Analysis of a tumor model as a multicomponent deformable porous medium

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Abstract. We propose a diffuse interface model to describe a tumor as a multicomponent deformable porous medium. We include mechanical effects in the model by coupling the mass balance equations for the tumor species and the nutrient dynamics to a mechanical equilibrium equation with phase-dependent elasticity coefficients. The resulting PDE system couples two Cahn–Hilliard type equations for the tumor phase and the healthy phase with a PDE linking the evolution of the interstitial fluid to the pressure of the system, a reaction-diffusion type equation for the nutrient proportion, and a quasistatic momentum balance. We prove here that the corresponding initial-boundary value problem has a solution in appropriate function spaces.

1. Introduction

Tumor growth is nowadays one of the most active areas of scientific research, especially due to the impact on the quality of life for cancer patients. Starting with the seminal work of Burton [9] and Greenspan [35], many mathematical models have been proposed to describe the complex biological and chemical processes that occur in tumor growth with the aim of better understanding and ultimately controlling the behavior of cancer cells. In recent years, there has been a growing interest in the mathematical modeling of cancer, see for example [1,2,5,10,16,20,22,50,52]. Mathematical models for tumor growth may have different analytical features: in the present work we are focusing on the subclass of continuum models, namely diffuse interface models. There are various ways to model the interaction between the tumor and surrounding host tissue. A classical approach is to represent the interfaces between the tumor and healthy tissues as idealized surfaces of zero thickness, leading to a sharp interface description that differentiates the tumor and the surrounding host tissue cell-by-cell. These sharp interface models are often difficult to analyze mathematically, and may fail when the interface undergoes a topological change. Metastasis, which is the spreading of cancer to other parts of the body, is one important example of a change of topology. In such an event, the interface can no longer be represented as a mathematical surface, and thus the sharp interface models do not properly describe the reality anymore.

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On the other hand, diffuse interface models consider the interface between the tumor and the healthy tissues as a layer of noninfinitesimal thickness in which tumor and healthy cells can coexist. The main advantage of this approach is that the mathematical description is less sensitive to topological changes. This is the reason why recent efforts in the mathematical modeling of tumor growth have been mostly focused on diffuse interface models, see for example [15, 16, 21, 30, 33, 36, 43, 51] and their numerical simulations demonstrating complex changes in tumor morphologies due to mechanical stresses and interactions with chemical species such as nutrients or toxic agents. Regarding the recent literature on the mathematical analysis of diffuse interface models for tumor growth, we can further refer to [11–13, 18, 24, 25, 28, 29, 31] as mathematical references for Cahn–Hilliard type models and [6, 27, 34, 37, 41, 48, 49] for models also including a transport effect described by Darcy's law.

A further class of diffuse interface models that also include chemotaxis and transport effects has been subsequently introduced (cf. [30, 33]); moreover, in some cases the sharp interface limits of such models have been investigated generally by using formal asymptotic methods (cf. [42, 45]).

Including mechanics in the model is clearly an important issue that has been discussed in several modeling papers, but that has been very poorly studied analytically. Hence, the main aim of this paper is to find a compromise between the applications and the rigorous analysis of the resulting PDE system: we would like to introduce here an applicationsignificant model which is also tractable analytically. Regarding the existing literature on this subject, we can quote paper [46], where, using multiphase porous media mechanics, the authors represent a growing tumor as a multiphase medium containing an extracellular matrix, tumor and host cells, and interstitial liquid. Numerical simulations are also performed that characterize the process of cancer growth in terms of the initial tumorto-healthy cell density ratio, nutrient concentration, mechanical strain, cell adhesion, and geometry. However, referring to [47] for more details on this topic, we mention here that many models in the literature are based on the assumption that the tumor mass presents a particular geometry, the so-called spheroid, and in that case the models mainly focus on the evolution of the external radius of the spheroid. The resulting mathematical problem is an integro-differential free boundary problem, which has been proved to have solutions (cf. [8,23]) and to predict the evolution of the system. Variants of this approach have been considered, e.g., in [17], differentiating between viable cells and the necrotic core. Further extensions of the model introduced in [47] can be found in [44].

Very recently in [32] a new model for tumor growth dynamics including mechanical effects has been introduced in order to generalize the previous works [38,39] with the goal of taking into account cell-cell adhesion effects with the help of a Ginzburg–Landau type energy. In their model, an equation of Cahn–Hilliard type is then coupled to the system of linear elasticity and a reaction-diffusion equation for a nutrient concentration, and several questions regarding well-posedness and regularity of solutions are investigated.

In this paper, following the approach of [47], we introduce a diffuse interface multicomponent model for tumor growth, where we include mechanics in the model, assuming that the tumor is a porous medium. In [47] the tumor is regarded as a mixture of various interacting components (cells and extracellular material) whose evolution is ruled by coupled mass and momentum balances. The cells usually are subdivided into subpopulations of proliferating, quiescent and necrotic cells (cf., e.g., [15, 16]) and the interactions between species are determined by the availability of some nutrients. Here, we restrict to the case where we distinguish only healthy and tumor cells, even if we could, without affecting the analysis, treat the case where we differentiate also between necrotic and proliferating tumor cells. Hence, we represent the tumor as a porous medium consisting of three phases: healthy tissue φ_1 , tumor tissue φ_2 , and interstitial fluid φ_0 satisfying proper mass balance equations including mass source terms depending on the nutrient variable ρ . The nutrient satisfies a reaction-diffusion equation nonlinearly coupled with the tumor and healthy tissue phases by a coefficient characterizing the different consumption rates of the nutrient by the different cell types. We couple the phases and nutrient dynamics with a mechanical equilibrium equation. This relation is further coupled with the phase dynamics through the elasticity modulus depending on the proportion of healthy and tumor phases. We refer to [19] for a mathematical model of a multicomponent flow in deformable porous media, from which we take inspiration. The mass balance relations are derived from a free energy functional $\mathcal{F} = \mathcal{F}(\varphi_0, \varphi_1, \varphi_2, w, \rho)$ which, in the domain Ω where the evolution takes place, can be written as

$$\mathcal{F} = \int_{\Omega} \left(\widehat{F}(\varphi_0 - w) + \frac{|\nabla \varphi_1|^2}{2} + \frac{|\nabla \varphi_2|^2}{2} + (\psi + g)(\varphi_1, \varphi_2) + \frac{\varrho^2}{2} + \frac{E(\varphi_1, \varphi_2)w^2}{2} \right) \mathrm{d}x,$$
(1.1)

where w denotes the volume difference with respect to the referential state, E is the elasticity modulus of the tissue, and \hat{F} is a suitable nonnegative function defined below in (2.12). The sum $\psi + g$ represents the interaction potential of a typically double-well character between tumor and healthy phases, with dominant component ψ which is convex with bounded domain, while g is its smooth nonconvex perturbation. The quantity ϱ represents the mass content of the nutrient. Notice that the gradient terms in the free energy are due to the modeling assumption that the interface between healthy and tumor phases is diffuse (we take the parameters in front of the gradients equal to one here for simplicity, but, in practice, they determine the thickness of the interface and have to be chosen properly). The quantities φ_0 , φ_1 , φ_2 are relative mass contents, so that only their nonnegative values are meaningful. We also assume that all the other substances present in the system are of negligible mass, that is, the identity $\varphi_0 + \varphi_1 + \varphi_2 = 1$ is to be satisfied as part of the problem. Hence, we choose the domain of ψ to be included in the set $\Theta := \{(\varphi_1, \varphi_2) \in \mathbb{R}^2 : \varphi_1 \ge 0, \ \varphi_2 \ge 0, \ \varphi_1 + \varphi_2 \le 1\}$. Classically, ψ can be taken as the indicator function of Θ or a logarithmic type potential (cf. [26]).

Under proper assumptions on the data, we prove the existence of weak solutions for the resulting PDE system that we will introduce in Section 2, coupled with suitable initial and boundary conditions. The PDEs consist of two Cahn–Hilliard type equations for the tumor phase and the healthy phase with a PDE linking the evolution of the interstitial fluid to the pressure of the system, with a reaction-diffusion type equation for the nutrient proportion

and the momentum balance. The technique of the proof is based on a regularization of the system, where, in particular, the nonsmooth potential ψ is replaced by its Yosida approximation ψ_{ε} . Then, we prove the existence of a solution to the approximated problem by means of a Faedo–Galerkin scheme and we pass to the limit by proving suitable uniform (in ε) a priori estimates and applying monotonicity and compactness arguments. A key point in the estimation consists in proving that the mean value of the phases are in the interior of the domain Θ of ψ , which in turns leads to the estimate of the mean value of the corresponding chemical potentials in the two Cahn–Hilliard type equations (cf. [14, 26]). The uniqueness could be proved only in very particular situations, for example, for smooth potentials ψ satisfying suitable growth conditions and under some restrictions on the interaction coefficients in the Cahn–Hilliard type equations for the phase. We prefer to leave this argument for further studies on the model.

Plan of the paper. In the next section, we introduce the model deduced from the modeling hypothesis of [47]. In Section 3, we state the mathematical problem and the main results of the paper concerning the existence of suitable weak solutions for the corresponding PDE system. The proof relies on the passage to the limit (in Section 5) in a regularized problem, whose well-posedness is obtained in Section 4.

2. Modeling

We follow the modeling hypotheses of [47] and represent the tumor as a porous medium consisting of three phases: healthy tissue, tumor tissue, and interstitial fluid. We choose the Lagrangian formalism, and assume that the evolution of the system takes place in a bounded domain $\Omega \subset \mathbb{R}^3$ with Lipschitzian boundary.

The state of the system is described by the following scalar quantities:

- φ_0 : Relative mass content of the interstitial fluid.
- φ_1 : Relative mass content of the healthy tissue.
- φ_2 : Relative mass content of the tumor tissue.
- μ_1 : Chemical potential controlling the growth of the healthy tissue.
- μ_2 : Chemical potential controlling the growth of the tumor tissue.
- *p*: Fluid pressure.
- w: Volume difference with respect to the referential state.
- ϱ : Mass content of the nutrients.

We consider the following evolution system in a given time interval (0, T):

$$\dot{\phi}_i + \sum_{j=0}^2 c_{ij} \operatorname{div} \xi_j = S_i, \quad i = 0, 1, 2,$$
(2.1)

$$\dot{\varrho} + \operatorname{div} \zeta + A(\varphi_1, \varphi_2) \, \varrho = 0, \qquad \zeta = -D \, \nabla \varrho,$$
(2.2)

$$\nu \dot{w} + E(\varphi_1, \varphi_2) w - p = \frac{1}{|\Omega|} \int_{\Omega} (E(\varphi_1, \varphi_2) w - p) \, \mathrm{d}x,$$
(2.3)

$$\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix} \in -\begin{pmatrix} \Delta \varphi_1 \\ \Delta \varphi_2 \end{pmatrix} + \partial \psi(\varphi_1, \varphi_2) + \nabla_{\!\varphi} g(\varphi_1, \varphi_2) + \nabla_{\!\varphi} E(\varphi_1, \varphi_2) \frac{w^2}{2}, \tag{2.4}$$

$$S_0 = -\gamma(\varrho)\,\overline{\varphi}_0(1-\varphi_0), \qquad S_1 = \gamma(\varrho)\,\overline{\varphi}_0\varphi_1, \qquad S_2 = \gamma(\varrho)\,\overline{\varphi}_0\varphi_2, \qquad (2.5)$$

$$\xi_j = -\nabla \mu_j, \quad j = 0, 1, 2,$$
 (2.6)

$$\mu_0 = p, w = \varphi_0 - f(p), \tag{2.7}$$

where the dot denotes the derivative with respect to $t \in (0, T)$, $\partial \psi$ is the subdifferential of a convex potential ψ , g is a smooth bounded possibly nonconvex perturbation of ψ , ∇ is the gradient with respect to the space variable $x = (x_1, x_2, x_3)$, ∇_{φ} is the gradient with respect to $\varphi = (\varphi_1, \varphi_2)$, Δ is the Laplace operator, f is an empirical increasing function of the pressure, and ξ_j , ζ are fluxes of the components φ_j , ϱ , respectively.

The physical meaning of (2.7) is the following: At constant volume w, the pressure p increases when the fluid content φ_0 increases. Similarly, at constant pressure, the volume increases when the fluid content increases, and at constant fluid content, the pressure increases when the volume decreases.

The above system is coupled with initial and boundary conditions

$$\varphi_{i}(0) = \varphi_{i}^{0} \quad \text{for } i = 1, 2, \\ w(0) = w^{0}, \\ \varrho(0) = \varrho^{0}$$
 in Ω , (2.8)

and

$$\begin{array}{l} \nabla \varphi_i \cdot n = 0 \quad \text{for } i = 1, 2, \\ \xi_i \cdot n = 0 \quad \text{for } i = 0, 1, 2, \\ \zeta \cdot n = \kappa (\varrho - \varrho^*) \end{array} \right\} \quad \text{on } \partial \Omega \times (0, T),$$

$$(2.9)$$

where n = n(x) is the unit outward normal vector at the point $x \in \partial \Omega$.

In (2.5) as well as in what follows, for arbitrary $t \in (0, T)$ and a generic function $v \in L^1(\Omega \times (0, T))$ we denote by

$$\overline{v}(t) = \frac{1}{|\Omega|} \int_{\Omega} v(x,t) \,\mathrm{d}x \tag{2.10}$$

the mean value of v over Ω .

Equations (2.4) and (2.7) can be derived from the potential (1.1) according to a standard "Cahn–Hilliard" theory, namely,

$$\mu_i \in \partial_{\varphi_i} \mathcal{F}(\varphi_0, \varphi_1, \varphi_2, w, \varrho), \quad i = 0, 1, 2,$$

$$(2.11)$$

where ∂_{φ_i} denotes a suitable (e. g., Clarke) concept of subdifferential, provided we set

$$\widehat{F}(z) = \int_{z_0}^{z} f^{-1}(s) \,\mathrm{d}s \tag{2.12}$$

with z_0 from Hypothesis 3.1 (iv). Equation (2.1) then represents the mass balance for the three components φ_0 , φ_1 , φ_2 of the system, where c_{ij} are the constant interaction coefficients. The source terms S_i are given by (2.5), where $\gamma(\rho)$ represents the speed of the growth rate depending on the nutrient concentration ρ . Equation (2.2) is a diffusion equation describing the mass balance for the nutrient concentration with a constant positive diffusion coefficient D > 0 and with a nonnegative coefficient A depending on φ_1 , φ_2 and characterizing the different consumption rates of the nutrient by the different cell types. The coefficient $\kappa > 0$ in the boundary condition (2.9) for ζ is the diffusivity of the boundary for the nutrients, and ρ^* is the (given) nutrient concentration outside the domain. Equation (2.3) is the mechanical equilibrium equation with constant viscosity coefficient $\nu > 0$ and with positive elasticity modulus $E(\varphi_1, \varphi_2)$ of the tissue, which can be different proportions of φ_1 and φ_2 . The constitutive functions A, E, f, γ , the convex potential ψ , the interaction constants, and the initial and boundary conditions satisfy Hypothesis 3.1 below.

The system (2.1)–(2.7) is thermodynamically consistent. Indeed, the balance between the power supplied to the system $\int_{\Omega} \sum_{i=0}^{2} \dot{\varphi}_{i} \mu_{i} dx$ and the potential increment $\dot{\mathcal{F}}$ formally gives

$$\int_{\Omega} \sum_{i=0}^{2} \dot{\varphi}_{i} \mu_{i} \, \mathrm{d}x - \frac{\mathrm{d}}{\mathrm{d}t} \mathcal{F}(\varphi_{0}, \varphi_{1}, \varphi_{2}, w, \varrho) = \int_{\Omega} (\dot{w} p - E(\varphi_{1}, \varphi_{2}) \dot{w} w - \dot{\varrho} \varrho) \, \mathrm{d}x$$
$$= \int_{\Omega} (v |\dot{w}|^{2} + D |\nabla \varrho|^{2} + A(\varphi_{1}, \varphi_{2}) \varrho^{2}) \, \mathrm{d}x$$
$$\geq 0,$$
(2.13)

which shows that the dissipation rate is positive during the process.

3. Statement of the problem

The quantities $\varphi_0, \varphi_1, \varphi_2$ are relative mass contents, so that only their nonnegative values are meaningful. We also assume that all the other substances present in the system are of negligible mass, that is, the identity $\varphi_0 + \varphi_1 + \varphi_2 = 1$ is to be satisfied as part of the problem. The convex functional ψ has to be chosen in such a way that the closure $\overline{\text{Dom }\psi}$ of its domain Dom ψ is the set

$$\overline{\operatorname{Dom}\psi} = \Theta := \left\{ \varphi = (\varphi_1, \varphi_2) \in \mathbb{R}^2 : \varphi_1 \ge 0, \ \varphi_2 \ge 0, \ \varphi_1 + \varphi_2 \le 1 \right\},$$
(3.1)

and for $\delta \in (0, 1 - (1/\sqrt{2}))$ we define

$$\Theta_{\delta} := \{ \varphi \in \operatorname{Int} \Theta : \operatorname{dist}(\varphi, \partial \Theta) \ge \delta \}.$$
(3.2)

Let us first specify the hypothesis about the data of the problem.

Hypothesis 3.1. We fix a constant $K \ge 1$ and assume the following hypotheses to hold:

(i) For all $j = 0, 1, 2, \sum_{i=0}^{2} c_{ij} = 0$, for all $i = 0, 1, 2, \sum_{j=0}^{2} c_{ij} = 0$, and there exists $\hat{c} > 0$ such that

$$-\sum_{i\neq j} c_{ij} |\xi_i - \xi_j|^2 \ge \hat{c} (|\xi_1 - \xi_0|^2 + |\xi_2 - \xi_0|^2)$$

for all $\xi_0, \xi_1, \xi_2 \in \mathbb{R}^3$;

- (ii) the functions $E, A : \mathbb{R}^2 \to [0, K]$ are Lipschitz continuous;
- (iii) the function $\gamma : \mathbb{R} \to [-K, K]$ is continuously differentiable and $|\gamma'(\varrho)| \le K$ for all $\rho \in \mathbb{R}$;
- (iv) the function $f : \mathbb{R} \to \mathbb{R}$ is continuously differentiable, $f_1 \ge f'(p) \ge f_0$ for some $f_1 > f_0 > 0$ and all $p \in \mathbb{R}$, $z_0 = f(0)$;
- (v) the function $\psi : \mathbb{R}^2 \to [0, +\infty]$ is proper convex lower semicontinuous, satisfying (3.1). We further assume that there exist positive constants δ, b', c', r' such that when putting $\delta_T = \delta e^{-KT-2}$, the following implications hold:
 - (v1) dist $(\hat{\varphi}, \Theta_{\delta_T}) \leq \delta_T/2 \implies |\hat{\xi}| \leq b' \quad \forall \hat{\xi} \in \partial \psi(\hat{\varphi});$
 - (v2) $\hat{\varphi} \in \Theta_{\delta_T}, \ |\varphi \hat{\varphi}| \ge \delta_T / 4, \ \varphi \in \Theta \implies r' |\xi \hat{\xi}| \le \langle \xi \hat{\xi}, \varphi \hat{\varphi} \rangle + c'$ $\forall \xi \in \partial \psi(\varphi), \quad \forall \hat{\xi} \in \partial \psi(\hat{\varphi});$
- (vi) the given function $g: \Theta \to \mathbb{R}$ is of class C^2 ;
- (vii) the functions $\varphi_0^0, \varphi_1^0, \varphi_2^0, w^0, \varrho^0 \in W^{1,2}(\Omega) \cap L^{\infty}(\Omega)$ are given initial data such that $\overline{w^0} = 0, (\varphi_1^0, \varphi_2^0) \in \Theta_{\delta}$ with δ from Hypothesis (v), $\varphi_0^0(x) + \varphi_1^0(x) + \varphi_2^0(x) = 1$ for a.e. $x \in \Omega$;
- (viii) the function $\varrho^* \in L^{\infty}(\partial \Omega \times (0, T))$ is such that $\dot{\varrho}^* \in L^2(\partial \Omega \times (0, T))$.

Conditions (v1), (v2) need some comments. They slightly differ from those in [14, Proposition 2.10], but it is easy to check they are still satisfied if, for example, ψ is the indicator function of the set Θ . Indeed, (v1) holds trivially. To verify that (v2) holds, take any $\varphi \in \Theta$ and $\xi \in \partial \psi(\varphi)$. We first notice that $\hat{\xi} = 0$, and

$$\langle \xi, \varphi - v \rangle \ge 0 \quad \forall v \in \Theta.$$

We are done if $\xi = 0$. Otherwise,

$$v = \hat{\varphi} + \delta_T \frac{\xi}{|\xi|}$$

is an admissible choice, and we obtain

$$\langle \xi, \varphi - \widehat{\varphi} \rangle \ge \delta_T |\xi|,$$

which is precisely (v2) with $r' = \delta_T$ and c' = 0.

In the proof, we extend the function g to the whole of \mathbb{R}^2 in such a way that

$$C_g := \sup\left\{|g(\varphi)|, |\nabla_{\!\varphi}g(\varphi)|, |\langle\nabla_{\!\varphi}g(\varphi), \varphi\rangle| : \varphi \in \mathbb{R}^2\right\} < \infty.$$
(3.3)

The main result of the paper reads as follows.

Theorem 3.2. Let Hypothesis 3.1 hold. Then the system (2.1)–(2.9) admits a solution with the regularity $\varphi_i \in L^{\infty}(\Omega \times (0,T))$, $\nabla \varphi_i \in L^{\infty}(0,T;L^2(\Omega))$, $\dot{\varphi}_i \in L^2(0,T;W^{-1,2}(\Omega))$, $\mu_i, \nabla \mu_i \in L^2(\Omega \times (0,T))$ for $i = 0, 1, 2, (\varphi_1(x,t), \varphi_2(x,t)) \in \Theta$ a.e., $\varphi_0 + \varphi_1 + \varphi_2 =$ 1 a.e., $w \in L^{\infty}(\Omega \times (0,T))$, $\dot{w}, \nabla w, \nabla \dot{w} \in L^{\infty}(0,T;L^2(\Omega))$, $\dot{\varrho} \in L^2(\Omega \times (0,T))$, $\varrho, \nabla \varrho \in L^{\infty}(0,T;L^2(\Omega))$. Equations (2.3), (2.5)–(2.7) and the initial conditions (2.8) are satisfied almost everywhere in $\Omega \times (0,T)$ and in Ω , respectively, and the relations (2.1)–(2.2) and (2.4) are to be interpreted respectively as

$$\int_{\Omega} \left(\dot{\varphi}_i \, v_i + \sum_{j=0}^2 c_{ij} \langle \nabla \mu_j, \nabla v_i \rangle \right) \mathrm{d}x = \int_{\Omega} S_i \, v_i \, \mathrm{d}x, \quad i = 0, 1, 2, \tag{3.4}$$

$$\int_{\Omega} \left(\dot{\varrho} \hat{v} + D \langle \nabla \varrho, \nabla \hat{v} \rangle + A(\varphi_1, \varphi_2) \varrho \hat{v} \right) dx + \kappa \int_{\partial \Omega} (\varrho - \varrho^*) \, \hat{v} \, ds(x) = 0, \qquad (3.5)$$

and

$$\begin{split} \int_{\Omega} \left\langle \left(\begin{array}{c} \mu_1 \\ \mu_2 \end{array} \right) - \nabla_{\varphi} g(\varphi_1, \varphi_2) - \nabla_{\varphi} E(\varphi_1, \varphi_2) \frac{w^2}{2}, \left(\begin{array}{c} v_1 \\ v_2 \end{array} \right) - \left(\begin{array}{c} \varphi_1 \\ \varphi_2 \end{array} \right) \right\rangle dx \\ &- \int_{\Omega} \left(\langle \nabla \varphi_1, \nabla (v_1 - \varphi_1) \rangle + \langle \nabla \varphi_2, \nabla (v_2 - \varphi_2) \rangle \right) dx \\ &\leq \int_{\Omega} (\psi(v_1, v_2) - \psi(\varphi_1, \varphi_2)) dx, \end{split}$$
(3.6)

for a.e. $t \in (0, T)$ and for all test functions $v_0, v_1, v_2, \hat{v} \in W^{1,2}(\Omega)$.

The proof of Theorem 3.2 is divided into several steps. We introduce a small regularizing parameter $\varepsilon > 0$ and approximate the convex potential ψ by its Yosida approximation ψ^{ε} defined by the formula

$$\psi^{\varepsilon}(\varphi) = \min_{z \in \mathbb{R}^2} \Big\{ \frac{1}{2\varepsilon} |\varphi - z|^2 + \psi(z) \Big\}.$$
 (3.7)

Let us recall the main properties of the Yosida approximation (see [3, 4, 7] for proofs).

Proposition 3.3. The mapping $\psi^{\varepsilon} : \mathbb{R}^2 \to [0, \infty)$ is convex and continuously differentiable, and the so-called resolvent J^{ε} of $\partial \psi$, defined as

$$J^{\varepsilon} = (I + \varepsilon \,\partial\psi)^{-1}, \tag{3.8}$$

where I is the identity, is nonexpansive in \mathbb{R}^2 . The mapping $\nabla_{\varphi}\psi^{\varepsilon}$ is monotone and Lipschitz continuous, and has for every $\varphi \in \mathbb{R}^2$ the following properties:

$$\nabla_{\!\varphi}\psi^{\varepsilon}(\varphi) = \frac{1}{\varepsilon}(\varphi - J^{\varepsilon}\varphi) \in \partial\psi(J^{\varepsilon}\varphi) \quad \forall \varepsilon > 0,$$
(3.9)

$$\varphi \in \text{Dom}\,\partial\psi \implies \begin{cases} |\nabla_{\!\varphi}\psi^{\varepsilon}(\varphi) - m(\partial\psi(\varphi))| \to 0\\ |\nabla_{\!\varphi}\psi^{\varepsilon}(\varphi)| \nearrow |m(\partial\psi(\varphi))| \end{cases} \quad as \ \varepsilon \searrow 0, \qquad (3.10)$$

$$\psi^{\varepsilon}(\varphi) = \frac{\varepsilon}{2} |\nabla_{\!\varphi} \psi^{\varepsilon}(\varphi)|^2 + \psi(J^{\varepsilon} \varphi) \quad \forall \varepsilon > 0,$$
(3.11)

$$\psi^{\varepsilon}(\varphi) \nearrow \psi(\varphi) \quad as \ \varepsilon \searrow 0,$$
 (3.12)

where $m(\partial \psi(\varphi))$ is the element of $\partial \psi(\varphi)$ with minimal norm.

From (3.9)–(3.11) it follows that for every $\varphi \in \mathbb{R}^2$ and every $\varepsilon > 0$ we have

$$\psi^{\varepsilon}(\varphi) = \frac{1}{2\varepsilon} |\varphi - J^{\varepsilon}\varphi|^2 + \psi(J^{\varepsilon}\varphi).$$
(3.13)

For every $\varphi \in \mathbb{R}^2$ and $\varepsilon > 0$ we have $J^{\varepsilon}(\varphi) \in \Theta$, so that $\psi(J^{\varepsilon}\varphi) \ge 0 \ge |J^{\varepsilon}\varphi|^2 - 1$. Furthermore, the Young inequality yields that

$$2\langle \varphi, J^{\varepsilon}\varphi \rangle \leq \frac{1}{2\varepsilon+1} |\varphi|^2 + (2\varepsilon+1) |J^{\varepsilon}\varphi|^2,$$

and we obtain

$$\psi^{\varepsilon}(\varphi) \ge \frac{1}{2\varepsilon + 1} |\varphi|^2 - 1 \quad \forall \varphi \in \mathbb{R}^2.$$
(3.14)

We consider the following weak formulation of the regularized problem (2.1)–(2.9):

$$\int_{\Omega} \left(\dot{\varphi}_i \, v_i + \sum_{j=0}^2 c_{ij} \langle \nabla \mu_j, \nabla v_i \rangle \right) \mathrm{d}x = \int_{\Omega} S_i \, v_i \, \mathrm{d}x, \quad i = 0, 1, 2, \tag{3.15}$$

$$\int_{\Omega} \left(\dot{\varrho} \hat{v} + D \langle \nabla \varrho, \nabla \hat{v} \rangle + A(\varphi_1, \varphi_2) \, \varrho \hat{v} \right) \mathrm{d}x + \kappa \int_{\partial \Omega} (\varrho - \varrho^*) \, \hat{v} \, \mathrm{d}s(x) = 0, \tag{3.16}$$

$$\nu \dot{w} + E(\varphi_1, \varphi_2)w - \frac{p}{|\varphi_0| + |\varphi_1| + |\varphi_2|} = \frac{1}{|\Omega|} \int_{\Omega} \left(E(\varphi_1, \varphi_2)w - \frac{p}{|\varphi_0| + |\varphi_1| + |\varphi_2|} \right) \mathrm{d}x,$$
(3.17)

$$\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix} = -\begin{pmatrix} \Delta\varphi_1 \\ \Delta\varphi_2 \end{pmatrix} + \nabla_{\varphi} \left(\psi^{\varepsilon}(\varphi_1, \varphi_2) + g(\varphi_1, \varphi_2)\right) + \nabla_{\varphi} E(\varphi_1, \varphi_2) \frac{w^2}{2},$$
(3.18)

$$S_0 = -Q (1 - \varphi_0), \qquad S_1 = Q \varphi_1, \qquad S_2 = Q \varphi_2, \tag{3.19}$$

$$Q = \frac{\gamma(Q)\phi_0}{(|\varphi_0| + |\varphi_1| + |\varphi_2|)(|\bar{\varphi}_0| + |\bar{\varphi}_1| + |\bar{\varphi}_2|)},$$
(3.20)

$$\xi_j = -\nabla \mu_j, \quad j = 0, 1, 2,$$
(3.21)

$$\mu_0 = p, \qquad w = \varphi_0 - f(p),$$
(3.22)

for a.e. $t \in (0, T)$ and for all test functions $v_0, v_1, v_2, \hat{v} \in W^{1,2}(\Omega)$.

Assuming that the system (3.15)–(3.22), (2.8) has a solution, choosing $v_0 = v_1 = v_2 = v$ in (3.15), and summing up over i = 0, 1, 2, we obtain formally from Hypothesis 3.1 (i) the identity

$$\int_{\Omega} \left(\sum_{i=0}^{2} \dot{\varphi}_{i} \right) v \, \mathrm{d}x = \int_{\Omega} Q\left(\sum_{i=0}^{2} \varphi_{i} - 1 \right) v \, \mathrm{d}x$$

for all $v \in W^{1,2}(\Omega)$. Putting $y(x,t) = \sum_{i=0}^{2} \varphi_i(x,t) - 1$, we see that this is an identity of the form $\dot{y}(x,t) = Q(x,t)y(x,t)$ with initial condition y(x,0) = 0 according to Hypothesis 3.1 (vii). Hence, still formally,

$$\sum_{i=0}^{2} \varphi_i(x,t) = 1$$
(3.23)

for all x and t. In particular, the denominators in (3.17) and (3.20) are greater than or equal to one. We show below that in the limit $\varepsilon \to 0$, all φ_i will be nonnegative, and the denominators will all be equal to one.

4. Galerkin approximations

We solve the problem (3.15)–(3.22), (2.8) by Galerkin approximations. We choose the orthonormal basis $\{e_k : k \in \mathbb{N} \cup \{0\}\}$ in $L^2(\Omega)$ such that

 $-\Delta e_k = \lambda_k e_k \quad \text{in } \Omega, \qquad \nabla e_k \cdot n = 0 \quad \text{on } \partial \Omega \text{ for } k \in \mathbb{N} \cup \{0\}, \qquad \lambda_0 = 0,$

and for $m \in \mathbb{N}$ we introduce the functions

$$\varphi_i^{(m)}(x,t) = \sum_{k=0}^m \widetilde{\varphi}_{ik}(t) e_k(x),$$

$$\mu_i^{(m)} = \sum_{k=0}^m \widetilde{\mu}_{ik}(t) e_k(x) \quad \text{for } i = 0, 1, 2,$$

$$\varrho^{(m)}(x,t) = \sum_{k=0}^m \widetilde{\varrho}_k(t) e_k(x),$$

with time dependent coefficients $\tilde{\varphi}_{ik}(t)$, $\tilde{\mu}_{ik}(t)$, $\tilde{\varrho}_k(t)$ which are to be found as solutions of the following ODE system for k = 0, 1, ..., m:

$$\begin{split} &\int_{\Omega} \left(\dot{\varphi}_{i}^{(m)} e_{k} + \sum_{j=0}^{2} c_{ij} \langle \nabla \mu_{j}^{(m)}, \nabla e_{k} \rangle \right) \mathrm{d}x = \int_{\Omega} S_{i}^{(m)} e_{k} \,\mathrm{d}x, \quad i = 0, 1, 2, \qquad (4.1) \\ &\int_{\Omega} \left(\dot{\varphi}^{(m)} e_{k} + D \langle \nabla \varphi^{(m)}, \nabla e_{k} \rangle + A(\varphi_{1}^{(m)}, \varphi_{2}^{(m)}) \,\varrho^{(m)} e_{k} \right) \mathrm{d}x \\ &\quad + \kappa \int_{\partial \Omega} (\varphi^{(m)} - \varphi^{*}) e_{k} \,\mathrm{d}s(x) = 0, \qquad (4.2) \\ &v \dot{w}^{(m)} + E(\varphi_{1}^{(m)}, \varphi_{2}^{(m)}) \,w^{(m)} - \frac{f^{-1}(\varphi_{0}^{(m)} - w^{(m)})}{|\varphi_{0}^{(m)}| + |\varphi_{1}^{(m)}| + |\varphi_{2}^{(m)}|} \\ &= \frac{1}{|\Omega|} \int_{\Omega} \left(E(\varphi_{1}^{(m)}, \varphi_{2}^{(m)}) \,w^{(m)} - \frac{f^{-1}(\varphi_{0}^{(m)} - w^{(m)})}{|\varphi_{0}^{(m)}| + |\varphi_{1}^{(m)}| + |\varphi_{2}^{(m)}|} \right) \mathrm{d}x, \qquad (4.3) \end{split}$$

$$\mu_{0}^{(m)} = P_{m}(f^{-1}(\varphi_{0}^{(m)} - w^{(m)})), \qquad (4.4)$$

$$\mu_{i}^{(m)} = -\Delta\varphi_{i}^{(m)} + P_{m}\left(\partial_{i}\psi^{\varepsilon}(\varphi_{1}^{(m)},\varphi_{2}^{(m)}) + \partial_{i}g(\varphi_{1}^{(m)},\varphi_{2}^{(m)}) + \partial_{i}E(\varphi_{1}^{(m)},\varphi_{2}^{(m)})\frac{|w^{(m)}|^{2}}{2}\right), \quad i = 1, 2, \qquad (4.5)$$

$$S_0^{(m)} = -Q^{(m)} (1 - \varphi_0^{(m)}), \qquad S_1^{(m)} = Q^{(m)} \varphi_1^{(m)}, \qquad S_2^{(m)} = Q^{(m)} \varphi_2^{(m)}, \quad (4.6)$$

$$Q^{(m)} = \frac{\gamma(\varrho^{(m)})\,\varphi_0^{(m)}}{\left(|\varphi_0^{(m)}| + |\varphi_1^{(m)}| + |\varphi_2^{(m)}|\right)\left(|\bar{\varphi}_0^{(m)}| + |\bar{\varphi}_1^{(m)}| + |\bar{\varphi}_2^{(m)}|\right)},\tag{4.7}$$

where $P_m : L^2(\Omega) \to H_m := \text{Span}(e_0, \dots, e_m)$ is the orthogonal projection of $L^2(\Omega)$ onto H_m , the symbol ∂_i denotes the partial derivative $\partial/\partial \varphi_i$ for i = 1, 2, and

$$\overline{\varphi}_i^{(m)} = \frac{1}{|\Omega|} \int_{\Omega} \varphi_i^{(m)} \,\mathrm{d}x$$

The initial conditions are

$$\tilde{\varphi}_{ik}(0) = \int_{\Omega} \varphi_i^0(x) \, e_k(x) \, \mathrm{d}x, \quad \tilde{\varrho}_k(0) = \int_{\Omega} \varrho^0(x) \, e_k(x) \, \mathrm{d}x, \quad w^{(m)}(x,0) = w^0(x).$$
(4.8)

System (4.1)–(4.2) is a locally well-posed system of 4(m + 1) differential equations of the first order for 4(m + 1) scalar unknowns $\tilde{\varrho}_k, \tilde{\varphi}_{ik}, i = 0, 1, 2, k = 0, 1, \ldots, m$, while it is convenient to interpret (4.3)–(4.6) as constitutive relations. We shall see below in equation (4.13) that the expressions in the denominators of (4.3) and (4.7) are greater than or equal to one, hence the formulas are meaningful. In particular, since f^{-1} is Lipschitz continuous by Hypothesis 3.1 (iv), equation (4.3) defines a Lipschitz continuous solution operator $W : C([0, T]; \mathbb{R}^{3(m+1)}) \rightarrow C^1([0, T]; W^{1,2}(\Omega))$, which with given functions $\tilde{\varphi}_{ik}, i = 0, 1, 2, k = 0, 1, \ldots, m$ associates the solution $w^{(m)}$ of (4.3). The existence of a unique local solution of (4.1)–(4.6) is therefore guaranteed on a nondegenerate time interval $[0, T_m), 0 < T_m \leq T$.

In order to show that the solution of (4.1)–(4.6) is global, we derive some estimates for the solution on the whole interval $[0, T_m)$.

4.1. Estimates independent of *m*

In the series of estimates which we derive in the formulas below, we denote by *C* any positive constant independent of *m* and ε , and by C^{ε} any constant independent of *m* and depending possibly on ε . For simplicity, we denote by $|\cdot|_H$ the norm in $L^2(\Omega)$, and by $\|\cdot\|_V$ the norm in $W^{1,2}(\Omega)$.

We first handle equation (4.2), which is easy. We multiply it by $\tilde{\varrho}_k$ and sum up over $k = 0, \ldots, m$ to obtain

$$\frac{\mathrm{d}}{\mathrm{d}t}\frac{1}{2}\int_{\Omega}|\varrho^{(m)}|^{2}\,\mathrm{d}x+D\int_{\Omega}|\nabla\varrho^{(m)}|^{2}\,\mathrm{d}x+\frac{\kappa}{2}\int_{\partial\Omega}|\varrho^{(m)}|^{2}\,\mathrm{d}s(x)\leq C.$$
(4.9)

We proceed similarly, multiplying (4.2) by $\dot{\tilde{\varrho}}_k$ and summing up over k = 0, ..., m to obtain that

$$\int_{\Omega} |\dot{\varrho}^{(m)}|^2 \,\mathrm{d}x + \frac{\mathrm{d}}{\mathrm{d}t} \Big(D \int_{\Omega} |\nabla \varrho^{(m)}|^2 \,\mathrm{d}x + \kappa \int_{\partial \Omega} |\varrho^{(m)}|^2 \,\mathrm{d}s(x) \Big) \le C \Big(1 + \int_{\Omega} |\varrho^{(m)}|^2 \,\mathrm{d}x \Big),\tag{4.10}$$

hence,

$$\int_{0}^{T_{m}} \int_{\Omega} |\dot{\varrho}^{(m)}|^{2} \,\mathrm{d}x \,\mathrm{d}t + \sup_{t \in (0, T_{m})} \left(\int_{\Omega} |\nabla \varrho^{(m)}|^{2}(t) \,\mathrm{d}x + \int_{\partial \Omega} |\varrho^{(m)}|^{2}(t) \,\mathrm{d}s(x) \right) \le C.$$
(4.11)

We further sum up equation (4.1) over i = 0, 1, 2. From Hypothesis 3.1 (i) it follows that

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_{\Omega} \left(\varphi_0^{(m)} + \varphi_1^{(m)} + \varphi_2^{(m)}\right) e_k \,\mathrm{d}x = \int_{\Omega} \left(S_0^{(m)} + S_1^{(m)} + S_2^{(m)}\right) e_k \,\mathrm{d}x$$
$$= \int_{\Omega} Q^{(m)}(x,t) \left(\varphi_0^{(m)} + \varphi_1^{(m)} + \varphi_2^{(m)} - 1\right) e_k \,\mathrm{d}x$$
(4.12)

for all k = 0, ..., m. In terms of the functions

$$y_k(t) = \int_{\Omega} \left(\varphi_0^{(m)} + \varphi_1^{(m)} + \varphi_2^{(m)} - 1 \right) e_k \, \mathrm{d}x = \tilde{\varphi}_{0,k} + \tilde{\varphi}_{1,k} + \tilde{\varphi}_{2,k} - \delta_{0,k},$$

where $\delta_{0,k}$ is the Kronecker symbol, we rewrite (4.12) in the form

$$\dot{y}_k(t) = \sum_{l=0}^m a_{kl}(t) y_l(t),$$

with bounded coefficients $a_{kl}(t)$. This is a linear ODE system with zero initial conditions (by Hypothesis 3.1 (vii)), so that all functions $y_k(t)$ vanish in the whole interval of existence. Hence,

$$\varphi_0^{(m)}(x,t) + \varphi_1^{(m)}(x,t) + \varphi_2^{(m)}(x,t) = 1$$
(4.13)

for all $(x, t) \in \Omega \times [0, T_m)$.

Next, we prove that $w^{(m)}$ as a solution of the ODE (4.3) admits, together with its time derivative, an L^{∞} -bound independent of *m* and ε , namely

$$\sup_{(x,t)\in\Omega\times(0,T_m)} \sup (|w^{(m)}(x,t)| + |\dot{w}^{(m)}(x,t)|) \le C.$$
(4.14)

Indeed, we first add to both the left-hand side and the right-hand side of (4.3) the term

$$\frac{f^{-1}(\varphi_0^{(m)})}{|\varphi_0^{(m)}| + |\varphi_1^{(m)}| + |\varphi_2^{(m)}|},$$

which is bounded, by Hypothesis 3.1 (iv) and (4.13). Note that by (4.3), we have that $\int_{\Omega} \dot{w}^{(m)} dx = 0$, hence $\int_{\Omega} w^{(m)} dx = 0$ by Hypothesis 3.1 (vii). Next, we multiply (4.3)

by $w^{(m)}$, use the fact that the mean value of $w^{(m)}$ is zero and the fact that $(f^{-1}(\varphi_0^{(m)}) - f^{-1}(\varphi_0^{(m)} - w^{(m)})) w^{(m)} \ge 0$, integrate over Ω , and obtain

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_{\Omega} |w^{(m)}(x,t)|^2 \,\mathrm{d}x \le C \int_{\Omega} |w^{(m)}(x,t)| \,\mathrm{d}x$$

for a.e. $t \in (0, T_m)$, hence, $\int_{\Omega} |w^{(m)}(x, t)|^2 dx \leq C$ for $t \in [0, T_m)$. In particular, the right-hand side of (4.3) is bounded independently of m and ε . We now repeat the same procedure, multiplying (4.3) by sign $w^{(m)}$ without integration over Ω . Note that for a.e. $x \in \Omega$, the function $t \mapsto w^{(m)}(x, t)$ is absolutely continuous, so that

$$\dot{w}^{(m)}(x,t)$$
 sign $w^{(m)}(x,t) = \frac{\partial}{\partial t} |w^{(m)}(x,t)|$ a.e

Furthermore, $(f^{-1}(\varphi_0^{(m)}) - f^{-1}(\varphi_0^{(m)} - w^{(m)}))$ sign $w^{(m)} \ge 0$, and we get

$$\nu \frac{\partial}{\partial t} |w^{(m)}(x,t)| + E(\varphi_1^{(m)}, \varphi_2^{(m)})|w^{(m)}(x,t)| \le C \quad \text{a.e. in } \Omega \times (0, T_m)$$

with $|w^{(m)}(x, 0)| \leq C$. Integrating from 0 to t we get a uniform upper bound for $|w^{(m)}(x, t)|$, and, by comparison with (4.3), we conclude that (4.14) holds.

Further estimates are more delicate. We multiply the (i, k)-th equation of (4.1) by $\tilde{\mu}_{ik}$ and sum up over i = 0, 1, 2 and k = 0, 1, ..., m to obtain

$$\sum_{i=0}^{2} \int_{\Omega} \dot{\varphi}_{i}^{(m)} \mu_{i}^{(m)} \,\mathrm{d}x + \sum_{i,j=0}^{2} c_{ij} \int_{\Omega} \langle \nabla \mu_{j}^{(m)}, \nabla \mu_{i}^{(m)} \rangle \,\mathrm{d}x = \sum_{i=0}^{2} \int_{\Omega} S_{i}^{(m)} \,\mu_{i}^{(m)} \,\mathrm{d}x.$$
(4.15)

We treat the three integrals in (4.15) separately. We first define a reduced potential $\mathcal{F}_0^{\varepsilon} = \mathcal{F}_0^{\varepsilon}(\varphi_0, \varphi_1, \varphi_2, w)$ by the formula

$$\mathcal{F}_{0}^{\varepsilon} = \int_{\Omega} \left(\widehat{F}(\varphi_{0} - w) + \psi^{\varepsilon}(\varphi_{1}, \varphi_{2}) + g(\varphi_{1}, \varphi_{2}) + E(\varphi_{1}, \varphi_{2}) \frac{w^{2}}{2} + \frac{|\nabla\varphi_{1}|^{2}}{2} + \frac{|\nabla\varphi_{2}|^{2}}{2} \right) dx, \qquad (4.16)$$

with \widehat{F} as in (2.12). Then the first integral on the left-hand side of (4.15) can be rewritten as

$$\sum_{i=0}^{2} \int_{\Omega} \dot{\varphi}_{i}^{(m)} \mu_{i}^{(m)} dx = \frac{d}{dt} \mathcal{F}_{0}^{\varepsilon}(\varphi_{0}^{(m)}, \varphi_{1}^{(m)}, \varphi_{2}^{(m)}, w^{(m)}) + \int_{\Omega} \dot{w}^{(m)}(f^{-1}(\varphi_{0}^{(m)} - w^{(m)}) - E(\varphi_{1}^{(m)}, \varphi_{2}^{(m)})w^{(m)}) dx \geq \frac{d}{dt} \mathcal{F}_{0}^{\varepsilon}(\varphi_{0}^{(m)}, \varphi_{1}^{(m)}, \varphi_{2}^{(m)}, w^{(m)}) - C \int_{\Omega} |\varphi_{0}^{(m)}| dx, \qquad (4.17)$$

with a constant C independent of m and ε , as a consequence of (4.14).

To estimate the second integral in (4.15), we use the vector formula

$$\langle u, v \rangle = -\frac{1}{2}(|u - v|^2 - |u|^2 - |v|^2)$$

to conclude, using Hypothesis 3.1 (i), that

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$$\sum_{i,j=0}^{2} c_{ij} \langle \nabla \mu_{j}^{(m)}, \nabla \mu_{i}^{(m)} \rangle = -\frac{1}{2} \sum_{i \neq j} c_{ij} |\nabla \mu_{j}^{(m)} - \nabla \mu_{i}^{(m)}|^{2}$$
$$\geq \frac{\hat{c}}{2} \sum_{i=1}^{2} |\nabla \mu_{i}^{(m)} - \nabla \mu_{0}^{(m)}|^{2}.$$
(4.18)

Finally, the integral on the right-hand side of (4.15) can be rewritten in the form

$$\sum_{i=0}^{2} \int_{\Omega} S_{i}^{(m)} \mu_{i}^{(m)} dx = -\sum_{i=1}^{2} \int_{\Omega} S_{i}^{(m)} \Delta \varphi_{i}^{(m)} dx + \int_{\Omega} S_{0}^{(m)} f^{-1}(\varphi_{0}^{(m)} - w^{(m)}) dx + \sum_{i=1}^{2} \int_{\Omega} S_{i}^{(m)} P_{m} \Big(\partial_{i} \psi^{\varepsilon}(\varphi_{1}^{(m)}, \varphi_{2}^{(m)}) + \partial_{i} g(\varphi_{1}^{(m)}, \varphi_{2}^{(m)}) + \partial_{i} E(\varphi_{1}^{(m)}, \varphi_{2}^{(m)}) \frac{|w^{(m)}|^{2}}{2} \Big) dx.$$
(4.19)

The first term on the right-hand side of (4.19) can be estimated using integration by parts as follows:

$$-\sum_{i=1}^{2} \int_{\Omega} S_{i}^{(m)} \Delta \varphi_{i}^{(m)} dx = \sum_{i=1}^{2} \int_{\Omega} \langle \nabla S_{i}^{(m)}, \nabla \varphi_{i}^{(m)} \rangle dx$$
$$\leq C \left(|\nabla \varrho^{(m)}|_{H}^{2} + |\nabla \varphi_{1}^{(m)}|_{H}^{2} + |\nabla \varphi_{2}^{(m)}|_{H}^{2} \right).$$
(4.20)

To estimate the remaining terms, notice that the function $Q^{(m)}$ defined in (4.7) is bounded in absolute value by the constant K from Hypothesis 3.1 (iii), and also

$$|S_i^{(m)}(x,t)| \le K \quad \text{for all } x \in \Omega, \ t \in [0, T_m), \ i = 0, 1, 2.$$
(4.21)

By Proposition 3.3, the gradient $\nabla_{\varphi}\psi^{\varepsilon}$ of ψ^{ε} is Lipschitz continuous with a constant depending on ε . We thus obtain from (4.19)–(4.21) that

$$\sum_{i=0}^{2} \int_{\Omega} S_{i}^{(m)} \mu_{i}^{(m)} dx \leq C^{\varepsilon} \left(1 + |\varphi_{0}^{(m)}|_{H} + |\varphi_{1}^{(m)}|_{H} + |\varphi_{2}^{(m)}|_{H} + |\nabla \varrho_{2}^{(m)}|_{H}^{2} + |\nabla \varphi_{2}^{(m)}|_{H}^{2} + |\nabla \varphi_{2}^{(m)}|_{H}^{2}\right).$$
(4.22)

Combining (4.15)–(4.22), we thus obtain

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathcal{F}_{0}^{\varepsilon}(\varphi_{0}^{(m)},\varphi_{1}^{(m)},\varphi_{2}^{(m)},w) + \int_{\Omega} \left(\sum_{i=1}^{2} |\nabla\mu_{i}^{(m)} - \nabla\mu_{0}^{(m)}|^{2}\right) \mathrm{d}x \\
\leq C^{\varepsilon} \left(1 + |\nabla\varrho^{(m)}|^{2}_{H} + |\nabla\varphi_{1}^{(m)}|^{2}_{H} + |\nabla\varphi_{2}^{(m)}|^{2}_{H} + |\varphi_{0}^{(m)}|^{2}_{H} + |\varphi_{1}^{(m)}|^{2}_{H} + |\varphi_{2}^{(m)}|^{2}_{H}\right). \tag{4.23}$$

By Hypothesis 3.1 (iv), we have $\widehat{F}(z) \ge \frac{z^2}{4f_1} - C$ for all $z \in \mathbb{R}$ and some constant C > 0. Hence, using (4.16), (3.14), (4.11), (4.14), and Gronwall's argument, we derive from (4.23) the estimate

$$\sup_{t \in (0,T_m)} \sup_{t \in (0,T_m)} \left(|\varphi_0^{(m)}|_H^2(t) + |\varphi_1^{(m)}|_H^2(t) + |\varphi_2^{(m)}|_H^2(t) + |\nabla\varphi_1^{(m)}|_H^2(t) + |\nabla\varphi_2^{(m)}|_H^2(t) \right) \\ + \int_0^{T_m} \int_\Omega \left(\sum_{i=1}^2 |\nabla\mu_i^{(m)} - \nabla\mu_0^{(m)}|^2 \right) (x,t) \, \mathrm{d}x \, \mathrm{d}t \le C^{\varepsilon}.$$

$$(4.24)$$

Furthermore, differentiating (4.3) with respect to the spatial variables we obtain that

$$\nu \nabla \dot{w}^{(m)} + E(\varphi_1^{(m)}, \varphi_2^{(m)}) \nabla w^{(m)} + w^{(m)} \left(\partial_1 E(\varphi_1^{(m)}, \varphi_2^{(m)}) \nabla \varphi_1^{(m)} \right. \\ \left. + \partial_2 E(\varphi_1^{(m)}, \varphi_2^{(m)}) \nabla \varphi_2^{(m)} \right) + \left(\nabla w^{(m)} - \nabla \varphi_0^{(m)} \right) \frac{(f^{-1})'(\varphi_0^{(m)} - w^{(m)})}{|\varphi_0^{(m)}| + |\varphi_1^{(m)}| + |\varphi_2^{(m)}|} \\ = f^{-1}(\varphi_0^{(m)} - w^{(m)}) \nabla \left(\frac{1}{|\varphi_0^{(m)}| + |\varphi_1^{(m)}| + |\varphi_2^{(m)}|} \right).$$
(4.25)

Testing (4.25) by $\nabla w^{(m)}$ and using the inequality $|\varphi_0^{(m)}| + |\varphi_1^{(m)}| + |\varphi_2^{(m)}| \ge 1$, Hypotheses 3.1 (ii), (iv), and the estimate (4.14), we find that

$$\frac{\mathrm{d}}{\mathrm{d}t} |\nabla w^{(m)}|_{H}^{2} + c |\nabla w^{(m)}|_{H}^{2} \le C \left(1 + |\nabla \varphi_{0}^{(m)}|_{H}^{2} + |\nabla \varphi_{1}^{(m)}|_{H}^{2} + |\nabla \varphi_{2}^{(m)}|_{H}^{2}\right) \quad (4.26)$$

with some constants $C > c \ge 0$. From (4.13) we immediately obtain the pointwise bound

$$|\nabla \varphi_0^{(m)}| \le |\nabla \varphi_1^{(m)}| + |\nabla \varphi_2^{(m)}|$$
 a.e. (4.27)

It follows from (4.24), (4.26), and by comparison with (4.25) that

$$\sup_{t \in (0,T_m)} \exp\left(|\nabla \dot{w}^{(m)}|_H + |\nabla w^{(m)}|_H\right) \le C.$$
(4.28)

By virtue of (4.4) we have

$$|\nabla \mu_0^{(m)}| \le |\nabla \varphi_1^{(m)}| + |\nabla \varphi_2^{(m)}| + |\nabla w^{(m)}| \quad \text{a.e.}$$
(4.29)

Since $\nabla_{\varphi} \psi^{\varepsilon}$ is Lipschitz continuous for every $\varepsilon > 0$, we obtain from (4.5) and (4.14) that

$$|\overline{\mu}_{i}^{(m)}(t)| \leq C^{\varepsilon} \left(1 + \int_{\Omega} \sum_{i=1}^{2} |\varphi_{i}^{(m)}|^{2}(x,t) \,\mathrm{d}x\right)^{1/2}$$
(4.30)

and

$$\int_{\Omega} |\mu_0^{(m)}|^2 \,\mathrm{d}x \le C \Big(1 + \int_{\Omega} |\varphi_0^{(m)}|^2 \,\mathrm{d}x \Big). \tag{4.31}$$

We now summarize the above computations in (4.24)–(4.31) and obtain for all $t \in (0, T_m)$ that

$$\int_{\Omega} \left(\sum_{i=0}^{2} \left(|\varphi_{i}^{(m)}|^{2} + |\nabla \varphi_{i}^{(m)}|^{2} \right) + |\varrho^{(m)}|^{2} + |\nabla \varrho^{(m)}|^{2} + |\nabla w^{(m)}|^{2} + |\nabla \dot{w}^{(m)}|^{2} \right) (x, t) \, \mathrm{d}x \\ + \int_{0}^{t} \int_{\Omega} \left(\sum_{i=0}^{2} \left(|\mu_{i}^{(m)}|^{2} + |\nabla \mu_{i}^{(m)}|^{2} \right) + |\dot{\varrho}^{(m)}|^{2} \right) (x, \tau) \, \mathrm{d}x \, \mathrm{d}\tau \le C^{\varepsilon}, \quad (4.32)$$

with a constant $C^{\varepsilon} > 0$ independent of m, and the uniform estimate (4.14) holds. By comparison with (4.5), we have a bound for $\Delta \varphi_i^{(m)}$ in $L^2(\Omega \times (0, T))$ which is independent of m, i = 1, 2. Finally, by comparison with (4.1), we obtain bounds in $L^2(0, T; W^{-1,2}(\Omega))$ independent of m for $\dot{\varphi}_i^{(m)}, i = 0, 1, 2$. We thus have sufficient estimates which on the one hand guarantee that the solution exists on the whole time interval [0, T] and, on the other hand, enable us to pass to the limit as $m \to \infty$ in (4.1)–(4.7) and check that the following statement holds:

Proposition 4.1. Let Hypothesis 3.1 hold and let $\varepsilon > 0$ be given. Then system (3.15)– (3.22), (2.8) admits a solution with the regularity μ_i , $\nabla \mu_i$, $\Delta \varphi_i \in L^2(\Omega \times (0, T))$, φ_i , $\nabla \varphi_i \in L^{\infty}(0, T; L^2(\Omega))$, $\dot{\varphi}_i \in L^2(0, T; W^{-1,2}(\Omega))$ for $i = 0, 1, 2, \varphi_0 + \varphi_1 + \varphi_2 = 1$ *a.e.*, $w, \dot{w} \in L^{\infty}(\Omega \times (0, T))$, $\nabla w, \nabla \dot{w} \in L^{\infty}(0, T; L^2(\Omega))$, $\dot{\varrho} \in L^2(\Omega \times (0, T))$, $\varrho, \nabla \varrho \in L^{\infty}(0, T; L^2(\Omega))$.

We can indeed pass to the limit in the initial conditions for ρ and w by virtue of (4.11) and (4.28). For the initial conditions for φ_i , the argument is standard as well. It is easy to check for each i = 0, 1, 2 that

$$\forall \eta > 0 \ \forall v_i \in L^2(\Omega) \ \exists t_\eta > 0 : t \in (0, t_\eta)$$

$$\Longrightarrow \ \exists m_\eta \in \mathbb{N} \ \forall m > m_\eta : \left| \int_{\Omega} (\varphi_i^{(m)}(x, t) - \varphi_i^{(m)}(x, 0)) v_i(x) \, \mathrm{d}x \right| < \eta,$$

$$(4.33)$$

so that the initial condition is satisfied in the weak sense. Note that this is related to the so-called Aubin–Lions lemma; see [40, Theorem 5.1] for the original reference.

5. Limit as $\varepsilon \to 0$

In the previous section we have proved that system (3.15)–(3.22), (2.8) admits a global solution. The estimates that we have derived so far depend on ε . We split this section into two subsections. In Section 5.1, we derive estimates independent of ε of the solution of (3.15)–(3.22), and in Section 5.2 we prove Theorem 3.2 by passing to the limit as $\varepsilon \rightarrow 0$.

5.1. Estimates independent of ϵ

Let us start with the following simple modification of [14, Propositions 2.10, 2.13].

Proposition 5.1. Let ψ satisfy Hypothesis 3.1 (v). Then there exist $\overline{\varepsilon} > 0$ and positive constants b, c, r such that for $\varepsilon \in (0, \overline{\varepsilon})$, the Yosida approximations ψ^{ε} of ψ have the following properties:

- (i) dist $(\hat{\varphi}, \Theta_{\delta_T}) \leq \delta_T/2 \implies |\nabla_{\!\!\varphi} \psi^{\varepsilon}(\hat{\varphi})| \leq b;$
- (ii) $\hat{\varphi} \in \Theta_{\delta_T}, \, \varphi \in \mathbb{R}^2, \, |\varphi \hat{\varphi}| \ge \delta_T/2 \implies r |\nabla_{\!\!\varphi} \psi^{\varepsilon}(\varphi) \nabla_{\!\!\varphi} \psi^{\varepsilon}(\hat{\varphi})| \le \langle \nabla_{\!\!\varphi} \psi^{\varepsilon}(\varphi) \nabla_{\!\!\varphi} \psi^{\varepsilon}(\hat{\varphi}), \varphi \hat{\varphi} \rangle + c.$

Proof. We prove the statement for b = b', r = r', c = c' + 2r'b', where b', c', r' are as in Hypothesis 3.1 (v). Let us start with part (i), and consider $\hat{\varphi} \in \mathbb{R}^2$ such that $dist(\hat{\varphi}, \Theta_{\delta_T}) \leq \delta_T/2$. For $\varepsilon > 0$ we define $J^{\varepsilon}\hat{\varphi}$ as in Proposition 3.3, and choose any $\hat{\xi} \in \partial \psi(\hat{\varphi})$. We have by (3.9) that

$$\widehat{\xi}^{\varepsilon} := \nabla_{\!\!\varphi} \psi^{\varepsilon}(\widehat{\varphi}) = \frac{1}{\varepsilon} (\widehat{\varphi} - J^{\varepsilon} \widehat{\varphi}) \in \partial \psi(J^{\varepsilon} \widehat{\varphi}),$$

hence

$$-\varepsilon\langle\hat{\xi}^{\varepsilon}-\hat{\xi},\hat{\xi}^{\varepsilon}\rangle=\langle\hat{\xi}^{\varepsilon}-\hat{\xi},J^{\varepsilon}\hat{\varphi}-\hat{\varphi}\rangle\geq0$$

by the monotonicity of $\partial \psi$. We thus have $|\hat{\xi}^{\varepsilon}| \leq b'$ by Hypothesis 3.1 (v), and part (i) is proved.

To prove part (ii), let $\hat{\varphi} \in \Theta_{\delta_T}$ be given, and put $\overline{\varepsilon} = \delta_T / (4b')$. For $\varepsilon < \overline{\varepsilon}$ we have

$$|\widehat{\varphi} - J^{\varepsilon}\widehat{\varphi}| = \varepsilon |\widehat{\xi}^{\varepsilon}| < \frac{\delta_T}{4}$$

by virtue of part (i). Hence, $\operatorname{dist}(J^{\varepsilon}\widehat{\varphi}, \Theta_{\delta_T}) < \delta_T/4$. Additionally, let $|\varphi - \widehat{\varphi}| \ge \delta_T/2$ for some $\varphi \in \mathbb{R}^2$. We denote $\xi^{\varepsilon} = \nabla_{\varphi} \psi^{\varepsilon}(\varphi)$. We have either

$$|J^{\varepsilon}\varphi - J^{\varepsilon}\widehat{\varphi}| < \frac{\delta_T}{4},\tag{5.1}$$

or

$$|J^{\varepsilon}\varphi - J^{\varepsilon}\widehat{\varphi}| \ge \frac{\delta_T}{4}.$$
(5.2)

In case (5.1), we have dist $(J^{\varepsilon}\hat{\varphi}, \Theta_{\delta_T}) < \delta_T/2$, and we obtain from part (i) simply that

$$r|\xi^{\varepsilon} - \hat{\xi}^{\varepsilon}| \le r(|\xi^{\varepsilon}| + |\hat{\xi}^{\varepsilon}|) \le 2rb.$$

If (5.2) holds, then we have by Hypothesis 3.1 (v) that

$$\begin{split} r|\xi^{\varepsilon} - \widehat{\xi}^{\varepsilon}| &\leq \langle \xi^{\varepsilon} - \widehat{\xi}^{\varepsilon}, J^{\varepsilon}\varphi - J^{\varepsilon}\widehat{\varphi} \rangle + c' \\ &= \langle \xi^{\varepsilon} - \widehat{\xi}^{\varepsilon}, \varphi - \widehat{\varphi} \rangle - \varepsilon |\xi^{\varepsilon} - \widehat{\xi}^{\varepsilon}|^{2} + c' \\ &\leq \langle \xi^{\varepsilon} - \widehat{\xi}^{\varepsilon}, \varphi - \widehat{\varphi} \rangle + c'. \end{split}$$

Combining the two inequalities and using the monotonicity of $\nabla_{\varphi} \psi^{\varepsilon}$, we obtain the assertion.

We actually need the following consequence of Proposition 5.1.

Corollary 5.2. Let $\psi, \overline{\varepsilon}, b, c, r$ be as in Proposition 5.1. Then there exists a constant $\hat{c} > 0$ with the property that for every $\varepsilon < \overline{\varepsilon}$, for every $\hat{\varphi} \in L^2(\Omega)$ such that $\hat{\varphi}(x) \in \Theta_{\delta_T}$ a.e., and for every $\varphi \in L^2(\Omega)$, we have

$$r \int_{\Omega} |\nabla_{\varphi} \psi^{\varepsilon}(\varphi(x)) - \nabla_{\varphi} \psi^{\varepsilon}(\widehat{\varphi}(x))| \, \mathrm{d}x$$

$$\leq \int_{\Omega} \langle \nabla_{\varphi} \psi^{\varepsilon}(\varphi(x)) - \nabla_{\varphi} \psi^{\varepsilon}(\widehat{\varphi}(x)), \varphi(x) - \widehat{\varphi}(x) \rangle \, \mathrm{d}x + \widehat{c}.$$
(5.3)

Proof. Let $\varphi \in L^2(\Omega)$ be arbitrarily chosen. We define

$$\Omega_+ := \{ x \in \Omega : \operatorname{dist}(\varphi(x), \Theta_{\delta_T}) \ge \delta_T / 4 \},\$$

and $\Omega_{-} = \Omega \setminus \Omega_{+}$. For a.e. $x \in \Omega_{-}$, we have by Proposition 5.1 (i) that

$$|\nabla_{\!\varphi}\psi^{\varepsilon}(\varphi(x))-\nabla_{\!\varphi}\psi^{\varepsilon}(\widehat{\varphi}(x))|\leq 2b.$$

For a.e. $x \in \Omega_+$, Proposition 5.1 (ii) yields that

$$r|\nabla_{\!\varphi}\psi^{\varepsilon}(\varphi(x)) - \nabla_{\!\varphi}\psi^{\varepsilon}(\widehat{\varphi}(x))| \le \langle \nabla_{\!\varphi}\psi^{\varepsilon}(\varphi(x)) - \nabla_{\!\varphi}\psi^{\varepsilon}(\widehat{\varphi}(x)), \varphi(x) - \widehat{\varphi}(x) \rangle + c.$$

Using the fact that $\langle \nabla_{\varphi} \psi^{\varepsilon}(\varphi(x)) - \nabla_{\varphi} \psi^{\varepsilon}(\widehat{\varphi}(x)), \varphi(x) - \widehat{\varphi}(x) \rangle \ge 0$ a.e., we can combine the two inequalities and obtain that

$$r \int_{\Omega} |\nabla_{\varphi} \psi^{\varepsilon}(\varphi(x)) - \nabla_{\varphi} \psi^{\varepsilon}(\widehat{\varphi}(x))| \, \mathrm{d}x$$

$$\leq \int_{\Omega} \langle \nabla_{\varphi} \psi^{\varepsilon}(\varphi(x)) - \nabla_{\varphi} \psi^{\varepsilon}(\widehat{\varphi}(x)), \varphi(x) - \widehat{\varphi}(x) \rangle \, \mathrm{d}r + c |\Omega_{+}| + 2rb |\Omega_{-}|.$$

Putting $\hat{c} := |\Omega|(c + 2rb)$, we complete the proof.

Let us come back to Problem (3.15)–(3.22) with initial conditions (2.8) and estimate the distance of the functions $\overline{\varphi}_i(t)$ from the boundary of Θ . To this end, we choose $v_0 = v_1 = v_2 = 1$ and put

$$\Gamma = \frac{\gamma(\varrho)}{\left(|\varphi_0| + |\varphi_1| + |\varphi_2|\right)\left(|\overline{\varphi}_0| + |\overline{\varphi}_1| + |\overline{\varphi}_2|\right)},$$

We obtain

$$\dot{\overline{\varphi}}_0(t) = -\frac{\overline{\varphi}_0(t)}{|\Omega|} \int_{\Omega} \Gamma(x,t) \left(1 - \varphi_0(x,t)\right) \mathrm{d}x, \tag{5.4}$$

$$\dot{\overline{\varphi}}_1(t) = \frac{\overline{\varphi}_0(t)}{|\Omega|} \int_{\Omega} \Gamma(x,t) \,\varphi_1(x,t) \,\mathrm{d}x, \tag{5.5}$$

$$\dot{\overline{\varphi}}_2(t) = \frac{\overline{\varphi}_0(t)}{|\Omega|} \int_{\Omega} \Gamma(x,t) \,\varphi_2(x,t) \,\mathrm{d}x.$$
(5.6)

From Hypothesis 3.1 (iii) it follows that $|\Gamma(x,t)(1-\varphi_0(x,t))| \le |\Gamma(x,t)| (|\varphi_1(x,t)| + |\varphi_2(x,t)|) \le K$ for a.e. $(x,t) \in \Omega \times (0,T)$. By Hypothesis 3.1 (vii) we have $\overline{\varphi}_0(0) \ge \delta/\sqrt{2} > 0$, hence,

$$\overline{\varphi}_0(t) \ge \overline{\varphi}_0(0) \,\mathrm{e}^{-Kt} > 0 \quad \text{for all } t \in [0, T].$$
(5.7)

Lower bounds for $\overline{\varphi}_1, \overline{\varphi}_2$ are more delicate to obtain. These functions are continuously differentiable. There exists, therefore, $T_{\varepsilon} \in [0, T]$ such that

$$\overline{\varphi}_i(t) \ge \delta \,\mathrm{e}^{-KT-1} \quad \text{for all } t \in [0, T_{\varepsilon}], \ i = 1, 2. \tag{5.8}$$

Put $T_{\varepsilon}^* = \max\{T_{\varepsilon} \in [0, T] : \text{ inequality (5.8) holds}\}$, and assume that $T_{\varepsilon}^* < T$ for some $\varepsilon < \overline{\varepsilon}$. For definiteness, we can assume that

$$\overline{\varphi}_1(T_{\varepsilon}^*) = \delta \,\mathrm{e}^{-KT-1}.\tag{5.9}$$

Taking into account (5.7), we have $1 - \overline{\varphi}_1(t) - \overline{\varphi}_2(t) = \overline{\varphi}_0(t) > (\delta/2) e^{-Kt}$ in $[0, T_{\varepsilon}^*]$. Hence, denoting $\varphi = (\varphi_1, \varphi_2)$ we have

$$\operatorname{dist}(\overline{\varphi}(t), \partial \Theta) \geq (\delta/2) \operatorname{e}^{-KT-1} > \delta_T,$$

so that $\overline{\varphi}(t) \in \Theta_{\delta_T}$ for all $t \in [0, T_{\varepsilon}^*]$.

Recall that we have the bound

$$\sup_{(x,t)\in\Omega\times(0,T_{\varepsilon}^{*})} \sup\left(|w(x,t)| + |\dot{w}(x,t)|\right) \le C$$
(5.10)

as a consequence of (4.14). Let us denote $\overline{\mu} = (\overline{\mu}_1, \overline{\mu}_2)$. From (5.10), (3.18), and (3.3), it follows that

$$\begin{aligned} |\overline{\mu}(t)| &\leq \int_{\Omega} \left(|\nabla_{\varphi} \psi^{\varepsilon}(\varphi)| + |\nabla_{\varphi} g(\varphi)| + \frac{1}{2} |\nabla_{\varphi} E(\varphi)| w^{2} \right) \mathrm{d}x \\ &\leq \int_{\Omega} |\nabla_{\varphi} \psi^{\varepsilon}(\varphi) - \nabla_{\varphi} \psi^{\varepsilon}(\overline{\varphi})| \,\mathrm{d}x + \widetilde{C} |\Omega| \end{aligned}$$
(5.11)

with $\widetilde{C} = b + C_g + \frac{1}{2} \sup |\nabla_{\varphi} E(\varphi)| w^2$, where we have used Hypothesis 3.1 (ii), (vi), and Proposition 5.1 (i). We further obtain from Corollary 5.2 and (3.18) that

$$\begin{split} |\overline{\mu}(t)| &\leq \frac{1}{r} \int_{\Omega} \langle \nabla_{\varphi} \psi^{\varepsilon}(\varphi) - \nabla_{\varphi} \psi^{\varepsilon}(\overline{\varphi}), \varphi - \overline{\varphi} \rangle \, \mathrm{d}x + \widetilde{C} |\Omega| + \frac{c}{r} \\ &= \frac{1}{r} \int_{\Omega} \langle \nabla_{\varphi} \psi^{\varepsilon}(\varphi), \varphi - \overline{\varphi} \rangle \, \mathrm{d}x + \widetilde{C} |\Omega| + \frac{c}{r} \\ &= \frac{1}{r} \Big(-\int_{\Omega} |\nabla\varphi|^2 \, \mathrm{d}x - \int_{\Omega} \langle \nabla_{\varphi} g(\varphi), \varphi - \overline{\varphi} \rangle \, \mathrm{d}x + \int_{\Omega} \langle \mu, \varphi - \overline{\varphi} \rangle \, \mathrm{d}x \Big) + \widetilde{C} |\Omega| + \frac{c}{r}. \end{split}$$
(5.12)

We now use again (3.3), the fact that

$$\int_{\Omega} \langle \mu, \varphi - \overline{\varphi} \rangle \, \mathrm{d}x = \int_{\Omega} \langle \mu - \overline{\mu}, \varphi - \overline{\varphi} \rangle \, \mathrm{d}x,$$

and the elementary inequalities

$$\int_{\Omega} |\varphi - \overline{\varphi}|^2 \, \mathrm{d}x \le C \int_{\Omega} |\nabla \varphi|^2 \, \mathrm{d}x, \quad \int_{\Omega} |\mu - \overline{\mu}|^2 \, \mathrm{d}x \le C \int_{\Omega} |\nabla \mu|^2 \, \mathrm{d}x \tag{5.13}$$

to conclude that there exists a constant M independent of ε such that for all $t \in [0, T_{\varepsilon}^*]$ we have

$$\left|\overline{\mu}(t)\right| \le M \left(1 + \left(\int_{\Omega} |\nabla \varphi|^2(x,t) \,\mathrm{d}x \right)^{1/2} \left(\int_{\Omega} |\nabla \mu|^2(x,t) \,\mathrm{d}x \right)^{1/2} \right). \tag{5.14}$$

We now repeat the estimation procedure from Section 4.1. We test the *i*-th equation in (3.15) by $v_i = \mu_i$, and sum up to obtain, similar to (4.15)–(4.18), that

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_{\Omega} \mathcal{F}_{0}^{\varepsilon}(\varphi_{0}, \varphi_{1}, \varphi_{2}, w) \,\mathrm{d}x + \frac{c}{2} \int_{\Omega} \sum_{i=1}^{2} (|\nabla \mu_{i} - \nabla \mu_{0}|^{2}) \,\mathrm{d}x$$
$$\leq \sum_{i=0}^{2} \int_{\Omega} S_{i} \mu_{i} \,\mathrm{d}x + C \left(1 + \int_{\Omega} |\varphi_{0}| \,\mathrm{d}x\right) \tag{5.15}$$

for a.e. $t \in (0, T_{\varepsilon}^*)$ with $\mathcal{F}_0^{\varepsilon}$ defined in (4.16), and with some constants C > c > 0 independent of ε . We further estimate the right-hand side by

$$\sum_{i=0}^{2} \int_{\Omega} S_{i} \mu_{i} \, \mathrm{d}x \leq C \sum_{i=0}^{2} \int_{\Omega} |\varphi_{i}| |\mu_{i}| \, \mathrm{d}x$$

to obtain, by virtue of (5.13), (5.14), and the hypotheses on \widehat{F} and g, that

$$\int_{\Omega} \left(|\varphi_0|^2 + \psi^{\varepsilon}(\varphi) + |\nabla\varphi|^2 \right) (x,t) \, \mathrm{d}x + \int_0^t \int_{\Omega} \sum_{i=1}^2 \left(|\nabla\mu_i - \nabla\mu_0|^2 \right) (x,\tau) \, \mathrm{d}x \, \mathrm{d}\tau$$

$$\leq C \left(1 + \int_0^t \int_{\Omega} \left(|\nabla\varphi|^2 + |\varphi_0|^2 + |\nabla\mu_1|^2 + |\nabla\mu_2|^2 \right) (x,t) \, \mathrm{d}x \, \mathrm{d}\tau \right). \tag{5.16}$$

We have for all points $(x, t) \in \Omega \times [0, T_{\varepsilon}^*]$ the identity $\varphi_0 + \varphi_1 + \varphi_2 = 1$ and $\nabla \varphi_0 = -\nabla \varphi_1 - \nabla \varphi_2$, hence, $|\nabla \mu_0| \le C(|\nabla \varphi_0| + |\nabla w|)$. Note that repeating the computations leading to (4.28), we derive the estimates

$$\sup_{t \in (0,T_{\varepsilon}^*)} \operatorname{ess}\left(|\nabla \dot{w}|_H + |\nabla w|_H \right) \le C, \tag{5.17}$$

with C independent of ε . The Gronwall argument and (3.14) now yield

$$\int_{\Omega} \left(\psi^{\varepsilon}(\varphi) + \sum_{i=0}^{2} \left(|\varphi_{i}|^{2} + |\nabla\varphi_{i}|^{2} \right) \right)(x,t) dx$$
$$+ \int_{0}^{t} \int_{\Omega} \sum_{i=1}^{2} \left(|\mu_{i}|^{2} + |\nabla\mu_{i}|^{2} \right)(x,\tau) dx d\tau \leq C^{*}$$
(5.18)

for every $t \in [0, T_{\varepsilon}^*]$ with a constant $C^* > 0$ independent of ε . By comparison with (3.15) we get the bound

$$\int_{0}^{T_{\varepsilon}^{*}} \|\dot{\varphi}_{i}(t)\|_{W^{-1,2}(\Omega)}^{2} \,\mathrm{d}t \leq C, \quad i = 0, 1, 2.$$
(5.19)

To make the list of estimates complete, recall that the upper bound in (4.9)–(4.10) is independent of *m* and ε , so that

$$\sup_{t \in (0,T_{\varepsilon}^*)} \operatorname{ess}\left(|\varrho(t)|_H + |\nabla \varrho(t)|_H\right) \le C, \quad \int_0^{T_{\varepsilon}^*} |\dot{\varrho}(t)|_H^2 \,\mathrm{d}t \le C.$$
(5.20)

The next step consists in proving that $T_{\varepsilon}^* = T$. To this end, we split for each $t \in [0, T_{\varepsilon}^*]$ the domain Ω into three parts, namely

$$\Omega_0(t) = \{ x \in \Omega : \varphi_1(x,t) \ge 0 \},$$

$$\Omega_1(t) = \{ x \in \Omega : 0 > \varphi_1(x,t) \ge -\varepsilon^{1/4} \},$$

$$\Omega_2(t) = \{ x \in \Omega : -\varepsilon^{1/4} > \varphi_1(x,t) \}.$$

Let us start with $\Omega_2(t)$. By definition (3.7) of ψ^{ε} , we have for $x \in \Omega_2(t)$ that

$$\psi^{\varepsilon}(\varphi(x,t)) \ge \frac{1}{2\varepsilon} \min_{z \in \Theta} |\varphi_1(x,t) - z_1|^2 \ge \frac{1}{2\sqrt{\varepsilon}}.$$
(5.21)

By virtue of (5.18), we have

$$|\Omega_2(t)| \le 2C^* \sqrt{\varepsilon}. \tag{5.22}$$

We now rewrite equation (5.5) in the form

$$\dot{\overline{\varphi}}_1(t) = \frac{\overline{\varphi}_0(t)}{|\Omega|} \Big(\int_{\Omega_0(t)} + \int_{\Omega_1(t)} + \int_{\Omega_2(t)} \Big) \Gamma(x,t) \varphi_1(x,t) \, \mathrm{d}x,$$

where

$$\begin{split} \int_{\Omega_1(t)} \Gamma(x,t) \,\varphi_1(x,t) \,\mathrm{d}x &\geq -K |\Omega| \varepsilon^{1/4}, \\ \int_{\Omega_2(t)} \Gamma(x,t) \,\varphi_1(x,t) \,\mathrm{d}x &\geq -K \int_{\Omega_2(t)} |\varphi_1(x,t)| \,\mathrm{d}x \\ &\geq -K |\Omega_2(t)|^{1/2} \bigg(\int_{\Omega} |\varphi_1(x,t)|^2 \,\mathrm{d}x \bigg)^{1/2} \\ &\geq -\sqrt{2} K C^* \varepsilon^{1/4}, \\ \int_{\Omega_0(t)} \Gamma(x,t) \,\varphi_1(x,t) \,\mathrm{d}x &\geq -K \int_{\Omega_0(t)} \varphi_1(x,t) \,\mathrm{d}x \\ &= -K |\Omega| \overline{\varphi}_1(t) + K \Big(\int_{\Omega_1(t)} + \int_{\Omega_2(t)} \Big) \varphi_1(x,t) \,\mathrm{d}x \\ &\geq -K |\Omega| \overline{\varphi}_1(t) - K(1 + \sqrt{2}C^*) \, \varepsilon^{1/4}. \end{split}$$

Using the fact that $0 \le \overline{\varphi}_0(t) \le 1$ for $t \in [0, T_{\varepsilon}^*]$, we have that

$$\dot{\overline{\varphi}}_{1}(t) = \frac{\overline{\varphi}_{0}(t)}{|\Omega|} \int_{\Omega} \Gamma(x,t) \varphi_{1}(x,t) \,\mathrm{d}x \ge -K(\overline{\varphi}_{1}(t) + \Lambda \varepsilon^{1/4}), \tag{5.23}$$

with a constant $\Lambda > 0$ independent of ε . We thus obtain a lower bound for $\overline{\varphi}_1(t)$, namely (note that $\overline{\varphi}_1(0) \ge \delta$ by Hypothesis 3.1 (vii)),

$$\overline{\varphi}_1(t) \ge \delta \,\mathrm{e}^{-Kt} - \Lambda \varepsilon^{1/4} (1 - \mathrm{e}^{-Kt}) \ge \delta \,\mathrm{e}^{-Kt} - \Lambda \varepsilon^{1/4} \tag{5.24}$$

for $t \in [0, T_{\varepsilon}^*]$. We see that for $\varepsilon > 0$ sufficiently small, condition (5.9) is violated. Hence, by (5.8), $T_{\varepsilon}^* = T$ and the estimate (5.18) holds globally in [0, T].

5.2. Proof of Theorem 3.2

We show that by passing to the limit as $\varepsilon \to 0$ in (3.15)–(3.22), we obtain a solution to (2.1)–(2.7) in the sense of Theorem 3.2. We label here the solution $(\mu_i, \varphi_i, w, \varrho)$ of (3.15)–(3.22) with the upper index ε in order to emphasize the dependence on ε .

The estimates (5.18)–(5.20) are independent of ε and hold globally on [0, T]. We can therefore extract a subsequence $\varepsilon \to 0$ such that

- $\nabla \varphi_i^{\varepsilon} \to \nabla \varphi_i$ for $i = 0, 1, 2, \nabla \varrho^{\varepsilon} \to \nabla \varrho, \nabla w^{\varepsilon} \to \nabla w$ weakly-star in $L^{\infty}(0, T; L^2(\Omega));$
- $\dot{\varrho}^{\varepsilon} \rightarrow \dot{\varrho}, \mu_i^{\varepsilon} \rightarrow \mu, \nabla \mu_i^{\varepsilon} \rightarrow \nabla \mu_i \text{ for } i = 0, 1, 2, \dot{w}^{\varepsilon} \rightarrow \dot{w} \text{ weakly in } L^2(\Omega \times (0, T));$
- $\dot{\varphi}_i^{\varepsilon} \rightarrow \dot{\varphi}_i$ for i = 0, 1, 2 weakly in $L^2(0, T; W^{-1,2}(\Omega))$.

Using the Sobolev embedding theorems, the trace theorem, and the Lions compactness lemma [40, Theorem 5.1] we obtain the convergences, passing again to a subsequence of $\varepsilon \rightarrow 0$ if necessary,

- $\varrho^{\varepsilon} \to \varrho, w^{\varepsilon} \to w$ strongly in $C([0, T]; L^2(\Omega));$
- $\varphi_i^{\varepsilon} \to \varphi_i$ for i = 0, 1, 2 strongly in $L^2(\Omega \times (0, T))$;
- $\varrho^{\varepsilon} \to \varrho$ strongly in $L^2(0, T; L^2(\partial \Omega))$.

We can pass to the limit in all terms in (3.15)–(3.22), and the limit initial condition (2.8) is obtained by an argument similar to (4.33). The variational inequality (3.6) needs to be paid some attention. Since ψ^{ε} is convex, we can rewrite (3.18) as

$$\begin{split} \int_{\Omega} & \left(\mu_{1}^{\varepsilon} - \partial_{1} g(\varphi_{1}^{\varepsilon}, \varphi_{2}^{\varepsilon}) - \partial_{1} E(\varphi_{1}^{\varepsilon}, \varphi_{2}^{\varepsilon}) \frac{w^{2}}{2} \right) (v_{1} - \varphi_{1}^{\varepsilon}) \, \mathrm{d}x \\ &+ \int_{\Omega} & \left(\mu_{2}^{\varepsilon} - \partial_{2} g(\varphi_{1}^{\varepsilon}, \varphi_{2}^{\varepsilon}) - \partial_{2} E(\varphi_{1}^{\varepsilon}, \varphi_{2}^{\varepsilon}) \frac{w^{2}}{2} \right) (v_{2} - \varphi_{2}^{\varepsilon}) \, \mathrm{d}x \\ &- \int_{\Omega} & \left(\langle \nabla \varphi_{1}^{\varepsilon}, \nabla (v_{1} - \varphi_{1}^{\varepsilon}) \rangle + \langle \nabla \varphi_{2}^{\varepsilon}, \nabla (v_{2} - \varphi_{2}^{\varepsilon}) \rangle \right) \, \mathrm{d}x \\ &\leq \int_{\Omega} & \left(\psi^{\varepsilon} (v_{1}, v_{2}) - \psi^{\varepsilon} (\varphi_{1}^{\varepsilon}, \varphi_{2}^{\varepsilon}) \right) \, \mathrm{d}x \end{split}$$
(5.25)

for a.e. $t \in (0, T)$ and for all test functions $v_1, v_2 \in W^{1,2}(\Omega)$. We now choose an arbitrary test function $\lambda \in L^2(0, T), \lambda(t) \ge 0$ a.e. From the above convergences it follows that

$$\liminf_{\varepsilon \to 0} \int_0^T \int_\Omega |\nabla \varphi_i^\varepsilon(x,t)|^2 \lambda(t) \, \mathrm{d}x \, \mathrm{d}t \ge \int_0^T \int_\Omega |\nabla \varphi_i(x,t)|^2 \lambda(t) \, \mathrm{d}x \, \mathrm{d}t,$$

and using (3.12) we obtain the pointwise limit $\lim_{\varepsilon \to 0} \psi^{\varepsilon}(v_1, v_2) = \psi(v_1, v_2)$. We multiply both sides of inequality (5.25) by $\lambda(t)$, integrate over $t \in (0, T)$ and pass to the limit to obtain

$$\int_{0}^{T} \int_{\Omega} \left(\mu_{1} - \partial_{1}g(\varphi_{1}, \varphi_{2}) - \partial_{1}E(\varphi_{1}, \varphi_{2}) \frac{w^{2}}{2} \right) (v_{1} - \varphi_{1})\lambda(t) \, \mathrm{d}x \, \mathrm{d}t \\ + \int_{0}^{T} \int_{\Omega} \left(\mu_{2} - \partial_{2}g(\varphi_{1}, \varphi_{2}) - \partial_{2}E(\varphi_{1}, \varphi_{2}) \frac{w^{2}}{2} \right) (v_{2} - \varphi_{2})\lambda(t) \, \mathrm{d}x \, \mathrm{d}t \\ - \int_{0}^{T} \int_{\Omega} \left(\langle \nabla\varphi_{1}, \nabla(v_{1} - \varphi_{1}) \rangle + \langle \nabla\varphi_{2}, \nabla(v_{2} - \varphi_{2}) \rangle \right) \lambda(t) \, \mathrm{d}x \, \mathrm{d}t \\ \leq \int_{0}^{T} \int_{\Omega} \psi(v_{1}, v_{2})\lambda(t) \, \mathrm{d}x \, \mathrm{d}t - \liminf_{\varepsilon \to 0} \int_{0}^{T} \int_{\Omega} \psi^{\varepsilon}(\varphi_{1}^{\varepsilon}, \varphi_{2}^{\varepsilon})\lambda(t) \, \mathrm{d}x \, \mathrm{d}t \quad (5.26)$$

for all test functions $v_1, v_2 \in W^{1,2}(\Omega)$. It remains to prove that we have

$$\liminf_{\varepsilon \to 0} \int_0^T \int_{\Omega} \psi^{\varepsilon}(\varphi_1^{\varepsilon}(x,t),\varphi_2^{\varepsilon}(x,t))\lambda(t) \,\mathrm{d}x \,\mathrm{d}t \\ \geq \int_0^T \int_{\Omega} \psi(\varphi_1(x,t),\varphi_2(x,t))\lambda(t) \,\mathrm{d}x \,\mathrm{d}t.$$
(5.27)

If (5.27) is fulfilled, then, on the one hand, (3.6) holds and, on the other hand, we conclude that $\psi(\varphi_1(x,t),\varphi_2(x,t)) < \infty$ almost everywhere. This means in particular that $(\varphi_1(x,t),\varphi_2(x,t)) \in \Theta$ for a.e. $(x,t) \in \Omega \times (0,T)$. Hence, as mentioned on the last line of Section 3, the identity $|\varphi_0| + |\varphi_1| + |\varphi_2| = \varphi_0 + \varphi_1 + \varphi_2 = 1$ holds almost everywhere, so that (3.17) coincides with (2.3), and (3.19)–(3.20) coincides with (2.5).

To prove (5.27), we first notice that by (5.15) we have

$$\sup_{t \in (0,T)} \sup \int_{\Omega} \psi^{\varepsilon}(\varphi^{\varepsilon}(x,t)) \, \mathrm{d}x \le C.$$

For simplicity, we omit for a moment the arguments (x, t) and write simply $\varphi^{\varepsilon}, \varphi$ instead of $\varphi^{\varepsilon}(x, t), \varphi(x, t)$. By (3.13), we have

$$\psi^{\varepsilon}(\varphi^{\varepsilon}) \ge \frac{1}{2\varepsilon} |\varphi^{\varepsilon} - J^{\varepsilon} \varphi^{\varepsilon}|^2 \quad \text{a.e.}$$
(5.28)

Hence, for a.e. $t \ge 0$,

$$\int_{\Omega} |\varphi^{\varepsilon} - J^{\varepsilon} \varphi^{\varepsilon}|^2 \, \mathrm{d}x \le 2\varepsilon \int_{\Omega} \psi^{\varepsilon}(\varphi^{\varepsilon}) \, \mathrm{d}x \le C\varepsilon.$$
(5.29)

We thus have for a.e. $t \ge 0$, by the triangle inequality,

$$|J^{\varepsilon}\varphi^{\varepsilon}(t) - \varphi(t)|_{H} \leq |J^{\varepsilon}\varphi^{\varepsilon}(t) - \varphi^{\varepsilon}(t)|_{H} + |\varphi^{\varepsilon}(t) - \varphi(t)|_{H}$$
$$\leq C\varepsilon + |\varphi^{\varepsilon}(t) - \varphi(t)|_{H}.$$
(5.30)

We know that φ^{ε} converges to φ in $L^2(\Omega \times (0, T))$. In particular, it follows from (5.30) that $J^{\varepsilon}\varphi^{\varepsilon}(x,t) \to \varphi(x,t)$ a.e. in $\Omega \times (0,T)$. On the other hand, by (3.11) we have

$$\psi^{\varepsilon}(\varphi^{\varepsilon}) \ge \psi(J^{\varepsilon}\varphi^{\varepsilon})$$
 a.e., (5.31)

and (5.27) follows from (5.30)–(5.31) and from the lower semicontinuity of ψ . We thus obtain the inequality

$$\int_{0}^{T} \int_{\Omega} \left(\left(\mu_{1} - \partial_{1}g(\varphi_{1}, \varphi_{2}) - \partial_{1}E(\varphi_{1}, \varphi_{2}) \frac{w^{2}}{2} \right) (v_{1} - \varphi_{1}) \right. \\ \left. + \left(\mu_{2} - \partial_{2}g(\varphi_{1}, \varphi_{2}) - \partial_{2}E(\varphi_{1}, \varphi_{2}) \frac{w^{2}}{2} \right) (v_{2} - \varphi_{2}) \right) \lambda(t) \, \mathrm{d}x \, \mathrm{d}t \\ \left. - \int_{0}^{T} \int_{\Omega} \left(\langle \nabla \varphi_{1}, \nabla (v_{1} - \varphi_{1}) \rangle + \langle \nabla \varphi_{2}, \nabla (v_{2} - \varphi_{2}) \rangle \right) \lambda(t) \, \mathrm{d}x \, \mathrm{d}t \right. \\ \left. \leq \int_{0}^{T} \int_{\Omega} \psi(v_{1}, v_{2}) \lambda(t) \, \mathrm{d}x \, \mathrm{d}t - \int_{0}^{T} \int_{\Omega} \psi(\varphi_{1}, \varphi_{2}) \lambda(t) \, \mathrm{d}x \, \mathrm{d}t,$$
 (5.32)

for all test functions $v_1, v_2 \in W^{1,2}(\Omega)$, $\lambda \in L^2(0, T)$, $\lambda(t) \ge 0$ a.e., which is equivalent to (3.6). This completes the proof of Theorem 3.2.

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References

- A. Agosti, C. Cattaneo, C. Giverso, D. Ambrosi, and P. Ciarletta, A computational framework for the personalized clinical treatment of glioblastoma multiforme. *ZAMM Z. Angew. Math. Mech.* 98 (2018), no. 12, 2307–2327 MR 3902306
- R. P. Araujo and D. L. S. McElwain, A history of the study of solid tumour growth: the contribution of mathematical modelling. *Bull. Math. Biol.* 66 (2004), no. 5, 1039–1091
 Zbl 1334.92187 MR 2253816

- [3] J.-P. Aubin and I. Ekeland, *Applied nonlinear analysis*. Pure Appl. Math. (N. Y.), John Wiley & Sons, Inc., New York, 1984 MR 749753
- [4] V. Barbu, Nonlinear semigroups and differential equations in Banach spaces. Editura Academiei Republicii Socialiste România, Bucharest; Noordhoff International Publishing, Leiden, 1976 MR 0390843
- [5] N. Bellomo, N. K. Li, and P. K. Maini, On the foundations of cancer modelling: selected topics, speculations, and perspectives. *Math. Models Methods Appl. Sci.* 18 (2008), no. 4, 593–646 Zbl 1151.92014 MR 2402885
- [6] S. Bosia, M. Conti, and M. Grasselli, On the Cahn-Hilliard-Brinkman system. *Commun. Math. Sci.* 13 (2015), no. 6, 1541–1567 Zbl 1330.35313 MR 3351441
- [7] H. Brézis, Opérateurs maximaux monotones et semi-groupes de contractions dans les espaces de Hilbert. North-Holland Math. Stud. No. 5, North-Holland Publishing Co., Amsterdam-London; Elsevier, New York, 1973 Zbl 0252.47055 MR 0348562
- [8] H. Bueno, G. Ercole, and A. Zumpano, Asymptotic behaviour of quasi-stationary solutions of a nonlinear problem modelling the growth of tumours. *Nonlinearity* 18 (2005), no. 4, 1629–1642 Zbl 1181.35023 MR 2150346
- [9] A. C. Burton, Rate of growth of solid tumors as a problem of diffusion. *Growth* **30** (1966), 157–176.
- [10] H. M. Byrne, T. Alarcon, M. R. Owen, S. D. Webb, and P. K. Maini, Modelling aspects of cancer dynamics: a review. *Philos. Trans. R. Soc. Lond. Ser. A Math. Phys. Eng. Sci.* 364 (2006), no. 1843, 1563–1578 MR 2248245
- [11] P. Colli, G. Gilardi, and D. Hilhorst, On a Cahn-Hilliard type phase field system related to tumor growth. *Discrete Contin. Dyn. Syst.* 35 (2015), no. 6, 2423–2442 Zbl 1342.35407 MR 3299006
- [12] P. Colli, G. Gilardi, E. Rocca, and J. Sprekels, Vanishing viscosities and error estimate for a Cahn-Hilliard type phase field system related to tumor growth. *Nonlinear Anal., Real World Appl.* 26 (2015), 93–108 Zbl 1334.35097 MR 3384327
- [13] P. Colli, G. Gilardi, E. Rocca, and J. Sprekels, Asymptotic analyses and error estimates for a Cahn-Hilliard type phase field system modelling tumor growth. *Discrete Contin. Dyn. Syst.*, *Ser. S* 10 (2017), no. 1, 37–54 Zbl 1360.35296 MR 3590170
- P. Colli, P. Krejčí, E. Rocca, and J. Sprekels, Nonlinear evolution inclusions arising from phase change models. *Czech. Math. J.* 57 (2007), no. 4, 1067–1098 Zbl 1174.35021 MR 2357581
- [15] V. Cristini, X. Li, J. S. Lowengrub, and S. M. Wise, Nonlinear simulations of solid tumor growth using a mixture model: invasion and branching. *J. Math. Biol.* 58 (2009), no. 4–5, 723–763 Zbl 1311.92039 MR 2471308
- [16] V. Cristini and J. Lowengrub, Multiscale modeling of cancer. An Integrated Experimental and Mathematical Modeling Approach. Cambridge University Press, 2010.
- [17] S. Cui and A. Friedman, Analysis of a mathematical model of the growth of necrotic tumors. J. Math. Anal. Appl. 255 (2001), no. 2, 636–677 Zbl 0984.35169 MR 1815805
- [18] M. Dai, E. Feireisl, E. Rocca, G. Schimperna, and M. E. Schonbek, Analysis of a diffuse interface model of multispecies tumor growth. *Nonlinearity* **30** (2017), no. 4, 1639–1658 Zbl 1367.35185 MR 3636313
- [19] B. Detmann and P. Krejčí, A multicomponent flow model in deformable porous media. *Math. Methods Appl. Sci.* 42 (2019), no. 6, 1894–1906 Zbl 1420.35233 MR 3937640
- [20] A. Fasano, A. Bertuzzi, and A. Gandolfi, Mathematical modelling of tumour growth and treatment. In *Complex systems in biomedicine*, pp. 71–108, Springer, Milan, 2006 Zbl 1387.92050 MR 2487998

- [21] H. B. Frieboes, F. Jin, Y.-L. Chuang, S. M. Wise, J. S. Lowengrub, and V. Cristini, Threedimensional multispecies nonlinear tumor growth. II: Tumor invasion and angiogenesis. J. *Theor. Biol.* 264 (2010), no. 4, 1254–1278 Zbl 1406.92049 MR 2980767
- [22] A. Friedman, Mathematical analysis and challenges arising from models of tumor growth. *Math. Models Methods Appl. Sci.* 17 (2007), Suppl., 1751–1772 Zbl 1135.92013 MR 2362763
- [23] A. Friedman and F. Reitich, Analysis of a mathematical model for the growth of tumors. J. Math. Biol. 38 (1999), no. 3, 262–284 Zbl 0944.92018 MR 1684873
- [24] S. Frigeri, M. Grasselli, and E. Rocca, On a diffuse interface model of tumour growth. *Eur. J. Appl. Math.* 26 (2015), no. 2, 215–243 Zbl 1375.92031 MR 3315054
- [25] S. Frigeri, K. F. Lam, and E. Rocca, On a diffuse interface model for tumour growth with nonlocal interactions and degenerate mobilities. In *Solvability, regularity, and optimal control of boundary value problems for PDEs*, pp. 217–254, Springer INdAM Ser. 22, Springer, Cham, 2017 Zbl 1382.35311 MR 3751643
- [26] S. Frigeri, K. F. Lam, E. Rocca, and G. Schimperna, On a multi-species Cahn-Hilliard-Darcy tumor growth model with singular potentials. *Commun. Math. Sci.* 16 (2018), no. 3, 821–856 Zbl 1404.35456 MR 3853909
- [27] H. Garcke and K. F. Lam, Global weak solutions and asymptotic limits of a Cahn-Hilliard-Darcy system modelling tumour growth. AIMS Math. 1 (2016), 318–360. Zbl 1434.35255
- [28] H. Garcke and K. F. Lam, Analysis of a Cahn-Hilliard system with non-zero Dirichlet conditions modeling tumor growth with chemotaxis. *Discrete Contin. Dyn. Syst.* 37 (2017), no. 8, 4277–4308 Zbl 1360.35042 MR 3642265
- [29] H. Garcke and K. F. Lam, Well-posedness of a Cahn-Hilliard system modelling tumour growth with chemotaxis and active transport. *Eur. J. Appl. Math.* 28 (2017), no. 2, 284–316 Zbl 1375.92011 MR 3613312
- [30] H. Garcke, K. F. Lam, R. Nürnberg, and E. Sitka, A multiphase Cahn-Hilliard-Darcy model for tumour growth with necrosis. *Math. Models Methods Appl. Sci.* 28 (2018), no. 3, 525–577 Zbl 1380.92029 MR 3747020
- [31] H. Garcke, K. F. Lam, and E. Rocca, Optimal control of treatment time in a diffuse interface model of tumor growth. *Appl. Math. Optim.* 78 (2018), no. 3, 495–544 Zbl 1403.35139 MR 3868741
- [32] H. Garcke, K. F. Lam, and A. Signori, On a phase field model of Cahn-Hilliard type for tumour growth with mechanical effects. *Nonlinear Anal. Real World Appl.* 57 (2021), paper no. 103192 Zbl 1456.35091 MR 4126782
- [33] H. Garcke, K. F. Lam, E. Sitka, and V. Styles, A Cahn-Hilliard-Darcy model for tumour growth with chemotaxis and active transport. *Math. Models Methods Appl. Sci.* 26 (2016), no. 6, 1095–1148 Zbl 1336.92038 MR 3484570
- [34] A. Giorgini, M. Grasselli, and H. Wu, The Cahn-Hilliard-Hele-Shaw system with singular potential. Ann. Inst. Henri Poincaré, Anal. Non Linéaire 35 (2018), no. 4, 1079–1118 Zbl 1394.35356 MR 3795027
- [35] H. P. Greenspan, Models for the growth of a solid tumor by diffusion. *Stud. Appl. Math.* 51 (1972), 317–340. Zbl 0257.92001
- [36] A. Hawkins-Daarud, K. G. van der Zee, and J. T. Oden, Numerical simulation of a thermodynamically consistent four-species tumor growth model. *Int. J. Numer. Methods Biomed. Eng.* 28 (2012), no. 1, 3–24 Zbl 1242.92030 MR 2898905
- [37] J. Jiang, H. Wu, and S. Zheng, Well-posedness and long-time behavior of a non-autonomous Cahn-Hilliard-Darcy system with mass source modeling tumor growth. J. Differ. Equations 259 (2015), no. 7, 3032–3077 Zbl 1330.35039 MR 3360665

- [38] E. A. B. F. Lima, J. T. Oden, D. A. Hormuth II, T. E. Yankeelov, and R. C. Almeida, Selection, calibration, and validation of models of tumor growth. *Math. Models Methods Appl. Sci.* 26 (2016), no. 12, 2341–2368 Zbl 1349.92075 MR 3564593
- [39] E. A. B. F. Lima, J. T. Oden, B. Wohlmuth, A. Shahmoradi, D. A. Hormuth II, T. E. Yankeelov, L. Scarabosio, and T. Horger, Selection and validation of predictive models of radiation effects on tumor growth based on noninvasive imaging data. *Comput. Methods Appl. Mech. Eng.* 327 (2017), 277–305 Zbl 1439.92110 MR 3725771
- [40] J.-L. Lions, Quelques méthodes de résolution des problèmes aux limites non linéaires. Dunod; Gauthier-Villars, Paris, 1969 MR 0259693
- [41] J. Lowengrub, E. Titi, and K. Zhao, Analysis of a mixture model of tumor growth. *Eur. J. Appl. Math.* 24 (2013), no. 5, 691–734 Zbl 1292.35153 MR 3104287
- [42] S. Melchionna and E. Rocca, Varifold solutions of a sharp interface limit of a diffuse interface model for tumor growth. *Interfaces Free Bound.* 19 (2017), no. 4, 571–590 Zbl 1390.35431 MR 3757089
- [43] J. T. Oden, A. Hawkins, and S. Prudhomme, General diffuse-interface theories and an approach to predictive tumor growth modeling. *Math. Models Methods Appl. Sci.* 20 (2010), no. 3, 477– 517 Zbl 1186.92024 MR 2647029
- [44] L. Preziosi and A. Tosin, Multiphase modelling of tumour growth and extracellular matrix interaction: mathematical tools and applications. J. Math. Biol. 58 (2009), no. 4–5, 625–656 Zbl 1311.92029 MR 2471305
- [45] E. Rocca and R. Scala, A rigorous sharp interface limit of a diffuse interface model related to tumor growth. J. Nonlinear Sci. 27 (2017), no. 3, 847–872 Zbl 1370.92076 MR 3638323
- [46] G. Sciumè, S. Shelton, W. G. Gray, C. T. Miller, F. Hussain, M. Ferrari, P. Decuzzi, and B. A. Schrefler, A multiphase model for three-dimensional tumor growth. *New J. Phys.* 15 (2013), 015005
- [47] A. Tosin, Multiphase modeling and qualitative analysis of the growth of tumor cords. *Netw. Heterog. Media* 3 (2008), no. 1, 43–83 Zbl 1144.35476 MR 2379886
- [48] X. Wang and H. Wu, Long-time behavior for the Hele-Shaw-Cahn-Hilliard system. Asymptotic Anal. 78 (2012), no. 4, 217–245 Zbl 1246.35164 MR 3012658
- [49] X. Wang and Z. Zhang, Well-posedness of the Hele-Shaw-Cahn-Hilliard system. Ann. Inst. Henri Poincaré Anal. Non Linéaire 30 (2013), no. 3, 367–384 Zbl 1291.35240 MR 3061427
- [50] S. M. Wise, J. S. Lowengrub, and V. Cristini, An adaptive multigrid algorithm for simulating solid tumor growth using mixture models. *Math. Comput. Modelling* 53 (2011), no. 1–2, 1–20 Zbl 1211.65123 MR 2739241
- [51] S. M. Wise, J. S. Lowengrub, H. B. Frieboes, and V. Cristini, Three-dimensional multispecies nonlinear tumor growth. I: Model and numerical method. *J. Theor. Biol.* 253 (2008), no. 3, 524–543 Zbl 1398.92135 MR 2964567
- [52] X. Wu, G. J. van Zwieten, and K. G. van der Zee, Stabilized second-order convex splitting schemes for Cahn-Hilliard models with application to diffuse-interface tumor-growth models. *Int. J. Numer. Methods Biomed. Eng.* **30** (2014), no. 2, 180–203 MR 3164683

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