla h - \nabla h_k) \rightharpoonup 0$ in $\mathcal{L}^2(0, T; \mathcal{L}^2(\Omega))$.

Using the same argumentation as for (3.18) above, now with $f(M_k, h_k, e_k) := \mu_h(1 - h_k)\frac{M_k}{1+M_k} - \delta_h h_k e_k$, we find

$$\int_0^T \int_\Omega \phi \left(\mu_h (1 - h_k) \frac{M_k}{1 + M_k} - \delta_h h_k e_k - \mu_h (1 - h) \frac{M}{1 + M} + \delta_h h e \right) \mathrm{d}x \, \mathrm{d}t \to 0.$$

$$(3.22)$$

Combining (3.19)-(3.22), we obtain

$$-\int_0^T \int_\Omega \phi_t h \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0, \cdot) \, h_0 \, \mathrm{d}x$$

$$= -\int_0^T \int_\Omega D_h \nabla\phi \cdot \nabla h \, \mathrm{d}x \, \mathrm{d}t + \int_0^T \int_\Omega \phi \left(\mu_h (1 - h) \frac{M}{1 + M} - \delta_h h e \right) \mathrm{d}x \, \mathrm{d}t.$$

We repeat the procedure for equation (3.6c). It holds

$$-\int_0^T \int_\Omega \phi_t \, e_k \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0, \cdot) \, e_0 \, \mathrm{d}x = -\int_0^T \int_\Omega D_e \nabla\phi \cdot \nabla e_k \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \int_0^T \int_\Omega \varsigma_e e_k (1 - e_k) \nabla\phi \cdot \nabla h_k \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \int_0^T \int_\Omega \phi \, G_e(h_k, M_k) e_k (1 - e_k) \, \mathrm{d}x \, \mathrm{d}t.$$

$$(3.23)$$

As was done above, we find

$$\left| \int_0^T \int_\Omega \phi_t (e - e_k) \, \mathrm{d}x \, \mathrm{d}t \right| \leq c \int_0^T \int_\Omega |e - e_k| \, \mathrm{d}x \, \mathrm{d}t \to 0. \qquad (3.24)$$

Analogously to equation (3.21), we obtain

$$\int_0^T \int_\Omega D_e \nabla \phi (\nabla e - \nabla e_k) \, \mathrm{d}x \, \mathrm{d}t \to 0. \tag{3.25}$$

As $e_k \to e$ in $\mathcal{L}^2(0, T; \mathcal{L}^2(\Omega))$ and $e_k \in [0, 1]$, corollary 3.1.12 implies the existence of a subsequence $(e_{k_n})_n$ with $e_{k_n}(1 - e_{k_n}) \to e(1 - e)$ in $\mathcal{L}^2(0, T; \mathcal{L}^2(\Omega))$. For shortness, we drop the subindex, and with $\nabla h_k \rightharpoonup \nabla h$ in $\mathcal{L}^2(0; T; \mathcal{L}^2(\Omega))$ we obtain

$$\left| \int_0^T \int_\Omega (e(1-e)\nabla h - e_k(1-e_k)\nabla h_k) \, \nabla \phi \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$\leq \left| \int_0^T \int_\Omega (e(1-e) - e_k(1-e_k)) \, \nabla h_k \nabla \phi \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$+ \left| \int_0^T \int_\Omega e(1-e) \, (\nabla h - \nabla h_k) \, \nabla \phi \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$\leq \|e(1-e) - e_k(1-e_k)\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \|\nabla h_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \|\nabla \phi\|_{C([0,T] \times \bar{\Omega})}$$

$$+ \left| \int_0^T \int_\Omega \nabla \phi e(1-e)(\nabla h - \nabla h_k) \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$\to 0$$

$$\tag{3.26}$$

Finally, with $f(h_k, e_k, M_k) := G_e(h_k, M_k)e_k(1 - e_k) = \mu_e \frac{h_k M_k}{1 + h_k M_k} e_k(1 - e_k)$ we conclude in the same way as we did for (3.18)

$$\int_0^T \int_\Omega \phi \left(\mu_e \frac{hM}{1 + hM} e(1-e) - \mu_e \frac{h_k M_k}{1 + h_k M_k} e_k(1-e_k) \right) \mathrm{d}x \, \mathrm{d}t \to 0. \tag{3.27}$$

Combining (3.23)-(3.27) yields

$$-\int_0^T \int_\Omega \phi_t \, e \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0, \cdot) \, e_0 \, \mathrm{d}x = -\int_0^T \int_\Omega D_e \nabla \phi \cdot \nabla e \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \int_0^T \int_\Omega \varsigma_e e(1-e) \nabla \phi \cdot \nabla h \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \int_0^T \int_\Omega \phi \, G_e(h, M) e(1-e) \, \mathrm{d}x \, \mathrm{d}t. \tag{3.28}$$

So far, we proved that (M,Q,h,e) fulfills (3.5a)-(3.5c). To prove, that it is also a solution to (3.5d), we will need the following convergence result:

Lemma 3.1.13. *Let $\Omega \subset \mathbb{R}^N$ be a bounded domain, let $T > 0$, and let $(f_k)_k$ be a sequence of functions in $C(0, T; W^{2,2}(\Omega))$ with $\nabla f_k \cdot \nu = 0$ on $(0, T) \times \partial\Omega$. Let further*

$$f_k \to f \text{ in } \mathcal{L}^2(0, T; \mathcal{L}^2(\Omega)) \quad \text{and} \quad \nabla f_k \rightharpoonup \nabla f \text{ in } \mathcal{L}^2(0, T; \mathcal{L}^2(\Omega)),$$

and let $\|\Delta f_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \leq c$ for some constant c, which is independent of k. Then there exists a subsequence $(f_{k_n})_n$ of $(f_k)_k$, such that $\nabla f_{k_n} \to \nabla f$ in $\mathcal{L}^2(0, T; \mathcal{L}^2(\Omega))$.

Proof. By weak convergence of $(\nabla f_k)_k$ to ∇f in $\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))$, it holds

$$\int_0^T \int_\Omega \nabla f_k \nabla f \, \mathrm{d}x \, \mathrm{d}t \to \int_0^T \int_\Omega |\nabla f|^2 \, \mathrm{d}x \, \mathrm{d}t. \tag{3.29}$$

Now consider the following difference of integrals:

$$
\begin{aligned}
\left| \int_0^T \int_\Omega |\nabla f_k|^2 \, \mathrm{d}x \, \mathrm{d}t \right. & \left. - \int_0^T \int_\Omega \nabla f_k \nabla f \, \mathrm{d}x \, \mathrm{d}t \right| \\
&= \left| \int_0^T \int_\Omega \nabla f_k (\nabla f_k - \nabla f) \, \mathrm{d}x \, \mathrm{d}t \right| \\
&= \left| \int_0^T \int_\Omega \Delta f_k (f_k - f) \, \mathrm{d}x \, \mathrm{d}t \right| \\
&\leq \underbrace{\|\Delta f_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}}_{\leq c} \underbrace{\|f_k - f\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}}_{\to 0} \\
&\to 0.
\end{aligned}
\tag{3.30}
$$

Hence,

$$\int_0^T \int_\Omega |\nabla f_k|^2 \, \mathrm{d}x \, \mathrm{d}t - \int_0^T \int_\Omega \nabla f_k \nabla f \, \mathrm{d}x \, \mathrm{d}t \to 0,$$

which implies

$$\int_0^T \int_\Omega |\nabla f_k|^2 \, \mathrm{d}x \, \mathrm{d}t \to \int_0^T \int_\Omega |\nabla f|^2 \, \mathrm{d}x \, \mathrm{d}t$$

due to (3.29). Applying the theorem of Radon-Riesz, $\nabla f_k \rightharpoonup \nabla f$ in $\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))$ together with $\|\nabla f_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \to \|\nabla f\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}$ implies the existence of a strongly convergent subsequence $(\nabla f_{k_n})_n$ with $\nabla f_{k_n} \to \nabla f$ in $\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))$. □

Continuation of the proof of theorem 3.1.11. Consider equation (3.6d). We find

$$
\begin{aligned}
-\int_0^T \int_\Omega \phi_t \, M_k \, \mathrm{d}x \, \mathrm{d}t & - \int_\Omega \phi(0,\cdot) \, M_0 \, \mathrm{d}x \\
&= \int_0^T \int_\Omega M_k \nabla \phi \cdot g_k \, \mathrm{d}x \, \mathrm{d}t - \epsilon_k \int_0^T \int_\Omega \nabla \phi \cdot \nabla M_k \, \mathrm{d}x \, \mathrm{d}t \\
&\quad + \int_0^T \int_\Omega \phi \, G_M(h_{k-1}, s_k^*, y_k^*) M_k (1 - M_k) \, \mathrm{d}x \, \mathrm{d}t.
\end{aligned}
\tag{3.31}
$$

As was done above, we find

$$\left| \int_0^T \int_\Omega \phi_t (M - M_k) \, \mathrm{d}x \, \mathrm{d}t \right| \leq c \int_0^T \int_\Omega |M - M_k| \, \mathrm{d}x \, \mathrm{d}t \to 0. \tag{3.32}$$

For the third term on the right hand side, we need

$$s_k^* \to s^*, \quad y_k^* \to y^* \text{ in } \mathcal{L}^2(0,T;\mathcal{L}^2(\Omega)).$$

Using lemma 3.1.13, we obtain strong convergence of (a subsequence of) $(\nabla h_k)_k$. For strong convergence of a subsequence of $(\nabla Q_k)_k$, we have to check $\nabla Q_k(x) \cdot$

$\nu(x) = 0$ on $\partial\Omega$ in order to apply lemma 3.1.13:

Let $x \in \partial\Omega$ and consider the gradient of equation (3.6a). Remember that the ODE (3.6a) was defined on $\bar{\Omega}$. Multiplication by the outward unit normal vector $\nu(x)$ yields

$$\partial_t(\nabla Q_k \cdot \nu) = \mu_Q(1 - 2Q_k)\nabla Q_k \cdot \nu - \delta_Q \frac{h_{k-1}}{1 + h_{k-1}}\nabla Q_k \cdot \nu - \delta_Q \frac{\nabla h_{k-1} \cdot \nu}{(1 + h_{k-1})^2}Q_k$$

with initial condition $\nabla Q_k(0, x) \cdot \nu(x) = 0$. Setting $u(t) = \nabla Q_k(t, x) \cdot \nu(x)$ (note that $x \in \partial\Omega$ was fixed) and using $\nabla h_{k-1} \cdot \nu = 0$ by boundary condition, we find the ODE

$$\partial_t u = \mu_Q(1 - 2Q_k)u - \delta_Q \frac{h_{k-1}}{1 + h_{k-1}}u,$$

$$u(0) = 0.$$

This linear ODE has a unique solution, which is given by $u(t) = 0$ for all $t > 0$. Hence, $\nabla Q_k(t, x) \cdot \nu(x) = 0$ on $\partial\Omega$, and we can conclude strong convergence of (a subsequence of) $(\nabla Q_k)_k$ by applying lemma 3.1.13. Then by corollary 3.1.12, it holds

$$s_k^* \to s^*, \quad y_k^* \to y^* \text{ in } \mathcal{L}^2(0, T; \mathcal{L}^2(\Omega))$$

and hence

$$G_M(h_{k-1}, s_k^*, y_k^*)M_k(1 - M_k) \to G_M(h, s^*, y^*)M(1 - M) \text{ in } \mathcal{L}^2(0, T; \mathcal{L}^2(\Omega)),$$

so

$$\int_0^T \int_\Omega \phi \left(G_M(h_{k-1}, s_k^*, y_k^*)M_k(1 - M_k) - G_M(h, s^*, y^*)M(1 - M)\right) \,\mathrm{d}x \,\mathrm{d}t \to 0. \tag{3.33}$$

By $\epsilon_k \to 0$ and boundedness of ∇M_k in $\mathcal{L}^2(0, T; \mathcal{L}^2(\Omega))$, we find

$$\epsilon_k \int_0^T \int_\Omega \nabla\phi \cdot \nabla M_k \,\mathrm{d}x \,\mathrm{d}t \to 0.$$

We multiply the remaining integral by $\frac{a_2 s_{max}}{a_1}$ and split it into three terms:

$$\frac{a_2 s_{max}}{a_1} \int_0^T \int_\Omega \nabla\phi(Mg - M_k g_k) \,\mathrm{d}x \,\mathrm{d}t$$

$$= -\rho_2 \int_0^T \int_\Omega \nabla\phi \left(M(1 - M)\mathbb{D}_W \nabla M - M_k(1 - M_k)\mathbb{D}_W \nabla M_k\right) \,\mathrm{d}x \,\mathrm{d}t \quad \text{(A)}$$

$$-(1 - \rho_1) \int_0^T \int_\Omega \nabla\phi \left(M(1 - M)\mathbb{D}_W \frac{\nabla h}{\sqrt{1 + |\nabla h|^2}}\right.$$
$$\left. -M_k(1 - M_k)\mathbb{D}_W \frac{\nabla h_{k-1}}{\sqrt{1 + |\nabla h_{k-1}|^2}}\right) \,\mathrm{d}x \,\mathrm{d}t \quad \text{(B)}$$

$$+\rho_1 \int_0^T \int_\Omega \nabla\phi \left((1 - y^*)M(1 - M)\mathbb{D}_W \frac{\nabla Q}{\sqrt{1 + |\nabla Q|^2}}\right.$$
$$\left. -(1 - y_k^*)M_k(1 - M_k)\mathbb{D}_W \frac{\nabla Q_k}{\sqrt{1 + |\nabla Q_k|^2}}\right) \,\mathrm{d}x \,\mathrm{d}t. \quad \text{(C)}$$

For (A), we observe that $M_k(1 - M_k) \to M(1 - M)$ in $\mathcal{L}^2(0, T; \mathcal{L}^2(\Omega))$ due to corollary (3.1.12) (or at least this holds for a subsequence). With $\nabla M_k \rightharpoonup \nabla M$ in $\mathcal{L}^2(0, T; \mathcal{L}^2(\Omega))$, this implies (cf. (3.26))

$$\int_0^T \int_\Omega \nabla \phi M_k(1 - M_k) \, \mathbb{D}_W \nabla M_k \, \mathrm{d}x \, \mathrm{d}t \to \int_0^T \int_\Omega \nabla \phi M(1 - M) \, \mathbb{D}_W \nabla M \, \mathrm{d}x \, \mathrm{d}t.$$

Hence, $(A) \to 0$.
For (B), we use the strong convergence of (a subsequence of) $(\nabla h_k)_k$ obtained by lemma 3.1.13. Together with corollary 3.1.12, this implies

$$M_k(1 - M_k) \frac{\nabla h_{k-1}}{\sqrt{1 + |\nabla h_{k-1}|^2}} \to M(1 - M) \frac{\nabla h}{\sqrt{1 + |\nabla h|^2}} \text{ in } \mathcal{L}^2(0, T; \mathcal{L}^2(\Omega)).$$

Hence, $(B) \to 0$.
For the last term, we find analogously to the argumentation above

$$(1 - y_k^*) M_k(1 - M_k) \frac{\nabla Q_k}{\sqrt{1 + |\nabla Q_k|^2}} \to (1 - y^*) M(1 - M) \frac{\nabla Q}{\sqrt{1 + |\nabla Q|^2}}$$

in $\mathcal{L}^2(0, T; \mathcal{L}^2(\Omega))$, hence $(C) \to 0$. This proves

$$-\int_0^T \int_\Omega \phi_t \, M \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0, \cdot) \, M_0 \, \mathrm{d}x$$
$$= \int_0^T \int_\Omega M \nabla \phi \cdot g(y^*) \, \mathrm{d}x \, \mathrm{d}t + \int_0^T \int_\Omega \phi \, G_M(h, s^*, y^*) M(1 - M) \, \mathrm{d}x \, \mathrm{d}t.$$

Since this holds for all $T \in (0, \infty)$, the functions M, h, e, Q are a global weak solution in the sense of definition 3.1.5. The claimed bounds on M, h, e, Q are given by lemma 3.1.10. $\qquad \square$

By theorem 3.1.11, we also proved theorem 3.1.4.

3.1.5 Remark: Flux saturation in the diffusion term

For the presented analysis to work, we needed to drop the flux saturation in the diffusion term of M. Here, we shortly want to discuss the problems arising from the original model 2.1. Choosing the same decoupling as before, but choosing in b_k instead of $\rho_2 \nabla M_k$ now $\rho_2 \frac{\nabla M_k}{\sqrt{1 + |\nabla M_{k-1}|^2}}$ and in s_k the additional term $-\rho_2 \frac{\nabla M_{k-1}}{\sqrt{1 + |\nabla M_{k-1}|^2}}$, the proof for the a priori estimates given in lemma 3.1.7 works completely analogously up to inequality (3.12), which is now given by

$$\int_0^T \int_\Omega \frac{\nabla M_k \, \mathbb{D}_W \nabla M_k}{\sqrt{1 + |\nabla M_{k-1}|^2}} \, \mathrm{d}x \, \mathrm{d}t \leq c - \frac{1 - \rho_1 - \rho_2}{\rho_2} \int_0^T \int_{\Omega_0^t} \frac{\nabla M_k \, \mathbb{D}_W \nabla h_{k-1}}{\sqrt{1 + |\nabla h_{k-1}|^2}} \, \mathrm{d}x \, \mathrm{d}t$$
$$+ \int_0^T \int_{\Omega_0^t} \frac{\rho_1 (1 - y_k^*)}{\rho_2} \frac{\nabla M_k \, \mathbb{D}_W \nabla Q_k}{\sqrt{1 + |\nabla Q_k|^2}} \, \mathrm{d}x \, \mathrm{d}t,$$

$$(3.34)$$

In difference to (3.12), from (3.34) we cannot conclude an $\mathcal{L}^2$-bound on ∇M_k, but only obtain an $\mathcal{L}^1$-bound under the additional assumption $\rho_2 > \frac{\alpha_{max}}{\alpha_{max}+\alpha_{min}}$, where α_{max} and α_{min} denote the maximum and minimum of the eigenvalues of $\mathbb{D}_W(x)$. So in lemma 3.1.7, we only assume $\|\nabla M_{k-1}\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))} \leq c_M(T)$, aiming to conclude $\|\nabla M_k\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))} \leq c_M(T)$. As in the modeling chapter, we assume that $\rho_1, \rho_2 \in (0,1)$ fulfill $\rho_1 + \rho_2 < 1$. Then from (3.34) it follows

$$
\int_0^T \int_\Omega \frac{\alpha_{min}}{\sqrt{1+|\nabla M_{k-1}|^2}} |\nabla M_k|^2 \, \mathrm{d}x \, \mathrm{d}t
$$
$$
\leq c + \frac{1-\rho_1-\rho_2}{\rho_2} \int_0^T \int_{\Omega_0^t} \frac{\alpha_{max}|\nabla M_k||\nabla h_{k-1}|}{\sqrt{1+|\nabla h_{k-1}|^2}} \, \mathrm{d}x \, \mathrm{d}t
$$
$$
+ \frac{\rho_1(1-y_k^*)}{\rho_2} \int_0^T \int_{\Omega_0^t} \frac{\alpha_{max}|\nabla M_k||\nabla Q_k|}{\sqrt{1+|\nabla Q_k|^2}} \, \mathrm{d}x \, \mathrm{d}t
$$
$$
= c + \frac{1-\rho_1-\rho_2}{\rho_2} \int_0^T \int_{\Omega} \frac{\alpha_{max}|\nabla M_k||\nabla h_{k-1}|}{\sqrt{1+|\nabla h_{k-1}|^2}} \, \mathrm{d}x \, \mathrm{d}t
$$
$$
+ \frac{\rho_1(1-y_k^*)}{\rho_2} \int_0^T \int_{\Omega} \frac{\alpha_{max}|\nabla M_k||\nabla Q_k|}{\sqrt{1+|\nabla Q_k|^2}} \, \mathrm{d}x \, \mathrm{d}t,
$$

where we used again $\nabla M_k = 0$ on the interior of $\Omega \backslash \Omega_0^t$ (cf. proof of lemma 3.1.7). Furthermore, it holds

$$
\left(\int_0^T \int_\Omega |\nabla M_k| \, \mathrm{d}x \, \mathrm{d}t \right)^2
$$
$$
= \left(\int_0^T \int_\Omega \frac{|\nabla M_k|}{\sqrt[4]{1+|\nabla M_{k-1}|^2}} \cdot \sqrt[4]{1+|\nabla M_{k-1}|^2} \, \mathrm{d}x \, \mathrm{d}t \right)^2
$$
$$
\leq \int_0^T \int_\Omega \frac{|\nabla M_k|^2}{\sqrt{1+|\nabla M_{k-1}|^2}} \, \mathrm{d}x \, \mathrm{d}t \cdot \int_0^T \int_\Omega \sqrt{1+|\nabla M_{k-1}|^2} \, \mathrm{d}x \, \mathrm{d}t,
$$

from which we conclude

$$
\frac{\left(\int_0^T \int_\Omega |\nabla M_k| \, \mathrm{d}x \, \mathrm{d}t \right)^2}{\int_0^T \int_\Omega \sqrt{1+|\nabla M_{k-1}|^2} \, \mathrm{d}x \, \mathrm{d}t} \leq \int_0^T \int_\Omega \frac{|\nabla M_k|^2}{\sqrt{1+|\nabla M_{k-1}|^2}} \, \mathrm{d}x \, \mathrm{d}t.
$$

Together with

$$
\frac{\|\nabla M_k\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}^2}{\int_0^T \int_\Omega \sqrt{1+|\nabla M_{k-1}|^2} \, \mathrm{d}x \, \mathrm{d}t} \geq \frac{\|\nabla M_k\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}^2}{\int_0^T \int_\Omega (1+|\nabla M_{k-1}|) \, \mathrm{d}x \, \mathrm{d}t}
$$
$$
= \frac{\|\nabla M_k\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}^2}{|\Omega|T + \|\nabla M_{k-1}\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}}
$$

it follows

$$\alpha_{min}\frac{\|\nabla M_k\|^2_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}}{|\Omega|T + \|\nabla M_{k-1}\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}}$$

$$\leq c + \frac{1-\rho_1-\rho_2}{\rho_2}\int_0^T\int_\Omega \frac{\alpha_{max}|\nabla M_k||\nabla h_{k-1}|}{\sqrt{1+|\nabla h_{k-1}|^2}}\,\mathrm{d}x\,\mathrm{d}t$$

$$+ \frac{\rho_1(1-y_k^*)}{\rho_2}\int_0^T\int_\Omega \frac{\alpha_{max}|\nabla M_k||\nabla Q_k|}{\sqrt{1+|\nabla Q_k|^2}}\,\mathrm{d}x\,\mathrm{d}t$$

$$\leq c + \frac{1-\rho_1-\rho_2}{\rho_2}\int_0^T\int_\Omega \alpha_{max}|\nabla M_k|\,\mathrm{d}x\,\mathrm{d}t$$

$$+ \frac{\rho_1(1-y_k^*)}{\rho_2}\int_0^T\int_\Omega \alpha_{max}|\nabla M_k|\,\mathrm{d}x\,\mathrm{d}t$$

$$\leq c + \frac{1-\rho_1-\rho_2}{\rho_2}\alpha_{max}\|\nabla M_k\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}$$

$$+ \frac{\rho_1(1-y_k^*)}{\rho_2}\alpha_{max}\|\nabla M_k\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}.$$

Using $y_k^* \leq 1$ and hence $1 - \rho_2 - \rho_1 y_k^* > 0$, we conclude

$$\left(\|\nabla M_k\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))} - \frac{\alpha_{max}}{2\alpha_{min}}\frac{1-\rho_2-\rho_1 y_k^*}{\rho_2}(T|\Omega| + \|\nabla M_{k-1}\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))})\right)^2$$

$$\leq \frac{\alpha_{max}^2}{4\alpha_{min}^2}\frac{(1-\rho_2-\rho_1 y_k^*)^2}{\rho_2^2}\left(T|\Omega| + \|\nabla M_{k-1}\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}\right)^2$$

$$+ \frac{c}{\alpha_{min}}\left(T|\Omega| + \|\nabla M_{k-1}\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}\right)$$

$$\leq \frac{\alpha_{max}^2}{4\alpha_{min}^2}\frac{(1-\rho_2-\rho_1 y_k^*)^2}{\rho_2^2}(T|\Omega| + c_M(T))^2 + \frac{c}{\alpha_{min}}(T|\Omega| + c_M(T)),$$

which implies

$$\|\nabla M_k\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}$$

$$\leq \frac{\alpha_{max}}{2\alpha_{min}}\frac{1-\rho_2-\rho_1 y_k^*}{\rho_2}(T|\Omega| + \|\nabla M_{k-1}\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))})$$

$$+ \sqrt{\frac{\alpha_{max}^2}{4\alpha_{min}^2}\frac{(1-\rho_2-\rho_1 y_k^*)^2}{\rho_2^2}(T|\Omega| + c_M(T))^2 + \frac{c}{\alpha_{min}}(T|\Omega| + c_M(T))}$$

$$\leq \frac{\alpha_{max}}{2\alpha_{min}}\frac{1-\rho_2-\rho_1 y_k^*}{\rho_2}(T|\Omega| + c_M(T))$$

$$+ \sqrt{\frac{\alpha_{max}^2}{4\alpha_{min}^2}\frac{(1-\rho_2-\rho_1 y_k^*)^2}{\rho_2^2}(T|\Omega| + c_M(T))^2 + \frac{c}{\alpha_{min}}(T|\Omega| + c_M(T))}$$

$$\leq \frac{\alpha_{max}}{2\alpha_{min}}\frac{1-\rho_2}{\rho_2}(T|\Omega| + c_M(T))$$

$$+ \sqrt{\frac{\alpha_{max}^2}{4\alpha_{min}^2}\frac{(1-\rho_2)^2}{\rho_2^2}(T|\Omega| + c_M(T))^2 + \frac{c}{\alpha_{min}}(T|\Omega| + c_M(T))}$$

$$\leq \frac{\alpha_{max}}{2\alpha_{min}} \frac{1 - \rho_2}{\rho_2}(T|\Omega| + c_M(T)) + \frac{\alpha_{max}}{2\alpha_{min}} \frac{1 - \rho_2}{\rho_2}(T|\Omega| + c_M(T))$$
$$+ \sqrt{\frac{c}{\alpha_{min}}(T|\Omega| + c_M(T))}$$
$$\leq \frac{\alpha_{max}}{\alpha_{min}} \frac{1 - \rho_2}{\rho_2}c_M(T) + \sqrt{\frac{c}{\alpha_{min}}c_M(T)} + \frac{\alpha_{max}}{\alpha_{min}} \frac{1 - \rho_2}{\rho_2}T|\Omega|$$
$$+ \sqrt{\frac{c}{\alpha_{min}}T|\Omega|}.$$

Due to our additional assumption $\rho_2 > \frac{\alpha_{max}}{\alpha_{max} + \alpha_{min}}$, it holds $\frac{\alpha_{max}}{\alpha_{min}} \frac{1 - \rho_2}{\rho_2} < 1$. Hence, $c_M(T)$ can be chosen large enough such that

$$\|\nabla M_k\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))} \leq \frac{\alpha_{max}}{\alpha_{min}} \frac{1 - \rho_2}{\rho_2}c_M(T) + \sqrt{\frac{c}{\alpha_{min}}c_M(T)} + \frac{\alpha_{max}}{\alpha_{min}} \frac{1 - \rho_2}{\rho_2}T|\Omega|$$
$$+ \sqrt{\frac{c}{\alpha_{min}}T|\Omega|}$$
$$\leq c_M(T).$$

Note, that the choice of $c_M(T)$ does not depend on k.

Due to the missing $\mathcal{L}^2$ bound on the gradient of M_k, the theorem of Aubin-Lions cannot be applied on the same spaces as in the foregoing proof. Instead, we can define the space

$$W^{-1,1}(\Omega) := \left\{ u = u_0 + \sum_{k=1}^{3} \partial_{x_i} u_i \text{ for some } u_i \in \mathcal{L}^1(\Omega) \right\}$$

with corresponding norm

$$\|u\|_{W^{-1,1}(\Omega)} := \inf \left\{ \sum_{k=0}^{3} \|u_i\|_{\mathcal{L}^1(\Omega)} : u = u_0 + \sum_{k=1}^{3} \partial_{x_i} u_i, \, u_i \in \mathcal{L}^1(\Omega) \right\},$$

as was done in [86], and choose in theorem A.1.11 $X = W^{1,1}(\Omega)$, $B = \mathcal{L}^1(\Omega)$ and $Y = W^{-1,1}(\Omega)$. Proving boundedness of $(\partial_t M_k)_k$ in $\mathcal{L}^1(0,T;W^{-1,1}(\Omega))$, we find the existence of a convergent subsequence $(M_{k_n})_n$ with $M_{k_n} \to M$ in $\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))$.

Now, there remain two problems to be solved in order to show that the limit function M is indeed a weak solution: Since $\mathcal{L}^1$ is not reflexive, from the boundedness of $\|M_k\|_{\mathcal{L}^1(0,T;W^{1,1}(\Omega))}$ we cannot conclude the existence of a weakly convergent subsequence $M_{k_n} \rightharpoonup M$ in $\mathcal{L}^1(0,T;W^{1,1}(\Omega))$. For this, we would need a slightly stronger bound on ∇M_k. Further, for the convergence of the flux saturated taxis terms we used not only the $\mathcal{L}^2$-convergence of $(Q_k)_k$ and $(h_k)_k$ but also the weak convergence of their gradients as well as the boundedness of $(\Delta Q_k)_k$ and $(\Delta h_k)_k$, which ensured strong convergence of the gradients and hence gave the convergence of the flux-saturated terms. For the flux saturated diffusion term, we can here only conclude $\frac{\nabla M_{k_n}}{\sqrt{1+|\nabla M_{k_n-1}|^2}} \rightharpoonup f$ in $\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))$ for some unknown function f. The proof for $f = \frac{\nabla M}{\sqrt{1+|\nabla M|^2}}$ is a non-trivial task remaining for the completion of the existence proof for the original model with flux saturation in all diffusion and taxis terms of M.

3.2 Adaptations of the existence proof to the model variations presented in sections 2.2-2.4

The aim of this section is to adapt the existence proof presented in the foregoing section to the model variations presented in sections 2.2-2.4. For the go-or-grow model developed in section 2.3 we will confine ourselves to prove the boundedness of cancer cell density in case of an existing solution.

3.2.1 Analysis of the basic model with endothelial cells following $\nabla M / \nabla(hM)$

We consider a simplified version of model 2.2, where again we drop the flux saturation in the diffusion term of M and adapt s^* accordingly (cf. remark 3.1.2). As $\varsigma_e^{(1)}$ and $\varsigma_e^{(2)}$ are both constants, we will drop (i) in $\varsigma_e^{(i)}$ for simplicity of writing.

The first thing to be adapted is the definition of the weak solution. In definition 3.1.5 we simply replace equation (3.5c) by

$$
\begin{aligned}
-\int_0^T \int_\Omega \phi_t \, e \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0,\cdot)\, e_0 \, \mathrm{d}x = & -\int_0^T \int_\Omega D_e \nabla\phi \cdot \nabla e \, \mathrm{d}x \, \mathrm{d}t \\
& + \int_0^T \int_\Omega \varsigma_e e(1-e)\nabla\phi \cdot \nabla f^{(i)}(h,M) \, \mathrm{d}x \, \mathrm{d}t \\
& + \int_0^T \int_\Omega \phi \, G_e(h,M)e(1-e) \, \mathrm{d}x \, \mathrm{d}t.
\end{aligned}
$$
(3.35)

Theorem 3.2.1. *There exists a global weak solution of the simplified version of model 2.2 in the sense of definition 3.1.5, where (3.5c) is replaced by (3.35).*

Proof. As the proof of this theorem is in large parts identical to the one presented in section 3.1, we will only respond to the differences.

The decoupling in section 3.1.1 is basically maintained, replacing equation (3.6c) by

$$
\begin{aligned}
\partial_t e_k = & D_e \Delta e_k - \varsigma_e \nabla_x \cdot \Big(e_k(1-e_k)\nabla_x f^{(i)}(h_k, M_{k-1}) \Big) \\
& + G_e(h_k, M_k)e_k(1-e_k)
\end{aligned} \quad \text{in } \mathbb{R}^+ \times \Omega, \quad (3.36)
$$

and correspondingly (3.8c) by

$$
(D_e \nabla e_k - \varsigma_e e_k(1-e_k)\nabla f^{(i)}(h_k, M_{k-1})) \cdot \nu = 0 \quad \text{on } \mathbb{R}^+ \times \partial\Omega. \quad (3.37)
$$

Here, it is important to use the decoupling $f^{(i)}(h_k, M_{k-1})$ rather than $f^{(i)}(h_k, M_k)$ in order to get a bound on $\|\nabla e_k\|_{\mathcal{L}^2((0,T),\mathcal{L}^2(\Omega))}$.

Lemma 3.2.2. *Let $T > 0$ and $(Q_{k-1}, h_{k-1}, e_{k-1}, M_{k-1}) \in (C^\infty((0,T) \times \bar{\Omega}) \cap C([0,T] \times \bar{\Omega}))^4$ and let $(Q_k, h_k, e_k, M_k) \in (C^\infty((0,T) \times \bar{\Omega}) \cap C([0,T] \times \bar{\Omega}))^4$ be a corresponding solution to system (3.6)-(3.9), where (3.6c) is replaced by (3.36) and (3.8c) by (3.37), respectively. Let further the assumptions from lemma 3.1.7 on the boundedness of $Q_{k-1}, h_{k-1}, e_{k-1}, M_{k-1}$ be fulfilled. Then the estimates on Q_k, h_k, e_k, M_k stated in lemma 3.1.7 still hold.*

Proof. In the proof of this lemma, there are two points to be adapted:

- In the application of theorem A.1.1, we set for $j = 1, 2$

$$a_i(t, x) = \varsigma_e(1 - 2e_k)\partial_{x_i} f^{(j)}(h_k, M_{k-1}),$$
$$a(t, x) = -(1 - e_k)\left(-\varsigma_e \Delta f^{(j)}(h_k, M_{k-1}) + G_e(h_k, M_k)\right),$$

and the assumptions of the theorem are still fulfilled. Hence, we find $0 \le e_k \le 1$.

- For the bound on $\|\nabla e_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}$, we estimate in the same way as was done in the proof of 3.1.7, leading to

$$\|\nabla e_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}^2 \le \left(D_e - \frac{\epsilon}{2}\varsigma_e\right)^{-1} \left(\frac{1}{2}\|e_0\|_{\mathcal{L}^2(\Omega)}^2\right.$$
$$\left. + \varsigma_e \frac{1}{2\epsilon}\|\nabla f^{(i)}(h_k, M_{k-1})\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}^2 + T|\Omega|\mu_e\right).$$

Hence, by

$$\|f^{(1)}(h_k, M_{k-1})\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} = \|\nabla M_{k-1}\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \le c_M(T),$$
$$\|f^{(2)}(h_k, M_{k-1})\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} = \|\nabla(h_k M_{k-1})\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}$$
$$\le \|h_k \nabla M_{k-1}\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}$$
$$+ \|M_{k-1} \nabla h_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}$$
$$\le \|\nabla M_{k-1}\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}$$
$$+ \|\nabla h_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}$$
$$\le c_M(T) + T^{\frac{1}{2}}|\Omega|^{\frac{1}{4}} c_h(T)$$

we can find a bound $c_e(T)$ for $\|\nabla e_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}^2$ analogously to the proof of lemma 3.1.7.

$\square$

Also lemma 3.1.8 can be maintained almost unchanged:

Lemma 3.2.3. *Let $M_0, h_0, e_0 \in W^{1,4}(\Omega)$, $Q_0^{(k)} \in C^\infty(\bar{\Omega})$ with*

$$0 \le M_0, h_0, e_0, Q_0^{(k)} \le 1.$$

Let further $(Q_{k-1}, h_{k-1}, e_{k-1}, M_{k-1}) \in (C^\infty((0, \infty) \times \bar{\Omega}) \cap C([0, \infty) \times \bar{\Omega}))^4$ fulfill the bounds from lemma 3.2.2. Then system (3.6)-(3.9) with (3.6c) and (3.8c) replaced by (3.36) and (3.37), respectively, has a unique global solution $(Q_k, h_k, e_k, M_k) \in (C^\infty((0, \infty) \times \bar{\Omega}) \cap C([0, \infty) \times \bar{\Omega})^4$, which fulfills again the bounds from lemma 3.2.2.

Proof. To adapt the proof to the new system, we change the definitions of the following system coefficients, where we have to distinguish between $f^{(1)}$ and $f^{(2)}$:

- $f^{(1)}(M_{k-1}) = M_{k-1}$:

$$a_{ii}^{21} = 0 \text{ and } a_i^{22} = -\varsigma_e(\nabla_x u_3^{k-1})(1 - u_2^k),$$

- $f^{(2)}(h_k, M_{k-1}) = h_k M_{k-1}$:

$$a_{ii}^{21} = -\varsigma_e u_2^k (1 - u_2^k) u_3^{k-1} \quad \text{and} \quad a_i^{22} = -\varsigma_e (\nabla_x u_3^{k-1})(1 - u_2^k) u_1^k.$$

With these coefficients, theorems A.1.2, A.1.3, A.1.4 and A.1.5 can be applied in the same way as in section 3.1.3, so lemma 3.1.8 still holds true. □

Hence, we find an iterative sequence $(Q_k, h_k, e_k, M_k)_k$ with $Q_k, h_k, e_k, M_k \in C^\infty((0, \infty) \times \bar{\Omega}) \cap C([0, \infty) \times \bar{\Omega})$ of global solutions to system (3.6)-(3.9) with (3.6c) and (3.8c) replaced by (3.36) and (3.37).
Next, in lemma 3.1.10 it was shown that the sequence of solutions converges. The statement for the adapted system is formulated analogously:

Lemma 3.2.4. *Let $(Q_k, h_k, e_k, M_k)_k$ be the sequence of global solutions to system (3.6)-(3.9), where (3.6c) and (3.8c) are replaced by (3.36) and (3.37), respectively, constructed above. Then there exist*

$$M, h, e, Q : \mathbb{R}_0^+ \times \bar{\Omega} \to [0, 1]$$

such that for all $T > 0$ it holds

$$M, e \in \mathcal{L}^2(0, T; W^{1,2}(\Omega)), \qquad h, Q \in \mathcal{L}^\infty(0, T; W^{1,2}(\Omega))$$

and there exists a subsequence $(Q_{k_n}, h_{k_n}, e_{k_n}, M_{k_n})_n$ such that

$$M_{k_n} \to M \ \ in \ \ \mathcal{L}^2(0, T; \mathcal{L}^2(\Omega)), \qquad h_{k_n} \to h \ \ in \ \ \mathcal{L}^\infty(0, T; \mathcal{L}^2(\Omega)),$$
$$e_{k_n} \to e \ \ in \ \ \mathcal{L}^2(0, T; \mathcal{L}^2(\Omega)), \qquad Q_{k_n} \to Q \ \ in \ \ \mathcal{L}^\infty(0, T; \mathcal{L}^2(\Omega))$$

and

$$M_{k_n} \rightharpoonup M \ \ in \ \ \mathcal{L}^2(0, T; W^{1,2}(\Omega)), \qquad e_{k_n} \rightharpoonup e \ \ in \ \ \mathcal{L}^2(0, T; W^{1,2}(\Omega)),$$
$$h_{k_n} \rightharpoonup h \ \ in \ \ \mathcal{L}^2(0, T; W^{1,2}(\Omega)), \qquad h_{k_n} \overset{*}{\rightharpoonup} h \ \ in \ \ \mathcal{L}^\infty(0, T; W^{1,2}(\Omega)),$$
$$Q_{k_n} \rightharpoonup Q \ \ in \ \ \mathcal{L}^2(0, T; W^{1,2}(\Omega)), \qquad Q_{k_n} \overset{*}{\rightharpoonup} Q \ \ in \ \ \mathcal{L}^\infty(0, T; W^{1,2}(\Omega)).$$

Proof. The difference in the proof of this lemma between the original system and the varied system considered here lies in the estimate of the taxis term. For the varied system, we have to find a bound on

$$\varsigma_e \|\nabla f^{(i)}(h_k, M_{k-1})\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \|\nabla \phi\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}$$

instead of

$$\varsigma_e \|\nabla h_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \|\nabla \phi\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}.$$

Due to the boundedness of $\|\nabla h_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}, \|\nabla M_{k-1}\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}$ and $0 \le h_k, M_{k-1} \le 1$, we easily find boundedness by $C\|\phi\|_{\mathcal{L}^2(0,T;W^{1,2}(\Omega))}$. □

Finally, there remains to adapt the proof of theorem 3.1.11, where we have to show that the limits from lemma 3.2.4 are indeed a weak solution to the given system.

Theorem 3.2.5. *The limit functions M, h, e, Q constructed in the proof of lemma 3.2.4 are a global weak solution in the sense of definition 3.1.5, where (3.5c) is replaced by (3.35).*

Proof.   • For $f^{(1)}(h_k, M_{k-1}) = M_{k-1}$ the proof works completely analogously to the proof for the original system, replacing in the argumentation followed by equation (3.26) $\nabla h_k \rightharpoonup \nabla h$ in $\mathcal{L}^2(0, T; \mathcal{L}^2(\Omega))$ by $\nabla M_{k-1} \rightharpoonup \nabla M$ in $\mathcal{L}^2(0, T; \mathcal{L}^2(\Omega))$.

• For $f^{(2)}(h_k, M_{k-1}) = h_k M_{k-1}$, we have to prove

$$\left| \int_0^T \int_\Omega (e(1-e)\nabla(hM) - e_k(1-e_k)\nabla(h_k M_{k-1})) \, \nabla\phi \, \mathrm{d}x \, \mathrm{d}t \right| \to 0.$$

We find

$$\left| \int_0^T \int_\Omega (e(1-e)\nabla(hM) - e_k(1-e_k)\nabla(h_k M_{k-1})) \, \nabla\phi \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$\leq \underbrace{\left| \int_0^T \int_\Omega (e(1-e)h\nabla M - e_k(1-e_k)h_k \nabla M_{k-1}) \, \nabla\phi \, \mathrm{d}x \, \mathrm{d}t \right|}_{(A)}$$

$$+ \underbrace{\left| \int_0^T \int_\Omega (e(1-e)M\nabla h - e_k(1-e_k)M_{k-1} \nabla h_k) \, \nabla\phi \, \mathrm{d}x \, \mathrm{d}t \right|}_{(B)}.$$

We estimate the first term:

$$(A) \leq \left| \int_0^T \int_\Omega (e(1-e)h - e_k(1-e_k)h_k) \, \nabla M_{k-1} \nabla\phi \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$+ \left| \int_0^T \int_\Omega (e(1-e)h(\nabla M - \nabla M_{k-1}) \, \nabla\phi \, \mathrm{d}x \, \mathrm{d}t \right|$$

$$\leq \underbrace{\|e(1-e)h - e_k(1-e_k)h_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}}_{\to 0 \text{ by corollary 3.1.12}}$$

$$\cdot \underbrace{\|\nabla M_{k-1}\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}}_{\leq c_M(T)} \|\nabla\phi\|_{C([0,T]\times\bar\Omega)}$$

$$+ \left| \int_0^T \int_\Omega \left(\underbrace{\nabla\phi e(1-e)h}_{\in \mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \underbrace{(\nabla M - \nabla M_{k-1})}_{\to 0 \text{ in } \mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \right) \mathrm{d}x \, \mathrm{d}t \right|$$

$$\to 0.$$

Analogously, we find $(B) \to 0$.

$\square$

Hence, for the varied system in this subsection, there exists a global weak solution in the sense of definition 3.1.5, where (3.5c) is replaced by (3.35), which proves theorem 3.2.1. $\square$

3.2.2 Remarks about the analysis for the go-or-grow model

We do not show existence of a solution to the go-or-grow model 2.3. The adaptation of the proof from section 3.1 to model 2.3 comes up with several difficulties, beneath others the choice of a suitable decoupling such that bounds on M_k and P_k can be found, and the problem to extract a bound on ∇P_k from equation (2.63b), which does not contain diffusion but transport terms via $|g(h, Q, M, P, y^*)|^2$.

Still, we want to point out that a positive solution - if it exists and is sufficiently smooth - fulfills the biologically relevant bound $C = M + P \leq 1$, meaning that the carrying capacity K_C introduced in subsection 2.3.1 is indeed the maximum density of tumor cells. To this aim, we assume that the initial condition for C fulfills $0 \leq C_0(x) < 1$. Adding (2.63a) and (2.63b), we find

$$\partial_t C + \nabla \cdot (g(h, Q, M, P, y^*)M) = G_P(h, y^*)(1 - C)P,$$

$$g(h, Q, M, P, y^*) = \frac{a_1}{a_2 s_{max}}(1 - C)\mathbb{D}_W b(h, Q, M, P, y^*),$$

$$b(h, Q, M, P, y^*) = (1 - \rho_1 - \rho_2)\frac{-\nabla h}{\sqrt{1 + |\nabla h|^2}} + \rho_1(1 - y^*)\frac{\nabla Q}{\sqrt{1 + |\nabla Q|^2}}$$

$$+ \rho_2 \frac{-\nabla C}{\sqrt{1 + |\nabla C|^2}}.$$

With $u = 1 - C$, we obtain

$$\partial_t u - \nabla \cdot \left((a_{ij})_{i,j=1}^N \nabla u\right) - \nabla \cdot \left((\tilde{a}_i)_{i=1}^N u\right) + a_0 u = 0,$$

where

$$a_{ij} = \frac{a_1 \rho_2}{a_2 s_{max}} \frac{M}{\sqrt{1 + |\nabla C|^2}} u(\mathbb{D}_W)_{ij},$$

$$\tilde{a}_i = \frac{a_1}{a_2 s_{max}} M \left(\mathbb{D}_W \left((1 - \rho_1 - \rho_2)\frac{-\nabla h}{\sqrt{1 + |\nabla h|^2}} + \rho_1(1 - y^*)\frac{\nabla Q}{\sqrt{1 + |\nabla Q|^2}}\right)\right)_i,$$

$$a_0 = G_P(h, y^*)P = \frac{y^*(1 - y^*)}{1 + h}P, \ y^* = \frac{\kappa Q}{1 + \kappa Q}.$$

Let $D_0 = \left(-\frac{1}{2}, \frac{3}{2}\right)$. Then we find that $D = \left(0, \frac{3}{2}\right)$ is nonempty and it holds $t\eta \in D_0$ for all $\eta \in D, t \in [0, 1]$. Further, due to the supposed nonnegativity of h and Q we find that all coefficients are sufficiently smooth. Hence, by application of theorem A.1.6 we find that for $u(0, x) = 1 - C_0(x) > 0$ it holds $u \geq 0$, i.e. $C \leq 1$.

3.2.3 Analysis of the basic model with therapy by gliadel wafers

In this subsection, we prove existence of a global weak solution to a simplified version of model 2.4, where we drop again the diffusion limitation for M. We further make a technical simplification, replacing the diffusion tensor in the equation for carmustine by a scalar diffusion constant. The considered system is then given by

Model 3.2: Therapy by gliadel wafers, simplified

$$\partial_t Q = \mu_Q Q(1-Q) - \delta_Q \frac{h}{1+h} Q - \delta_{QC} \frac{C}{1+C} Q, \tag{3.38a}$$

$$\partial_t h = D_h \Delta h + \mu_h(1-h)\frac{M}{1+M} - \delta_h he, \tag{3.38b}$$

$$\partial_t e = D_e \Delta e - \varsigma_e \nabla \cdot (e(1-e)\nabla h) + G_e(h,M)e(1-e), \tag{3.38c}$$

$$\partial_t C = D_C \Delta C - (k_{bbb}e + k_d)C + \frac{2a}{5} C_{\text{total}}(x)Ce^{-a\int_0^t C(s,x)\,\mathrm{d}s}, \tag{3.38d}$$

$$\partial_t M + \nabla \cdot (g(h,Q,M,y^*)M)$$
$$= G_M(h,s^*,y^*)(1-M)M - \delta_M(s^*)\frac{C}{1+C}M(1-M) \tag{3.38e}$$

in $\mathbb{R}^+ \times \Omega$ (in $\mathbb{R}^+ \times \bar{\Omega}$ for equation (3.38a)), where

$$g(h,Q,M,y^*) = \frac{a_1}{a_2 s_{max}}(1-M)\mathbb{D}_W b(h,Q,M,y^*), \tag{3.39a}$$

$$b(h,Q,M,y^*) = (1-\rho_1)\frac{-\nabla h}{\sqrt{1+|\nabla h|^2}} + \rho_1(1-y^*)\frac{\nabla Q}{\sqrt{1+|\nabla Q|^2}} \tag{3.39b}$$
$$- \rho_2 \nabla M,$$

$$G_M(h,s^*,y^*) = \frac{(1-s^*)(y^* - (y^*)^2)}{1+h}, \tag{3.39c}$$

$$G_e(h,M) = \mu_e \frac{hM}{1+hM}, \tag{3.39d}$$

$$\delta_M(s^*) = \sigma(1-s^*), \tag{3.39e}$$

$$s^* = \left| \frac{a_1}{a_2 s_{max}}(1-M)\mathbb{D}_W \left((1-\rho_1)\frac{-\nabla h}{\sqrt{1+|\nabla h|^2}} \right.\right.$$
$$\left.\left. + \rho_1(1-y^*)\frac{\nabla Q}{\sqrt{1+|\nabla Q|^2}} \right) \right|, \tag{3.39f}$$

$$y^* = \frac{\kappa Q}{1+\kappa Q}, \tag{3.39g}$$

with zero flux boundary conditions

$$Mg(h,Q,M,y^*) \cdot \nu = 0 \quad \text{on } \partial\Omega,\ t > 0, \tag{3.40a}$$
$$D_h \nabla h \cdot \nu = 0 \quad \text{on } \partial\Omega,\ t > 0, \tag{3.40b}$$
$$(D_e \nabla e - \varsigma_e e(1-e)\nabla h) \cdot \nu = 0 \quad \text{on } \partial\Omega,\ t > 0, \tag{3.40c}$$
$$D_C \nabla C \cdot \nu = 0 \quad \text{on } \partial\Omega,\ t > 0 \tag{3.40d}$$

and initial data

$$Q(0,x) = Q_0(x) \in C^1(\bar{\Omega}) \cap W^{2,2}(\Omega), \quad h(0,x) = h_0(x) \in W^{1,4}(\Omega),$$
$$e(0,x) = e_0(x) \in W^{1,4}(\Omega), \quad M(0,x) = M_0(x) \in W^{1,4}(\Omega), \quad (3.41)$$
$$C(0,x) = C_0(x) \in W^{1,4}(\Omega),$$

with $Q_0(x), h_0(x), e_0(x), M_0(x) \in [0,1]$, $C_0(x) \in [0,H]$, $H := \max\limits_{x\in\bar{\Omega}} C_{\text{total}}(x)$, for all $x \in \Omega$, and $\nabla Q_0(x) \cdot \nu = 0$ for all $x \in \partial\Omega$, where Ω is a sufficiently smooth bounded domain of $\mathbb{R}^N$ with $N \leq 3$.

Remark 3.2.6. In simulations later on, the initial data describe the situation directly after surgery. Hence, initial data as well as the water diffusion tensor $\mathbb{D}_W$ are supposed to differ from those in the foregoing models. For the subsequent analysis, however, we will assume a certain regularity of coefficients and initial data. This assumption can be justified by the idea, that in practice a surgical cut is not arbitrarily sharp, so we expect some smoothening effect on the cell densities at the border of the cavity. (In practice, of course, all cell densities have to be discrete at a very close look, no matter what the initial situation is.) We further suppose that the same holds true for the water diffusion tensor, which is in the following supposed to be sufficiently smooth.

We aim to show that there exists a global weak solution in the following sense:

Definition 3.2.7. We call

$$(Q,h,e,C,M) : \mathbb{R}_0^+ \times \bar{\Omega} \to [0,1]^3 \times [0,H] \times [0,1]$$

a global weak solution to system (3.38)-(3.41), if for all $T \in (0,\infty)$ it holds

$$Q, h, C \in \mathcal{L}^\infty(0,T;W^{1,2}(\Omega)), \ e, M \in \mathcal{L}^\infty([0,T) \times \Omega) \cap \mathcal{L}^2(0,T;W^{1,2}(\Omega))$$

and

$$-\int_0^T \int_\Omega \phi_t \, Q \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0, \cdot) \, Q_0 \, \mathrm{d}x$$

$$= \int_0^T \int_\Omega \phi \left(\mu_Q Q(1-Q) - \delta_Q \frac{h}{1+h} Q - \delta_{QC} \frac{C}{1+C} Q \right) \mathrm{d}x \, \mathrm{d}t, \tag{3.42a}$$

$$-\int_0^T \int_\Omega \phi_t \, h \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0, \cdot) \, h_0 \, \mathrm{d}x$$

$$= -\int_0^T \int_\Omega D_h \nabla \phi \cdot \nabla h \, \mathrm{d}x \, \mathrm{d}t \tag{3.42b}$$

$$+ \int_0^T \int_\Omega \phi \left(\mu_h (1-h) \frac{M}{1+M} - \delta_h h e \right) \mathrm{d}x \, \mathrm{d}t,$$

$$-\int_0^T \int_\Omega \phi_t \, e \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0, \cdot) \, e_0 \, \mathrm{d}x$$

$$= -\int_0^T \int_\Omega D_e \nabla \phi \cdot \nabla e \, \mathrm{d}x \, \mathrm{d}t + \int_0^T \int_\Omega \varsigma_e e(1-e) \nabla \phi \cdot \nabla h \, \mathrm{d}x \, \mathrm{d}t \tag{3.42c}$$

$$+ \int_0^T \int_\Omega \phi \, \mu_e \frac{hM}{1+hM} e(1-e) \, \mathrm{d}x \, \mathrm{d}t,$$

$$-\int_0^T \int_\Omega \phi_t \, C \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0, \cdot) \, C_0 \, \mathrm{d}x$$

$$= -\int_0^T \int_\Omega D_C \nabla \phi \cdot \nabla C \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \int_0^T \int_\Omega \phi \left(\frac{2a}{5} C_{\text{total}}(x) C e^{-a \int_0^t C(s,x) \, \mathrm{d}s} - (k_{bbb} e + k_d) C \right) \mathrm{d}x \, \mathrm{d}t,$$

$$\tag{3.42d}$$

$$-\int_0^T \int_\Omega \phi_t \, M \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0, \cdot) \, M_0 \, \mathrm{d}x$$

$$= \int_0^T \int_\Omega M \nabla \phi \cdot g(y^*) \, \mathrm{d}x \, \mathrm{d}t$$

$$+ \int_0^T \int_\Omega \phi \, G_M(h, s^*) M(1-M) - \delta_M(s^*) \frac{C}{1+C} M(1-M) \, \mathrm{d}x \, \mathrm{d}t,$$

$$\tag{3.42e}$$

for all $\phi \in C_0^\infty([0, T) \times \Omega)$.

Remark 3.2.8. On $\mathbb{D}_W(x)$ we make the same assumptions as in section 3.1, i.e. $\mathbb{D}_W(x)$ is positive definite for all $x \in \bar{\Omega}$ and sufficiently smooth.
Further, we assume $k_d \geq \frac{2a}{5} H$.

Theorem 3.2.9. *There exists a global weak solution to model 3.2 in the sense of definition 3.2.7.*

Again, we follow the proof presented in section 3.1 and constrain on presenting the differences. As before, we start by regularizing and decoupling system (3.38) iteratively. The a priori estimates of lemma 3.1.7 are adjusted to the new system and complemented by estimates on C_k. The proof of the existence

of a unique solution to the decoupled system is adapted. Finally, the proof of convergence of the sequences of the solutions components to a weak solution of the original system is adapted/complemented.

Proof of theorem 3.2.9. Choosing $(Q_0^{(k)})_k$ and $(\epsilon_k)_k$ as in section 3.1, we define the decoupling as follows:

$$\partial_t Q_k = \mu_Q Q_k (1 - Q_k) - \delta_Q \frac{h_{k-1}}{1 + h_{k-1}} Q_k - \delta_{QC} \frac{C_{k-1}}{1 + C_{k-1}} Q_k, \qquad (3.43a)$$

$$\partial_t h_k = D_h \Delta h_k + \mu_h (1 - h_k) \frac{M_k}{1 + M_k} - \delta_h h_k e_k, \qquad (3.43b)$$

$$\partial_t e_k = D_e \Delta e_k - \varsigma_e \nabla \cdot (e_k (1 - e_k) \nabla h_k) + G_e(h_k, M_k) e_k (1 - e_k), \qquad (3.43c)$$

$$\partial_t C_k = D_C \Delta C_k - (k_{bbb} e_k + k_d) C_k + \frac{2a}{5} C_{\text{total}}(x) C_k e^{-a \int_0^t C_{k-1} \, ds}, \qquad (3.43d)$$

$$\partial_t M_k + \nabla \cdot (g_k M_k) - \epsilon_k \Delta M_k$$
$$= G_M(h_{k-1}, s_k^*, y_k^*) M_k (1 - M_k) - \delta_M(s_k^*) \frac{C_{k-1}}{1 + C_{k-1}} M_k (1 - M_k), \qquad (3.43e)$$

in $\mathbb{R}^+ \times \Omega$ (in $\mathbb{R}^+ \times \bar{\Omega}$ for equation (3.43a)), where

$$g_k = \frac{a_1}{a_2 s_{max}} (1 - M_k) \mathbb{D}_W b_k, \qquad (3.44a)$$

$$b_k = (1 - \rho_1) \frac{-\nabla h_{k-1}}{\sqrt{1 + |\nabla h_{k-1}|^2}} + \rho_1 (1 - y_k^*) \frac{\nabla Q_k}{\sqrt{1 + |\nabla Q_k|^2}} - \rho_2 \nabla M_k, \qquad (3.44b)$$

$$y_k^* = \frac{\kappa Q_k}{\kappa Q_k + 1}, \qquad (3.44c)$$

$$s_k^* = \left| \frac{a_1}{a_2 s_{max}} M_k (1 - M_k) \mathbb{D}_W \left((1 - \rho_1) \frac{-\nabla h_{k-1}}{\sqrt{1 + |\nabla h_{k-1}|^2}} \right. \right.$$
$$\left. \left. + \rho_1 (1 - y_k^*) \frac{\nabla Q_k}{\sqrt{1 + |\nabla Q_k|^2}} \right) \right| \qquad (3.44d)$$

with corresponding boundary conditions

$$(M_k g_k - \epsilon_k \nabla M_k) \cdot \nu = 0 \qquad \text{on } \partial\Omega, \, t > 0, \qquad (3.45a)$$

$$D_h \nabla h_k \cdot \nu = 0 \qquad \text{on } \partial\Omega, \, t > 0, \qquad (3.45b)$$

$$(D_e \nabla e_k - \varsigma_e e_k (1 - e_k) \nabla h_k) \cdot \nu = 0 \qquad \text{on } \partial\Omega, \, t > 0, \qquad (3.45c)$$

$$D_C \nabla C_k \cdot \nu = 0 \qquad \text{on } \partial\Omega, \, t > 0, \qquad (3.45d)$$

and fulfilling the initial data in (3.41) (for $Q_k(0, x)$ we consider the approximated initial data $Q_0^{(k)}(x)$):

$$Q_k(0, x) = Q_0^{(k)}(x) \in C^\infty(\bar{\Omega}), \quad h_k(0, x) = h_0(x) \in W^{1,4}(\Omega),$$
$$e_k(0, x) = e_0(x) \in W^{1,4}(\Omega), \quad M_k(0, x) = M_0(x) \in W^{1,4}(\Omega), \qquad (3.46)$$
$$C_k(0, x) = C_0(x) \in W^{1,4}(\Omega),$$

with $Q_0^{(k)}(x), h_0(x), e_0(x), M_0(x) \in [0,1]$, $C_0(x) \in [0,H]$ for all $x \in \Omega$, and $\nabla Q_0^{(k)}(x) \cdot \nu = 0$ for all $x \in \partial\Omega$.

For the proof of existence, we first have to find a priori estimates. We expand lemma 3.1.7:

Lemma 3.2.10. *Let $T > 0$ and $(Q_{k-1}, h_{k-1}, e_{k-1}, C_{k-1}, M_{k-1}) \in (C^\infty((0,T) \times \bar\Omega) \cap C([0,T] \times \bar\Omega))^5$ and let $(Q_k, h_k, e_k, C_k, M_k) \in (C^\infty((0,T) \times \bar\Omega) \cap C([0,T] \times \bar\Omega))^5$ be a corresponding solution to system (3.43)-(3.46). Then there exist constants $c_Q(T), c_h(T), c_e(T), c_C(T), c_M(T), c_{QQ}(T), c_{hh}(T), c_{CC}(T)$, depending on time and initial data only, such that the following implication holds:*
If $Q_{k-1}, h_{k-1}, e_{k-1}, C_{k-1}, M_{k-1}$ fulfill

$$0 \leq Q_{k-1}, h_{k-1}, e_{k-1}, M_{k-1} \leq 1,\ 0 \leq C_{k-1} \leq H,$$
$$\|\nabla Q_{k-1}\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^4(\Omega))} \leq c_Q(T),\ \|\nabla h_{k-1}\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^4(\Omega))} \leq c_h(T),$$
$$\|\nabla e_{k-1}\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \leq c_e(T),\ \|\nabla C_{k-1}\|_{\mathcal{L}^\infty(0,T;\mathcal{L}^4(\Omega))} \leq C_C(T),$$
$$\|\nabla M_{k-1}\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \leq c_M(T),\ \|\Delta Q_{k-1}\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^2(\Omega))} \leq c_{QQ}(T),$$
$$\|\Delta h_{k-1}\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \leq c_{hh}(T),\ \|\Delta C_{k-1}\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \leq c_{CC}(T),$$

then it holds

$$0 \leq Q_k, h_k, e_k, M_k \leq 1,\ 0 \leq C_k \leq H,$$
$$\|\nabla Q_k\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^4(\Omega))} \leq c_Q(T),\ \|\nabla h_k\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^4(\Omega))} \leq c_h(T),$$
$$\|\nabla e_k\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \leq c_e(T),\ \|\nabla C_k\|_{\mathcal{L}^\infty(0,T;\mathcal{L}^4(\Omega))} \leq C_C(T),$$
$$\|\nabla M_k\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \leq c_M(T),\ \|\Delta Q_k\|_{\mathcal{L}^\infty((0,T);\mathcal{L}^2(\Omega))} \leq c_{QQ}(T),$$
$$\|\Delta h_k\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \leq c_{hh}(T),\ \|\Delta C_k\|_{\mathcal{L}^2((0,T);\mathcal{L}^2(\Omega))} \leq c_{CC}(T).$$

Proof. The proof of the bounds on h_k and e_k and their derivatives remains unchanged. The proof of the bounds on Q_k and its derivatives works completely analogously to the proof of lemma 3.1.7, since the loss term by carmustine is identical to that by acidity. The bound on M_k can be computed similarly as we did in the proof of lemma 3.1.7: Theorem A.1.6 is still applicable, so we find $0 \leq M_k \leq 1$.
For the boundedness of C_k, we apply theorem A.1.1: In the notations of the theorem, replacing a by $\tilde{a}$ to avoid confusion, we have

$$a_{ij} = D_C I_{ij},\ a_j = 0,\ \tilde{a} = (k_{bbb} e_k + k_d) - \frac{2a}{5} C_{\text{total}}(x) e^{-a \int_0^t C_{k-1}(s,x)\,\mathrm{d}s},$$

and $C_k(t,x) \geq 0$ follows directly from $C_k(0,x) \geq 0$. To obtain $C_k(t,x) \leq H$, we set $u = H - C_k$ and find the equation

$$\partial_t u - D_C \Delta u + \tilde{a} u = \tilde{a} H \geq 0$$

due to the assumption $k_d \geq \frac{2a}{5} H = \frac{2a}{5} \max_{x \in \bar\Omega} C_{\text{total}}(x)$ in remark 3.2.8. Hence, we can conclude $u \geq 0$, i.e. $C_k(t,x) \leq H$.

Next, we aim to find a bound on ∇C_k. Interpreting

$$f_k(t,x) = -(k_{bbb} e_k + k_d) C_k + \frac{2a}{5} C_{\text{total}}(x) C_k e^{-a \int_0^t C_{k-1}(s,x)\,\mathrm{d}s}$$

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as a function of t and x rather than a function of e_k and C_k, we use again the Neumann heat semigroup to find

$$C_k(t,x) = e^{tD_C\Delta}C_0(x) + \int_0^t e^{(t-s)D_C\Delta}f_k(s,x)\,\mathrm{d}s.$$

By boundedness of f_k and theorem A.1.10, we conclude

$$\|\nabla C_k(t,\cdot)\|_{\mathcal{L}^4(\Omega)} \leq \|\nabla\left(e^{tD_C\Delta}C_0(\cdot)\right)\|_{\mathcal{L}^4(\Omega)}$$
$$+ \int_0^t \|\nabla\left(e^{(t-s)D_C\Delta}f_k(s,\cdot)\right)\|_{\mathcal{L}^4(\Omega)}\,\mathrm{d}s$$
$$\leq c_1 e^{-\lambda_1 D_C t}\|\nabla C_0\|_{\mathcal{L}^4(\Omega)}$$
$$+ c_2 \int_0^t (1+((t-s)D_C)^{-\frac{1}{2}})e^{-\lambda_1(t-s)D_C}\|f_k(s,\cdot)\|_{\mathcal{L}^4(\Omega)}\,\mathrm{d}s$$
$$\leq c_1\|\nabla C_0\|_{\mathcal{L}^4(\Omega)} + c_3 \int_0^t (1+((t-s)D_C)^{-\frac{1}{2}})e^{-\lambda_1(t-s)D_C}\,\mathrm{d}s$$
$$\leq c_1\|\nabla C_0\|_{\mathcal{L}^4(\Omega)} + c_4(T)$$
$$=: c_C(T),$$

where $\lambda_1 > 0$ denotes the first nonzero eigenvalue of $-\Delta$ under Neumann boundary conditions. Hence, $\|\nabla C_k\|_{\mathcal{L}^\infty(0,T;\mathcal{L}^4(\Omega))} \leq c_C(T)$.
The proof of the bound on ∇M_k works analogously to its proof in lemma 3.1.7: In equation (3.10), we have to add on the right hand side the term

$$-\sigma \int_\gamma^{T-\gamma}\int_{\Omega_\delta^t} f_\delta(M_k)(1-s_k^*)\frac{C_{k-1}}{1+C_{k-1}}M_k(1-M_k)\,\mathrm{d}x\,\mathrm{d}t$$
$$-\sigma \int_\gamma^{T-\gamma}\int_{\Omega\setminus\Omega_\delta^t} f_\delta(M_k)(1-s_k^*)\frac{C_{k-1}}{1+C_{k-1}}M_k(1-M_k)\,\mathrm{d}x\,\mathrm{d}t.$$

Now we have to derive the limit of these additional terms for $\delta \to 0$. With the same argumentation as in the proof of 3.1.7, we find

$$\lim_{\delta\to 0}\int_\gamma^{T-\gamma}\int_{\Omega_\delta^t} f_\delta(M_k)(1-s_k^*)\frac{C_{k-1}}{1+C_{k-1}}M_k(1-M_k)\,\mathrm{d}x\,\mathrm{d}t$$
$$=\int_\gamma^{T-\gamma}\int_{\Omega_0^t} f_0(M_k)(1-s_k^*)\frac{C_{k-1}}{1+C_{k-1}}M_k(1-M_k)\,\mathrm{d}x\,\mathrm{d}t.$$

For the other term, we estimate

$$\left|\lim_{\delta\to 0}\int_\gamma^{T-\gamma}\int_{\Omega\setminus\Omega_\delta^t} f_\delta(M_k)(1-s_k^*)\frac{C_{k-1}}{1+C_{k-1}}M_k(1-M_k)\,\mathrm{d}x\,\mathrm{d}t\right|$$
$$\leq \lim_{\delta\to 0}\int_\gamma^{T-\gamma}\int_{\Omega\setminus\Omega_\delta^t} |f_\delta(M_k)M_k(1-M_k)|\,\mathrm{d}x\,\mathrm{d}t$$
$$= \lim_{\delta\to 0}\int_\gamma^{T-\gamma}\int_{\Omega\setminus\Omega_0^t} |f_\delta(M_k)M_k(1-M_k)|\,\mathrm{d}x\,\mathrm{d}t$$
$$+ \lim_{\delta\to 0}\int_\gamma^{T-\gamma}\int_{\Omega_0^t\setminus\Omega_\delta^t} |f_\delta(M_k)M_k(1-M_k)|\,\mathrm{d}x\,\mathrm{d}t,$$

which was already proven to be zero in the proof of 3.1.7. Hence, we find

$$\lim_{\delta \to 0} \int_\gamma^{T-\gamma} \int_{\Omega \setminus \Omega_\delta^t} f_\delta(M_k)(1 - s_k^*) \frac{C_{k-1}}{1 + C_{k-1}} M_k(1 - M_k) \, \mathrm{d}x \, \mathrm{d}t = 0.$$

For $\gamma \to 0$, we obtain the following limit inequality:

$$\int_\Omega F_0(M_k(\cdot, T)) \, \mathrm{d}x - \int_\Omega F_0(M_k(\cdot, 0)) \, \mathrm{d}x - \frac{a_1}{a_2 s_{max}} \int_0^T \int_{\Omega_0^t} \nabla M_k \mathbb{D}_W b_k \, \mathrm{d}x \, \mathrm{d}t$$

$$\leq \int_0^T \int_{\Omega_0^t} f_0(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1 - M_k) \, \mathrm{d}x \, \mathrm{d}t$$

$$- \sigma \int_0^T \int_{\Omega_0^t} f_0(M_k)(1 - s_k^*) \frac{C_{k-1}}{1 + C_{k-1}} M_k(1 - M_k) \, \mathrm{d}x \, \mathrm{d}t.$$

As was done in (3.11), we estimate the right hand side of the limit equation, now obtaining

$$\left(\int_0^T \int_{\Omega_0^t} f_0(M_k) G_M(h_{k-1}, s_k^*, y_k^*) M_k(1 - M_k) \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega F_0(M_k(\cdot, T)) \, \mathrm{d}x \right.$$

$$\left. + \int_\Omega F_0(M_k(\cdot, 0)) \, \mathrm{d}x \right) - \sigma \int_0^T \int_{\Omega_0^t} f_0(M_k)(1 - s_k^*) \frac{C_{k-1}}{1 + C_{k-1}} M_k(1 - M_k) \, \mathrm{d}x \, \mathrm{d}t$$

$$\leq c(T).$$

Proceeding then as in the original proof, we obtain

$$\|\nabla M_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \leq c_M(T).$$

Finally, we need to show the boundedness of $\|\Delta C_k\|_{\mathcal{L}^2(\Omega)}$. To this aim, we multiply equation (3.43d) by ΔC and integrate with respect to t and x. Using partial integration, we find

$$D_C \|\Delta C_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}^2$$

$$= -\frac{1}{2} \|\nabla C_k(T, \cdot)\|_{\mathcal{L}^2(\Omega)}^2 + \frac{1}{2} \|\nabla C_k(0, \cdot)\|_{\mathcal{L}^2(\Omega)}^2$$

$$\underbrace{- \int_0^T \int_\Omega \nabla C_k \cdot \nabla((k_{bbb} e_k + k_d) C_k) \, \mathrm{d}x \, \mathrm{d}t}_{A}$$

$$+ \underbrace{\int_0^T \int_\Omega \nabla C_k \cdot \nabla \left(\frac{2a}{5} C_{\text{total}}(x) C_k e^{-a \int_0^t C_{k-1}(s, \cdot) \, \mathrm{d}s} \right) \, \mathrm{d}x \, \mathrm{d}t}_{B}.$$

We estimate the third and fourth term on the right hand side:

$$(A) = \int_0^T \int_\Omega \nabla C_k \cdot \nabla((k_{bbb} e_k + k_d) C_k) \, \mathrm{d}x \, \mathrm{d}t$$

$$\leq \int_0^T \int_\Omega |\nabla C_k|^2 (k_{bbb} e_k + k_d) \, \mathrm{d}x \, \mathrm{d}t + \int_0^T \int_\Omega k_{bbb} C_k \nabla C_k \cdot \nabla e_k \, \mathrm{d}x \, \mathrm{d}t$$

$$\leq c \|\nabla C_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}^2 + c \|\nabla C_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \|\nabla e_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))},$$

$$\leq c(T)$$

and

$$
(B) = \int_0^T \int_\Omega \nabla C_k \cdot \nabla \left(\frac{2a}{5} C_{\text{total}}(x) C_k e^{-a \int_0^t C_{k-1}(s,\cdot)\,\mathrm{d}s} \right) \, \mathrm{d}x \, \mathrm{d}t
$$

$$
\leq \frac{2a}{5} \int_0^T \int_\Omega |\nabla C_k|^2 C_{\text{total}}(x) e^{-a \int_0^t C_{k-1}(s,\cdot)\,\mathrm{d}s} \, \mathrm{d}x \, \mathrm{d}t
$$

$$
+ \frac{2a}{5} \int_0^T \int_\Omega \nabla C_k \cdot \nabla C_{\text{total}}(x) C_k e^{-a \int_0^t C_{k-1}(s,\cdot)\,\mathrm{d}s} \, \mathrm{d}x \, \mathrm{d}t
$$

$$
- \frac{2a^2}{5} \int_0^T \int_\Omega C_{\text{total}}(x) C_k \nabla C_k \cdot \int_0^t \nabla C_{k-1}(s,\cdot)\,\mathrm{d}s \, e^{-a \int_0^t C_{k-1}(s,\cdot)\,\mathrm{d}s} \, \mathrm{d}x \, \mathrm{d}t
$$

$$
\leq c\|\nabla C_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}^2 + c\|\nabla C_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}\|\nabla C_{\text{total}}\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}
$$

$$
+ c\|\nabla C_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}\|T \sup_{t \in (0,T)} |\nabla C_{k-1}(t,\cdot)|\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))}
$$

$$
\leq c + c\|\nabla C_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} T^{\frac{3}{2}} \|\nabla C_{k-1}\|_{\mathcal{L}^\infty(0,T;\mathcal{L}^2(\Omega))}
$$

$$
\leq c(T).
$$

Hence, we find

$$
\|\Delta C_k\|_{\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))} \leq c_{CC}(T).
$$

$\square$

Next, we have to adapt lemma 3.1.8:

Lemma 3.2.11. *Let* $M_0, h_0, e_0, C_0 \in W^{1,4}(\Omega)$, $Q_0^{(k)} \in C^\infty(\bar\Omega)$ *with*

$$
0 \leq M_0, h_0, e_0, Q_0^{(k)} \leq 1, \, 0 \leq C_0 \leq H.
$$

Let further $(Q_{k-1}, h_{k-1}, e_{k-1}, C_{k-1}, M_{k-1}) \in (C^\infty((0,\infty) \times \bar\Omega) \cap C([0,\infty) \times \bar\Omega))^5$ *fulfill the bounds from lemma 3.2.10. Then system (3.43)-(3.46) has a unique global solution* $(Q_k, h_k, e_k, C_k, M_k) \in (C^\infty((0,\infty) \times \bar\Omega) \cap C([0,\infty) \times \bar\Omega))^5$, *which fulfills again the bounds from lemma 3.2.10.*

Proof. Again, global existence of Q_k is obtained from equation (3.43a) by applying standard theory for ODEs, using the boundedness of Q_k. The postulated smoothness properties can be deduced from remark A.1.9.

Now consider system (3.43b)-(3.43e). Using the notations of theorem A.1.2 with

$u^k = \begin{pmatrix} h_k \\ e_k \\ C_k \\ M_k \end{pmatrix}$, the system coefficients are as follows:

- From equation (3.43b)

$$a_{ii}^{11} = D_h \ \text{ for } i = 1, ..., N,$$
$$a_{ij}^{11} = 0 \ \text{ for } i \neq j,$$
$$a_{ij}^{12} = a_{ij}^{13} = a_{ij}^{14} = 0 \ \text{ for } i, j = 1, ..., N,$$
$$a_i^{1r} = b_i^{1r} = 0 \ \text{ for } i = 1, ..., N, \ r = 1, 2, 3, 4,$$
$$a_0^{12} = a_0^{13} = a_0^{14} = 0,$$
$$a_0^{11} = \delta_h u_2^k,$$
$$f_1 = \mu_h (1 - u_1^k) \frac{u_4^k}{1 + u_4^k}.$$

- From equation (3.43c)

$$a_{ii}^{22} = D_e \ \text{ for } i = 1, ..., N,$$
$$a_{ij}^{22} = 0 \ \text{ for } i \neq j,$$
$$a_{ii}^{21} = -\varsigma_e u_2^k (1 - u_2^k) \ \text{ for } i = 1, ..., N,$$
$$a_{ij}^{21} = 0 \ \text{ for } i \neq j,$$
$$a_{ij}^{23} = a_{ij}^{24} = 0 \ \text{ for } i, j = 1, ..., N,$$
$$a_i^{2r} = b_i^{2r} = 0 \ \text{ for } i = 1, ..., N, \ r = 1, 2, 3, 4,$$
$$a_0^{21} = a_0^{23} = a_0^{24} = 0,$$
$$a_0^{22} = -\mu_e \frac{u_1^k u_4^k}{1 + u_1^k u_4^k} (1 - u_2^k),$$
$$f_2 = 0.$$

- From equation (3.43d)

$$a_{ii}^{33} = D_C \ \text{ for } i = 1, ..., N,$$
$$a_{ij}^{33} = 0 \ \text{ for } i \neq j,$$
$$a_{ij}^{31} = a_{ij}^{32} = a_{ij}^{34} = 0 \ \text{ for } i, j = 1, ..., N,$$
$$a_i^{3r} = b_i^{3r} = 0 \ \text{ for } i = 1, ..., N, \ r = 1, 2, 3, 4$$
$$a_0^{31} = a_0^{32} = a_0^{34} = 0,$$
$$a_0^{33} = k_{bbb} u_2^k + k_d,$$
$$f_3 = \frac{2a}{5} C_{\text{total}}(x) u_3^k e^{-a \int_0^t u_3^{k-1} \, ds}.$$

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- From equation (3.43e)

$$a_{ij}^{44} = \frac{a_1 \rho_2}{a_2 s_{max}} u_4^k (1 - u_4^k)(\mathbb{D}_W)_{ij} + \epsilon_k I_{ij} \ \text{ for } i, j = 1, ..., N,$$

$$a_{ij}^{41} = a_{ij}^{42} = a_{ij}^{43} = 0 \ \text{ for } i, j = 1, ..., N,$$

$$a_i^{41} = a_i^{42} = a_i^{43} = 0 \ \text{ for } i = 1, ..., N,$$

$$b_i^{4r} = 0 \ \text{ for } i = 1, ..., N, \ r = 1, 2, 3, 4,$$

$$a_i^{44} = \frac{a_1 (1 - \rho_1)}{a_2 s_{max}} \frac{1 - u_4^k}{\sqrt{1 + \|\nabla u_1^{k-1}\|^2}} (\mathbb{D}_W \nabla u_1^{k-1})_i$$

$$\qquad - \frac{a_1 \rho_1}{a_2 s_{max}} (1 - y_k^*) \frac{1 - u_4^k}{\sqrt{1 + \|\nabla Q_k\|^2}} (\mathbb{D}_W \nabla Q_k)_i \ \text{ for } i = 1, ..., N,$$

$$a_0^{41} = a_0^{42} = a_0^{43} = 0,$$

$$a_0^{44} = -y_k^* (1 - y_k^*) \frac{1 - s_k^*}{1 + u_1^{k-1}} (1 - u_4^k) + \sigma (1 - s_k^*) \frac{u_3^{k-1}}{1 + u_3^{k-1}} (1 - u_4^k),$$

$$f_4 = 0.$$

We check the assumptions of theorem A.1.2:

Let $D_0 := (-\frac{1}{2}, \frac{3}{2})^2 \times (-\frac{1}{2}, H+1) \times (-\frac{1}{2}, \frac{3}{2})$. Then all coefficients of $\mathcal{A}$ and $\mathcal{B}$ are C^∞-smooth w.r.t. x, t and u. Further note, that the set $D \subset D_0$ is nonempty: For example consider

$$a_{ij}(0, 0, 0, 0) = \begin{pmatrix} D_h I_{ij} & 0 & 0 & 0 \\ 0 & D_e I_{ij} & 0 & 0 \\ 0 & 0 & D_C I_{ij} & 0 \\ 0 & 0 & 0 & \epsilon_k I_{ij} \end{pmatrix},$$

where due to the positivity of D_h, D_e, D_C and ϵ_k we find that

$$\left(\sum_{i,j=1}^N a_{ij}^{kl}(0, 0, 0, 0) \xi_i \xi_j \right)_{k,l=1}^4$$

is positive definite for all $\xi \in \mathbb{R}^N \backslash \{0\}$. Hence, $(0, 0, 0, 0) \in D$. f is C^∞-smooth on $((\mathbb{R}_0^+ \times \bar{\Omega} \times D_0) \times \mathbb{R}^{4 \times N}, \mathbb{R}^4)$, hence also on $((\mathbb{R}_0^+ \times \bar{\Omega} \times D) \times \mathbb{R}^{4 \times N}, \mathbb{R}^4)$. Furthermore, f is independent of the gradient of u. Choosing $p = 4$, the condition $\frac{N}{p} < 1 < (1 + \frac{1}{p}) \wedge (2 - \frac{N}{p})$ is fulfilled with $N \leq 3$. Since it further holds $g = 0$ and the initial data are all at least in $W^{1,4}(\Omega)$, by theorems A.1.2, A.1.3 and A.1.4 there exists a unique solution $u^k \in C^\infty((0, t^+) \times \bar{\Omega}, \mathbb{R}^4)$ for some $t^+ > 0$. Due to the positivity of ϵ_k, there is some $\delta > 0$ such that $(a_{ij}^{44})_{ij}$ is positive definite for $u_4^k \in (-\delta, 1 + \delta)$, hence by $0 \leq h_k, e_k, M_k \leq 1$ and $0 \leq C_k \leq H$, u^k is bounded away from ∂D. Then by theorem A.1.5 we find $t^+ = \infty$.

The proclaimed bounds are given by lemma 3.2.10. $\qquad \square$

Now, we have to prove that the constructed sequence of solutions converges, i.e.

Lemma 3.2.12. *Let $(Q_k, h_k, e_k, C_k, M_k)_k$ be the sequence of global solutions to system (3.43)-(3.46) constructed above. Then there exist*

$$M, h, e, Q : \mathbb{R}_0^+ \times \bar{\Omega} \to [0, 1], \; C : \mathbb{R}_0^+ \times \bar{\Omega} \to [0, H],$$

such that for all $T > 0$ it holds

$$M, e \in \mathcal{L}^2(0, T; W^{1,2}(\Omega)), \qquad h, Q, C \in \mathcal{L}^\infty(0, T; W^{1,2}(\Omega)),$$

and there exists a subsequence $(Q_{k_n}, h_{k_n}, e_{k_n}, C_{k_n}, M_{k_n})_n$ such that

$$M_{k_n} \to M \; \text{in} \; \mathcal{L}^2(0, T; \mathcal{L}^2(\Omega)), \qquad h_{k_n} \to h \; \text{in} \; \mathcal{L}^\infty(0, T; \mathcal{L}^2(\Omega)),$$
$$e_{k_n} \to e \; \text{in} \; \mathcal{L}^2(0, T; \mathcal{L}^2(\Omega)), \qquad Q_{k_n} \to Q \; \text{in} \; \mathcal{L}^\infty(0, T; \mathcal{L}^2(\Omega)),$$
$$C_{k_n} \to C \; \text{in} \; \mathcal{L}^\infty(0, T; \mathcal{L}^2(\Omega)),$$

and

$$M_{k_n} \rightharpoonup M \; \text{in} \; \mathcal{L}^2(0, T; W^{1,2}(\Omega)), \qquad e_{k_n} \rightharpoonup e \; \text{in} \; \mathcal{L}^2(0, T; W^{1,2}(\Omega)),$$
$$h_{k_n} \rightharpoonup h \; \text{in} \; \mathcal{L}^2(0, T; W^{1,2}(\Omega)), \qquad h_{k_n} \overset{*}{\rightharpoonup} h \; \text{in} \; \mathcal{L}^\infty(0, T; W^{1,2}(\Omega)),$$
$$Q_{k_n} \rightharpoonup Q \; \text{in} \; \mathcal{L}^2(0, T; W^{1,2}(\Omega)), \qquad Q_{k_n} \overset{*}{\rightharpoonup} Q \; \text{in} \; \mathcal{L}^\infty(0, T; W^{1,2}(\Omega)),$$
$$C_{k_n} \rightharpoonup C \; \text{in} \; \mathcal{L}^2(0, T; W^{1,2}(\Omega)), \qquad C_{k_n} \overset{*}{\rightharpoonup} C \; \text{in} \; \mathcal{L}^\infty(0, T; W^{1,2}(\Omega)).$$

Proof. We adapt the proof of lemma 3.1.10. The adaptation of the proof for $(M_k)_k$ and $(Q_k)_k$ is straightforward. What is left to do, is the proof of $C_{k_n} \to C$ in $\mathcal{L}^\infty(0, T; \mathcal{L}^2(\Omega)), C_{k_n} \rightharpoonup C$ in $\mathcal{L}^2(0, T; W^{1,2}(\Omega))$, and $C_{k_n} \overset{*}{\rightharpoonup} C$ in $\mathcal{L}^\infty(0, T; W^{1,2}(\Omega))$.

To this aim, we choose $X = W^{1,2}(\Omega)$, $B = \mathcal{L}^2(\Omega)$ and $Y = W^{-1,2}(\Omega)$. We have to check the boundedness of $(\partial_t C_k)_k$ in $\mathcal{L}^2(0, T; W^{-1,2}(\Omega)) = (\mathcal{L}^2(0, T; W_0^{1,2}(\Omega)))^*$ (the boundedness of $(C_k)_k$ in $\mathcal{L}^\infty(0, T; W^{1,2}(\Omega))$ is given by the estimates above). Let $\phi \in \mathcal{L}^2(0, T; W_0^{1,2}(\Omega))$. Multiplying (3.43d) by ϕ and integrating over Ω yields

$$\left| \int_\Omega \partial_t C_k \cdot \phi \, dx \right| \leq \left| \int_\Omega D_C \Delta C_k \phi \, dx \right| + \left| \int_\Omega k_C(e_k) C_k \phi \, dx \right|$$
$$+ \left| \int_\Omega \frac{2a}{5} C_{\text{total}}(x) C_k e^{-a \int_0^t C_{k-1} \, ds} \phi \, dx \right|$$
$$\leq D_C \int_\Omega |\nabla C_k| |\nabla \phi| \, dx + \int_\Omega (k_{bbb} e_k + k_d) C_k |\phi| \, dx$$
$$+ \frac{2a}{5} H^2 \int_\Omega |\phi| \, dx$$
$$\leq D_C \|\nabla C_k\|_{\mathcal{L}^2(\Omega)} \|\nabla \phi\|_{\mathcal{L}^2(\Omega)} + (k_{bbb} + k_d) H |\phi|_{\mathcal{L}^1(\Omega)}$$
$$+ \frac{2a}{5} H^2 \|\phi\|_{\mathcal{L}^1(\Omega)}$$
$$\leq C(T) \|\phi\|_{W^{1,2}(\Omega)}.$$

Hence, $(\partial_t C_k)_k$ is bounded in $\mathcal{L}^2(0, T; W^{-1,2}(\Omega))$ and by theorem A.1.11 we conclude the existence of a subsequence $(C_{k_n})_n$ with $C_{k_n} \to C$ in $\mathcal{L}^\infty(0, T; \mathcal{L}^2(\Omega))$. By boundedness of $(C_{k_n})_n$ in $\mathcal{L}^\infty(0, T; W^{1,2}(\Omega))$, there exists a subsubsequence $(C_{k_{n_l}})_l$ with $C_{k_{n_l}} \rightharpoonup C$ in $\mathcal{L}^2(0, T; W^{1,2}(\Omega))$ and $C_{k_{n_l}} \overset{*}{\rightharpoonup} C$ in $\mathcal{L}^\infty(0, T; W^{1,2}(\Omega))$. $\square$

Finally, it has to be proven that the constructed limit functions are indeed a weak solution to the given problem.

Theorem 3.2.13. *The limit functions M, h, e, C, Q constructed in the proof of theorem 3.2.12 are a global weak solution to (3.38)-(3.41) in the sense of definition 3.2.7.*

Proof. The main part of the proof of theorem 3.1.11 remains unchanged. In equation (3.31) we have to add the term

$$-\int_0^T \int_\Omega \sigma(1-s_k^*)\frac{C_{k-1}}{1+C_{k-1}}M_k(1-M_k)\phi\,\mathrm{d}x\,\mathrm{d}t$$

on the right hand side. By corollary 3.1.12 and lemma 3.1.13, we find

$$(1-s_k^*)\frac{C_{k-1}}{1+C_{k-1}}M_k(1-M_k) \to (1-s^*)\frac{C}{1+C}M(1-M) \text{ in } \mathcal{L}^2(0,T;\mathcal{L}^2(\Omega)),$$

hence

$$\int_0^T \int_\Omega \sigma(1-s_k^*)\frac{C_{k-1}}{1+C_{k-1}}M_k(1-M_k)\phi\,\mathrm{d}x\,\mathrm{d}t$$
$$\to \int_0^T \int_\Omega \sigma(1-s^*)\frac{C}{1+C}M(1-M)\phi\,\mathrm{d}x\,\mathrm{d}t.$$

Now consider equation (3.43d). It holds

$$-\int_0^T \int_\Omega \phi_t C_k \,\mathrm{d}x\,\mathrm{d}t - \int_\Omega \phi(0,\cdot)\,C_0 \,\mathrm{d}x$$
$$= -\int_0^T \int_\Omega D_C \nabla\phi \cdot \nabla C_k \,\mathrm{d}x\,\mathrm{d}t \tag{3.47}$$
$$+ \int_0^T \int_\Omega \phi\left(\frac{2a}{5}C_{\text{total}}(x)C_k e^{-a\int_0^t C_{k-1}\,\mathrm{d}s} - (k_{bbb}e_k + k_d)C_k\right)\,\mathrm{d}x\,\mathrm{d}t.$$

As we did for equation (3.16), we find

$$\left|\int_0^T \int_\Omega \phi_t(C-C_k)\,\mathrm{d}x\,\mathrm{d}t\right| \le c\int_0^T \int_\Omega |C-C_k|\,\mathrm{d}x\,\mathrm{d}t \to 0. \tag{3.48}$$

It further holds

$$\int_0^T \int_\Omega D_C \nabla\phi(\nabla C - \nabla C_k)\,\mathrm{d}x\,\mathrm{d}t \to 0, \tag{3.49}$$

since $\nabla\phi \in \mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))$ and $(\nabla C - \nabla C_k) \rightharpoonup 0$ in $\mathcal{L}^2(0,T;\mathcal{L}^2(\Omega))$. For the decay terms, we find

$$\int_0^T \int_\Omega \phi\left(-(k_{bbb}e+k_d)C + (k_{bbb}e_k+k_d)C_k\right)\,\mathrm{d}x\,\mathrm{d}t$$
$$= -\int_0^T \int_\Omega \phi k_{bbb}(eC - e_kC_k)\,\mathrm{d}x\,\mathrm{d}t - \int_0^T \int_\Omega \phi k_d(C-C_k)\,\mathrm{d}x\,\mathrm{d}t \tag{3.50}$$
$$\to 0,$$

where we used the same argumentation as for equation (3.18).

Finally, we have to show that

$$\int_0^T \int_\Omega \phi \left(\frac{2a}{5} C_{\text{total}}(x) C e^{-a \int_0^t C \, ds} - \frac{2a}{5} C_{\text{total}}(x) C_k e^{-a \int_0^t C_{k-1} \, ds} \right) dx \, dt$$

converges to zero. Due to $C_k \to C$ in $\mathcal{L}^\infty(0,T;\mathcal{L}^2(\Omega))$ and hence also in $\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))$, it holds $\int_0^t C_k \, ds \to \int_0^t C \, ds$ in $\mathcal{L}^\infty(0,T;\mathcal{L}^1(\Omega))$:

$$\sup_{t \in (0,T)} \left\| \int_0^t C_k(s,\cdot) \, ds - \int_0^t C(s,\cdot) \, ds \right\|_{\mathcal{L}^1(\Omega)}$$

$$\leq \sup_{t \in (0,T)} \int_\Omega \int_0^t |C_k(s,x) - C(s,x)| \, ds \, dx$$

$$= \|C_k - C\|_{\mathcal{L}^1(0,T;\mathcal{L}^1(\Omega))}$$

$$\to 0.$$

Together with continuity and boundedness of $C_{\text{total}}(x)$, it follows by corollary 3.1.12 (for simplicity, we drop the subindices for the subsequence as before)

$$\frac{2a}{5} C_{\text{total}}(x) C_k e^{-a \int_0^t C_{k-1} \, ds} \to \frac{2a}{5} C_{\text{total}}(x) C e^{-a \int_0^t C \, ds} \text{ in } \mathcal{L}^2(0,T;\mathcal{L}^2(\Omega)),$$

which implies

$$\int_0^T \int_\Omega \phi \left(\frac{2a}{5} C_{\text{total}}(x) C e^{-a \int_0^t C \, ds} - \frac{2a}{5} C_{\text{total}}(x) C_k e^{-a \int_0^t C_{k-1} \, ds} \right) dx \, dt \to 0. \tag{3.51}$$

Combining (3.47)-(3.51), we obtain

$$-\int_0^T \int_\Omega \phi_t C \, dx \, dt - \int_\Omega \phi(0,\cdot) C_0 \, dx$$

$$= -\int_0^T \int_\Omega D_C \nabla \phi \cdot \nabla C \, dx \, dt$$

$$+ \int_0^T \int_\Omega \phi \left(\frac{2a}{5} C_{\text{total}}(x) C e^{-a \int_0^t C \, ds} - (k_{bbb} e + k_d) C \right) dx \, dt.$$

$\square$

This proves the existence of a global weak solution as stated in theorem 3.2.9. $\square$

3.2.4 Analysis of the basic model with classical chemotherapy

Making the same simplifications as before, i.e. dropping the flux saturation in the diffusion term of M and replacing $\mathbb{D}_W$ in the temzolomide-equation by a scalar diffusion constant, the analysis for this modeling approach is a simpler version of the analysis for the model of gliadel wafers. The only difference lies in the source term $s(t)$ in the description of temozolomide, which is here given by a bounded C^∞-function. Hence, we confine ourselves here to state the result:

Theorem 3.2.14. *There exists a global weak solution to the simplified version of model 2.5 in the sense of definition 3.2.7, where now $H := \sup\limits_{t \in (0,\infty)} \frac{s(t)}{d_C}$, and (3.42d) is replaced by*

$$-\int_0^T \int_\Omega \phi_t \, C \, \mathrm{d}x \, \mathrm{d}t - \int_\Omega \phi(0, \cdot) \, C_0 \, \mathrm{d}x$$
$$= -\int_0^T \int_\Omega D_C \nabla \phi \cdot \nabla C \, \mathrm{d}x \, \mathrm{d}t + \int_0^T \int_\Omega \phi \, (s(t)e - d_C C) \, \mathrm{d}x \, \mathrm{d}t$$

with

$$s(t) = \sum_{i=1}^n s_i(t), \ s_i(t) = \begin{cases} d_i e^{-\frac{\sigma_i}{b_i^2 - (t_i - t)^2}} & \text{for } |t_i - t| < b_i, \\ 0 & \text{otherwise.} \end{cases}$$

Remark 3.2.15. In the same way as we proved $C \leq H$ in the foregoing section, we can show $C \leq \sup\limits_{t \in (0,\infty)} \frac{s(t)}{d_C}$.

Chapter 4

Simulation results

In this section, the macroscopic evolution of a tumor according to the different modeling approaches presented in chapter 2 is simulated.

The code for the models developed in sections 2.1 and 2.2 was implemented by Niklas Kolbe and Nikolaos Sfakianakis [18]. Within the scope of this thesis, some changes and extensions of the code were made in order to adapt it to the models presented in sections 2.3 and 2.4.

The code by Kolbe and Sfakianakis is based on a second order finite volume scheme, using the minimized-central slope limiter [74], and the implicit-explicit midpoint scheme from [57] for time stepping [18]. For more details about the code see [18]. All algorithms were originally implemented in MATLAB R2019b, adaptation of the code and generation of the figures was done in MATLAB R2021b.

We want to consider the following settings:

1. untreated glioblastoma

   - according to model 2.1 with dominating haptotaxis
   - according to model 2.1 with dominating pH-taxis
   - according to model 2.1, but dropping the flux limiter in the diffusion of M in (2.25a)
   - according to model 2.1, but dropping all flux limiters in (2.25a)
   - with endothelial cells following $\nabla M / \nabla(hM)$ according to model 2.2
   - according to the go-or-grow model 2.3

2. glioblastoma according to model 2.1 treated by surgery

3. glioblastoma treated by surgery and gliadel wafers (model 2.4)

4. glioblastoma treated by surgery and classical chemotherapy (model 2.5)

   - for standard dosing scheme applied by the University Medical Center Munich
   - for metronomic chemotherapy
   - for the dosing scheme one-week-on-one-week-off

Parameter	value	source
acid diffusion D_h	10^{-5}	estimated[1]
endothelial cell diffusion D_e	10^{-6}	[11]
acidotaxis of endothelial cells ζ_e	1	[11]
weight of haptotaxis in glioma migration ρ_1	7.5×10^{-1}	estimated[1]
weight of diffusion in glioma migration ρ_2	1.5×10^{-2}	estimated[1]
tissue proliferation μ_Q	3×10^{-4}	estimated[1]
acid production by glioma μ_h	10^{-3}	[47]
endothelial cell proliferation μ_e	1	[54]
acid degradation of tissue δ_Q	5×10^{-3}	estimated[1]
acid uptake by endothelial cells δ_h	8×10^{-3}	estimated[1]

Table 4.1: Non-dimensionalized parameters

4.1 Evolution of glioblastoma without treatment

In the first section we want to consider the evolution of an untreated glioblastoma in different settings. For the macroscopic basic model 2.1, we study the influence of the taxis terms by comparing simulations for dominating haptotaxis with simulations for dominating pH-taxis. In the setting of dominating haptotaxis, we examine further variations of the basic model: Dropping the flux limiter for the diffusion of M, we compare the differences between the simulations of the basic model 2.1 and the simplified basic model 3.1 used in the analysis section. Next, we drop all flux limitations (hence now also the limitations in the taxis terms) for M in the basic model and compare the result with the original basic model. Further, we examine the taxis term in the equation for endothelial cells. Here, we compare the basic model containing pH-taxis of endothelial cells with taxis along the gradients of M (hM, respectively) according to model 2.2. Finally, we consider a splitting of the cancer population into migrating and proliferating cells according to the go-or-grow dichotomy (model 2.3).

If not stated otherwise, the parameters used in this section are given by table 4.1. Simulations are made for $t \in [0, 5]$. For the chosen non-dimensionalization of time, this corresponds to a time interval of approximately ten weeks. All simulations are performed over the spatial domain $\Omega = [0, 1] \times [0, 1.2155]$. Initial data are chosen as follows: For the tumor, we choose a symmetric initial distribution:

$$M_0(x) = \frac{1}{2} e^{-\frac{(x-0.3)^2 + (y-0.65)^2}{0.0008}}.$$

Since it is not clear how initial data for h should be chosen according to the given initial data of the tumor, we set h_0 to be the pH-value present in average in a healthy brain. Due to acid production by the tumor, pH-value is not supposed to be constant in the initial situation. One could choose for example an initial condition like $h_0(x) = a \cdot M_0(x) + 10^{-2.8}$ for some $a > 0$ as was done in [18]. The effect on tumor evolution compared to a constant initial pH is small, though. Hence, instead of guessing some pH-level fitting to the initial tumor, we choose

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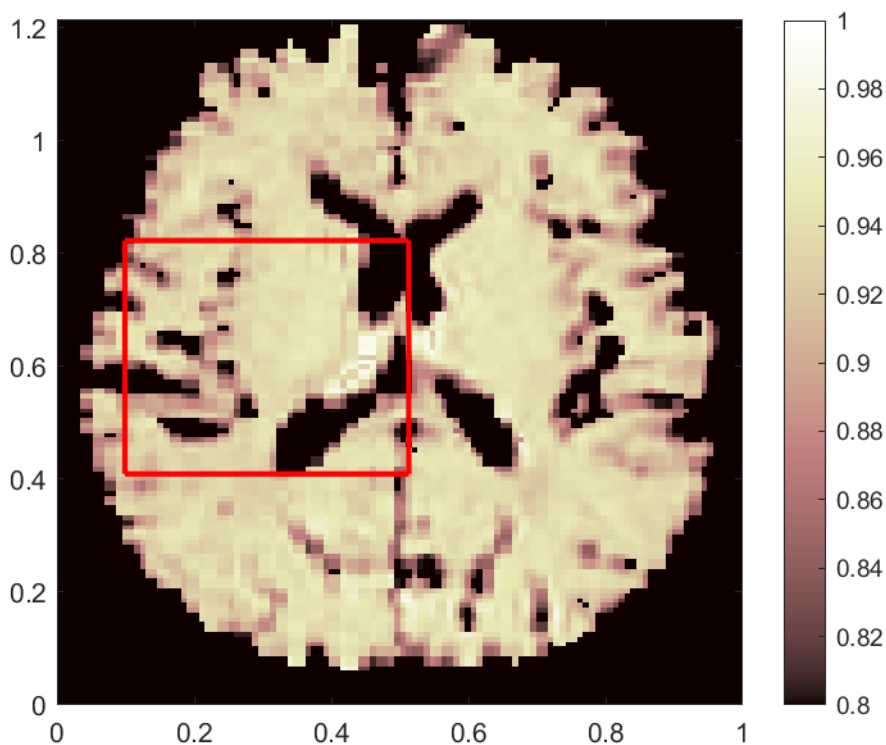
[1]Estimated in correspondence to [18].

Figure 4.1: Cutout of the simulation domain

a constant level in order to see better how acidity production by the tumor happens according to our developed models. Thus, we choose

$$h_0(x) = 10^{-2.8} \;\; \text{for } x \in \Omega. \tag{4.1}$$

Choosing $K_h = 10^{-4.6} \frac{mol}{l}$ for non-dimensionalization, this corresponds to $pH = -\log_{10}(K_h \cdot h_0) = 7.4$ in healthy brain tissue [44].

A realistic initial condition for endothelial cells is difficult to obtain. There are several large arteries supplying the brain with nutrients and oxygen, which could be modeled in the initial data. The exact position of single blood vessels around the tumor, though, remains unclear. Since we have no such data available, we simply choose three spots near the tumor with an accumulation of endothelial cells, such that we can qualitatively examine the proclaimed spread of blood vessels into the tumor. We choose

$$e_0(x) = e^{-\frac{(x-0.35)^2+(y-0.65)^2}{0.00008}} + e^{-\frac{(x-0.25)^2+(y-0.65)^2}{0.00008}} + e^{-\frac{(x-0.3)^2+(y-0.6)^2}{0.00008}} \;\; \text{for } x \in \Omega. \tag{4.2}$$

Initial data for Q are given by equation (2.5).

The figures presented in this chapter show a cutout of the simulation domain Ω, which is given by $[0.0991, 0.5129] \times [0.4095, 0.8233]$ (cf. figure 4.1).

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4.1.1 Experiment 1: The basic model 2.1 with dominant haptotaxis

We consider model 2.1. Parameters are given in table 4.1. To see more details in the evolution of tissue, for $t = 1$ and $t = 5$ the difference in tissue density to the initial density at $t = 0$ is plotted.

In figure 4.2, the spread of the tumor according to the brain structure can be seen. pH in the region of the tumor is significantly decreased. The pH level in the inner part of the tumor coincides with the one known from literature [44]. As expected, the endothelial cells spread into direction of low pH, i.e. into the tumor. For a realistic vascularization of the tumor we would need appropriate initial data. Still, we can qualitatively observe the process of vascularization. Tissue is degraded in the acidic regions. The tissue growth observed in the simulation in regions of low density is due to the constantly chosen carrying capacity. Here, a space dependent carrying capacity could give a more precise prognosis of tissue development.

4.1.2 Experiment 2: The basic model 2.1 with dominant pH-taxis

Again, we consider model 2.1. Except the parameter ρ_1, which is here chosen as $\rho_1 = 0.25$, all parameters coincide with those from experiment 1, which are given in table 4.1.

As can be seen in figure 4.3, the spread of cancer cells in experiment 2 proves to be much more diffusive than observed in experiment 1. Due to the diffusive behavior of the protons, a dominant pH-taxis in the description of cancer cells leads to a more diffusive behavior of the tumor, i.e. a larger tumor volume with reduced density. In the consequence, maximal pH decrease is smaller than in experiment 1, while the region of decreased pH is larger. The same behavior can be observed for the changes in tissue density. The behavior of endothelial cells is similar to experiment 1.

4.1.3 Experiment 3: The simplified basic model 3.1

In this experiment, we consider model 3.1, used in the first section of the analysis chapter. Remember, that model 3.1 coincides with the basic model 2.1 without flux limitation in the diffusion term of M: Instead of (2.25b), we choose

$$b(h, Q, M, y^*) = (1 - \rho_1 - \rho_2)\frac{-\nabla h}{\sqrt{1 + |\nabla h|^2}} + \rho_1(1 - y^*)\frac{\nabla Q}{\sqrt{1 + |\nabla Q|^2}} - \rho_2 \nabla M,$$

and $s^* = |g(h, Q, M, y^*)|$ is adapted according to the new $b(h, Q, M, y^*)$. The parameters are given in table 4.1. In figure 4.4 we observe that compared with experiment 1 the tumor is less compact, due to the stronger diffusion. As was to be expected, in comparison with experiment 1 the structure of brain tissue is less cognizable in the form of the glioma as here diffusion dominates hapto- and chemotaxis. Again, we observe that as a consequence of the less compact tumor, maximal pH decrease is smaller than in experiment 1, while the region of decreased pH is larger. The effect observed here is stronger than in experiment 2. The same behavior is observed for tissue evolution. For the endothelial cells,
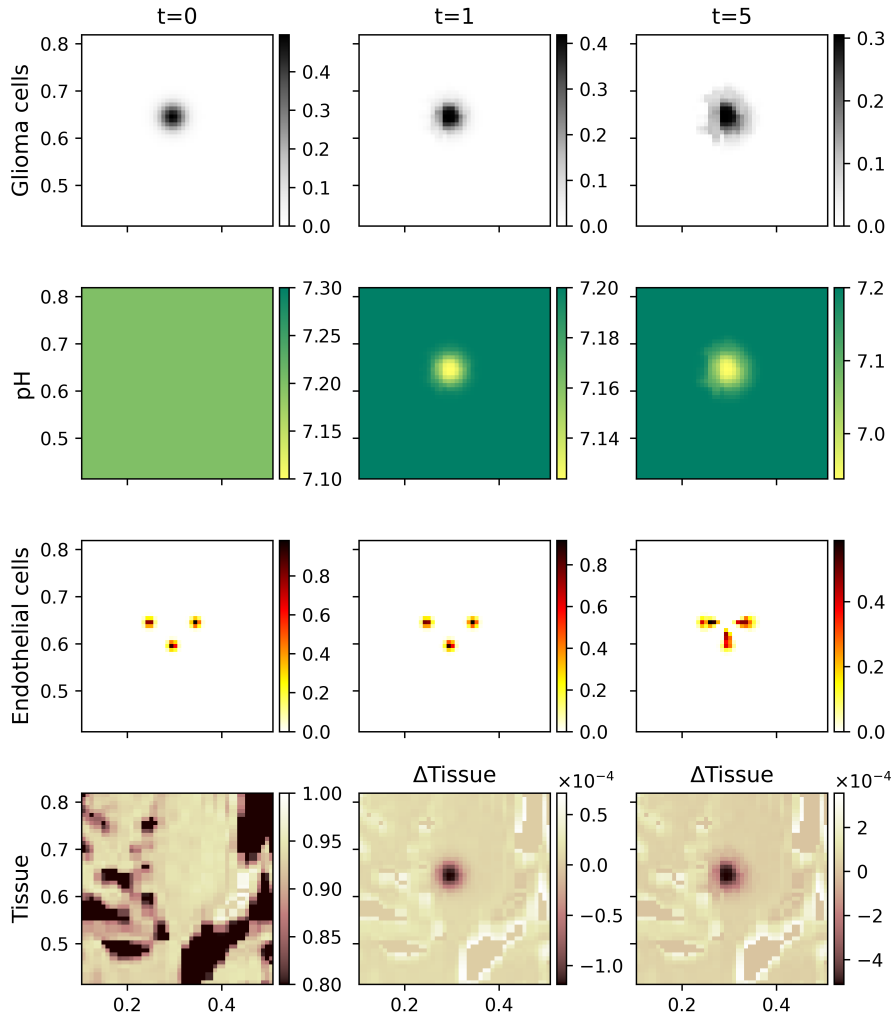
Figure 4.2: Experiment 1: Basic model 2.1 with dominant haptotaxis. For $t = 1$ and $t = 5$, instead of tissue density, the changes $Q(t, x) - Q(0, x)$ in tissue density are plotted.
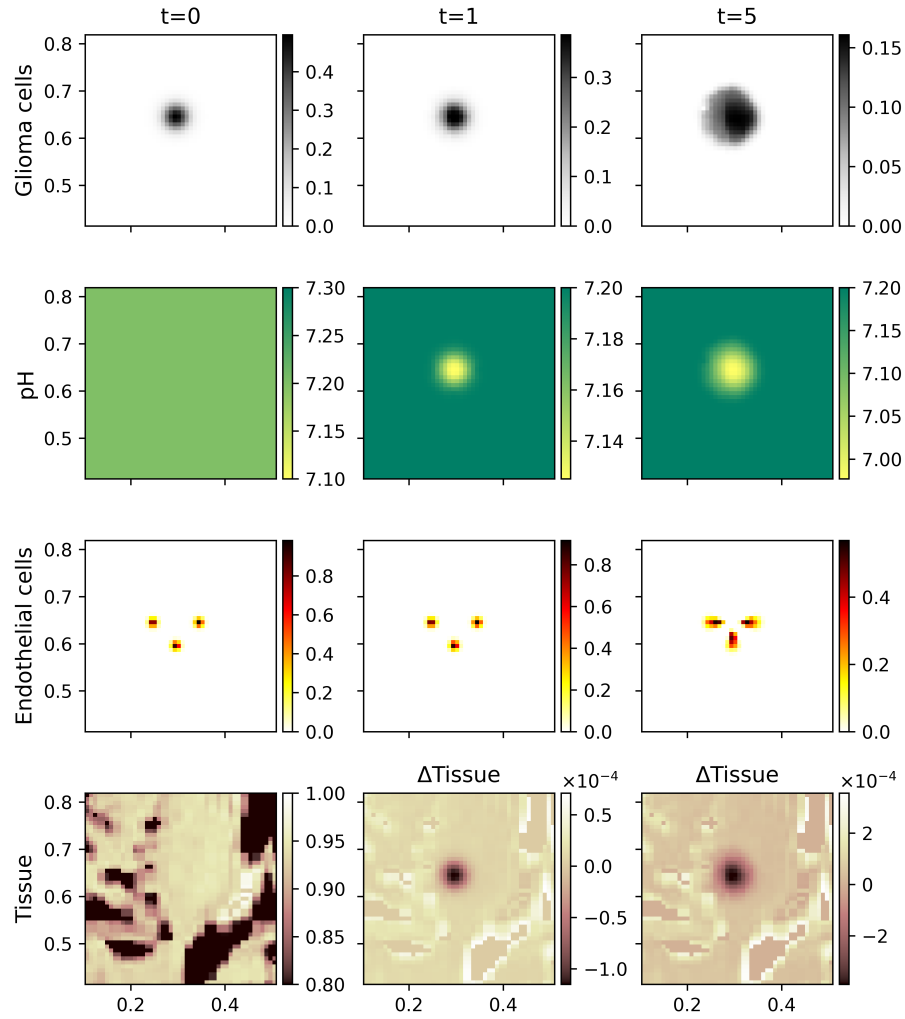
Figure 4.3: Experiment 2: Basic model 2.1 with dominant pH-taxis. For $t = 1$ and $t = 5$, instead of tissue density, the changes $Q(t, x) - Q(0, x)$ in tissue density are plotted.
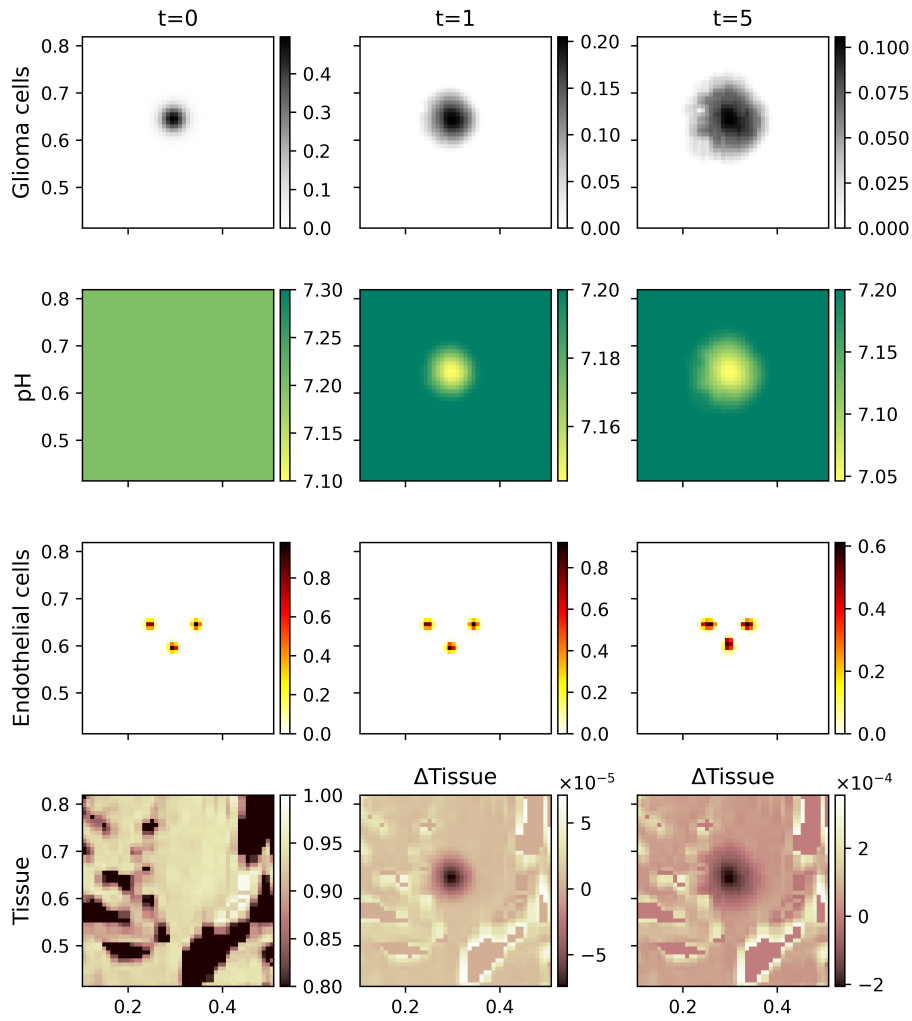
Figure 4.4: Experiment 3: Simplified basic model 3.1. For $t = 1$ and $t = 5$, instead of tissue density, the changes $Q(t, x) - Q(0, x)$ in tissue density are plotted.

we observe a slower spread than in experiment 1. This is caused by weaker pH-taxis due to the more evenly distributed proton concentration.

4.1.4 Experiment 4: The basic model 2.1 with no flux limitation

In this experiment, we consider another variation of the basic model 2.1. In (2.25b) now all flux limitations are dropped. Hence, instead of (2.25b) we choose

$$b(h, M, q, y^*) = -(1 - \rho_1 - \rho_2)\nabla h + \rho_1(1 - y^*)\nabla Q - \rho_2 \nabla M.$$

$s^* = |g(h, Q, M, y^*)|$ is adapted according to the new $b(h, Q, M, y^*)$. The parameters are given in table 4.1. As was to be expected, the drift of the tumor cells observed in figure 4.5 is stronger than in experiment 1, leading to a larger tumor volume with decreased density. In contrast to experiment 3, where diffusion was the dominating process, diffusion and haptotaxis are now more balanced. On the tumor density plot, the effect of brain structure is well observable, which suggests that haptotaxis is a relevant factor for the behavior of the glioma cells in this model. Similar to experiment 3, due to the reduced compactness of the tumor, we observe a wider region of decreased pH and tissue than in experiment 1, while at the same time observing less maximal decrease. Also the behavior of the endothelial cells is similar to that in experiment 3.

4.1.5 Experiment 5: Endothelial cells following ∇M ($\nabla(hM)$) (model 2.2)

In experiment 5, we consider model 2.2, where the endothelial cells now follow the gradient of M, respectively hM, instead of h. Again, the parameters are given in table 4.1. It is not obvious how the taxis sensitivity parameter ς_e should be chosen. Note, that it does not make sense to simply multiply the original parameter by $\frac{K_M}{K_h}$, as might be intuitive with regard to the non-dimensionalization in section 2.2. The model for endothelial growth is not developed from single cell dynamics but set up phenomenologically on the macroscopic scale. Hence, the parameter ς_e does not have a clear biological interpretation with a fixed value. It is chosen heuristically in dependence on the chosen model such that the latter covers biological observations. Hence, the parameters ς_e in section 2.1 and section 2.2 differ. In the following, ς_e is chosen such that the velocity of endothelial spread is similar in experiments 1, 5a and 5b, such that a qualitative comparison between the model variants is possible.

Experiment 5a: $f_1 = M$

In experiment 5a, we choose $f_1 = M$ in equation (2.29), meaning that the endothelial cells follow the gradient of M. As the spread of cancer cells is less diffusive than the dispersion of protons, the gradient of M is supposed to be considerably larger. Hence, to obtain comparable results, we have to lower ς_e. All other parameters coincide with those of experiment 1. We choose $\varsigma_e = 3 \cdot 10^{-3}$.
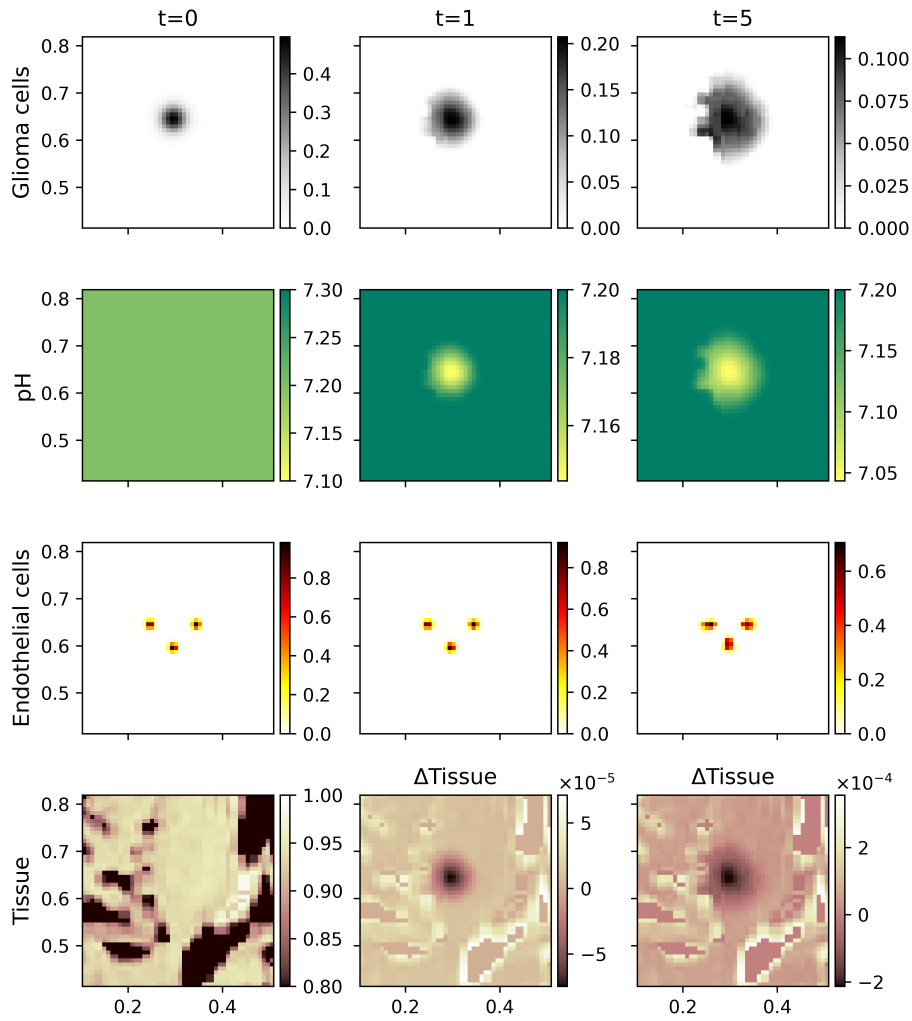
Figure 4.5: Experiment 4: No flux limitation in the basic model 2.1. For $t = 1$ and $t = 5$, instead of tissue density, the changes $Q(t, x) - Q(0, x)$ in tissue density are plotted.

Experiment 5b: $f_2 = hM$

In experiment 5b, we choose $f_2 = hM$, i.e. the endothelial cells follow the gradient of hM. Again, we use the parameters given in table 1 (including $\zeta_e = 1$).

Results

The results of experiment 5a and 5b are summarized in figure 4.6. In both experiments we observe a sharper localization of endothelial cells than in experiment 1. Since tumor cells are less diffusive than protons, taxis along M and hM leads to a less homogeneous spread of the endothelial cells than taxis along h. Qualitatively, the spread of endothelial cells in experiment 5a and experiment 5b is similar.

As was already mentioned in the modeling section 2.2, from a biological point of view, endothelial cells follow neither the gradient of M nor of hM nor of h. Instead, endothelial spread is expected along gradients of VEGF. We discussed the pros and cons of approximating VEGF by h, M or hM: By replacing in the taxis term of the endothelial cells VEGF by h, we can expect that the diffusive behavior of VEGF is approximated well. On the other hand, choosing hM instead of h gives a more precise modeling of the production of VEGF by tumor cells in contact with low pH. While taxis of endothelial cells along the gradient of M seems to be a too strong simplification, representing neither the diffusivity of VEGF nor its production, the two other modeling approaches are both possible choices. However, we have to be aware that even those two are only approximations for the real tactic process, both having their assets and drawbacks as described above. For a more precise description, we would have to model VEGF in a separate equation, where we can combine diffusion with a large diffusion coefficient as given for h with a proliferation term including the product hM.

4.1.6 Experiment 6: The go-or-grow model 2.3

In experiment 6, we consider model 2.3, where the population of glioma cells is split into a migrating and a proliferating subpopulation. For the non-dimensionalized switch parameters α_1 and α_2, we choose $\alpha_1 = 0.2$ and $\alpha_2 = 4$ in correspondence to [22]. All other parameters are given in table 4.1. For the initial conditions of migrating and proliferating cells, we each choose half of the initial density of cancer cells considered so far, i.e.

$$M_0(x) = \frac{1}{4}e^{-\frac{(x-0.3)^2+(y-0.65)^2}{0.0008}},$$
$$P_0(x) = \frac{1}{4}e^{-\frac{(x-0.3)^2+(y-0.65)^2}{0.0008}}.$$

Considering figure 4.7, we observe for the migrating subpopulation M the expected invasive behavior, where the density in the inner of the tumor decreases while the surrounding tissue is invaded. For the proliferative subpopulation we observe increasing density of the tumor as a consequence of cell proliferation. At the same time, though, we see that the area, where proliferative cells are found, increases. This is due to the switch of part of the migrational population back to proliferative stage as a consequence of weaker tactic signals received at the peripheral region of the tumor.
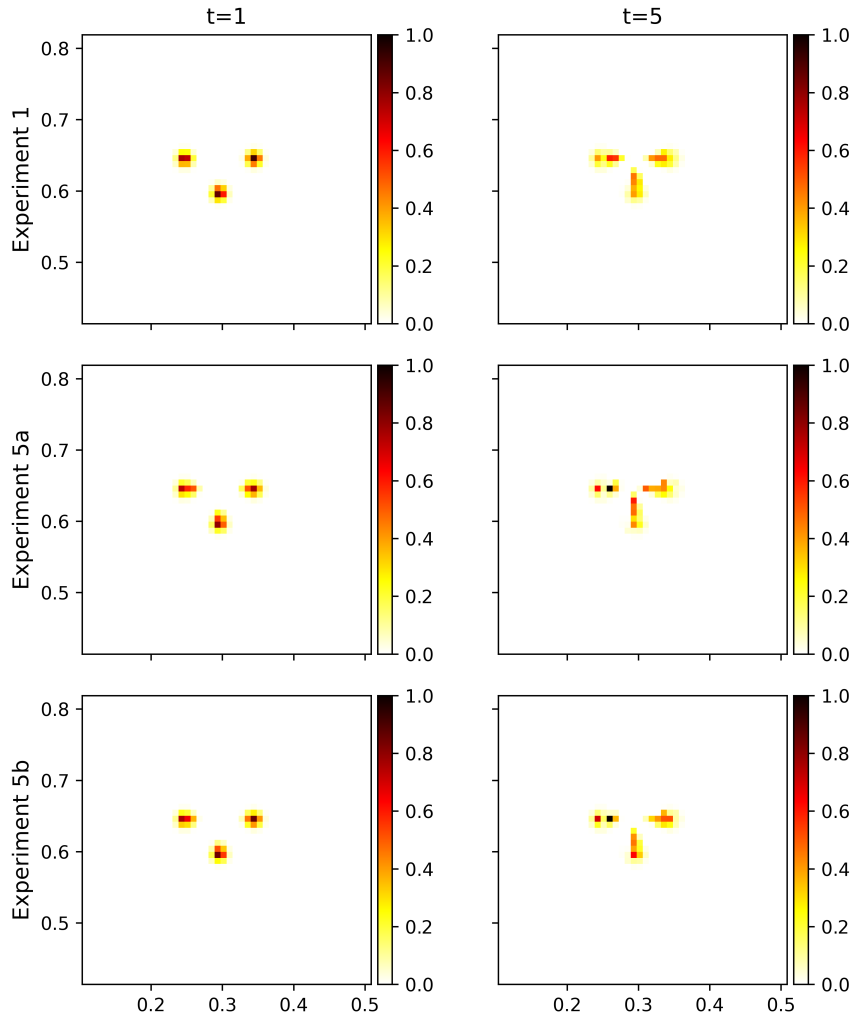
Figure 4.6: Comparison between experiment 1 and experiment 5a/b: Endothelial cells following $\nabla h \backslash \nabla M \backslash \nabla(hM)$ (model 2.2)
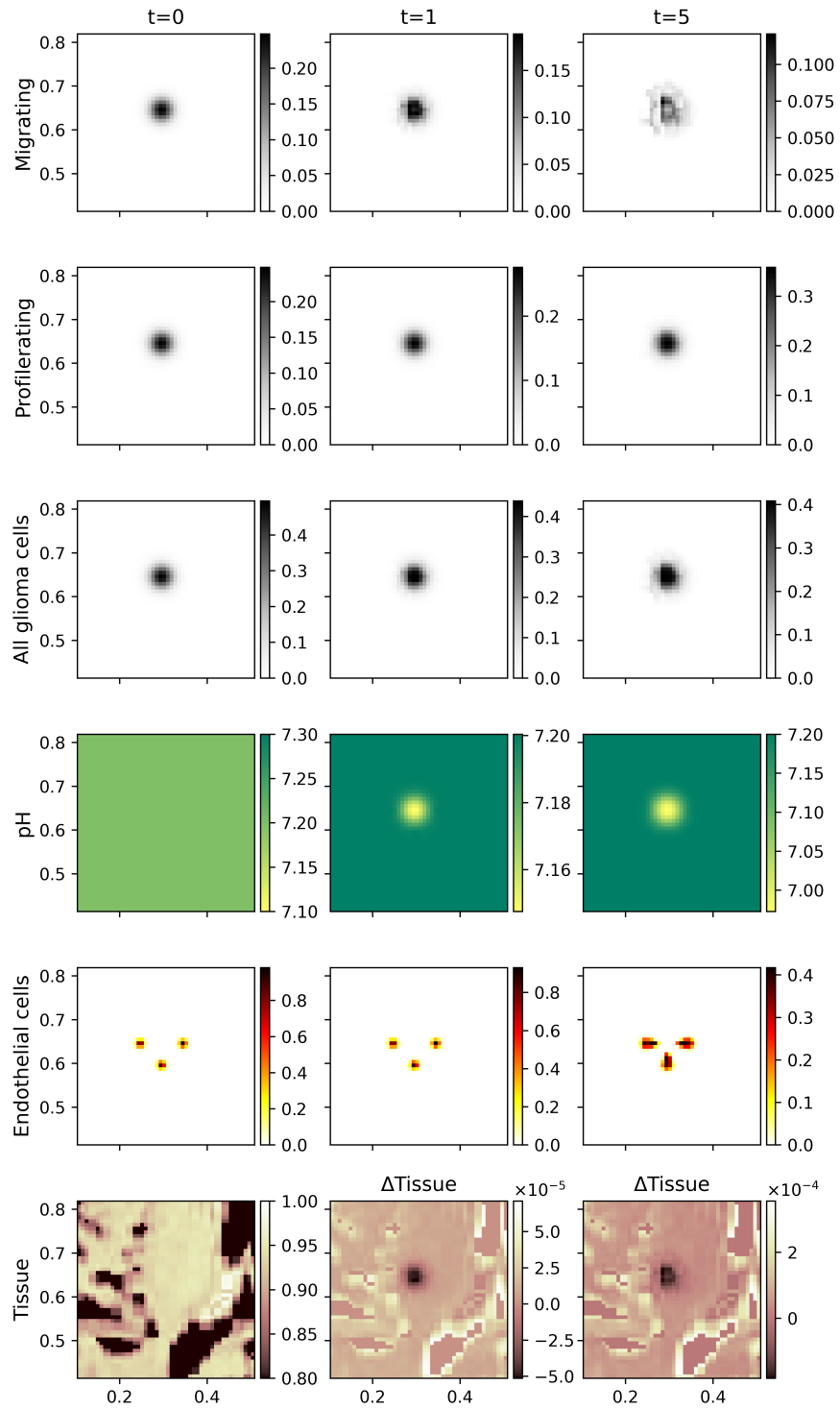
Figure 4.7: Experiment 6: The go-or-grow model 2.3. For $t = 1$ and $t = 5$, instead of tissue density, the changes $Q(t, x) - Q(0, x)$ in tissue density are plotted.

4.2 Evolution of glioblastoma with therapy

In this section, we want to consider the evolution of a glioblastoma under different therapies. We consider surgery alone, surgery with implantation of gliadel wafers, and surgery followed by classical chemotherapy in different settings. The not therapy-specific parameters used in this section are again given by table 4.1. Therapy-specific parameter values are given in the respective subsections.

Simulation time is adapted to the therapy periods and hence prolonged to $[0, 20]$, which corresponds to approximately 40 weeks, the time needed for the standard dosing scheme of classical chemotherapy [66]. As before, all simulations are performed over the spatial domain $\Omega = [0, 1] \times [0, 1.2155]$. All initial data, except those for endothelial cells, are chosen as in section 4.1. So far, we considered initial data for endothelial cells such that their growth and taxis behavior became visible. Since we do not consider therapy by anti-angiogenic factors here, the growth of blood vessels is not object of closer observation in this section. Instead, we have to choose a more realistic network of blood vessels, which is responsible for the transport of chemotherapeutic agent. Since no data about the initial distribution of blood vessels are available, we choose a normal distribution of endothelial cell densities in the range $[0, 0.1]$. Surgery is performed at time $t = 2.5$. The background of this choice is that the invasive shape of the tumor leads to problems regarding the complete removal; after a simulation period of five weeks ($t = 2.5$), such an invasive shape can be expected. Note that the time span of five weeks is chosen only for the technical reason stated above. It is not to be interpreted as the time between diagnosis and resection, which should be considerably smaller [62].

Again, the figures presented in this chapter show a cutout of the simulation domain Ω, which is given by $[0.0991, 0.5129] \times [0.4095, 0.8233]$ (see figure 4.1). A table with a direct comparison between the effectivity of the different treatment approaches according to our simulations is presented at the end of this section.

4.2.1 Experiment 7: The basic model 2.1 with therapy by partial removal of the tumor

We repeat experiment 1 on the time interval $[0, 2.5]$. At $t = 2.5$, part of the tumor is removed. Afterwards, the simulation is resumed on the time interval $[2.5, 20]$.

The removal of the tumor is simulated as follows: In experiment 7a, at $t = 2.5$ all parts of the tumor with densities of more than 0.05 are removed. In experiment 7b, additionally, all tumor cells within a radius of 0.5 cm of those high density locations are removed (a procedure called supramaximal or supratotal resection, which is to ensure that also tumor cells not visible during surgery are resected [33, 83]). In both experiments, tissue and blood vessels at the respective locations are removed as well.

The results are summarized in figures 4.8 and 4.9. Clearly, supramaximal resection lowers the tumor density not only directly but also 35 weeks after resection. Still, it has to be taken into account that the removed healthy brain tissue is appreciably larger for supramaximal resection. Comparing tumor and tissue mass directly before and after surgery, we find that in experiment 7a by resection the tumor mass is decreased by 89.1% and the tissue mass by 1.0%,
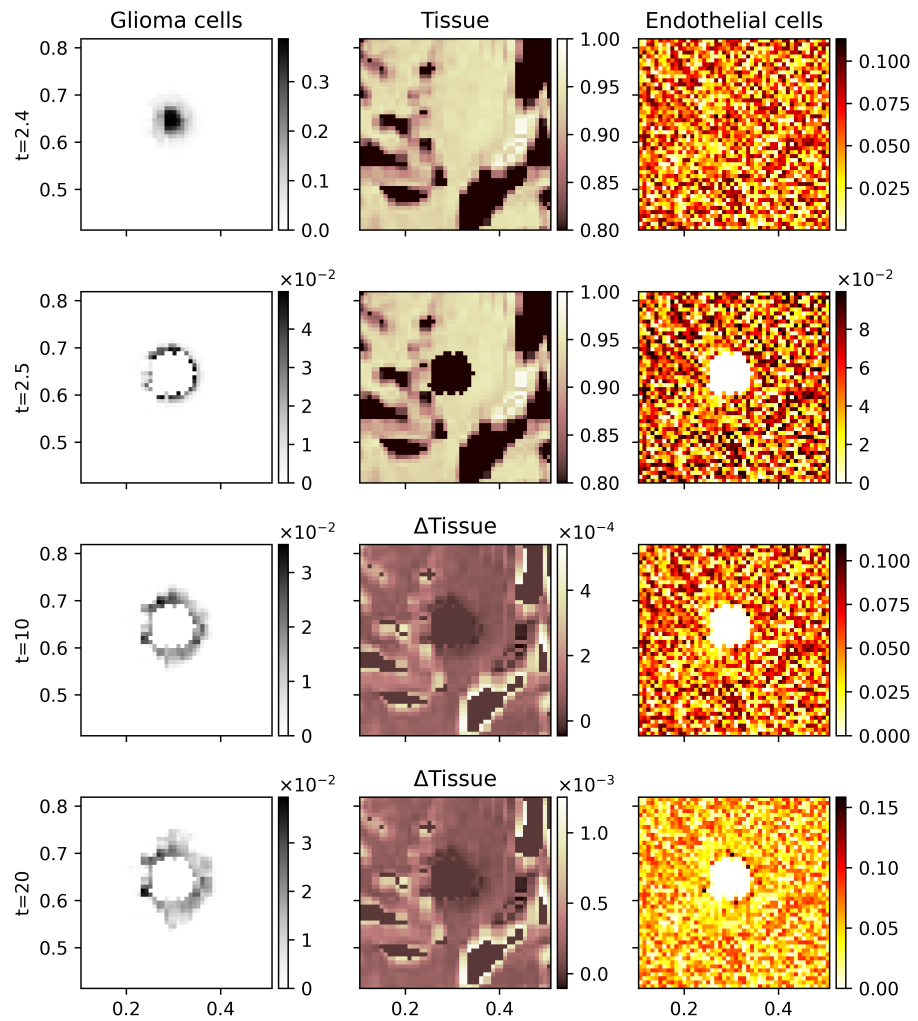
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Figure 4.8: Experiment 7a: Basic model 2.1 with removal of glioblastoma at $t = 2.5$ with surgery threshold 0.05. For $t = 10$ and $t = 20$, instead of tissue density, the changes $Q(t, x) - Q(2.5, x)$ in tissue density after resection are plotted.
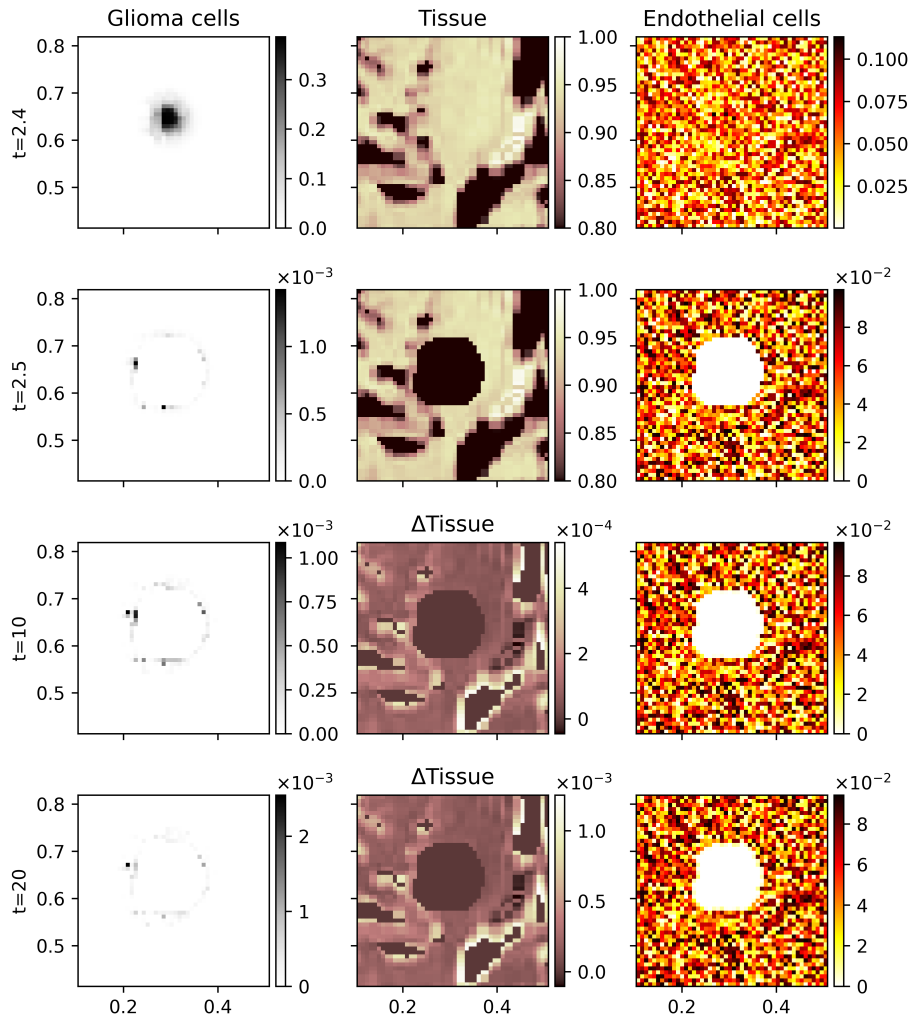
Figure 4.9: Experiment 7b: Basic model 2.1 with removal of glioblastoma at $t = 2.5$ with surgery threshold 0.05 and safety radius 0.5 cm. For $t = 10$ and $t = 20$, instead of tissue density, the changes $Q(t, x) - Q(2.5, x)$ in tissue density after resection are plotted.
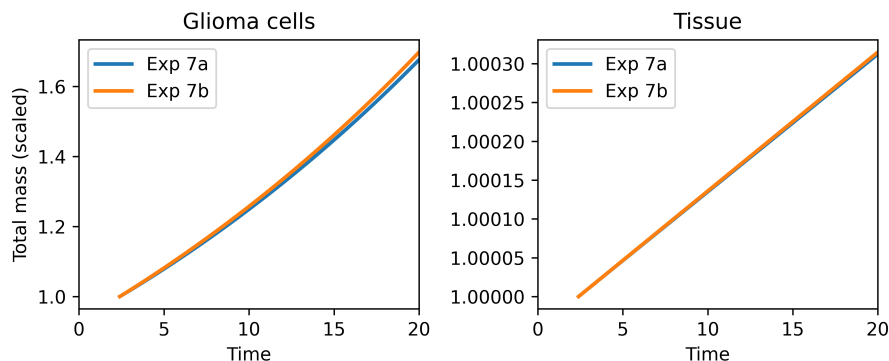
Figure 4.10: Experiment 7: Total masses of tumor and tissue in relation to total masses immediately after surgery at $t = 2.5$

respectively. In contrast, in experiment 7b the tumor mass is removed almost completely (by 99.9%), but also the tissue is reduced by 2.5%. Depending on the location of the tumor, there has to be a profound consideration of the medical advantages and disadvantages of those options [62]. In our simulations, the tissue does not reenter the resection cavity. This is due to our modeling approach, which suggests an ODE for tissue evolution.

The evolution of total masses of tumor and tissue in relation to the reference values of total masses of tumor and tissue immediately after surgery in experiments 7a and 7b, which can be seen in figure 4.10, are almost identical. In relation to the reference values, we observe a slightly faster regrowth of tumor mass in experiment 7b. This behavior has its origin in the lower cell density after surgery combined with the logistic growth of the cancer cells. Note, though, that the almost identical curves in figure 4.10 only describe the evolution of the total masses in relation to the total masses at $t = 2.5$, which differ in experiments 7a and 7b. There is, of course, a considerable difference between the non-scaled total masses in experiment 7a and experiment 7b (cf. the values stated above).

4.2.2 Experiment 8: Therapy by partial removal of the tumor and implantation of gliadel wafers (model 2.4)

We repeat experiment 1 on the time interval $[0, 2.5]$. At $t = 2.5$, part of the tumor is removed as in experiment 7a and gliadel wafers are implanted. Afterwards, the simulation is resumed for model 2.4 on the time interval $[2.5, 20]$.

For the simulation, wafers are implanted around the border of the resection cavity with a thickness of 1.5 mm. For therapy by gliadel wafers, no reliable data sets are available, hence many of the parameters given in table 4.2 are only estimates. We lay the focus here on a qualitative comparison between the different therapy approaches, choosing similar parameters for experiments 8 and 9. Since carmustine as well as temozolomide, used for classical chemotherapy in experiment 9, attack cells during the cell cycle, we assume a larger degradation rate for the fast proliferating tumor cells than for normal tissue. Not therapy-specific parameters are again given in table 4.1.

Parameter	value	source
carmustine diffusion D_C	10	[50]
tumor degradation by carmustine σ	10^2	estimated
tissue degradation by carmustine δ_{QC}	10	estimated
carmustine uptake by endothelial cells k_{bbb}	5	estimated
natural decay of carmustine k_d	5	estimated
degradation of wafer a	1	estimated
maximum carmustine concentration $\max C_{total}(x)$	8×10^{-2}	[1]

Table 4.2: Non-dimensionalized parameters

In figure 4.11 we observe a local degradation of tumor cells as well as of healthy brain tissue by the carmustine diffusing from the gliadel wafers. In figure 4.12, we see that the loss of brain tissue due to carmustine is small against the loss of tumor mass, though. In comparison with experiment 7a (same setting for resection, but no implantation of wafers), total tumor mass at $t = 20$ is 20.0% lower, while tissue mass is only 0.024% lower. Interestingly, the maximal tumor cell density at a single spot in experiment 8 is larger than in experiment 7a. This could be due to the local destruction of tissue, leading to larger gradients ∇Q and hence a more stringent haptotactic behavior of the tumor cells, which in turn leads to locally high accumulations of tumor cells.

4.2.3 Experiment 9: Therapy by partial removal of the tumor and classical chemotherapy according to different dosing schemes (model 2.5)

Again, we repeat experiment 1 on the time interval $[0, 2.5]$. At $t = 2.5$, part of the tumor is removed as in experiment 7a. Afterwards, the simulation is resumed for model 2.5 in different settings on the time interval $[2.5, 20]$. The parameters are given in table 4.1 and 4.3.

Parameter	value	source
temozolomide diffusion D_C	10	estimated[1]
tumor degradation by temozolomide σ	10^2	estimated[1]
tissue degradation by temozolomide δ_{QC}	10	estimated[1]
natural decay of temozolomide d_C	5	estimated[1]
administration width b_i for all i	5×10^{-3}	[6]

Table 4.3: Non-dimensionalized parameters

Experiment 9a: Standard dosing scheme

We consider the standard dosing scheme [66] of six weeks with daily dose 75 mg temozolomide per m^2 body surface, followed by four weeks of break, followed by six five-days-on-23-days-off cycles. In the first cycle, the daily dose amounts to 150 mg temozolomide per m^2 body surface, in the consequent cycles 200 mg

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[1]Again, due to a lack of reliable data, paramaters can only be estimated. For a better qualitative comparison of the two therapy approaches, we choose these parameters in accordance to those for carmustine.
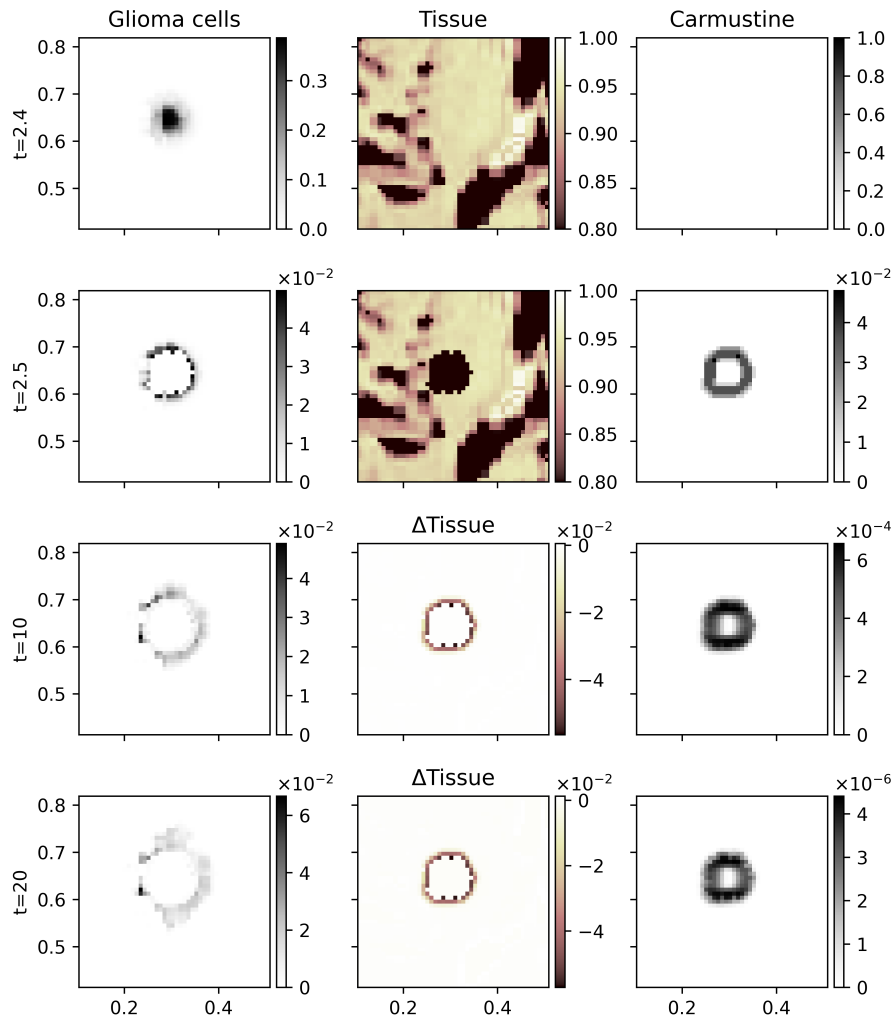
Figure 4.11: Experiment 8: Removal of glioblastoma at $t = 2.5$ with simultaneous implantation of gliadel wafers (model 2.4). For $t = 10$ and $t = 20$, instead of tissue density, the changes $Q(t, x) - Q(2.5, x)$ in tissue density after resection are plotted.
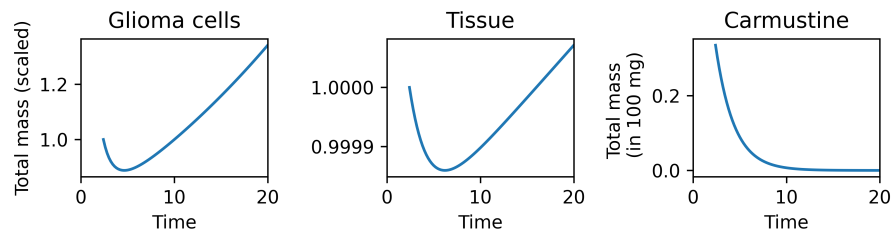

Figure 4.12: Experiment 8: Total masses of tumor and tissue in relation to total masses immediately after surgery at $t = 2.5$, total mass of carmustine

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temozolomide per m^2 body surface. Assuming a body surface area of 2 m^2[76] and choosing $K_C = 100\ mg$, we find for the non-dimensionalized administration parameters

$$d_i = 10.4\ \text{ for } i = 1, 2, ..., 42,$$
$$d_i = 20.8\ \text{ for } i = 71, ..., 75,$$
$$d_i = 27.7\ \text{ for } i = j + 28k,\ j = 99, ..., 103,\ k = 1, ..., 4,$$
$$d_i = 0\ \text{ otherwise}$$

with $t_i \approx \frac{i}{14}$.

In figure 4.13, we see that in contrast to experiment 8 the tissue and the tumor are not reduced locally but over the whole simulation domain, depending on the density of drug-transporting blood vessels. At the first glance, the figures for temozolomide concentration appear unexpected. Remember that the initial distribution of endothelial cell density is given by a normal distribution as plotted in figures 4.8 and 4.9. Since temozolomide is transported to the brain via these blood vessels, the plot of its concentration has a similar appearance, though blurred due to the diffusivity of the chemotherapeutic agent.

In figure 4.14, we observe tumor growth with decreased growth rate in comparison to experiment 7a (on the time interval $[2.5, 20]$ the tumor mass increases by 12.3% in experiment 9a in comparison to 67.6% in experiment 7a, respectively). At the same time, the tissue mass is degraded by 0.40% in contrast to an increase of 0.03% in experiment 7a. In the six cycles following daily administration, after some decay during the first five days of drug administration, tumor mass increases with each cycle. In our experiments, tumor growth is slowed down but not stopped.

Experiment 9b: Metronomic scheme

We consider a metronomic scheme with daily doses. For a better comparison of the different dosing schemes applied in experiments 9a, 9b and 9c, we choose the totally administered dose to be the same in each experiment. For a daily dose of 75 mg per m^2 body surface, this gives 58 days of dose administration without break. This leads to the non-dimensionalized administration parameters

$$d_i = 10.4 \qquad\qquad \text{for } i = 1, 2, ..., 58,$$
$$d_i = 0 \qquad\qquad \text{for } i = 59, 60, ...,$$

with $t_i \approx \frac{i}{14}$. The results are given in figures 4.15 and 4.16. Though at time $t = 10$ in experiment 9b therapy is already finished, we observe a barely smaller tumor mass than in experiment 9a (on $[2.5, 10]$ we find a gain in tumor mass of 3.5% in contrast to 3.6%). After the complete interval of observation, the standard dosing scheme proves to attack the cancer cells more efficiently (on $[2.5, 20]$ we find a gain in tumor mass of 39.8% in experiment 9b and a gain of 12.3% in experiment 9a). Here, the treatment with high doses proves to be more effective. On the other hand, it must not be neglected that less tumor growth comes along with increased tissue degradation (while in experiment 8a 0.4% of healthy tissue are lost, the degradation in experiment 9b amounts only to 0.17%).

Figure 4.13: Experiment 9a: Removal of glioblastoma at $t = 2.5$ followed by chemotherapy (model 2.5) with standard dosing scheme. For $t = 10$ and $t = 20$, instead of tissue density, the changes $Q(t, x) - Q(2.5, x)$ in tissue density after resection are plotted.

Figure 4.14: Experiment 9a: Total masses of tumor and tissue in relation to total masses immediately after surgery at $t = 2.5$, total mass of temozolomide
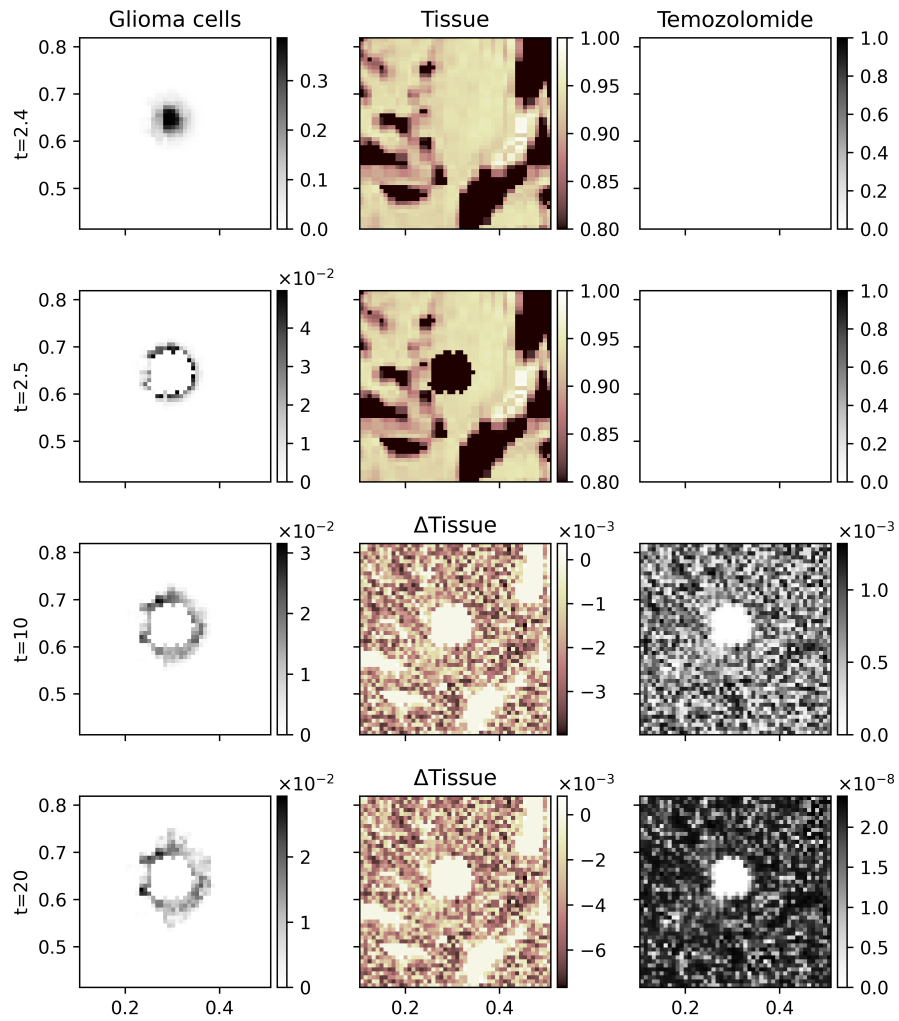
Figure 4.15: Experiment 9b: Removal of glioblastoma at $t = 2.5$ followed by chemotherapy (model 2.5) with metronomic dosing scheme. For $t = 10$ and $t = 20$, instead of tissue density, the changes $Q(t, x) - Q(2.5, x)$ in tissue density after resection are plotted.
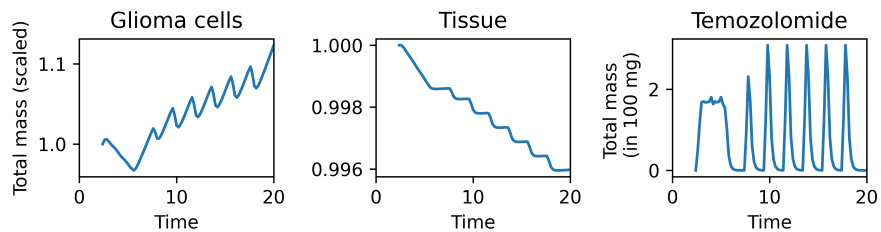

Figure 4.16: Experiment 9b: Total masses of tumor and tissue in relation to total masses immediately after surgery at $t = 2.5$, total mass of temozolomide
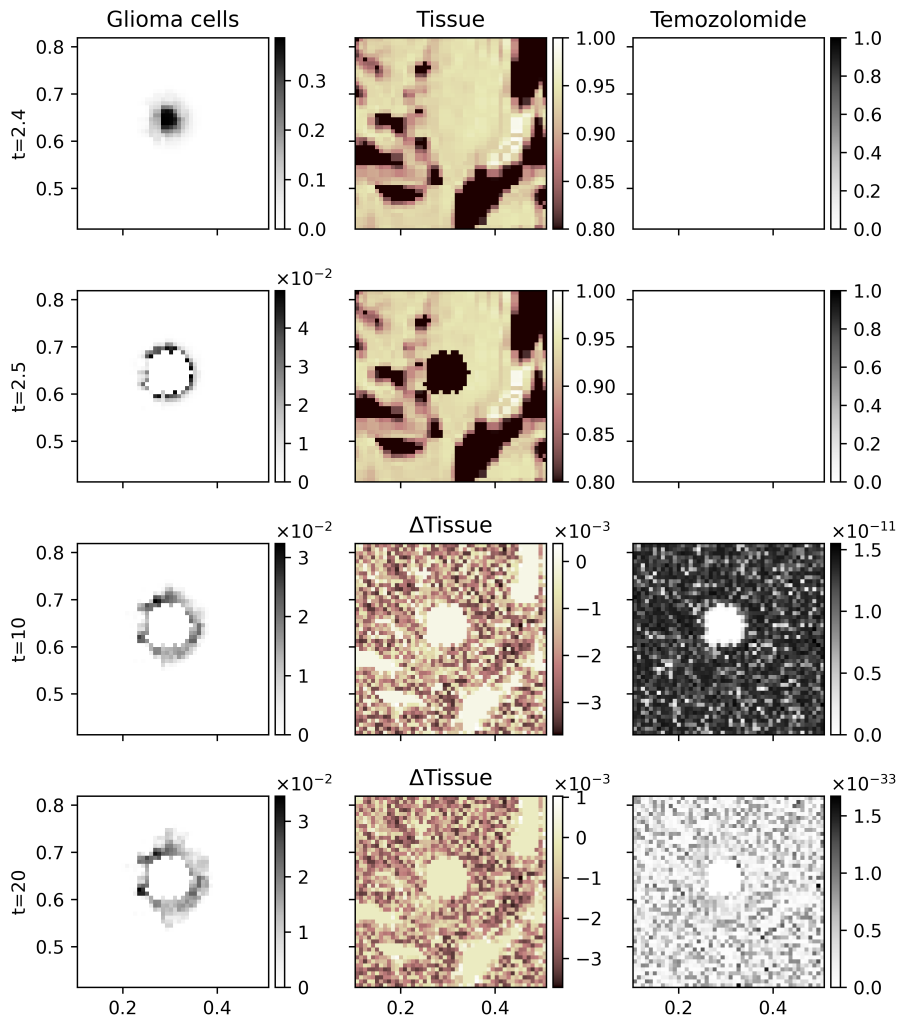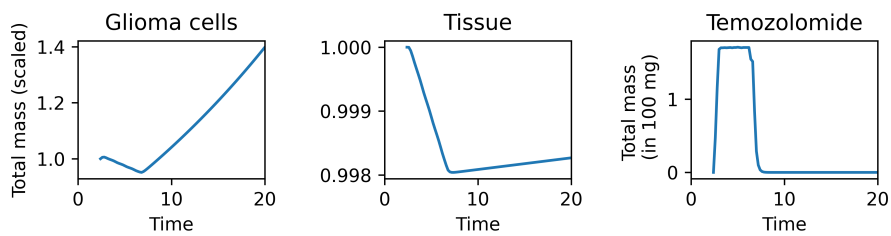
Experiment 9c: One-week-on-one-week-off

Finally, we consider the scheme studied in [26, 73], which is one-week-on-one-week-off. Again, we choose the totally administered dose to be the same as in the experiments before. Assuming that the weakly breaks allow a slightly higher daily dose than in experiment 9b, we choose 100 mg per m^2 body surface for days of drug administration. To obtain the same dose in total as before, we apply this scheme for six weeks. We obtain the non-dimensionalized administration parameters

$$d_i = 13.9 \text{ for } i = j + 14k, \ j = 1, ..., 7, \ k = 0, ..., 5,$$
$$d_i = 0 \text{ otherwise.}$$

In figure 4.17, we see the evolution of the tumor. In figure 4.18, we observe the decrease of tumor mass during the time span of the six therapy cycles with small ascents in the drug free weeks. The pattern we observe in total mass in figure 4.17 is similar to that in the 5-days-on-23-days-off cycles of experiment 9a, but due to the shorter drug free intervals with a decrease in tumor mass in each treatment cycle. This leads, however, also to a stronger degradation of tissue during the administration cycles. Further, due to the shorter therapy period (after eleven weeks, no further temozolomide is applied), the resulting tumor mass 35 weeks after therapy start is with an increase of 38.5% considerably larger than in experiment 9a.

4.2.4 Comparison of the different treatment approaches

In table 4.4, the gain and loss of tumor and tissue mass are compared for the different therapies. To this aim, we choose experiment 7a (surgery without further treatment) as a reference. In the first two columns of table 4.4, gain and loss of total mass in relation to the state immediately after surgery are summarized, i.e.

$$\frac{\int_\Omega M(20, x) - M(2.5, x)\, \mathrm{d}x}{\int_\Omega M(2.5, x)\, \mathrm{d}x} \quad \text{and} \quad \frac{\int_\Omega Q(20, x) - Q(2.5, x)\, \mathrm{d}x}{\int_\Omega Q(2.5, x)\, \mathrm{d}x}.$$

In the third and fourth column, we present the relative differences in total mass between experiment 7a and the other experiments, i.e.

$$\frac{\int_\Omega M_{ex\,i}(20, x) - M_{ex\,7a}(20, x)\, \mathrm{d}x}{\int_\Omega M_{ex\,7a}(20, x)\, \mathrm{d}x} \quad \text{and} \quad \frac{\int_\Omega Q_{ex\,i}(20, x) - Q_{ex\,7a}(20, x)\, \mathrm{d}x}{\int_\Omega Q_{ex\,7a}(20, x)\, \mathrm{d}x}.$$

All values are measured at $t = 20$.

	gain in relation to state after surgery		changes in relation to ex 7a	
	tumor mass	tissue mass	tumor mass	tissue mass
ex 7a	67.6%	+0.03%	−	−
ex 8	34.1%	+0.006%	−20.0%	−0.024%
ex 9a	12.3%	−0.40%	−33.0%	−0.43%
ex 9b	39.8%	−0.17%	−16.6%	−0.20%
ex 9c	38.5%	−0.18%	−17.4%	−0.21%

Table 4.4: Comparison of the different therapy strategies
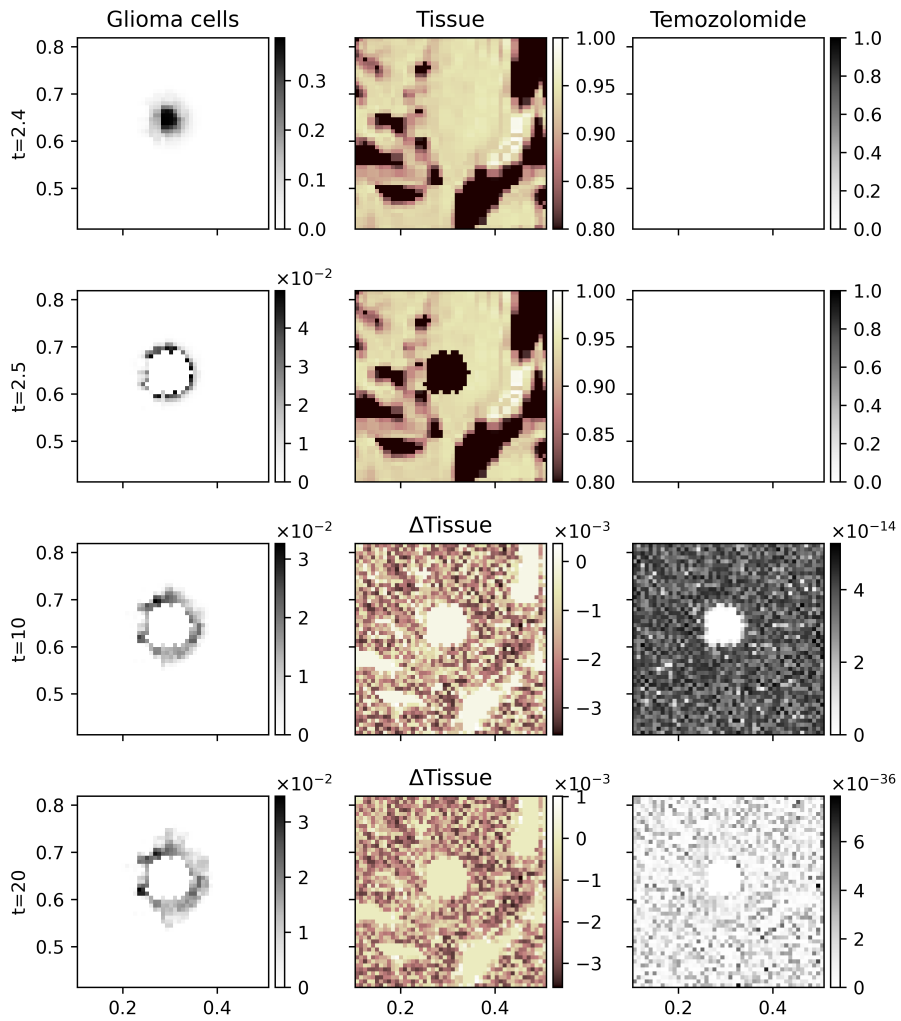
Figure 4.17: Experiment 9c: Removal of glioblastoma at $t = 2.5$ followed by chemotherapy (model 2.5) with one-week-on-one-week-off dosing scheme. For $t = 10$ and $t = 20$, instead of tissue density, the changes $Q(t,x) - Q(2.5,x)$ in tissue density after resection are plotted.

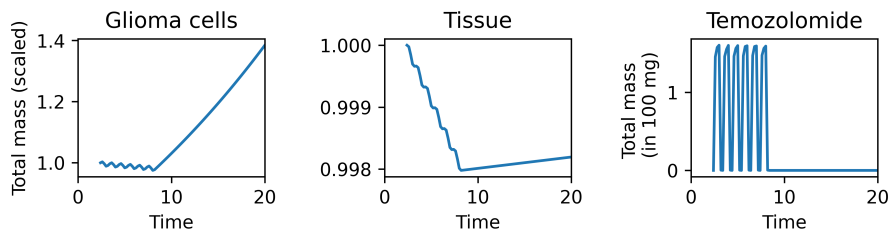

Figure 4.18: Experiment 9c: Total masses of tumor and tissue in relation to total masses immediately after surgery at $t = 2.5$, total mass of temozolomide

Comparing the ratios of the loss of tumor mass and tissue mass, each measured in relation to experiment 7a, i.e. the entries of the third column divided by the entries of the fourth column, we find that in experiment 9a, 9b and 9c the relative losses of tumor mass divided by the relative losses of tissue mass are almost equal, experiment 9a providing a slightly better result than experiments 9b and 9c (cf. table 4.5).

	ex 8	ex 9a	ex 9b	ex 9c
rel. loss in tumor mass / rel. loss in tisue mass	833.3	76.7	83.0	82.9

Table 4.5: Ratios of the loss of tumor mass and tissue mass, each measured in relation to experiment 7a

This result suggests that from a mathematical point of view, there is no clear preference for one of the dosing schemes - higher degradation of tumor mass comes along with similarly higher degradation of healthy brain tissue. A higher total degradation can always be reached by an increase of the administration dose. However, in the decision of the individually suitable dosing scheme also other effects like side effects of high doses have to be considered.
For therapy by gliadel wafers, the ratio of decreased tumor mass and lost brain tissue looks promising at the first glance. The reduced degradation of tissue is due to the local action of the chemotherapeutic agent, which is the clear advantage of gliadel wafers over classical chemotherapy. In the standard therapy by temozolomide, the drug acts on the whole brain, so mainly in regions where no tumor cells are to be expected, damaging tissue unnecessarily. What must not be neglected when drawing a comparison between therapy by gliadel wafers and therapy by classical chemotherapy, though, are the high risks of adverse reactions after implantation of gliadel wafers like cerebral edema, wound healing abnormalities, or depression [1]. Further, invasive tumor cells in a certain distance from the resected tumor can not be reached, which might be one of the reasons why therapy by surgery and gliadel wafers alone is indicated only in case of recurrent glioma. For newly diagnosed glioma, it is indicated only as an adjunct to surgery and radiation [1].

Chapter 5

Discussion

Modeling

Multiscale modeling facilitates the combination of microscopic dynamics, describing for example processes in the cancer cell or on its surface, with macroscopic processes like the evolution of the tumor environment. Thereby, it enables a far more detailed description than the modeling on a single (usually macroscopic) scale. Especially for the description of cancer invasion, where attachment to the ECM plays a major role, many effects cannot be modeled on a macroscopic level alone.

In the presented multiscale model, we combined the dynamics of tissue binding cell surface receptors as well as velocity dynamics with a macroscopic description of the tumor environment. A closed system of momentum equations was developed, from which an equation for the macroscopic tumor cell density was derived via scaling methods. In the resulting system, consisting of equations for the tumor cell density as well as different components of the tumor environment (pH, tissue density and endothelial cell density), the effects of microscopic cell behavior are still contained via the coefficient functions in the equation for cancer cell density. At the same time, the equation can be handled numerically without the problems arising for equations with different scales and a higher dimension.

Approaches similar to the model presented in this thesis have been made, e.g. [13, 14, 15, 20, 21, 22, 32, 41, 55]. In difference to these works, we described changes in direction of cancer cells not by a turning kernel but directly modeled the velocity dynamics by an ODE. This has the advantage that not only changes in direction are possible but also in speed, which opens new possibilities of modeling. We used this approach to include effects of population density pressure into the velocity dynamics by decreasing speed in crowded regions. In view of the interpretation of corresponding simulations, the resulting boundedness of cancer cell density by the biological carrying capacity is of great practical interest. A similar approach based on the publication of chapter 2 was done in [42]. Also from an analytical point of view, this proceeding leads to interesting equations, in our case causing degeneracy and flux saturation of diffusion and taxis terms. For the derivation of a macroscopic equation, we made as usual some approximating assumptions on the second order moments. While in earlier mod-

els no closed system of moment equations was developed but the macroscopic equation was derived via scaling methods (see e.g. [13, 14, 15, 20, 21, 22, 32] again), by an additional assumption on the divergence of one of the second order moments we could derive a closed system of moment equations. The subsequent scalings for the derivation of a single macroscopic equation for tumor density are naturally given by the biological parameters.

There are many possible extensions of the presented model. So far, we considered only one activity variable, the state of cell surface receptor binding to the extracellular matrix. The effect of pH on cell proliferation was modeled by a macroscopic term. Since acidification plays a major role in tumor progression, it could be interesting to include a further activity variable describing intracellular pH of the single cancer cells or modeling the transmembrane units mediating the exchange between outer and inner pH, e.g. as in [41]. However, this will lead to an even more complex model on the micro-meso-level. Challenges are to be expected for the derivation of a macroscopic model, especially since also the so far macroscopic equation describing extracellular pH will be concerned by the microscopic dynamics. A further possible extension could be the modeling of necrotic tissue as was done for example in [13, 15, 48]

Some extensions of the basic model were made in sections 2.2-2.4. While the discussion of the best taxis term for endothelial cells is a question of detail and could be circumvented by introducing a further equation for vascular endothelial growth factor, the definition of subpopulations of migrating and proliferating cancer cells facilitates a more detailed description of the tumor dynamics, however leading to several problems regarding the analysis.

The benefit of extending the basic model by therapy terms is obvious. While there already exists a variety of models for radiation and classical chemotherapy, the focus in this work was laid upon therapy by gliadel wafers, an approach that has rarely been modeled yet. Here, we focused on the therapy by resection of the tumor with subsequent implantation of gliadel wafers without further therapies, as is indicated for patients with recurrent glioblastoma. In case of newly diagnosed high-grade glioma, the implantation of gliadel wafers is recommended in adjunction with radiation. Since the latter is not supposed to effect carmustine concentration, for a corresponding extension of the model radiation terms could simply be added in the equation describing glioma cell density.

Also for the modeling of therapy by gliadel wafers or classical chemotherapy, the introduction of an additional activity variable could be of interest. In our models, the microscopic dynamics are included via the cell speed into the macroscopic decay terms of cancer cell density by carmustine and temozolomide (which was due to the idea that fast migrating cells do not proliferate and are hence less affected by chemotherapeutic agents). A description of different classes of cell surface receptors binding not only to ECM but also to soluble components would facilitate a more precise description of drug absorption by the cancer cells (however, with the above mentioned drawbacks regarding additional activity variables).

Analysis

We proved the existence of a global weak solution to a simplified version of the basic model developed in section 2.1, dropping the flux limitation in the diffu-

sion term of M but still retaining it in the taxis terms. The major challenge of the analysis lay in handling the strongly degenerate diffusion term in the equation for M and the nonlinear coupling of the PDE-ODE-system, including flux saturation in the taxis terms. After regularizing the system, as was done for example in [80, 81, 82, 85, 86], and decoupling it, a sequence of solutions was constructed using theory by Amann. The bounds on the gradients of M_k needed for convergence of the sequence could be found by choosing a suitable set of multiplier functions f_δ and considering domains of degeneracy and nondegeneracy separately. Beneath the existence of a global weak solution, we could verify that the components of the solution are nonnegative and do not exceed the biologically expected values. What remains open is the question of uniqueness of the weak solution.

The next step would be the existence of a weak solution to the original problem, i.e. model 2.1 with flux limited diffusion. By flux saturation in the diffusion term, problems arise concerning the regularity of M. We already addressed this topic in subsection 3.1.5.

While the existence of a global weak solution to a simplified version of the models developed in sections 2.2 and 2.4 could be shown, the existence of a solution to the go-or-grow model from section 2.3 remains an open topic. Beyond the problems addressed above, arising from flux limitation and degeneracy, the model comes up with several analytical challenges. Trying to adapt our original proof, first problems arise with the choice of a suitable decoupling, such that boundedness and nonnegativity of M_k and P_k are ensured. While this problem might be circumvented by a different approach not based on a decoupling of the system, the major challenge lies in the equation for the proliferating cells P. Due to the signal dependent switch terms on the microscale, the macroscopic equation for P depends on the function g, which contains gradients of M, P, h and Q. Hence, we have an equation including a transport-like term but containing no diffusion, which could ensure regularity. Especially if the flux saturation in the diffusion term is dropped to simplify the equation for M, this further complicates the problem, as it makes the term g even more irregular.

Simulations

In simulations we illustrated the resulting cell densities for different settings of the basic model, using a code developed by N. Kolbe and N. Sfakianakis. The effects of dominating haptotaxis versus dominating pH-taxis were compared, showing the expected differences in anisotropy of the spread. We further illustrated the differences between the original model developed in section 2.1, the simplified version used in the analysis section, and a version without any flux saturation. As expected, we observed a more diffusive behavior of the simplified model when compared to the original version and the version without flux saturation, and saw that without flux limitation the tumor spread is more invasive. For the tissue, we observed in all settings a slight increase in the density in regions not concerned with tumor growth. This from a biological point of view unexpected growth is due to the carrying capacity having been chosen constant. A proper knowledge of a spatially variant carrying capacity would solve this inaccuracy but is difficult to realize in a quantitative manner. Apart from that, the simulations coincide with the expected behavior of the tumor and its envi-

ronment.

The code was adapted to the model variations, including different tactic behavior of endothelial cells as well as the go-or-grow model. We observed that taxis of endothelial cells along M leads to a more distinct formation of blood vessels, while taxis along h or hM leads to a wider spread of vasculature.

Finally, we compared the different therapies, considering gliadel wafers as well as various dosing schemes for classical chemotherapy. Here, especially the advantages of the local action of gliadel wafers in comparison with classical chemotherapy became obvious, while the comparison between the dosing schemes only revealed quantitative differences, which can - from a mathematical point of view - easily be adjusted by lowering or raising the administered dose. In order to choose the best treatment for single patients, knowledge about the individual dose limitation by medical aspects would be needed.

Further, for a prognostic simulation near to reality, refillment of the resection cavity has to be modeled. However, this needs a completely different modeling approach, where tissue is not described by an ODE anymore but changes its location as a consequence of surrounding pressure. Beside this, a precise modeling of resection has to take into account further aspects like the formation of edema.

To get more realistic simulations, beside the problem of resection modeling, data about the initial distribution of blood vessels are needed, as they are responsible for the transport of drug into the tumor and away from it and hence play an important role for therapy outcome. Though essential for a precise prognosis of drug distribution in the brain, these kind of data are unfortunately very difficult to obtain.

The next step would be the validation of our simulations with real patient data. Confirming our modeling approach by medical data would be another small step in the understanding and modeling of glioma dynamics and therapy effects.

Appendix A

A.1 Theorems

Theorem A.1.1 ([16, theorem 13.5]). *Let $u \in W_p^{1,2}([0,T] \times \Omega)$ for some $p > n + 2$, where*

$$W_p^{1,2}([0,T] \times \Omega) := \{u \in \mathcal{L}^p([0,T] \times \Omega) : \partial_t u, \partial_x^\alpha u \in \mathcal{L}^p([0,T] \times \Omega) \text{ for } |\alpha| \leq 2\},$$

such that

$$u_t - \sum_{i,j=1}^n a_{ij}(t,x)u_{x_i x_j} + \sum_{i=1}^n a_i(t,x)u_{x_i} + a(t,x)u \geq 0 \ \ in \ \ (0,T] \times \Omega,$$

$$\partial_\nu u \geq 0 \ \ on \ \ (0,T] \times \partial\Omega,$$
$$u(0,\cdot) \geq 0 \ \ in \ \Omega,$$

where ν denotes the outward unit normal, and $a_{ij} = a_{ji}, a_i, a \in C([0,T] \times \bar{\Omega})$ and $\sum_{i,j=1}^n a_{ij}(t,x)\xi_i\xi_j \geq \alpha |\xi|^2$ for some $\alpha > 0$.
Then $u \geq 0$ in $[0,T] \times \bar{\Omega}$.

Theorem A.1.2 ([4, theorem 14.4 with remark 12.2 a)]). *Let D_0 be a nonempty open subset of $\mathbb{R}^n$ and assume that*

$$a_{ij}, a_i, b_i, a_0 \in C^{2-}(\mathbb{R}_0^+ \times \bar{\Omega} \times D_0, \mathbb{R}^{n \times n}), \ \ 1 \leq i,j \leq N,$$

where for $k \in \mathbb{N}$

$$C^{k-}(X,E) := \{u \in C^{k-1}(X,E) : D^\alpha u \text{ is Lipschitz continuous for } |\alpha| \leq k-1\}.$$

Then we consider the following quasilinear parabolic boundary value problem:

$$\partial_t u + \mathcal{A}(u)u = f(\cdot,\cdot,u,\partial u) \ \ in \ \mathbb{R}^+ \times \Omega,$$
$$\mathcal{B}(u)u = g(\cdot,\cdot,u) \ \ on \ \mathbb{R}^+ \times \partial\Omega, \hspace{2cm} \text{(A.1)}$$
$$u(\cdot,0) = u_0 \ \ on \ \Omega,$$

where

$$\mathcal{A}(\eta)u = -\sum_{i,j=1}^N \partial_i \left(a_{ij}(\cdot,\cdot,\eta)\partial_j u\right) - \sum_{i=1}^N \partial_i \left(a_i(\cdot,\cdot,\eta)u\right) + \sum_{i=1}^N b_i(\cdot,\cdot,\eta)\partial_i u + a_0(\cdot,\cdot,\eta)u,$$

$$\mathcal{B}(\eta)u = \sum_{i,j=1}^N \nu^i \gamma_\partial \left(a_{ij}(\cdot,\cdot,\eta)\partial_j u + a_i(\cdot,\cdot,\eta)u\right),$$

γ_∂ *denoting the trace operator for $\partial\Omega$. Assume that*

$$D = \left\{ \eta \in D_0 : \left(\sum_{i,j=1}^{N} a_{ij}^{kl}(\cdot,\cdot,\eta)\xi_i\xi_j \right)_{k,l=1}^{n} \text{ is positive definite for all } \xi \in \mathbb{R}^N \backslash\{0\} \right\} \tag{A.2}$$

is nonempty. Further, suppose that

$$f \in C^{1-,2-}((\mathbb{R}_0^+ \times \bar{\Omega} \times D) \times \mathbb{R}^{n \times N}, \mathbb{R}^n)$$

and that for each compact subset K of D there exists a constant c_K s.t.

$$|\partial_\zeta f(t,x,\eta,\zeta)| \leq c_K(1 + |\zeta|) \text{ for all } (t,x,\eta,\zeta) \in \mathbb{R}_0^+ \times \bar{\Omega} \times K \times \mathbb{R}^{n \times N}.$$

Finally, assume that

$$g \in C^{1-}(\mathbb{R}_0^+ \times \partial\Omega \times D, \mathbb{R}^n).$$

If $\frac{N}{p} < 1 < (1 + \frac{1}{p}) \wedge (2 - \frac{N}{p})$ and f is independent of the gradient, then the boundary value problem (A.1) has for each $u_0 \in W^{1,p}(\Omega, D)$ a unique weak solution $u \in C(J; W^{1,p}(\Omega))$, $J = [0, t^+)$ for some $t^+ > 0$.

Theorem A.1.3 ([4, theorem 14.6]). *Suppose the assumptions of theorem A.1.2 are fulfilled. Additionally, let $g = 0$. Then u is a classical solution of (A.1), that is,*

$$u \in C(J \times \bar{\Omega}, D) \cap C^{1,2}(\dot{J} \times \bar{\Omega}, \mathbb{R}^n),$$

where $\dot{J} = J \backslash \{0\}$, and u satisfies (A.1) pointwise.

Theorem A.1.4 ([4, corollary 14.7]). *Let the assumptions of theorem A.1.2 be fulfilled. If $g = 0$ and f and all coefficients of $(\mathcal{A}, \mathcal{B})$ are C^∞-smooth, then*

$$u \in C^\infty(\dot{J} \times \bar{\Omega}, \mathbb{R}^n).$$

The following theorem is a special case of theorem 15.5, [4].

Theorem A.1.5 ([4, theorem 15.5]). *Suppose that $(\mathcal{A}, \mathcal{B})$ is lower triangular and that either*

- *each a_{ij} is a diagonal matrix and*

$$|f_r(u, \partial u)| \leq c(|u|)(1 + |\nabla u_r|), \ 1 \leq r \leq n$$

  or

- *the r-th row of each a_{ij} is independent of u_s for $s > r$, and*

$$|f_r(u, \partial u)| \leq c(|u|)(1 + |\nabla u_r| + \sum_{s<r} |\nabla u_s|^2), \ 1 \leq r \leq n.$$

Also suppose, that

$$\|u(t)\|_{\mathcal{L}^\infty} \leq c(T), \ 0 \leq t \leq T < \infty, \ t < t^+.$$

Then $t^+ = \infty$ if $u|_{[0,T]}$ is bounded away from ∂D for each $T > 0$.

The following comparison principle is a special case of theorem 15.1, [4].

Theorem A.1.6 ([4, theorem 15.1]). *Consider the parabolic boundary value problem (A.1) from theorem A.1.2 for $n = 1$. Let all assumptions of theorem A.1.2 be fulfilled. Further, let $t\eta \in D_0$ for all $\eta \in D, t \in [0,1]$, let $f \in C^1(\bar{\Omega} \times D_0, \mathbb{R})$, $g \in C^1(\partial\Omega \times D_0, \mathbb{R})$ with $f(\cdot, 0), g(\cdot, 0) \geq 0$ and let $u(0, \cdot) \geq 0$.*
Then for the solution u from theorem A.1.2 it holds $u(t, \cdot) \geq 0$ for $t \in J$.

Theorem A.1.7 ([59, chapter 2.3, theorem 2]). *Let E be an open subset of $\mathbb{R}^{n+m}$ containing the point (u_0, μ_0), where $u_0 \in \mathbb{R}^n$ and $\mu_0 \in \mathbb{R}^m$, and assume that $f \in C^1(E)$. Then there exist $a, \delta > 0$ such that for all $y \in B_\delta(u_0), \mu \in B_\delta(\mu_0)$ the initial value problem*

$$\dot{u} = f(u, \mu), \ u(0) = y$$

has a unique solution $u(t, y, \mu) \in C^1(G)$, where $G = [-a, a] \times B_\delta(y_0) \times B_\delta(\mu_0)$.

Remark A.1.8. In case of a nonautonomous problem $\dot{u} = f(t, u, \mu)$, we set $\tilde{u} = (t, u)^T$ and obtain the equation $\dot{\tilde{u}} = (1, f(t, u, \mu))^T =: \tilde{f}(\tilde{u}, \mu)$. Hence, the theorem can also be applied to nonautonomous equations.

Remark A.1.9. By [59, chapter 2.3, remark 1], the solution $u(t, y, \mu)$ from theorem A.1.7 has the same smoothness properties as f.

Theorem A.1.10 ([79, lemma 1.3 (ii) and (iii)]). *Let $(e^{r\Delta})_{r\geq 0}$ be the Neumann heat semigroup in Ω and let $\lambda_1 > 0$ denote the first nonzero eigenvalue of $-\Delta$ in Ω under Neumann boundary conditions. Then, there exists $C > 0$ depending on Ω only with the following property:*

(i) *For $1 \leq p \leq \infty$ it holds for all $w \in \mathcal{L}^p(\Omega)$*

$$\|\nabla e^{r\Delta} w\|_{\mathcal{L}^p(\Omega)} \leq C(1 + r^{-\frac{1}{2}})e^{-\lambda_1 r}\|w\|_{\mathcal{L}^p(\Omega)} \ \forall r > 0.$$

(ii) *For $2 \leq p < \infty$ it holds for all $w \in W^{1,p}(\Omega)$*

$$\|\nabla e^{r\Delta} w\|_{\mathcal{L}^p(\Omega)} \leq Ce^{-\lambda_1 r}\|\nabla w\|_{\mathcal{L}^p(\Omega)} \ \forall r > 0.$$

Theorem A.1.11 ([52]). *Let $I \subset \mathbb{R}$ be some interval and let $\Omega \subset \mathbb{R}^n$ be an open bounded set. Let further B be some Banach space of functions defined on Ω. If*

1. $(u_n)_n$ *is bounded in $\mathcal{L}^p(I, X)$,*

2. $(\partial_t u_n)_n$ *is bounded in $\mathcal{L}^r(I, Y)$,*

3. X *embeds compactly in B, which embeds continuously in Y,*

then $(u_n)_n$ has a strongly convergent subsequence in $\mathcal{L}^p(I; B)$, provided $p < \infty$ or $r > 1$.

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Akademischer Werdegang

seit 02/2017	Promotion Mathematik, Technische Universität Kaiserslautern
10/2014 - 12/2016	Masterstudium Mathematik mit Nebenfach Physik, Technische Universität Kaiserslautern
08/2013 - 12/2013	Auslandssemester LTH (Lund, Schweden)
10/2011 - 10/2014	Bachelorstudium Mathematik mit Nebenfach Physik, Technische Universität Kaiserslautern
05/2011	Abitur, Alexander-von-Humboldt Schule Lauterbach

Academic curriculum vitae

since 02/2017	PhD student in mathematics, Technische Universität Kaiserslautern
10/2014 - 12/2016	Master studies in mathematics with minor subject physics, Technische Universität Kaiserslautern
08/2013 - 12/2013	Semester abroad, LTH (Lund, Sweden)
10/2011 - 10/2014	Bachelor studies in mathematics with minor subject physics, Technische Universität Kaiserslautern
05/2011	Abitur, Alexander-von-Humboldt Schule Lauterbach