Analysis of a diffuse interface model of multispecies tumor growth

Mimi Dai* Eduard Feireisl † Elisabetta Rocca‡ Giulio Schimperna§
Maria E. Schonbek¶

July 22, 2015

Abstract

We consider a diffuse interface model for tumor growth recently proposed in [3]. In this new approach sharp interfaces are replaced by narrow transition layers arising due to adhesive forces among the cell species. Hence, a continuum thermodynamically consistent model is introduced. The resulting PDE system couples four different types of equations: a Cahn-Hilliard type equation for the tumor cells (which include proliferating and dead cells), a Darcy law for the tissue velocity field, whose divergence may be different from 0 and depend on the other variables, a transport equation for the proliferating (viable) tumor cells, and a quasi-static reaction diffusion equation for the nutrient concentration. We establish existence of weak solutions for the PDE system coupled with suitable initial and boundary conditions. In particular, the proliferation function at the boundary is supposed to be nonnegative on the set where the velocity $\mathbf{u}$ satisfies $\mathbf{u} \cdot \nu > 0$, where ν is the outer normal to the boundary of the domain. We also study a singular limit as the diffuse interface coefficient tends to zero.

Key words: tumor growth, diffuse interface model, Cahn-Hilliard equation, reaction-diffusion equation, Darcy law, existence of weak solutions, singular limits.

AMS (MOS) Subject Classification: 35B25, 35D30, 35K35, 35K57, 35Q92, 74G25, 78A70, 92C17.

1 Introduction

Mathematical modeling and analysis of tumor growth processes give important insights on cancer growth progression. The models are expected to help to provide optimal treatment strategies. The behavior of tumors is a complex biological phenomenon, influenced by many factors, such as cell–cell and cell–matrix adhesion, mechanical stress, cell motility and transport of oxygen, nutrients and growth factors. In recent years, many mathematical models of cancer have been proposed and various numerical simulations have been carried out (cf., e.g., the recent reviews [2, 7, 8, 9]). A variety of models are available to investigate different characteristics of cancer: single-phase continuum and multiphase mixture models, and methods that combine both continuum and discrete components (cf., e.g., [7, Chap. 7]).

We will address the problem of existence of weak solutions for a PDE system for a tumor growth model introduced in [3] (cf. also [18] and [17]) and analyze a singular limit of that model. The

*Department of Mathematics, University of Illinois at Chicago, 851 S. Morgan Street, Chicago, IL 60607-7045, USA. E-mail: *mdai@uic.edu*.

†Institute of Mathematics of the Academy of Sciences of the Czech Republic, Žitná 25, CZ-115 67 Praha 1, Czech Republic. E-mail: *feireisl@math.cas.cz*.

‡Weierstrass Institute for Applied Analysis and Stochastics, Mohrenstr. 39, D-10117 Berlin, Germany. E-mail: *rocca@wias-berlin.de* and Dipartimento di Matematica "F. Enriques", Università degli Studi di Milano, Milano I-20133, Italy. E-mail: *elisabetta.rocca@unimi.it*.

§Dipartimento di Matematica "F. Casorati", Università degli Studi di Pavia, via Ferrata 1, Pavia I-27100, Italy. E-mail: *giusch04@unipv.it*.

¶Department of Mathematics, University of California, Santa Cruz, CA 95064, USA. E-mail: *schonbek@ucsc.edu*.

works listed above can be framed in the continuum tumor growth models category. This modeling approach has become central in the studies of tumor development in applied mathematics (cf. also [1, 14]). Actually, the translation of biological processes into models generally turns out to be simpler for discrete models than for continuum approaches. Nevertheless, discrete models can be difficult to study analytically because the associated computational cost rapidly increases with the number of cells modeled. This makes it difficult to simulate millimeter or greater sized tumors. For this reason, in larger scale systems (millimeter to centimeter scale), continuum methods provide a good modeling alternative. Mixture models, on the other hand, provide the capability of simulating in detail the interactions among multiple cell species.

In the framework of continuum models, the diffuse interface method turns out to be particularly useful to describe multi-species tumor growth processes. In this approach the sharp interfaces are replaced by narrow transition layers arising due to the adhesion forces among different cell-species. This choice is quite effective since it avoids to introduce complicated boundary conditions across the tumor/host tissue and other species/species interfaces. This would have been the case when considering sharp interface models. Moreover, the diffuse interface approach eliminates the need of tracking the position of the interfaces, which is one one of the main issues of such models.

The model derived in [3] consists of a Cahn-Hilliard system with transport and reaction terms which governs various types of cell concentrations. The reaction terms depend on the nutrient concentration (e.g., oxygen) which obeys to a quasi-static advection-reaction-diffusion equation coupled to the Cahn-Hilliard equations. The cell velocities satisfy a generalized Darcy's law where, besides the pressure gradient, appears also the so-called Korteweg force due to the cell concentration.

Numerical simulations of diffuse-interface models for tumor growth have been carried out in several papers (see, for instance, [7, Chap. 8] and references therein). However, a rigorous mathematical analysis of the resulting PDEs is still in its beginning. To the best of our knowledge, the first related papers are concerned with a simplified model, the so-called Cahn-Hilliard-Hele-Shaw system (see [13], cf. also [15, 16]) in which the nutrient n, the source of tumor S_T and the fraction S_D of the dead cells are neglected. Moreover, very recent contributions (see [4, 10, 5, 6]) are devoted to the analysis of a newly proposed simpler model in [12] (see also [19]). In this model, velocities are set to zero and the state variables are reduced to the tumor cell fraction and the nutrient-rich extracellular water fraction.

In what follows we briefly introduce the model proposed in [3], where a complete description as well as numerical simulations are provided. Our multi-species tumor model includes the mechanical interaction between different species. The following notation will be used:

- $\phi_i, i = 1, 2, 3$: *the volume fractions of the cells:* $\phi_1 = P$*: proliferating cell fraction;* $\phi_2 = \phi_D$*: dead cell fraction;* $\phi_3 = \phi_H$*: host cell fraction;*
- Π: *the cell-to-cell pressure*;
- $\mathbf{u}{:=}\mathbf{u}_i, i = 1, 2, 3$: *the tissue velocity field. We assume that the cells are tightly packed and they march together*;
- n: *the nutrient concentration*;
- $\Phi = \phi_D + P$: *the volume fraction of the tumor cells which is split into the sum of the dead tumor cells and of the proliferating cells*;
- $\mathbf{J}_i$: *the fluxes that account for mechanical interactions among the species*;
- $S_i, i = 1, 2, 3$: *account for inter-component mass exchange as well as gains due to proliferation of cells and loss due to cell death.*

The variables above are naturally constrained by the relation $\phi_H + \Phi = 1$.
The volume fractions obey the mass conservation (advection-reaction-diffusion) equations:

$$\partial_t \phi_i + \mathrm{div}_x(\mathbf{u}\phi_i) = -\mathrm{div}_x \mathbf{J}_i + \Phi S_i. \tag{1.1}$$

We have assumed that the densities of the components are matched. Notice that unlike in [3], for simplicity, the variable ϕ_W standing for the volume fraction of water has been omitted. The total energy adhesion, supposed independent of ϕ_H, has the form

$$E = \int_\Omega \left(\mathcal{F}(\Phi) + \frac{1}{2}|\nabla_x \Phi|^2 \right) \, \mathrm{d}x,$$

where $\mathcal{F}$ is a logarithmic type mixing potential (cf. (2.4) in Subsection 2.1). Then, we define the fluxes $\mathbf{J}_\Phi$ and $\mathbf{J}_H$ as follows:

$$\begin{aligned}
\mathbf{J}_\Phi &= \mathbf{J}_1 + \mathbf{J}_2 := -\nabla_x \left(\frac{\delta E}{\delta \Phi} \right) = -\nabla_x \left(\mathcal{F}'(\Phi) - \Delta\Phi \right) := -\nabla_x \mu, \\
\mathbf{J}_H &= \mathbf{J}_3 := -\nabla_x \left(\frac{\delta E}{\delta \phi_H} \right) = \nabla_x \left(\frac{\delta E}{\delta \Phi} \right),
\end{aligned}$$

where we have used in the last equality the fact that $\phi_H = 1 - \Phi$ and where μ is the chemical potential of the system. For the source of mass in the host tissue we have the following relations:

- $S_T = S_D + S_P := S_2 + S_1$,
- $\Phi S_H := \Phi S_3 = \phi_H S_T = (1 - \Phi) S_T$.

Assuming the mobility of the system to be constant, then the tumor volume fraction Φ and the host tissue volume fraction ϕ_H obey the following mass conservation equations (cf. (1.1)):

$$\partial_t \Phi + \mathrm{div}_x(\mathbf{u}\Phi) = -\mathrm{div}_x \mathbf{J}_\Phi + \Phi(S_2 + S_1), \tag{1.2}$$
$$\partial_t \phi_H + \mathrm{div}_x(\mathbf{u}\phi_H) = -\mathrm{div}_x \mathbf{J}_H + \Phi S_3. \tag{1.3}$$

Using now the fact that $S_T = S_1 + S_2$ and recalling that $\phi_H + \Phi = 1$, we can forget of the equation for ϕ_H and we recover the equation for Φ in the form

$$\partial_t \Phi + \mathrm{div}_x(\mathbf{u}\Phi) - \mathrm{div}_x(\nabla_x \mu) = \Phi S_T, \;\; \mu = \mathcal{F}'(\Phi) - \Delta\Phi. \tag{1.4}$$

As in [18], we suppose the net source of tumor cells S_T to be given by

$$S_T = S_T(n, P, \Phi) = \lambda_M n P - \lambda_L(\Phi - P),$$

where $\lambda_M \geq 0$ is the mitotic rate and $\lambda_L \geq 0$ is the lysing rate of dead cells. The volume fraction of dead tumor cells ϕ_D would satisfy an equation similar to (1.4), namely

$$\partial_t \phi_D + \mathrm{div}_x(\mathbf{u}\phi_D) - \mathrm{div}_x(\nabla_x \mu) = \Phi S_D,$$

where the source of dead cells is taken as

$$S_D = S_D(n, P, \Phi) = \left(\lambda_A + \lambda_N H(n_N - n)\right) P - \lambda_L(\Phi - P).$$

However, we prefer to couple the equation for Φ with the one for $P = \Phi - \phi_D$ which then reads

$$\partial_t P + \mathrm{div}_x(\mathbf{u}P) = \Phi(S_T - S_D).$$

Here $\lambda_A P$ describes the death of cells due to apoptosis (cf. [3, p. 730]) with rate $\lambda_A \geq 0$ and the term $\lambda_N H(n_N - n)P$ models the death of cells due to necrosis with rate $\lambda_N \geq 0$. In [18] H was originally taken as the Heaviside function. Here, for mathematical reasons, we smooth it out by taking it as a regular and nonnegative function of n. The term n_N represents the necrotic limit, at which the tumor tissue dies due to lack of nutrients.

The tumor velocity field $\mathbf{u}$ (given by the mass-averaged velocity of all the components) is assumed to fulfill Darcy's law:

$$\mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi,$$

where, for simplicity, the motility has been taken constant and equal to 1. Summing up equations (1.1), we end up with the following constraint for the velocity field:

$$\mathrm{div}_x \mathbf{u} = S_T.$$

Since the time scale for nutrient diffusion is much faster than the rate of cell proliferation, the nutrient is assumed to evolve quasi-statically:

$$-\Delta n + \nu_U n P = T_c(n, \Phi),$$

where the nutrient capillarity term T_c is

$$T_c(n, \Phi) = [\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)]\,(n_c - n),$$

ν_U represents the nutrient uptake rate by the viable tumor cells, ν_1, ν_2 denote the nutrient transfer rates for preexisting vascularization in the tumor and host domains, and n_c is the nutrient level of capillaries. The function $Q(\Phi)$ is assumed to be regular and to satisfy $\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi) \geq 0$ (cf. (3.2) below).

Remark 1.1. *We chose the boundary conditions proposed in [3] for Φ, μ, Π and n. On the other hand, under the homogeneous Neumann boundary conditions suggested in [3] for P, we could not show that the system is well-posed. For this reason, we chose the boundary conditions (1.13), which are natural in connection with the transport equation (1.8) for P. In particular, the proliferation function at the boundary has to be nonnegative on the set where the velocity $\mathbf{u}$ satisfies $\mathbf{u}\cdot\nu > 0$, with ν denoting the outer normal unit vector to the boundary of our domain Ω. By maximum principle, this implies in particular that $P \geq 0$ in Ω, which is an information we need for proving well-posedness of the system.*

In summary, let $\Omega \subset \mathbb{R}^3$ be a bounded domain and $T > 0$ the final time of the process. For simplicity, choose $\lambda_M = \nu_U = 1$, $\lambda_A = \lambda_1$, $\lambda_N = \lambda_2$, $\lambda_L = \lambda_3$. Then, in $\Omega \times (0, T)$, we have the following system of equations:

$$\partial_t \Phi + \mathrm{div}_x(\mathbf{u}\Phi) - \mathrm{div}_x(\nabla_x \mu) = \Phi S_T,\ \ \mu = -\Delta\Phi + \mathcal{F}'(\Phi), \tag{1.5}$$

$$\mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi, \tag{1.6}$$

$$\mathrm{div}_x \mathbf{u} = S_T, \tag{1.7}$$

$$\partial_t P + \mathrm{div}_x(\mathbf{u}P) = \Phi(S_T - S_D), \tag{1.8}$$

$$-\Delta n + nP = T_c(n, \Phi), \tag{1.9}$$

where

$$S_T(n, P, \Phi) = nP - \lambda_3(\Phi - P), \tag{1.10}$$

$$S_D(n, P, \Phi) = (\lambda_1 + \lambda_2 H(n_N - n))\,P - \lambda_3(\Phi - P),$$

$$T_c(n, \Phi) = [\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)]\,(n_c - n). \tag{1.11}$$

The functions Q, H and the constants λ_i, ν_i will be described in Section 2.1. System (1.5–1.9) will be coupled with the following boundary conditions on $\partial\Omega \times (0, T)$:

$$\mu = \Pi = 0,\ \ n = 1, \tag{1.12}$$

$$\nabla_x \Phi \cdot \nu = 0,\ \ P\mathbf{u}\cdot\nu \geq 0, \tag{1.13}$$

and with the initial conditions

$$\Phi(0) = \Phi_0, \quad P(0) = P_0 \text{ in } \Omega. \tag{1.14}$$

Note that, as $P \geq 0$, the second condition in (1.13) should be interpreted as $P = 0$ whenever $\mathbf{u}\cdot\nu < 0$, meaning on the part of the inflow part of the boundary. Moreover, in the weak formulation, that condition will be incorporated into equation (1.8) turning it into a variational inequality (cf. (2.18) below).

The different nature of the four equations as well as their nonlinear coupling (especially due to the Korteweg term in the pressure equation) make the analysis of the problem particularly challenging.

Moreover, we may notice that the singular limit studied in the last Section 6 as the interface energy coefficient is let tend to zero can be obtained only under more restrictive assumptions on the potential $\mathcal{F}$, which is required to be strictly convex, and under different boundary conditions for $\mathbf{u}$ (namely, we assume no-flux, rather than Dirichlet, conditions for Π). We refer the reader to Remark 6.1 below for further comments and for the discussion of related open problems.

Plan of the paper. The main results and assumptions are stated in Section 2. The subsequent Sections 3 and 4 are the core of the paper where we provide the a priori bounds for our solutions and we show the weak sequential stability properties. In Section 5, we construct an approximation scheme compatible with the apriori estimates and prove its well-posedness. In the last section, we analyze the singular limit problem mentioned above.

2 Assumptions and main results

2.1 Singular potential and initial data

We suppose that the potential $\mathcal{F}$ supports the natural bounds

$$0 \le \Phi(t, x) \le 1. \tag{2.1}$$

To this end, we take $\mathcal{F} = \mathcal{C} + \mathcal{B}$, where $\mathcal{B} \in C^2(\mathbb{R})$ and

$$\mathcal{C} : \mathbb{R} \mapsto [0, \infty] \text{ convex, lower-semi continuous, } \mathcal{C}(\Phi) = \infty \text{ for } \Phi < 0 \text{ or } \Phi > 1. \tag{2.2}$$

Moreover, we ask that

$$\mathcal{C} \in C^1(0, 1), \ \lim_{\Phi \to 0^+} \mathcal{C}'(\Phi) = \lim_{\Phi \to 1^-} \mathcal{C}'(\Phi) = \infty. \tag{2.3}$$

A typical example of such $\mathcal{C}$ is the *logarithmic potential*

$$\mathcal{C}(\Phi) = \begin{cases} \Phi \log(\Phi) + (1 - \Phi) \log(1 - \Phi) \text{ for } \Phi \in [0, 1], \\ \infty \text{ otherwise.} \end{cases} \tag{2.4}$$

Remark 2.1. *Condition* (2.3) *has mainly a technical character and is assumed just for the purpose of constructing a not too complicated approximation scheme (cf. also Remark 5.1). At the price of some additional technical work it could be avoided. One may, for instance, consider the case where* $\mathcal{C}(\Phi) = I_{[0,1]}(\Phi)$ *(the* indicator function *of* $[0, 1]$*), which does not satisfy* (2.3)*.*

Regarding the functions Q and H and the constants λ_i, ν_i appearing in the definitions of S_T and S_D, we assume $Q, H \in C^1(\mathbb{R})$ together with

$$\lambda_i \ge 0 \text{ for } i = 1, 2, 3, \quad H \ge 0. \tag{2.5}$$

$$[\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)] \ge 0, \quad 0 < n_c < 1. \tag{2.6}$$

Finally, we suppose Ω be a bounded domain with smooth boundary in $\mathbb{R}^3$ and impose the following conditions on the initial data:

$$\Phi_0 \in H^1(\Omega), \quad 0 \le \Phi_0 \le 1, \quad \mathcal{C}(\Phi_0) \in L^1(\Omega), \tag{2.7}$$

$$P_0 \in L^2(\Omega), \quad 0 \le P_0 \le 1 \quad \text{a.e. in } \Omega. \tag{2.8}$$

2.2 Main result

Before stating the main result, let us introduce a suitable weak formulation of the problem. We say that $(\Phi, \mathbf{u}, P, n)$ is a weak solution to problem (1.5–1.14) in $(0, T) \times \Omega$ if

(i) these functions belong to the regularity class:

$$\Phi \in C^0([0,T]; H^1(\Omega)) \cap L^2(0,T; W^{2,6}(\Omega)), \tag{2.9}$$

$$\mathcal{C}(\Phi) \in L^\infty(0,T; L^1(\Omega)), \text{ hence, in particular, } 0 \le \Phi \le 1 \text{ a.a. in } (0,T)\times\Omega; \tag{2.10}$$

$$\mathbf{u} \in L^2((0,T)\times\Omega;\mathbb{R}^3), \text{ div } \mathbf{u} \in L^\infty((0,T)\times\Omega); \tag{2.11}$$

$$\Pi \in L^2(0,T; W_0^{1,2}(\Omega)), \quad \mu \in L^2(0,T; W_0^{1,2}(\Omega)); \tag{2.12}$$

$$P \in L^\infty((0,T)\times\Omega),\ 0 \le P \le 1 \text{ a.a. in } (0,T)\times\Omega; \tag{2.13}$$

$$n \in L^2(0,T; W^{2,2}(\Omega)),\ 0 \le n \le 1 \text{ a.a. in } (0,T)\times\Omega; \tag{2.14}$$

(ii) the following integral identities hold:

$$\int_0^T \int_\Omega [\Phi\partial_t\varphi + \Phi\mathbf{u}\cdot\nabla_x\varphi + \mu\Delta\varphi + \Phi S_T\varphi]\ \mathrm{d}x\ \mathrm{d}t = -\int_\Omega \Phi_0\varphi(0,\cdot)\ \mathrm{d}x \tag{2.15}$$

for any $\varphi \in C_c^\infty([0,T)\times\Omega)$, where

$$\mu = -\Delta\Phi + \mathcal{F}'(\Phi),\ \mathbf{u} = -\nabla_x\Pi + \mu\nabla_x\Phi, \tag{2.16}$$

$$\mathrm{div}_x\mathbf{u} = S_T \text{ a.a. in } (0,T)\times\Omega; \quad \nabla_x\Phi\cdot\nu|_{\partial\Omega} = 0; \tag{2.17}$$

$$\int_0^T \int_\Omega [P\partial_t\varphi + P\mathbf{u}\cdot\nabla_x\varphi + \Phi(S_T - S_D)\varphi]\ \mathrm{d}x\ \mathrm{d}t \ge -\int_\Omega P_0\varphi(0,\cdot)\ \mathrm{d}x \tag{2.18}$$

for any $\varphi \in C_c^\infty([0,T)\times\overline{\Omega})$, $\varphi|_{\partial\Omega} \ge 0$;

$$-\Delta n + nP = T_c(n,\Phi) \text{ a.a. in } (0,T)\times\Omega;\ n|_{\partial\Omega} = 1. \tag{2.19}$$

Now, we are able to state the main result of the present paper:

Theorem 2.1. *Let $T > 0$ be given. Under the assumptions stated in Subsection 2.1, the variational formulation (2.15–2.19) of the initial-boundary value problem (1.5–1.14) admits at least one solution in the regularity class (2.9–2.14).*

Remark 2.2. *It is worth observing once more that the second boundary condition* (1.13) *is now incorporated into the variational inequality* (2.18).

3 A priori bounds

In this section we establish several formal a priori estimates for our solution. The procedure turns out to be rigorous when (smoother) solutions of the approximated problem (5.39–5.43) are considered. In particular, this happens for the regularized solution constructed in Section 5 below. In this section we refer to system (1.5–1.14) and not to the weak formulation (2.15–2.19) because actually the a-priori estimates should be performed on the regularized problem (5.39–5.43) whose solutions are more regular than the ones obtained at the limit.

We start with noticing that, as a direct consequence of our choice of the potential $\mathcal{F}$, the phase field function Φ satisfies (2.1).

3.1 Lower bound for P

The density function P satisfies the transport equation (1.8), which can be equivalently rewritten in the form

$$\begin{aligned}\partial_t P + \mathbf{u}\cdot\nabla_x P &= -PS_T + \Phi(S_T - S_D) \\ &= P\left[-S_T + \Phi\left(n - (\lambda_1 + \lambda_2 H(n_N - n))\right)\right].\end{aligned} \tag{3.1}$$

Thus, provided

$$P(0,\cdot) = P_0 \ge 0, \text{ and } P(t,x) \ge 0 \text{ for } x \in \partial\Omega,\ \mathbf{u}\cdot\nu \le 0,$$

we can deduce by maximum principle arguments that

$$P \ge 0.$$

3.2 Positivity and upper bound for n

In order to obtain positivity of n we need

$$-nP + T_c(n, \varphi) = -nP + [\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)] (n_c - n)$$

to be positive (non-negative) whenever $n < 0$; actually, this follows from the hypothesis (cf. (2.6) in Subsection 2.1)

$$[\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)] \geq 0, \ 0 < n_c < 1. \tag{3.2}$$

This assumption also implies that $n \leq 1$, so we may conclude that

$$0 \leq n(t, x) \leq 1. \tag{3.3}$$

3.3 Upper bound for P

Since $0 \leq \Phi \leq 1$ and $0 \leq n \leq 1$, by the assumptions provided in Subsection 2.1 we have

$$-\Phi \left(\lambda_1 + \lambda_2 H(n_N - n)\right) \leq 0.$$

Hence evaluating the expression on the right-hand side of (3.1) for $P = 1$ yields

$$P \left[-S_T + \Phi \left(n - (\lambda_1 + \lambda_2 H(n_N - n))\right)\right] \leq \lambda_3(\Phi - 1) + n(\Phi - 1).$$

Consequently, provided

$$0 \leq P(0, \cdot) = P_0 \leq 1, \text{ and } 0 \leq P(t, x) \leq 1 \text{ for } x \in \partial\Omega, \ \mathbf{u} \cdot \nu \leq 0,$$

it follows that

$$0 \leq P(t, x) \leq 1. \tag{3.4}$$

3.4 Estimates for the Cahn-Hilliard equation

The standard estimates are obtained via multiplication of (1.5) by μ:

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_\Omega \left[\frac{1}{2}|\nabla_x \Phi|^2 + \mathcal{F}(\Phi)\right] \ \mathrm{d}x + \int_\Omega |\nabla_x \mu|^2 \ \mathrm{d}x = -\int_\Omega \mathbf{u} \cdot \nabla_x \Phi \mu \ \mathrm{d}x, \tag{3.5}$$

where, by virtue of (1.6),

$$-\int_\Omega \mathbf{u} \cdot \nabla_x \Phi \mu \ \mathrm{d}x = -\int_\Omega |\mathbf{u}|^2 \ \mathrm{d}x + \int_\Omega \Pi \mathrm{div}_x \mathbf{u} \ \mathrm{d}x = -\int_\Omega |\mathbf{u}|^2 \ \mathrm{d}x + \int_\Omega \Pi S_T \ \mathrm{d}x.$$

Consequently, (3.5) reads

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_\Omega \left[\frac{1}{2}|\nabla_x \Phi|^2 + \mathcal{F}(\Phi)\right] \ \mathrm{d}x + \int_\Omega \left[|\nabla_x \mu|^2 + |\mathbf{u}|^2\right] \ \mathrm{d}x = \int_\Omega \Pi S_T \ \mathrm{d}x, \tag{3.6}$$

where

$$\left| \int_\Omega \Pi S_T \ \mathrm{d}x \right| \leq \|S_T\|_{L^\infty(\Omega)} \|\Pi\|_{L^1(\Omega)}.$$

Seeing that Π solves the Dirichlet problem

$$-\Delta \Pi = S_T - \mathrm{div}_x(\mu \nabla_x \Phi), \ \Pi|_{\partial\Omega} = 0,$$

we deduce that

$$\|\Pi(t, \cdot)\|_{H^1(\Omega)} \leq \|S_T(t, \cdot)\|_{L^2(\Omega)} + \|\mu \nabla_x \Phi\|_{L^2(\Omega;\mathbb{R}^3)},$$

where, by means of Gagliardo-Nirenberg interpolation inequality,

$$\|\mu \nabla_x \Phi\|_{L^2(\Omega;\mathbb{R}^3)} \leq \|\mu(t, \cdot)\|_{L^4(\Omega)} \|\nabla_x \Phi\|_{L^4(\Omega;\mathbb{R}^3)}$$

$$\leq c\|\mu(t,\cdot)\|_{L^4(\Omega)}\|\Phi(t,\cdot)\|^{1/2}_{L^\infty(\Omega)}\|\Delta\Phi(t,\cdot)\|^{1/2}_{L^2(\Omega)}$$

$$\leq c\|\mu(t,\cdot)\|_{L^4(\Omega)}\|\Phi(t,\cdot)\|^{1/2}_{L^\infty(\Omega)}\left(\|\mu\|^{1/2}_{L^2(\Omega)}+\|\nabla\Phi\|^{1/2}_{L^2(\Omega)}\right),$$

where the last inequality has been obtained testing the second (1.5) by Φ and using the properties of $\mathcal{F}$ (in particular, the monotonicity of $\mathcal{C}'$).

Thus, going back to (3.6) and applying a standard version of Grönwall's lemma, we deduce the bounds

$$\sup_{t\in(0,T)}\|\Phi\|_{H^1(\Omega)}\leq c, \tag{3.7}$$

$$\int_0^T\left[\|\nabla_x\mu\|^2_{L^2(\Omega;\mathbb{R}^3)}+|\mathbf{u}|^2\right]\ \mathrm{d}t\leq c. \tag{3.8}$$

3.4.1 More estimates on Φ

Knowing that

$$-\Delta\Phi+\mathcal{C}'(\Phi)=g=\mu-\mathcal{B}'(\Phi)\in L^2(0,T;H^1(\Omega)), \tag{3.9}$$

we may multiply this relation by $-\Delta\Phi$ and use once more the monotonicity of $\mathcal{C}'$ to deduce

$$\int_0^T\|\Phi\|^2_{W^{2,2}(\Omega)}\ \mathrm{d}t\leq c.$$

Next, take an increasing function h and multiply (3.9) by $h(\mathcal{C}'(\Phi))$ to obtain

$$\int_\Omega\left[h'(\mathcal{C}'(\Phi))\mathcal{C}''(\Phi)|\nabla_x\Phi|^2+h(\mathcal{C}'(\Phi))\mathcal{C}'(\Phi)\right]\ \mathrm{d}x=\int_\Omega gh(\mathcal{C}'(\Phi))\ \mathrm{d}x. \tag{3.10}$$

Choosing $h(\cdot)=(\cdot)^5$ and using that $g\in L^2(0,T;L^6(\Omega))$, we then easily deduce

$$\mathcal{C}'(\Phi)\text{ is bounded in }L^2(0,T;L^6(\Omega)),$$

whence, comparing terms in (3.9), we also infer

$$\int_0^T\|\Phi\|^2_{W^{2,6}(\Omega)}\ \mathrm{d}t\leq c. \tag{3.11}$$

3.4.2 Estimates on $\mathbf{u}$

Note that we already know

$$\mathrm{div}_x\mathbf{u}=S_T\text{ bounded in }L^\infty((0,T)\times\Omega)$$

and

$$\mathbf{u}\text{ bounded in }L^2((0,T)\times\Omega;\mathbb{R}^3).$$

Next, we compute

$$\mathbf{curl}_x\mathbf{u}=\nabla_x\mu\wedge\nabla_x\Phi\in L^2(0,T;L^1(\Omega))\cap L^1(0,T;L^2(\Omega)).$$

Hence, we may take a test function $\varphi\in C^\infty(\mathbb{R}^3)$ with support contained in Ω and apply [11, p. 51] to the function $\varphi\mathbf{u}$. In view of the fact that $\mathrm{div}_x(\varphi\mathbf{u})$ and $\mathbf{curl}(\varphi\mathbf{u})$ are bounded in $L^1(0,T;L^2(\mathbb{R}^3))$, we then obtain that $\varphi\mathbf{u}$ is bounded in $L^1(0,T;H^1(\mathbb{R}^3))$. Consequently, $\mathbf{u}$ satisfies

$$\int_0^T\|\mathbf{u}\|_{H^1_{\mathrm{loc}}(\Omega;\mathbb{R}^3)}\ \mathrm{d}t \tag{3.12}$$

4 Weak sequential stability

Suppose that

$$\{\Phi_\delta, \mathbf{u}_\delta, P_\delta, n_\delta\}_{\delta>0}$$

is a family of solutions complying with the *a priori* bounds obtained in the last section. Our goal is to show the precompactness of this family of solutions, that is to prove that

$$\left\{ \begin{array}{c} \Phi_\delta \to \Phi \text{ weakly-(*) in } L^\infty((0,T)\times\Omega), \\ \mathbf{u}_\delta \to \mathbf{u} \text{ weakly in } L^2((0,T)\times\Omega;\mathbb{R}^3), \\ P_\delta \to P \text{ weakly-(*) in } L^\infty((0,T)\times\Omega), \\ n_\delta \to n \text{ weakly-(*) in } L^\infty((0,T)\times\Omega), \end{array} \right\}$$

where the limits solve the same system of equations.

4.1 Compactness of the time derivatives

It follows from (1.5) and the a-priori estimates we have on Φ that

$$\partial_t \Phi_\delta \to \partial_t \Phi \text{ weakly in } L^2(0,T;W^{-1,2}(\Omega)),$$

whence, in accordance with (3.11) and the uniform bounds obtained before, we get

$$\nabla_x \Phi_\delta \to \nabla_x \Phi \text{ in } L^q((0,T)\times\Omega;\mathbb{R}^3) \text{ for a certain } q>2, \tag{4.1}$$

and

$$\Phi_\delta \to \Phi \text{ a.a. in } (0,T)\times\Omega. \tag{4.2}$$

Consequently, we can pass to the limit in (1.5), using the fact that $\mathrm{div}_x \mathbf{u}_\delta = S_{T,\delta}$ and the standard monotone operator theory to handle the limit in μ_δ.

Let us now test (1.8) by $\phi \in W_0^{1,2}(\Omega)$. Then, integrating by parts and using (3.8), we easily arrive at

$$\int_0^T \|P_t\|^2_{W^{-1,2}(\Omega)} \, \mathrm{d}t \le c. \tag{4.3}$$

Coupling this with (3.4), we infer

$$P_\delta \to P \text{ strongly in } L^2(0,T:W^{-\epsilon,2}(\Omega)) \text{ for every } \epsilon \in (0,1). \tag{4.4}$$

Let now $\phi \in C^\infty(\mathbb{R}^3)$ with support in Ω. Then, from (4.4) and (3.12), we obtain

$$\int_0^T \int_\Omega P_\delta \mathbf{u}_\delta \phi \, \mathrm{d}x \, \mathrm{d}t \to \int_0^T \int_\Omega P\mathbf{u}\phi \, \mathrm{d}x \, \mathrm{d}t,$$

whence we can identify the limit of the product

$$\mathbf{u}_\delta P_\delta \to \mathbf{u}P \text{ weakly in } L^2((0,T)\times\Omega;\mathbb{R}^3). \tag{4.5}$$

Next, testing (1.9) by n_δ and using (3.3) and (3.4), it is easy to infer

$$n_\delta \to n \text{ weakly in } L^2(0,T;W_0^{1,2}(\Omega)), \tag{4.6}$$

whence, using (4.4) again,

$$P_\delta n_\delta \to Pn \text{ weakly-(*) in } L^\infty((0,T)\times\Omega), \tag{4.7}$$

$$P_\delta b(n_\delta) \to P\overline{b(n)} \text{ weakly-(*) in } L^\infty((0,T)\times\Omega), \tag{4.8}$$

for any C^1 function b, where $\overline{b(n)}$ denotes a weak limit of $\{b(n_\delta)\}_{\delta>0}$.

4.2 Strong convergence of the nutrients

We finish the proof of compactness by showing strong (a.a.) pointwise convergence of the nutrients $\{n_\delta\}_{\delta>0}$. We have

$$\begin{aligned} -\Delta n_\delta + P n_\delta + [\nu_1(1-Q(\Phi)) + \nu_2 Q(\Phi)]\, n_\delta &= \\ = (P - P_\delta) n_\delta + [\nu_1(1-Q(\Phi_\delta)) + \nu_2 Q(\Phi_\delta)]\, n_c \\ +\Big([\nu_1(1-Q(\Phi)) + \nu_2 Q(\Phi)] - [\nu_1(1-Q(\Phi_\delta)) + \nu_2 Q(\Phi_\delta)] \Big) n_\delta, \end{aligned} \tag{4.9}$$

and, for the limit system,

$$-\Delta n + P n + [\nu_1(1-Q(\Phi)) + \nu_2 Q(\Phi)]\, n = [\nu_1(1-Q(\Phi)) + \nu_2 Q(\Phi)]\, n_c.$$

Thus, testing respectively by n_δ and n, integrating by parts, and making use of the relations (4.1–4.8) (in particular, (4.8) is exploited with the choice $b(n_\delta) = n_\delta^2$ in order to manage the first term on the right hand side of (4.9)), we may show that

$$\int_0^T \int_\Omega |\nabla_x n_\delta|^2 + P n_\delta^2 + [\nu_1(1-Q(\Phi)) + \nu_2 Q(\Phi)]\, n_\delta^2 \ \mathrm{d}x\ \mathrm{d}t$$

$$\to \int_0^T \int_\Omega |\nabla_x n|^2 + P n^2 + [\nu_1(1-Q(\Phi)) + \nu_2 Q(\Phi)]\, n^2 \ \mathrm{d}x\ \mathrm{d}t,$$

which yields the desired conclusion

$$\nabla_x n_\delta \to \nabla_x n,\ n_\delta \to n \text{ in } L^2((0,T)\times\Omega). \tag{4.10}$$

5 Approximation scheme

In this section we briefly introduce the approximated scheme needed to obtain rigorously the above described a priori estimates. This part is quite standard, hence some details are omitted.

5.1 Local existence by fixed point argument

Let

$$\overline{S} \in L^8(0,T;L^2(\Omega)),\ \|\overline{S}\|_{L^8(0,T;L^2(\Omega))} \le R_2, \tag{5.1}$$

where $R_2 > 0$ (this value can be chosen arbitrarily; for instance we can take $R_2 = 1$).

Replace $S_T + \lambda_3 \Phi$ with $\overline{S}$ and solve (1.5–1.7) locally in time by a fixed point argument. The following can be proven:

Lemma 5.1. *Let $\overline{S}$ be given by (5.1). Let $\delta \in (0,1/4)$ and $\Phi_{0\delta} \in W^{2,6}(\Omega)$, $\Phi_{0\delta} \in [\delta, 1-\delta]$. Then there exists $T_0 \in (0,T]$ possibly depending on δ such that the system*

$$a.\ \ \partial_t \Phi - \delta \Delta \mu_t + \mathbf{u}\cdot\nabla_x \Phi - \Delta\mu = 0, \quad b.\ \ \mu = -\Delta\Phi + \mathcal{F}'(\Phi), \tag{5.2}$$

$$\mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi, \tag{5.3}$$

$$-\Delta \Pi = -\mathrm{div}_x(\mu \nabla_x \Phi) + \overline{S} - \lambda_3 \Phi, \tag{5.4}$$

coupled with the initial and boundary conditions

$$\mu = \Pi = 0, \quad \nabla_x \Phi \cdot \nu = 0 \quad \text{on } \partial\Omega \times (0,T), \tag{5.5}$$

$$\mu(0) = 0, \quad \Phi(0) = \Phi_{0\delta}, \tag{5.6}$$

has at least one solution $(\Phi, \mu, \Pi, \mathbf{u})$ satisfying the regularity properties

$$\Phi \in H^1(0,T_0;H^1(\Omega)) \cap L^\infty(0,T_0;W^{2,6}(\Omega)), \tag{5.7}$$

$$\mu \in H^1(0,T_0;H^1(\Omega)) \cap L^\infty(0,T_0;H^2(\Omega)), \tag{5.8}$$

$$\Pi \in L^8(0,T;H^2(\Omega))\,. \tag{5.9}$$

Proof. Let $T_0 \in (0,T]$ to be chosen below and let

$$\overline{\Phi} \in L^4(0,T_0;W^{1,4}(\Omega)), \quad \overline{\mu} \in L^4((0,T_0)\times\Omega),$$

with

$$\|\overline{\Phi}\|_{L^4(0,T_0;W^{1,4}(\Omega))} + \|\overline{\mu}\|_{L^4((0,T_0)\times\Omega)} \le R_1.$$

This in particular implies

$$\|\overline{\mu}\nabla_x\overline{\Phi}\|_{L^2((0,T_0)\times\Omega)} \le Q(R_1).$$

Again, $R_1 > 0$ can be chosen arbitrarily. Here and below Q is a computable positive function, monotone increasing in each of its arguments.

Replace $\overline{\Phi}$, $\overline{\mu}$ and $\overline{S}$ in equation (5.4), which becomes

$$-\Delta\Pi = -\mathrm{div}_x(\overline{\mu}\nabla_x\overline{\Phi}) + \overline{S} - \lambda_3\overline{\Phi} \tag{5.10}$$

and is still endowed with the boundary condition $\Pi = 0$. Clearly, (5.10) has one and only one solution

$$\Pi \in L^2(0,T_0;H_0^1(\Omega)). \tag{5.11}$$

Moreover,

$$\|\Pi\|_{L^2(0,T_0;H_0^1(\Omega))} \le Q(R_1,R_2).$$

Set

$$\mathbf{u} := -\nabla_x\Pi + \overline{\mu}\nabla_x\overline{\Phi} \in L^2((0,T_0)\times\Omega;\mathbb{R}^3), \tag{5.12}$$

and replace it in (5.2). Once $\mathbf{u}$ is assigned we can easily prove existence of a solution to (5.2). Note that no regularization of $\mathcal{F}$ is required. The regularity class of the solution can be formally determined multiplying (5.2) a. by μ and (5.2) b. by Φ_t. Note that

$$\left|\int_\Omega \mathbf{u}\cdot\nabla_x\Phi\mu \,\mathrm{d}x\right| \le \|\mathbf{u}\|_{L^2(\Omega;\mathbb{R}^3)}\|\mu\|_{L^4(\Omega)}\|\nabla_x\Phi\|_{L^4(\Omega;\mathbb{R}^3)}$$

$$\le c\|\mathbf{u}\|^2_{L^2(\Omega;\mathbb{R}^3)}\|\mu\|^2_{H^1(\Omega)} + c\|\Phi\|^2_{H^2(\Omega)}$$

$$\le c\|\mathbf{u}\|^2_{L^2(\Omega;\mathbb{R}^3)}\|\mu\|^2_{H^1(\Omega)} + c\|\mu\|^2_{L^2(\Omega)} + c\|\Phi\|^2_{H^1(\Omega)},$$

The last inequality follows by multiplying (5.2) b. by $\Delta\Phi$ and using the monotonicity of $\mathcal{C}'$ (cf. Subsec. 2.1). Then, we can apply Grönwall's lemma to obtain

$$\|\Phi\|_{L^\infty(0,T_0;H^1(\Omega))} + \|\mu\|_{L^\infty(0,T_0;H^1(\Omega))} \le Q(R_1,R_2,\delta^{-1},T_0).$$

Next, multiplying (5.2) a. by μ_t, the time derivative of (5.2) b. by Φ_t, and summing the results, yields

$$\|\Phi\|_{H^1(0,T_0;H^1(\Omega))} + \|\mu\|_{H^1(0,T_0;H^1(\Omega))} \le Q(R_1,R_2,\delta^{-1},T_0). \tag{5.13}$$

Note that, to deduce (5.13) in a rigorous way, it would have been necessary to regularize $\mathcal{C}$ in order for its second derivative to be well defined. However this is a standard argument and the resulting estimate would be independent of the regularization since it just relies on the monotonicity of $\mathcal{C}'$. Hence, we omit giving details. Finally, the same argument used for the complete system yields (cf. (3.11))

$$\|\Phi\|_{L^\infty(0,T_0;W^{2,6}(\Omega))} \le Q(R_1,R_2,\delta^{-1},T_0). \tag{5.14}$$

Next, multiplying (5.2) a. by $\Delta\mu$ and using (5.14), it is not difficult to arrive at

$$\|\mu\|_{L^\infty(0,T_0;H^2(\Omega))} \le Q(R_1,R_2,\delta^{-1},T_0). \tag{5.15}$$

By Sobolev's embedding this implies that there exists $C_\delta > 0$ such that

$$-C_\delta \le \mu(t,x) \le C_\delta \text{ for a.e. } (t,x) \in (0,T)\times\Omega. \tag{5.16}$$

Thanks to assumption (2.3), recalling that $\Phi_{0\delta} \in [\delta, 1-\delta]$, and applying maximum principle arguments in (5.2), we deduce the following *separation property*: there exists $\kappa_\delta > 0$ such that

$$-1 + \kappa_\delta \leq \Phi(t,x) \leq 1 - \kappa_\delta \text{ for a.e. } (t,x) \in (0,T) \times \Omega. \tag{5.17}$$

Thanks to the above separation property, we can easily prove the uniqueness of the couple (Φ, μ). We already know that, once $\overline{S}$ is given, a unique Π solving (5.10) is determined. Hence we have a unique $\mathbf{u}$ given by (5.12). Assuming that, for this $\mathbf{u}$, a couple of pairs (Φ, μ) solve (5.2), we can test the difference of (5.2) a. by the difference of the μ's and the difference of (5.2) b. by the difference of the Φ_t's. Performing standard manipulations and using the separation property (5.17) it is then easy to deduce a contractive estimate. Hence, the couple (Φ, μ) is in fact unique.

The above argument permits us to define, for the *fixed* $\overline{S}$ given by (5.1), the map

$$\mathcal{M}_1 : B_{R_1} \to L^\infty(0,T_0; W^{2,6}(\Omega)) \times L^\infty(0,T_0; H^2(\Omega)),\ \mathcal{M}_1 : (\overline{\Phi}, \overline{\mu}) \mapsto (\Phi, \mu),$$

where B_{R_1} is the closed ball of radius R_1 in the space $L^4(0,T; W^{1,4}(\Omega)) \times L^4((0,T) \times \Omega)$. We aim to apply Schauder's fixed point theorem to the above map. To this purpose, we first observe that we can take T_0 small enough so that the map takes values into B_{R_1}. Moreover, $\mathcal{M}_1$ is compact by Sobolev's embeddings. Finally, the continuity of $\mathcal{M}_1$ can be shown by standard methods relying on the a priori estimates obtained above.

Hence, by Schauder's theorem, there exists a time $T_0 \leq T$, possibly depending on δ, such that system (5.2–5.4), coupled with the initial and boundary conditions, has at least one solution $(\Phi, \mu, \Pi, \mathbf{u})$, in the interval $(0, T_0)$. The regularity of this solution is specified by (5.11), (5.13), (5.14), and (5.15). To conclude the proof, it remains to improve the regularity of $\mathbf{u}$. Since we now know that Π solves (5.4), using (5.14) and (5.15) it is easy to check that

$$\| - \operatorname{div}_x(\mu \nabla_x \Phi)\|_{L^\infty(0,T_0;L^6(\Omega))} \leq Q(R_2, \delta^{-1}, T_0).$$

Hence, recalling (5.1) and applying elliptic regularity to (5.4), we arrive at

$$\|\Pi\|_{L^8(0,T_0;H^2(\Omega))} + \|\mathbf{u}\|_{L^8(0,T_0;H^1(\Omega;\mathbb{R}^3))} \leq Q(R_2, \delta^{-1}, T_0). \tag{5.18}$$

This gives (5.9) and concludes the proof of Lemma 5.1. □

Remark 5.1. *As already noted in Remark 2.1, assumption* (2.3) *is needed only for the sake of obtaining higher regularity of approximating functions. Indeed, it would be enough to assume it to hold in the approximation (for a suitable family $\mathcal{C}_\delta$ tending to $\mathcal{C}$ as $\delta \to 0$) and not necessarily for $\mathcal{C}$.*

Lemma 5.2. *For any $\overline{S}$ as in (5.1), the quadruple* $(\Phi, \mu, \Pi, \mathbf{u})$ *solving (5.2–5.4) with the initial and boundary conditions (5.5–5.6) is* unique.

Proof. A contractive estimate can be obtained simply by multiplying the difference of (5.2) a. by the difference of the μ's, the difference of (5.2) b. by the difference of the Φ_t's, and the difference of the (5.4) by the difference of the Π's. We leave the details to the reader. We note that the separation property (5.17) and the additional regularity (5.18) play a role in this argument. □

Thanks to the above Lemmas, given $\overline{S}$, there exists a *unique* quadruple $(\Phi, \mu, \Pi, \mathbf{u})$ solving (5.2–5.4). We now plug this quadruple into (a proper regularization of) system (1.8–1.9). Namely, we have the

Lemma 5.3. *Let $\overline{S}$ as in (5.1) and let T_0, Φ, μ, Π and $\mathbf{u}$ be given by Lemma 5.1. Let $P_{0\delta} \in H^1_0(\Omega)$, $P_{0\delta} \in [0,1]$ a.e.. Then there exists one and only one couple (P, n) satisfying the system*

$$\partial_t P - \delta \Delta P + \operatorname{div}_x(\mathbf{u}P) = \Phi\big(n - \lambda_1 - \lambda_2 H(n_N - n)\big)P, \tag{5.19}$$

$$-\Delta n + nP = T_c(n, \Phi), \tag{5.20}$$

over $(0, T_0)$, together with the initial and boundary conditions specified at the beginning (with P_0 replaced by $P_{0\delta}$) and the additional condition

$$\delta P = 0 \text{ on } \partial\Omega. \tag{5.21}$$

Moreover,

$$a.\ \ P(t,x) \geq 0,\ \ b.\ \ 0 \leq n(t,x) \leq 1 \textit{ for a.e. } (t,x) \in (0,T_0) \times \Omega \tag{5.22}$$

and the following regularity properties hold

$$\|P\|_{H^1(0,T_0;L^2(\Omega))} + \|P\|_{L^\infty(0,T_0;L^2(\Omega))} + \|P\|_{L^2(0,T_0;H^2(\Omega))} \leq Q(R_2, \delta^{-1}, T_0), \tag{5.23}$$

$$\|n\|_{H^1(0,T_0;H^1(\Omega))} + \|n\|_{L^\infty(0,T_0;H^2(\Omega))} \leq Q(R_2, \delta^{-1}, T_0), \tag{5.24}$$

Proof. Let us introduce the truncation operator $\mathcal{T}(r) = \max\{0, \min\{1, r\}\}$. Plugging $\mathcal{T}$ into the right hand side of (5.19), we obtain the elliptic-parabolic system

$$\partial_t P - \delta \Delta P + \operatorname{div}_x(\mathbf{u}P) = \Phi\big(\mathcal{T}(n) - \lambda_1 - \lambda_2 H(n_N - n)\big)P, \tag{5.25}$$

$$-\Delta n + nP = T_c(n, \Phi), \tag{5.26}$$

Existence of solutions to (the initial-boundary value problem) for (5.25–5.26) is standard. For instance, one may prove it by using the Faedo-Galerkin scheme. Hence, we omit the details. Rather, we point out which are the main a priori estimates involved, with the purpose of establishing sufficient regularity properties of solutions. We will also see, as a byproduct, that the component n turns out to take values in the interval $[0,1]$ so that the couple (n,P) will in fact solve (5.19–5.20) (without truncation).

To carry out this program, we start with multiplying (5.25) by P to get

$$\begin{aligned} &\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\|P\|^2_{L^2(\Omega)} + \delta\|\nabla_x P\|^2_{L^2(\Omega;\mathbb{R}^3)} \\ &\leq \int_\Omega P\mathbf{u} \cdot \nabla_x P \ \mathrm{d}x + \int_\Omega \Phi\big(\mathcal{T}(n) - \lambda_1 - \lambda_2 H(n_N - n)\big)P^2 \ \mathrm{d}x. \end{aligned}$$

where we used condition (5.21). In view of the smoothness of Φ and the presence of the truncation operator, the only term that needs to be estimated is the first one on the right hand side. By Poincaré's and Young's inequalities, we have

$$\begin{aligned} \int_\Omega P\mathbf{u} \cdot \nabla_x P \ \mathrm{d}x &\leq \|P\|_{L^4(\Omega)}\|\mathbf{u}\|_{L^4(\Omega;\mathbb{R}^3)}\|\nabla_x P\|_{L^2(\Omega)} \\ &\leq \|P\|^{7/4}_{H^1(\Omega)}\|P\|^{1/4}_{L^2(\Omega)}\|\mathbf{u}\|_{L^4(\Omega;\mathbb{R}^3)} \\ &\leq \frac{\delta}{2}\|\nabla_x P\|^2_{L^2(\Omega)} + c_\delta\|P\|^2_{L^2(\Omega)}\|\mathbf{u}\|^8_{L^4(\Omega;\mathbb{R}^3)}. \end{aligned} \tag{5.27}$$

Hence, by (5.18) and Grönwall's Lemma, we arrive at

$$\|P\|_{L^\infty(0,T_0;L^2(\Omega))} + \|P\|_{L^2(0,T_0;H^1(\Omega))} \leq Q(R_2, \delta^{-1}, T_0). \tag{5.28}$$

Combining this relation with (5.18) we infer

$$\|\operatorname{div}_x(\mathbf{u}P)\|_{L^{8/5}(0,T_0;L^{3/2}(\Omega))} \leq Q(R_2, \delta^{-1}, T_0), \tag{5.29}$$

whence, applying parabolic regularity theory to (5.25),

$$\|P_t\|_{L^{8/5}(0,T_0;L^{3/2}(\Omega))} + \|P\|_{L^{8/5}(0,T_0;W^{2,3/2}(\Omega))} \leq Q(R_2, \delta^{-1}, T_0). \tag{5.30}$$

In turn, by interpolation, this gives

$$\|P\|_{L^{8/3}(0,T_0;W^{\frac{3}{2}-\epsilon,3/2}(\Omega))} \leq Q(R_2, \delta^{-1}, T_0, \epsilon^{-1}). \tag{5.31}$$

for all $\epsilon \in (0,1)$, whence, by Sobolev's embeddings,

$$\|P\|_{L^{8/3}(0,T_0;L^{6-\epsilon}(\Omega))} + \|\nabla_x P\|_{L^{8/3}(0,T_0;L^{2-\epsilon}(\Omega))} \leq Q(R_2, \delta^{-1}, T_0, \epsilon^{-1}). \tag{5.32}$$

Consequently, by (5.18),

$$\|\mathrm{div}_x(\mathbf{u}P)\|_{L^2(0,T_0;L^{\frac{3}{2}-\epsilon}(\Omega))} \le Q(R_2,\delta^{-1},T_0,\epsilon^{-1}), \tag{5.33}$$

whence, going back to (5.25),

$$\|P_t\|_{L^2(0,T_0;L^{\frac{3}{2}-\epsilon}(\Omega))} + \|P\|_{L^2(0,T_0;W^{2,\frac{3}{2}-\epsilon}(\Omega))} \le Q(R_2,\delta^{-1},T_0,\epsilon^{-1}). \tag{5.34}$$

We proceed by bootstrapping. Actually, some more iterations (whose details are omitted for brevity) permit us to obtain (5.23). Once sufficient regularity is achieved, the same maximum principle argument used for the coupled system gives (5.22) a.

We now pass to equation (5.26). By elliptic regularity (i.e., multiplying by $n-1\in H^1_0(\Omega)$), we infer

$$\|n\|_{L^2(0,T_0;H^1(\Omega))} \le Q(R_2,\delta^{-1},T_0). \tag{5.35}$$

Next, using, as for the complete system, the sign condition on the right hand side, we get the second (5.22). This entails in particular that P solves (5.19), i.e., no truncation in fact occurs.
By (5.28), (5.22), and elliptic regularity, it follows that

$$\|n\|_{L^\infty(0,T_0;H^2(\Omega))} \le Q(R_2,\delta^{-1},T_0). \tag{5.36}$$

Now, we differentiate (5.20) in time. Recalling (1.11) we have

$$\begin{aligned} -\Delta n_t + n_t P + nP_t = &- [\nu_1(1-Q(\Phi)) + \nu_2 Q(\Phi)]\, n_t \\ &+ [-\nu_1 Q'(\Phi) + \nu_2 Q'(\Phi)]\, \Phi_t (n_c - n). \end{aligned} \tag{5.37}$$

Test the above relation by n_t and use the regularity given by (5.13) and (5.23) together with the second (5.22) and the positivity of the given term $[\nu_1(1-Q(\Phi))+\nu_2 Q(\Phi)]$, to obtain

$$\|n_t\|_{L^2(0,T_0;H^1(\Omega))} \le Q(R_2,\delta^{-1},T_0). \tag{5.38}$$

This, combined with (5.36), yields (5.24). Finally, we have to prove uniqueness of the solution (n,P). This in fact follows from a standard argument. Indeed, it is sufficient to test the difference of (5.19) by the difference of the P's and the difference of (5.20) by the difference of the n. Then, the transport term in (5.19) is treated in a way similar to (5.27), whereas the right hand side of (5.20) is easily controlled in view of the high regularity of Φ and of the sign condition. This concludes the proof of the lemma. □

We can now finalize our fixed point argument for the complete system.

Theorem 5.1. *Let $\delta\in(0,1/4)$, $\Phi_{0\delta}\in W^{2,6}(\Omega)$, $\Phi_{0\delta}\in[\delta,1-\delta]$, $P_{0\delta}\in H^1_0(\Omega)$, $P_{0\delta}\in[0,1]$ a.e.. Then there exists $T_1\in(0,T]$ possibly depending on δ such that the system*

$$\partial_t\Phi - \delta\Delta\mu_t + \mathbf{u}\cdot\nabla_x\Phi - \Delta\mu = 0, \quad \mu = -\Delta\Phi + \mathcal{F}'(\Phi), \tag{5.39}$$

$$\mathbf{u} = -\nabla_x\Pi + \mu\nabla_x\Phi, \tag{5.40}$$

$$-\mathrm{div}_x\mathbf{u} = S_T = nP - \lambda_3(\Phi - P), \tag{5.41}$$

$$\partial_t P - \delta\Delta P + \mathrm{div}_x(\mathbf{u}P) = \Phi\big(n - \lambda_1 - \lambda_2 H(n_N - n)\big)P, \tag{5.42}$$

$$-\Delta n + nP = T_c(n,\Phi), \tag{5.43}$$

coupled with the initial and boundary conditions (1.12–1.14) (with $\Phi_{0\delta}$ and $P_{0\delta}$ replacing Φ_0 and P_0) and (5.21), has at least one solution $(\Phi,\mu,\mathbf{u},P,n)$ defined over the time interval $(0,T_1)$ and satisfying the regularity properties (5.7–5.8), (5.18), (5.23–5.24).

Proof. We let $\overline{S}$ be as in (5.1), where the choice of $R_2 \geq 0$ is in fact arbitrary. Then, applying first Lemmas 5.1, 5.2 and then Lemma 5.3 we obtain a *unique* quintuple $(\Phi, \mu, \mathbf{u}, P, n)$. Thus, we can consider the map

$$\mathcal{M}_2 : \overline{S} \mapsto S := nP + \lambda_3 P. \tag{5.44}$$

In view of (5.23), (5.24) and Sobolev's embeddings, it is easy to check that

$$\|S\|_{L^\infty(0,T_0;L^2(\Omega))} \leq Q(R_2, \delta^{-1}, T_0), \tag{5.45}$$

In particular, we can choose $T_1 \in (0, T_0]$ such that S lies in the closed ball B_{R_2} of $L^8(0, T_1; L^2(\Omega))$. Moreover, continuity and compactness of the map $\mathcal{M}_2$ in the topology of $L^8(0, T_1; L^2(\Omega))$ are an easy consequence of the regularity properties (5.23), (5.24), the Lions-Aubin theorem, and the a priori estimates in Lemmas 5.1, 5.3. Hence we can apply once more Schauder's theorem to $\mathcal{M}_2$, which gives that

$$\overline{S} = S = nP + \lambda_3 P \text{ in } (0,T) \times \Omega. \tag{5.46}$$

Hence, (5.3–5.4) reduce to (1.6–1.7), where S_T is given by (1.10). This concludes the proof of the theorem. □

In order to complete the proof of Theorem 2.1, we need now to pass to the limit in the regularized system as $\delta \searrow 0$, assuming of course that $\Phi_{0\delta} \to \Phi_0$ and $P_{0\delta} \to P_0$ in suitable ways. We just briefly comment on the most delicate part of this step, which consists in the passage to the limit in (5.42) in order to recover (2.18). The other parts are indeed standard since it can be immediately seen that the a-priori estimates performed in Section 3 are still valid on the regularized system and they turn out to be also independent of δ.

Taking a test function φ as in (2.18) we multiply (5.42) by φ to obtain

$$\int_0^T \int_\Omega \left[P\partial_t\varphi + P\mathbf{u}\cdot\nabla_x\varphi + \Phi\left(n - \lambda_1 - \lambda_2 H(n_N - n)\right)\varphi \right] \,\mathrm{d}x\,\mathrm{d}t \tag{5.47}$$

$$= \delta \int_0^T \int_\Omega \nabla_x P \cdot \nabla_x \varphi \,\mathrm{d}x\,\mathrm{d}t - \int_\Omega P_0\varphi(0,\cdot)\,\mathrm{d}x + \int_0^T \int_{\partial\Omega} P\mathbf{u}\cdot\mathbf{n}\varphi \,\mathrm{dS}_x$$

$$-\delta \int_0^T \int_{\partial\Omega} \nabla_x P \cdot \mathbf{n}\varphi \,\mathrm{dS}_x,$$

where, as

$$P|_{\partial\Omega} = 0, \ P \geq 0 \text{ in } (0,T)\times\Omega,$$

$$\int_0^T \int_{\partial\Omega} P\mathbf{u}\cdot\mathbf{n}\varphi \,\mathrm{dS}_x = 0, \ -\delta \int_0^T \int_{\partial\Omega} \nabla_x P \cdot \mathbf{n}\varphi \,\mathrm{dS}_x \geq 0.$$

Letting $\delta \searrow 0$ in (5.47) we get (2.18).

Finally, let us notice that, by standard arguments, it is possible to show that the a priori estimates provide an extension of the local approximate solution up to the original final time T. Hence, in particular we have a global solution in the limit. This concludes the proof of Theorem 2.1.

6 Singular limit

In this section, we consider the problem obtained from (1.5–1.9) by taking $S_T = S_D = 0$. Hence we just consider the system of equations for Φ and $\mathbf{u}$, decoupled from the rest, of the form

$$\partial_t\Phi + \mathrm{div}_x(\mathbf{u}\Phi) - \mathrm{div}_x(\nabla_x\mu) = 0, \ \mu = -\varepsilon^2\Delta\Phi + \mathcal{F}'(\Phi), \tag{6.1}$$

$$\mathbf{u} = -\nabla_x\Pi + \mu\nabla_x\Phi, \tag{6.2}$$

$$\mathrm{div}_x\mathbf{u} = 0, \tag{6.3}$$

with the boundary conditions

$$\mathbf{u}\cdot\mathbf{n}|_{\partial\Omega} = 0, \ \nabla_x\Phi\cdot\mathbf{n}|_{\partial\Omega} = 0, \ \mu|_{\partial\Omega} = 0. \tag{6.4}$$

Notice that, in particular, we are considering here a no-flux condition for Π in place of the Dirichlet condition in (1.12).

Similarly to Section 3.4, we derive the energy balance

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega\left[\frac{\varepsilon^2}{2}|\nabla_x\Phi|^2+\mathcal{F}(\Phi)\right]\,\mathrm{d}x+\int_\Omega|\nabla_x\mu|^2+|\mathbf{u}|^2\,\mathrm{d}x=0. \tag{6.5}$$

Next,

$$\int_\Omega\left[\varepsilon^2|\Delta\Phi|^2+\mathcal{F}''(\Phi)|\nabla_x\Phi|^2\right]\,\mathrm{d}x=\int_\Omega\nabla_x\mu\cdot\nabla_x\Phi\,\mathrm{d}x.$$

Then, assuming strict convexity of $\mathcal{F}$, namely

$$\mathcal{F}''\geq\lambda>0, \tag{6.6}$$

the following estimates can be deduced

$$\int_0^T\|\varepsilon\Delta\Phi\|^2_{L^2(\Omega)}\,\mathrm{d}t\leq c,\ \int_0^T\|\nabla_x\Phi\|^2_{L^2(\Omega;\mathbb{R}^3)}\,\mathrm{d}t\leq c. \tag{6.7}$$

6.1 Compactness of the velocity

In view of (6.5) we may assume there is a subsequence such that

$$\mathbf{u}_\varepsilon\to\mathbf{u}\text{ weakly in }L^2((0,T)\times\Omega;\mathbb{R}^3).$$

Obviously,

$$\mathrm{div}_x\mathbf{u}=0,\ \mathbf{u}\cdot\mathbf{n}|_{\partial\Omega}=0. \tag{6.8}$$

We can now write

$$\mathbf{u}_\varepsilon=-\nabla_x\left(\Pi_\varepsilon-\mathcal{F}(\Phi_\varepsilon)\right)-\varepsilon^2\Delta\Phi_\varepsilon\nabla_x\Phi_\varepsilon;$$

whence, seeing that

$$\varepsilon^2\Delta\Phi_\varepsilon\nabla_x\Phi_\varepsilon\to0\text{ in }L^1((0,T)\times\Omega),$$

we conclude that

$$\mathbf{curl}_x\mathbf{u}=0,$$

which, combined with (6.8), yields

$$\mathbf{u}=0.$$

Therefore, taking $\varepsilon\to0$, system (6.1)–(6.3) converges to

$$\partial_t\Phi-\Delta\mu=0,\qquad\mu=\mathcal{F}'(\Phi), \tag{6.9}$$

which satisfies the energy law

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega\mathcal{F}(\Phi)\,\mathrm{d}x+\int_\Omega|\nabla_x\mu|^2\,\mathrm{d}x=0. \tag{6.10}$$

Summarizing, we have proved the

Theorem 6.1. *Let the assumptions given in Subsec. 2.1 hold, let $\mathcal{F}$ satisfy* (6.6)*, and let $(\Phi_\varepsilon,\mu_\varepsilon,\mathbf{u}_\varepsilon)$ denote a family of weak solutions to the system (6.1–6.3) complemented with the boundary conditions* (6.4) *and the Cauchy conditions. Then, as $\varepsilon\to0$, the functions $(\Phi_\varepsilon,\mu_\varepsilon,\mathbf{u}_\varepsilon)$ suitably tend to a triple $(\Phi,\mu,0)$ satisfying* (6.9) *together with the energy equality* (6.10) *and the initial and boundary conditions.*

Remark 6.1. *It would be interesting to investigate whether similar estimates could be derived for the singular flux*

$$\mathbf{u}=-\nabla_x\Pi+\frac{1}{\varepsilon}\mu\nabla_x\Phi.$$

However, the above argument does not seem to be easily adaptable to cover such a situation. For instance, we cannot prove uniform integrability of the product

$$\varepsilon\Delta\Phi\nabla_x\phi$$

in that case.

7 Acknowledgements

The research of E.F. leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ ERC Grant Agreement 320078. The Institute of Mathematics of the Academy of Sciences of the Czech Republic is supported by RVO:67985840. The work of E.R. and of G.S. was supported by the FP7-IDEAS-ERC-StG Grant #256872 (EntroPhase), by GNAMPA (Gruppo Nazionale per l'Analisi Matematica, la Probabilità e le loro Applicazioni) of INdAM (Istituto Nazionale di Alta Matematica), and by IMATI – C.N.R. Pavia.

References

[1] R.P. Araujo, D.L.S. McElwain, A History of the study of solid tumour growth: the contribution of mathematical modelling, Bull. Math. Biol. **66** (2004), 1039–1091.

[2] H.A. Byrne, T. Alarcón, M. Owen, S. Webb, P. Maini, Modeling aspects of cancer dynamics: a review, Philos. Trans. R. Soc. Lond. Ser. A Math. Phys. Eng. Sci. **364** (2006), 1563–1578.

[3] Y. Chen, S.M. Wise, V.B. Shenoy, J.S. Lowengrub, A stable scheme for a nonlinear, multiphase tumor growth model with an elastic membrane, Int. J. Numer. Methods Biomed. Eng. **30** (2014), 726–754.

[4] P. Colli, G. Gilardi, D. Hilhorst, On a Cahn-Hilliard type phase field system related to tumor growth, Discrete Contin. Dyn. Syst. **35** (2015), 2423–2442.

[5] P. Colli, G. Gilardi, E. Rocca, 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.

[6] P. Colli, G. Gilardi, E. Rocca, J. Sprekels, Asymptotic analyses and error estimates for a Cahn-Hilliard type phase field system modelling tumor growth, arXiv:1503.00927v1 (2015), 1–19, DCDS-S issue from the STAMM in Poitiers, to appear (2015).

[7] V. Cristini, J. Lowengrub, Multiscale modeling of cancer. An Integrated Experimental and Mathematical Modeling Approach, Cambridge Univ. Press, Cambridge, 2010.

[8] A. Fasano, A. Bertuzzi, A. Gandolfi, Mathematical modeling of tumour growth and treatment. Complex Systems in Biomedicine, Springer, Milan, 71–108, 2006.

[9] A. Friedman, Mathematical analysis and challenges arising from models of tumor growth, Math. Models Methods Appl. Sci. **17** (2007), 1751–1772.

[10] S. Frigeri, M. Grasselli, E. Rocca, On a diffuse interface model of tumor growth, European J. Appl. Math. **26** (2015), 215–243.

[11] V. Girault, P.-A. Raviart, Finite element methods for Navier-Stokes equations. Theory and algorithms, Springer Series in Computational Mathematics, 5. Springer-Verlag, Berlin, 1986.

[12] A. Hawkins-Daarud, K.G. van der Zee, J.T. Oden, Numerical simulation of a thermodynamically consistent four-species tumor growth model, Int. J. Numer. Meth. Biomed. Engng. **28** (2011), 3–24.

[13] J. Lowengrub, E. Titi, K. Zhao, Analysis of a mixture model of tumor growth, European J. Appl. Math. **24** (2013), 1–44.

[14] J.T. Oden, E.E. Prudencio, A. Hawkins-Daarud, Selection and assessment of phenomenological models of tumor growth, Math. Models Methods Appl. Sci. **23** (2013), 1309–1338.

[15] X. Wang, H. Wu, Long-time behavior for the Hele-Shaw-Cahn-Hilliard system, Asymptot. Anal. **78** (2012), 217–245.

[16] X. Wang, Z. Zhang, Well-posedness of the Hele-Shaw-Cahn-Hilliard system, Ann. Inst. H. Poincaré Anal. Non Linéaire, **30** (2013), 367–384.

[17] S.M. Wise, J.S. Lowengrub, V. Cristini, An adaptive multigrid algorithm for simulating solid tumor growth using mixture models, Math. Comput. Modelling **53** (2011), 1–20.

[18] S.M. Wise, J.S. Lowengrub, H.B. Frieboes, V. Cristini, Three-dimensional multispecies nonlinear tumor growth-I: Model and numerical method, J. Theoret. Biol. **253** (2008), 524–543.

[19] X. Wu, G.J. van Zwieten, K.G. van der Zee, Stabilized second-order convex splitting schemes for Cahn-Hilliard models with applications to diffuse-interface tumor-growth models, Int. J. Numer. Meth. Biomed. Engng. **30** (2014), 180–203.