On the long time behavior of a tumor growth model

Alain Miranville
Laboratoire de Mathématiques et Applications
UMR CNRS 7348, Equipe DACTIM-MIS
Université de Poitiers - SP2MI
Boulevard Marie et Pierre Curie
F-86962 Chasseneuil Futuroscope Cedex, France
Fudan University (Fudan Fellow), Shanghai, China
Xiamen University
School of Mathematical Sciences
Xiamen, Fujian, China
E-mail: Alain.Miranville@math.univ-poitiers.fr

Elisabetta Rocca
Dipartimento di Matematica, Università di Pavia, and IMATI - C.N.R.,
Via Ferrata 5, 27100 Pavia, Italy
E-mail: elisabetta.rocca@unipv.it

Giulio Schimperna
Dipartimento di Matematica, Università di Pavia, and IMATI - C.N.R.,
Via Ferrata 5, 27100 Pavia, Italy
E-mail: giusch04@unipv.it

October 30, 2018

Abstract

We consider the problem of the long time dynamics for a diffuse interface model for tumor growth. The model describes the growth of a tumor surrounded by host tissues in the presence of a nutrient and consists in a Cahn-Hilliard-type equation for the tumor phase coupled with a reaction-diffusion equation for the nutrient concentration. We prove that, under physically motivated assumptions on parameters and data, the corresponding initial-boundary value problem generates a dissipative dynamical system that admits the global attractor in a proper phase space.

Key words: Tumor growth; cancer treatment; phase field model; Cahn–Hilliard equation; reaction-diffusion equation; initial-boundary value problem; well-posedness; dissipativity; global attractor.

AMS (MOS) subject classification: 35D30; 35K57; 35Q92; 35B41; 37L30; 92C17

1 Introduction

One of the main examples of complex systems studied nowadays both in the biomedical and in the mathematical literature refers to tumor growth processes. In particular, there has been a recent surge in the development of phase field models for tumor growth. These models aim to describe the evolution of a tumor mass surrounded by healthy tissues by taking into account biological mechanisms such as proliferation of cells via nutrient consumption, apoptosis, chemotaxis and active transport of specific chemical species. In particular, we will consider here a model that fits into the framework of diffuse interface models for tumor growth. In this setting the evolution of the tumor is described by means of an order parameter \( \varphi \) that represents the local concentration of tumor cells; the interface between
the tumor and healthy cells, rather than being represented as a surface, is seen as a (narrow) layer separating the regions where $\varphi = \pm 1$, with $\varphi = 1$ denoting the tumor phase and $\varphi = -1$ the healthy phase. Note that in the case of an incipient tumor, i.e., before the development of quiescent cells, the representation of the tumor growth process is often given by a Cahn–Hilliard equation \cite{4} for $\varphi$ coupled with a reaction-diffusion equation for the nutrient $\sigma$ (cf., e.g., \cite{9,19,20,22}). We will consider here this type of situation; we just mention the fact that more sophisticated models may distinguish between different tumor phases (e.g., proliferating and necrotic), or, treating the cells as inertia-less fluids, include the effects of fluid flow into the evolution of the tumor, leading to (possibly multiphase) Cahn-Hilliard-Darcy systems \cite{8,15,31}.

In this work, our main purpose is to consider the long time dynamics of a Cahn-Hilliard-reaction-diffusion tumor growth model recently introduced in \cite{19}. On the other hand, in comparison with \cite{19}, we have neglected here the effects of chemotaxis and active transport (a more complete model including these effects may be the topic of a future work). Namely, we consider the following PDE system:

\begin{align}
\varphi_t - \Delta \mu &= (P\sigma - A)h(\varphi), \\
\mu &= -\Delta \varphi + \psi'(\varphi), \\
\sigma_t - \Delta \sigma &= -C\sigma h(\varphi) + B(\sigma_s - \sigma),
\end{align}

settled in $\Omega \times (0, +\infty)$, $\Omega$ being a smooth domain of $\mathbb{R}^3$, and complemented with the Cauchy conditions and with no-flux (i.e., homogeneous Neumann) boundary conditions for all unknowns. As already mentioned, $\varphi$ represents the tumor phase concentration, $\sigma$ is the concentration of a nutrient for the tumor cells (such as oxygen or glucose), and $\mu$ is the chemical potential of the “phase transition” from healthy to tumor cells. The parameters $P, A, B, C$ are assumed to be strictly positive constants, $\sigma_s \in (0, 1)$, and, in order to ensure dissipativity, some compatibility conditions will be needed (cf. Assumption \ref{assumption} below and Subsection \ref{subsec} for a detailed explanation of the effects of such conditions). More specifically, in applications, $P$ denotes the proliferation rate, $A$ the apoptosis rate, $C$ the nutrient consumption rate, and $B$ the nutrient supply rate. The term $P\sigma h(\varphi)$ models the proliferation of tumor cells which is proportional to the concentration of the nutrient, the term $Ah(\varphi)$ describes the apoptosis of tumor cells, and $C\sigma h(\varphi)$ models the consumption of the nutrient by the tumor cells. The constant $\sigma_s$ denotes the nutrient concentration in a pre-existing vasculature, and $B(\sigma_s - \sigma)$ models the supply of nutrient from the blood vessels if $\sigma_s > \sigma$ and the transport of nutrient away from the domain $\Omega$ if $\sigma_s < \sigma$. Moreover, $\psi'$ stands for the derivative of a double-well potential $\psi$ and $h$ is a smooth proliferation function. A typical example of potential, meaningful in view of applications, has the expression

$$\psi_{reg}(r) = \frac{1}{4}(r^2 - 1)^2, \quad r \in \mathbb{R},$$

but we may observe that in our analysis we can allow for more general regular potentials having at least cubic and at most exponential growth at infinity. Hence, the polynomial potentials normally associated to the Cahn-Hilliard energy are also admissible here. On the other hand, we may not consider here the so-called singular potentials, e.g. of logarithmic type, that are also popular in connection with Cahn-Hilliard-based models (see, e.g., \cite{26}, cf. also \cite{13} for an application of logarithmic potentials to multiphase tumor growth models).

Let us now give, without any claim of completeness, a short overview of the recent mathematical literature on diffuse-interface tumor growth models. Modeling tumor growth dynamics has recently become a major issue in applied mathematics (see, e.g., \cite{11,8,31}). Numerical simulations of diffuse interface models for tumor growth have been carried out in several papers (see, e.g., \cite{8} Ch. 8); nonetheless, a rigorous mathematical theory of the related systems of PDEs is still at its beginning and many important problems are still open. We may quote \cite{5,6,7,10,11,12,13,15,10} as mathematical references for Cahn-Hilliard-type models and \cite{5,14,23,24} 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. \cite{17,19}); moreover in some cases the sharp interface limits of such models have been investigated generally by using formal asymptotic methods. Rigorous sharp
interface limits have been however obtained in some special cases (see, e.g., the two recent works \[25, 29\]).

On the other hand, the problem of characterizing the long time behavior of solutions to tumor growth models is still in its infancy. Up to our knowledge, the only reference available to date for Cahn-Hilliard-reaction-diffusion models is the work \[11\], where existence of the global attractor is proved in a phase space characterized by an a priori bound on the physical energy. However, the model considered in \[11\] has some notable differences with respect to the present one (cf. \[20\] and see also \[22, 32\]). In particular, in \[11\] the right-hand sides of \((1.1)\) and \((1.3)\) contain the chemical potential \(\mu\) and this type of coupling implies that a total energy balance can actually be proved.

In this work, we prove the dissipativity of the system and the existence of a global attractor for the dynamical system generated by solutions of the initial-boundary value problem for \((1.1)-(1.3)\) taking values in the natural phase space which basically consists of the pairs \((\varphi, \sigma)\) having finite physical energy (cf. \[22,28\] below). The main mathematical difficulty in the proof stands in establishing the dissipativity of the dynamical process, i.e., existence of a uniformly absorbing set. Indeed, differently from standard Cahn-Hilliard models, here the spatial mean of \(\varphi\) (i.e., the total mass of the tumor) is not conserved in time, but the tumor may grow or shrink in a way that is essentially prescribed by the right-hand side of \((1.1)\) which can be seen as a source of tumor mass. It is then clear that, if this right-hand side remains, say, positive for large values of \(\varphi\), then the mass of \(\varphi\) may grow indefinitely and there can be no absorbing set. For this reason, dissipativity is only expected to hold under suitable compatibility conditions between the proliferation function \(h\) and the various coefficients \(A, B, C, P, \sigma\). Roughly speaking these conditions (which are thoroughly discussed below, see for instance Remark \[29\]) prescribe that, for large positive (negative) values of \(\varphi\), the right-hand side of \((1.1)\) must become negative (respectively, positive) in such a way that the tumor concentration is forced to remain bounded in the \(L^\infty\)-norm uniformly for large values of the time variable. For this reason we need to assume in particular that, at least for \(\varphi👀\, -1\), \(h(\varphi)\) stays strictly negative (and not equal to 0 as was generally assumed in former contributions); otherwise we cannot prove a uniform bound from below on \(\varphi\). We finally observe that, in view of our choice of no-flux boundary conditions, spatially homogeneous solutions exist. Their behavior is analyzed in Subsection \[4.4\] by means of simple ODE techniques and in particular this gives further evidence of the fact that in absence of compatibility conditions on the coefficients, dissipativity of the process may fail.

The paper is organized as follows: in the next section, we list our assumptions on the coefficients and data, state the problem in a precise form and present our main results. Then, the last section is devoted to the corresponding proofs and to a discussion on the mentioned compatibility conditions and on the behavior of spatially homogeneous solutions.

## 2 Main results

We let \(\Omega\) be a smooth bounded domain of \(\mathbb{R}^3\) with boundary \(\Gamma\). For simplicity, but with no loss of generality, we assume \(|\Omega| = 1\). We set \(H := L^2(\Omega)\) and \(V := H^1(\Omega)\). We will use the same symbols \(H\) and \(V\) for denoting vector valued functions (we may write, for instance, \(\nabla \varphi \in H\)). The standard scalar product in \(H\) will be noted as \((\cdot, \cdot)\). Since the immersion \(V \subset H\) is continuous and dense, identifying \(H\) with its topological dual \(H'\) through the above scalar product we obtain the Hilbert triplet \((V, H, V')\).

The duality pairing between a generic Banach space \(X\) and its dual \(X'\) will be generally noted as \((\cdot, \cdot)\).

We let \(R\) denote a weak form of the Laplace operator with Neumann boundary conditions. Namely, we set

\[
R : V \rightarrow V', \quad (Rv, z) := \int_{\Omega} \nabla v \cdot \nabla z \, dx. \tag{2.1}
\]

For a generic function (or functional) \(v\) defined over \(\Omega\), we will note its spatial mean value as

\[
v_\Omega := \frac{1}{|\Omega|}(v, 1) = (v, 1), \tag{2.2}
\]

the latter equality holding since \(|\Omega| = 1\). For, say, \(v \in V'\), the above holds replacing scalar products with duality pairings. We also recall the Poincaré-Wirtinger inequality

\[
\|v - v_\Omega\| \leq c_\Omega \|
\nabla v\| \quad \forall v \in V. \tag{2.3}
\]
Next, for any $\zeta \in V'$ we set
\[ V'_0 := \{ \zeta \in V' : \zeta_\Omega = 0 \}, \quad V_0 := V \cap V'_0. \] (2.4)

The above notation $V'_0$ is suggested just for the sake of convenience; indeed, we mainly see $V_0$, $V'_0$ as (closed) subspaces of $V$, $V'$, inheriting their norms, rather than as a pair of spaces in duality.

Clearly, $R$ maps $V$ onto $V'_0$ and its restriction to $V_0$ is an isomorphism of $V_0$ onto $V'_0$. We denote by $N : V'_0 \to V_0$ the inverse of $R$, so that for any $u \in V$ and $\zeta \in V'_0$ there holds
\[ \langle Ru, N\zeta \rangle = \langle RN\zeta, u \rangle = \langle \zeta, u \rangle. \] (2.5)

We can now introduce a set of assumptions on the coefficients and data that will be kept for the rest of the paper, noting that some results will in fact require more specific conditions.

**Assumption 2.1.** The coefficients are assumed to satisfy
\[ P, A, B, C > 0, \quad \sigma_\epsilon \in (0, 1). \] (2.6)

The configuration potential $\psi$ lies in $C^{1,1}_{\text{loc}}(\mathbb{R})$. Moreover its derivative is decomposed as a sum of a monotone part $\beta$ and a linear perturbation:
\[ \psi'(r) = \beta(r) - \lambda r, \quad \lambda \geq 0, \quad r \in \mathbb{R}. \] (2.7)

The monotone part $\beta$ is normalized so that $\beta(0) = 0$ and further complies with the growth condition
\[ \exists c_\beta > 0 : \quad |\beta(r)| \leq c_\beta(1 + \psi(r)) \quad \forall r \in \mathbb{R}, \] (2.8)

which is more or less equivalent to asking $\psi$ to have at most an exponential growth at infinity. It will also be convenient to indicate by $\hat{\beta}$ the antiderivative of $\beta$ such that $\hat{\beta}(0) = 0$. It then follows that $\hat{\beta}$ takes only nonnegative values; moreover, from (2.7), it turns out that $\psi(r) = \hat{\beta}(r) - \lambda r^2/2 + K$ for all $r \in \mathbb{R}$, where $K$ is an integration constant which, thanks to (2.8), can be chosen in such a way that $\min \psi = 0$. In order to avoid degenerate situations (such as $\beta = \psi \equiv 0$, $\lambda = 0$) we also ask a minimal growth condition at infinity for $\psi$, i.e. that
\[ \liminf_{|r| \to \infty} \frac{\psi(r)}{|r|} =: \ell \in (0, +\infty] \] (2.9)

Only for the sake of proving uniqueness, condition (2.8) has to be slightly reinforced: we ask that there exists $c > 0$ such that
\[ |\beta(r) - \beta(s)| \leq c|r - s|(1 + |\beta(r)| + |\beta(s)|) \quad \forall r, s \in \mathbb{R}. \] (2.10)

Note that this is still consistent with having at most an exponential growth of $\beta$. Next, we assume that $h$ is in $C^1(\mathbb{R})$, increasingly monotone and it satisfies at least $h(-1) = 0$ and $h(r) \equiv 1$ for all $r \geq 1$. Moreover, we ask that there exist $\underline{h} \geq 0$ and $\underline{\varphi} \leq -1$ such that $h(r) = -\underline{h}$ for all $r \leq \underline{\varphi}$. Note that, as a consequence, $h$ is globally Lipschitz continuous. Finally, we assume the initial data to satisfy
\[ \sigma_0 \in L^\infty(\Omega), \quad 0 \leq \sigma_0 \leq 1 \quad \text{a.e. in } \Omega, \] (2.11)
\[ \varphi_0 \in V, \quad \psi(\varphi_0) \in L^1(\Omega). \] (2.12)

We note that the second condition in (2.11) is not strictly necessary for proving existence. On the other hand, it makes sense to assume it in view of the physical interpretation of $\sigma$ as a nutrient concentration.

**Remark 2.2.** The simplest situation of a function $h$ satisfying the above assumption is given by the “symmetric” case corresponding to $\underline{h} = 0$ and $\underline{\varphi} = -1$. On the other hand we will see in what follows that dissipativity of trajectories may not hold in such a case. This motivates our choice to consider the possibility of having $\underline{h} > 0$. 

4
Remark 2.3. As mentioned in the introduction, it would also be significant to consider the case when $h(\varphi) = k\varphi + h_0(\varphi)$, where $k > 0$ and $h_0$ is smooth and uniformly bounded; namely, $h$ is decomposed as a main linear part plus a bounded perturbation. This situation is somehow simpler because, at least as long as we can guarantee that $P_\sigma - A < 0$, the linear part of $h$ drives some mass dissipation effect in $P_\sigma$.

Remark 2.4. As will be clear in a while when we discuss dissipativity, condition (2.12) corresponds to finiteness of the initial value of the “physical” energy (cf. (2.27) below). In particular, if $\psi$ grows at infinity as a polynomial of (possibly large) degree $p$, then the latter of (2.12) essentially prescribes that $\varphi_0 \in L^p(\Omega)$.

Remark 2.5. An explicit expression of a potential satisfying our hypotheses and having very slow (linear) growth at infinity is the following:

$$
\psi(r) = \begin{cases} 
\frac{1}{2} - r^2 & \text{if } |r| \leq \frac{1}{2}, \\
(r-1)^2 & \text{if } r \in \left(\frac{1}{2}, 2\right), \\
(r+1)^2 & \text{if } r \in \left(-2, -\frac{1}{2}\right), \\
2|r| - 3 & \text{if } |r| \geq 2.
\end{cases}
$$

Then, the conditions in Assumption 2.1 are satisfied with $\lambda = \ell = 2$. On the other hand, we will see below that a potential like that in (2.13) is not suitable for having dissipativity, which seems to require a faster than cubic (but at most exponential) growth rate at infinity. This growth rate is satisfied, for instance, by the standard double-well potential (1.4).

We are now ready to introduce our basic concept of weak solution:

Definition 2.6. We say that a triplet $(\varphi, \mu, \sigma) : (0, \infty) \times \Omega \to \mathbb{R}^3$ is a global weak solution to the tumor-growth model if the following conditions are satisfied:

(a) for every $T > 0$, there hold the regularity properties

$$
\varphi \in H^1(0, T; V') \cap C^0([0, T]; V) \cap L^2(0, T; H^2(\Omega)),
$$

$$
\beta(\varphi) \in L^2(0, T; H),
$$

$$
\mu \in L^2(0, T; V),
$$

$$
\sigma \in H^1(0, T; V') \cap C^0([0, T]; H) \cap L^2(0, T; V) \cap L^\infty(0, T; L^\infty(\Omega));
$$

(b) equations (1.1) - (1.3) are satisfied in the following weak sense:

$$
\varphi_t + R\mu = (P_\sigma - A)h(\varphi) \quad \text{in } V', \quad \text{a.e. in } (0, \infty),
$$

$$
\mu = R\varphi + \psi'(\varphi) \quad \text{in } H, \quad \text{a.e. in } (0, \infty),
$$

$$
\sigma_t + R\sigma = -C_\sigma h(\varphi) + B(\sigma_s - \sigma) \quad \text{in } V', \quad \text{a.e. in } (0, \infty);
$$

(c) there hold, a.e. in $\Omega$, the initial conditions

$$
\varphi|_{t=0} = \varphi_0, \quad \sigma|_{t=0} = \sigma_0.
$$

Note that the homogeneous Neumann boundary conditions are now incorporated in the equations by definition of the operator $R$ (cf. (2.1)). Observe also that (2.19) could in fact be interpreted as a pointwise relation (complemented with an explicit boundary condition) thanks to the regularity (2.14).

Our first result is devoted to proving well-posedness in the class of weak solutions:

Theorem 2.7. Let Assumption 2.1 hold. Then the tumor-growth model admits one and only one global in time weak solution in the sense of Definition 2.6. Moreover, for any $T > 0$ there exists $\overline{\varphi}_T \geq 1$ such that

$$
0 \leq \sigma(t, x) \leq \overline{\varphi}_T, \quad \text{for a.e. } (t, x) \in (0, T) \times \Omega,
$$

where we can take $\overline{\varphi}_T$ independent of time if $B - C_L h > 0$ and, in particular, $\overline{\varphi}_T = 1$ if $h = 0$. 

5
It is worth observing that existence and uniqueness hold without assuming any compatibility conditions on the parameters $P, A, B, C, \sigma$. On the other hand, as far as one wants to prove dissipativity of the dynamical process associated to weak solutions, it seems necessary to take more restrictive assumptions. Note, for instance, that (2.22) may allow the $L^\infty$-norm of $\sigma$ to increase in time. Hence, we introduce a new

**Assumption 2.8.** Let the parameters satisfy

\[ h > 0, \quad B - Ch > 0, \quad (2.23) \]
\[ \frac{B \sigma_s}{B - Ch} < 1, \quad (2.24) \]
\[ A - P \frac{B \sigma_s}{B - Ch} > 0. \quad (2.25) \]

Let also $\beta$ have a superquadratic behavior at infinity, namely

\[ \exists \kappa_\beta > 0, C_\beta \geq 0, p_\beta > 2 : \quad \beta(r) \text{sign } r \geq \kappa_\beta |r|^{p_\beta} - C_\beta \quad \forall r \in \mathbb{R}. \quad (2.26) \]

**Remark 2.9.** We remark that (2.23)-(2.24) essentially prescribe $h$ to be strictly positive, but small. The reason for such a condition will be clarified below.

Our next result is actually devoted to proving that, if both Assumptions 2.1 and 2.8 hold, then weak solutions eventually lie in a bounded absorbing set in a proper phase space. To define the latter, we introduce the usual Cahn-Hilliard energy functional

\[ E(\varphi) = \frac{1}{2} \|\nabla \varphi\|^2 + \int_\Omega \psi(\varphi) \, dx, \quad (2.27) \]

arising as the sum of the interfacial and configurational energy. Then, we can define the “energy space”

\[ \mathcal{X} := \{ (\varphi, \sigma) \in V \times L^\infty(\Omega) : \psi(\varphi) \in L^1(\Omega) \} \quad (2.28) \]

and we correspondingly introduce the “magnitude” of an element $(\varphi, \sigma) \in \mathcal{X}$ as

\[ \|(\varphi, \sigma)\|_\mathcal{X} := \|\varphi\|_V + \|\sigma\|_{L^\infty(\Omega)} + \|\psi(\varphi)\|_{L^1(\Omega)}. \quad (2.29) \]

Note that, in view of condition (2.22) (which holds with $\bar{\sigma}$ independent of $T$ thanks to (2.23)), we already know that the component $\sigma$ of any weak solution stays bounded in $L^\infty(\Omega)$ uniformly in time. Observe also that the quantity in (2.29) is not a true norm due to the occurrence of the nonlinear function $\psi$. On the other hand, convenience justifies the use of the above notation.

We can state our second result about dissipativity of the dynamical process generated by weak solutions:

**Theorem 2.10.** Let Assumptions 2.1 and 2.8 hold. Then there exists a positive constant $C_0$ independent of the initial data and a time $T_0$ depending only on the $\mathcal{X}$-magnitude of the initial data such that any weak solution satisfies

\[ \|(\varphi(t), \sigma(t))\|_\mathcal{X} \leq C_0 \quad \text{for every } t \geq T_0. \quad (2.30) \]

Combining the above property with asymptotic compactness of trajectories, we obtain the final result of this paper devoted to proving the existence of the global attractor. We refer the reader to, e.g., [2, 23, 29] for the related notions from the theory of infinite-dimensional dynamical systems.

**Theorem 2.11.** Let Assumptions 2.1 and 2.8 hold. Then the dynamical system generated by weak trajectories on the phase space $\mathcal{X}$ admits the global attractor $\mathcal{A}$. More precisely, $\mathcal{A}$ is a relatively compact subset of $\mathcal{X}$ which is also bounded in $H^2(\Omega) \times H^1(\Omega)$ and uniformly attracts the trajectories emanating from any bounded set $B \subset \mathcal{X}$.

**Remark 2.12.** In view of the fact that system (1.1)-(1.3) has a good parabolic structure, we expect the elements $(\varphi, \sigma) \in \mathcal{A}$ to be in fact smooth functions. More precisely their regularity may only be limited by the smoothness of the nonlinear functions $h$ and $\psi$. In particular, if $h$ and $\psi$ are $C^\infty$, then the elements of the attractor are expected to be infinitely differentiable as well.
3 Proofs

3.1 Proof of Theorem 2.7: Well-posedness

A priori estimates. The main ingredient of the proof of existence consists in a suitable set of a priori estimates. To obtain them, we proceed here in a formal way by working directly on equations (1.1)-(1.3). The argument may however be easily justified within the framework of some regularization scheme (e.g., Faedo-Galerkin). On the other hand, since the procedure works similarly with related models (cf. in particular [16]), we just provide the highlights leaving details to the reader.

In what follows we will note by \( c > 0 \) and \( \kappa > 0 \) some generic positive constants (whose specific value may vary on occurrence) depending only on the given parameters of the system (and neither on the initial data, nor on any hypothetic approximation parameter). The symbol \( \kappa \) will be used in estimates from below. Specific values of the constants will be noted as \( c_i, \kappa_i, i \geq 1 \). Constants depending on additional parameters will be noted using subscripts (e.g., \( c_T \) if the constant depends on the final time \( T \)).

To start with, we derive the basic boundedness properties for the nutrient. To this aim, we test (1.3) by \(-\sigma_-\) (with \( \sigma_- \geq 0 \) denoting the negative part of \( \sigma \)) to deduce

\[
\frac{1}{2} \frac{d}{dt} \| \sigma_- \|^2 + \| \nabla \sigma_- \|^2 \leq c \| \sigma_- \|^2. \tag{3.1}
\]

We used here the uniform boundedness of \( h \) and the fact that \( B(\sigma_s - \sigma) \) is positive for \( \sigma \leq 0 \) because \( \sigma_s > 0 \). Then, by (2.11) and the Gronwall lemma, we obtain that \( \sigma(t, x) \geq 0 \) for (almost) every \( t \geq 0 \) and \( x \in \Omega \).

To get an upper bound, we test (1.3) by \((\sigma - \overline{\sigma})_+\) with \( \overline{\sigma} \geq 1 \) to be chosen below. Using the assumptions on \( h \) and performing standard manipulations, we deduce

\[
\frac{1}{2} \frac{d}{dt} \| (\sigma - \overline{\sigma})_+ \|^2 + \| \nabla (\sigma - \overline{\sigma})_+ \|^2 = - \int_\Omega ((B - Ch)(\sigma - B\sigma_s) (\sigma - \overline{\sigma})_+ \ dx
\leq \int_\Omega |B - Ch| (\sigma - \overline{\sigma})_+ \ dx + \int_\Omega ((B - Ch)\overline{\sigma} - B\sigma_s) (\sigma - \overline{\sigma})_+ \ dx. \tag{3.2}
\]

We now have two cases. If \( B - Ch > 0 \), then we can always choose \( \overline{\sigma} \geq 1 \) large enough so that \((B - Ch|\overline{\sigma} - B\sigma_s \geq 0 \). As a consequence, the latter term on the right-hand side is nonpositive and we can apply Gronwall’s lemma to deduce that \( \sigma(t, x) \leq \overline{\sigma} \) for a.e. \((t, x) \in (0, \infty) \times \Omega \). Note that, if \( \overline{\sigma} = 0 \) the above certainly holds with \( \overline{\sigma} = 1 \) in view of the fact that \( \sigma_s < 1 \).

On the other hand, if \( B - Ch \leq 0 \), then the above procedure fails because we cannot control the last term in (3.2). Nevertheless, an \( L^\infty \)-estimate on \( \sigma \) on finite times intervals can be obtained also in that case. Indeed, one may test (1.3) by \( \sigma^{p-1} \) (recall that we already know that in any case \( \sigma \geq 0 \)) for a generic \( p > 1 \). Then the boundedness of \( h \) and easy computations give

\[
\frac{1}{p} \frac{d}{dt} \| \sigma \|_{L^p(\Omega)}^p \leq c (1 + \| \sigma \|_{L^p(\Omega)}^p), \tag{3.3}
\]

with \( c > 0 \) independent of \( p \). Hence, setting \( y_p := \| \sigma \|_{L^p(\Omega)}^p \), we obtain the differential inequality

\[
(1 + y_p)' \leq cp(1 + y_p), \tag{3.4}
\]

whence

\[
\| \sigma \|_{L^p(\Omega)}^p \leq 1 + y_p(0) \leq (1 + y_p(0)) e^{c_0 t} \leq 2e^{c_0 t}. \tag{3.5}
\]

Thus, taking the \( 1/p \)-power and then letting \( p \to \infty \), we get the desired conclusion. Summarizing, in any case we have obtained

\[
\| \sigma \|_{L^\infty(0,T;L^\infty(\Omega))} \leq c_T. \tag{3.6}
\]

This relation may be intended as a priori estimate independent of any hypothetic regularization parameter. Note that the constant on the right-hand side is independent of \( T \) if \( B - Ch > 0 \), and in particular it can be taken as \( c_T = 1 \) if \( \overline{\sigma} = 0 \).
As a next step, we derive the **Energy estimate** for the Cahn-Hilliard system. This is the basic a priori information that any hypothetic weak solution is expected to satisfy. To obtain it, we test \((1.1)\) by \(\mu\), \((1.2)\) by \(\varphi\), and sum up to obtain

\[
\frac{d}{dt} \left( \frac{1}{2} \| \nabla \varphi \|^2 + \int_{\Omega} \psi(\varphi) \, dx \right) + \| \nabla \mu \|^2 = \int_{\Omega} (P\sigma - A) h(\varphi) \mu \, dx.
\]  

(3.7)

Then let us replace the expression for \(\mu\) as given by \((1.2)\):

\[
\frac{d}{dt} \left( \frac{1}{2} \| \nabla \varphi \|^2 + \int_{\Omega} \psi(\varphi) \, dx \right) + \| \nabla \mu \|^2 = \int_{\Omega} (P\sigma - A) (h'(\varphi) \| \nabla \varphi \|^2 + h(\varphi) \beta(\varphi)) \, dx \\
+ \int_{\Omega} \lambda(A - P\sigma) h(\varphi) \, dx + P \int_{\Omega} h(\varphi) \nabla \sigma \cdot \nabla \varphi \, dx,
\]  

(3.8)

where \(h'(\varphi)\) has been decomposed according to \((2.7)\). Let us now control the terms on the right-hand side. First, as a consequence of Assumption \((2.1)\) \(|h(r)| + |h'(r)| \leq c\) for every \(r \in \mathbb{R}\). Hence, using also \((3.6)\),

\[
\int_{\Omega} (P\sigma - A) h'(\varphi) \| \nabla \varphi \|^2 \, dx \leq c(1 + \| \sigma \|_{L^\infty(\Omega)}) \| \nabla \varphi \|^2 \leq c_T \| \nabla \varphi \|^2.
\]  

(3.9)

Next, thanks to \((2.8)\),

\[
\int_{\Omega} (P\sigma - A) h(\varphi) \beta(\varphi) \, dx \leq c(1 + \| \sigma \|_{L^\infty(\Omega)}) \left( 1 + \int_{\Omega} \psi(\varphi) \, dx \right) \leq c_T \int_{\Omega} \psi(\varphi) \, dx.
\]  

(3.10)

Finally, using also Young’s inequality it is not difficult to deduce

\[
\int_{\Omega} \lambda(A - P\sigma) h(\varphi) \, dx + P \int_{\Omega} h(\varphi) \nabla \sigma \cdot \nabla \varphi \, dx \leq \frac{1}{2} \| \nabla \sigma \|^2 + c_T \left( 1 + \| \varphi \|_{L^1(\Omega)} + \| \nabla \varphi \|^2 \right).
\]  

(3.11)

Note that the above constants \(c_T\) depend on \(T\) only through the \(L^\infty\)-norm of \(\sigma\) (cf. \((3.6)\)). In order to control the first term on the right-hand side of \((3.11)\), we test \((1.3)\) by \(\sigma\). Then, straightforward calculations yield

\[
\frac{1}{2} \frac{d}{dt} \| \sigma \|^2 + \| \nabla \sigma \|^2 \leq c(1 + \| \sigma \|^2).
\]  

(3.12)

Summing \((3.8)\) to \((3.12)\) and using \((3.9)\) - \((3.11)\), we arrive at

\[
\frac{d}{dt} \left( \frac{1}{2} \| \nabla \varphi \|^2 + \int_{\Omega} \psi(\varphi) \, dx + \frac{1}{2} \| \sigma \|^2 \right) + \| \nabla \mu \|^2 + \frac{1}{2} \| \nabla \sigma \|^2 \\
\leq c_T \left( 1 + \| \varphi \|_{L^1(\Omega)} + \| \nabla \varphi \|^2 + \| \sigma \|^2 + \int_{\Omega} \psi(\varphi) \, dx \right).
\]  

(3.13)

Now, using the growth assumption \((2.9)\), it is clear that, for some \(\kappa, c > 0\),

\[
\frac{1}{2} \| \nabla \varphi \|^2 + \int_{\Omega} \psi(\varphi) \, dx \geq \kappa \| \varphi \|_{V} - c \quad \forall \varphi \in V.
\]  

(3.14)

Hence, by Gronwall’s lemma, \((3.13)\) provides the following set of a priori estimates:

\[
\| \varphi \|_{L^\infty(0,T;V)} \leq c_T, \\
\| \nabla \mu \|_{L^2(0,T;H)} \leq c_T, \\
\| \psi(\varphi) \|_{L^\infty(0,T;L^1(\Omega))} \leq c_T, \\
\| \varphi \|_{L^2(0,T,V) \cap L^\infty(0,T,H)} \leq c_T,
\]

(3.15)\text{--}(3.18)

with \(c_T\) as in \((3.6)\).

Next, integrating \((1.2)\) over \(\Omega\) and using once more \((2.8)\), we deduce

\[
|\mu_\Omega| = \left| \int_{\Omega} \mu \, dx \right| = \left| \int_{\Omega} (\beta(\varphi) - \lambda \varphi) \, dx \right| \leq c_T \left( 1 + \int_{\Omega} \psi(\varphi) \, dx \right),
\]

(3.19)
where we have used (3.15) to control the $\lambda$-term. Recalling (3.17) we then infer
\[ \|\mu\|_{L^\infty(0,T)} \leq cT, \] (3.20)
which, combined with (3.16), gives in turn
\[ \|\mu\|_{L^2(0,T;V)} \leq cT. \] (3.21)

Now, testing (1.2) by $\beta(\varphi)$ and using (3.15), (3.21) and the monotonicity of $\beta$, it is a standard matter to deduce
\[ \|\beta(\varphi)\|_{L^2(0,T;H)} \leq cT. \] (3.22)

Finally, we derive some estimates on the time derivatives of $\varphi$ and $\sigma$. Multiplying (1.1) by a generic nonzero test function $v \in V$ and using the previous estimates, we actually get
\[ \langle \varphi_t, v \rangle = (\nabla \mu, \nabla v) + \int_\Omega (P\sigma - A)h(\varphi)v \, dx, \] (3.24)
whence estimates (3.15), (3.21) and standard manipulations yield
\[ \|\varphi_t\|_{L^2(0,T;V')} \leq cT. \] (3.25)

Operating in an analogue way with equation (1.3) we similarly obtain
\[ \|\sigma_t\|_{L^2(0,T;V')} \leq cT. \] (3.26)

Remark 3.1. Using a more refined regularity argument in (1.2) and 3D Sobolev embeddings (see, e.g., [27]) one could improve (3.22)-(3.23) up to
\[ \|\beta(\varphi)\|_{L^2(0,T;L^6(\Omega))} + \|\varphi\|_{L^2(0,T;W^{2,6}(\Omega))} \leq cT. \] (3.27)

Weak sequential stability. We assume here to have a sequence of weak solutions $(\varphi_n, \mu_n, \sigma_n)$ satisfying the a priori estimates obtained above uniformly with respect to the approximation parameter $n$. In other words, the constants $c$ or $cT$ on the right-hand sides of the bounds are assumed independent of $n$. We then prove that, up to the extraction of subsequences, $(\varphi_n, \mu_n, \sigma_n)$ tends in a suitable way to a triplet $(\varphi, \mu, \sigma)$ solving the tumor growth model in the sense of Definition 2.6 on the assigned but otherwise arbitrary time interval $(0,T)$. This argument, generally noted as a “weak stability property”, may be seen as an abbreviated procedure for passing to the limit in some approximation, for instance a Faedo-Galerkin scheme, that may also involve the regularization of some terms (in particular of the function $\beta$). On the other hand, the procedure is so standard that we believe that giving very few highlights may suffice.

Actually, using the bounds (3.14), (3.15)-(3.18), (3.21)-(3.23), (3.25)-(3.26) and standard weak compactness argument, we are able to take a (nonrelabelled) subsequence of $n$ such that $(\varphi_n, \mu_n, \sigma_n) \to (\varphi, \mu, \sigma)$ in the sense of weak or weak star convergence in proper Sobolev spaces. Moreover, using (3.25), (3.26), and the Aubin-Lions lemma, we obtain that $(\varphi_n, \sigma_n)$ tends to $(\varphi, \sigma)$ strongly in some $L^p$-space, hence pointwise. This allows us to pass to the limit in the nonlinear terms thanks to continuity of $h$ and $\beta$. In particular, we may observe that, combining (3.22) with the pointwise convergence of $\varphi_n$ and using a generalized version of Lebesgue’s dominated convergence theorem, there follows
\[ \beta(\varphi_n) \to \beta(\varphi) \text{ weakly in } L^2(0,T;H). \] (3.28)

Actually, even if in the approximation $\beta$ is replaced by some regularization $\beta_n$ the above property still works (with $\beta_n(\varphi_n)$ in place of $\beta(\varphi_n)$ on the left-hand side) up to adaptations, provided that one assumes that $\beta_n$ tends to $\beta$ uniformly on compact subsets of $\mathbb{R}$. 

9
Uniqueness. We give here a proof of uniqueness. A different (and somehow simpler) proof is given in [18] (cf. also [15]) in the case where \( \psi \) has polynomial (of degree four) growth. On the other hand, the argument given here works also for exponential \( \psi \) (cf. [2.10]). Assume to have two solutions \((\varphi_1, \mu_1, \sigma_1)\) and \((\varphi_2, \mu_2, \sigma_2)\) corresponding to two sets of initial data \((\varphi_{1,0}, \sigma_{1,0})\) and \((\varphi_{2,0}, \sigma_{2,0})\). Then the differences \((\varphi, \mu, \sigma) := (\varphi_1 - \varphi_2, \mu_1 - \mu_2, \sigma_1 - \sigma_2)\) satisfy the following equations:

\[
\begin{align*}
\varphi_t + R\mu &= P\varphi h(\varphi_1) + (P\sigma_2 - A)(h(\varphi_1) - h(\varphi_2)) \quad \text{in } V', \text{ a.e. in } (0, \infty), \\
\mu &= R\varphi + \psi'(\varphi_1) - \psi'(\varphi_2) \quad \text{in } H, \text{ a.e. in } (0, \infty), \\
\sigma_t + R\sigma &= -C\sigma h(\varphi_1) - C\sigma_2(h(\varphi_1) - h(\varphi_2)) - B\sigma, \quad \text{in } V', \text{ a.e. in } (0, \infty);
\end{align*}
\]  

with the initial conditions

\[
\varphi|_{t=0} = \varphi_0, \quad \sigma|_{t=0} = \sigma_0,
\]  

where \( \varphi_0 := \varphi_{1,0} - \varphi_{2,0}, \sigma_0 := \sigma_{1,0} - \sigma_{2,0} \). In particular, integrating (3.29) over \( \Omega \), we obtain

\[
(\varphi_{1})_t = \int_\Omega P\varphi h(\varphi_1) \, dx + \int_\Omega (P\sigma_2 - A)(h(\varphi_1) - h(\varphi_2)) \, dx.
\]  

Testing the above by \( \varphi_{1} \) and using the boundedness of \( h \) and of \( \sigma_2 \) with the Lipschitz continuity of \( h \), we obtain

\[
\frac{1}{2} \frac{d}{dt} |\varphi_{1}|^2 \leq c(|\varphi_{1}|^2 + \|\sigma_2\|^2 + \|\varphi_{1}\|^2).
\]  

Next, let us take the difference of (3.29) and (3.31) and test it by \( N(\varphi - \varphi_{1}) \). Simpala calculations yield

\[
\frac{1}{2} \frac{d}{dt} \|\nabla(\varphi - \varphi_{1})\|^2 + \int_\Omega \mu(\varphi - \varphi_{1}) \, dx \leq c(|\varphi - \varphi_{1}|^2, \|\sigma\|^2 + \|\varphi_{1}\|^2).
\]  

Now, testing (3.30) by \( \varphi - \varphi_{1} \), we infer

\[
\|\nabla\varphi\|^2 = \int_\Omega \mu(\varphi - \varphi_{1}) \, dx - \int_\Omega (\psi'(\varphi_1) - \psi'(\varphi_2))(\varphi - \varphi_{1}) \, dx \\
\leq \int_\Omega (\varphi - \varphi_{1}) \, dx + \varphi_{1} \int_\Omega (\beta(\varphi_1) - \beta(\varphi_2)) \, dx + \lambda \|\varphi - \varphi_{1}\|^2,
\]  

where we also used the decomposition (2.7) and the monotonicity of \( \beta \). Next, testing (3.31) by \( \sigma \), using the Lipschitz continuity of \( h \) and performing standard manipulations, we deduce

\[
\frac{1}{2} \frac{d}{dt} \|\sigma\|^2 + \|\nabla\sigma\|^2 \leq c(|\sigma|^2 + \|\varphi_{1}\|^2).
\]  

Combining (3.34) – (3.37), we obtain

\[
\frac{1}{2} \frac{d}{dt} \left( |\varphi_{1}|^2 + \|\varphi - \varphi_{1}\|_{V'}^2 + \|\sigma\|_{V'}^2 + \|\nabla\varphi\|^2 + \|\nabla\sigma\|^2 \right) \\
\leq \varphi_{1} \int_\Omega (\beta(\varphi_1) - \beta(\varphi_2)) \, dx + c(|\varphi - \varphi_{1}|^2 + \|\sigma\|^2 + |\varphi_{1}|^2).
\]  

In order to control the terms on the right-hand side we first observe that, thanks to the Poincaré-Wirtinger inequality and to Ehrling’s lemma,

\[
c|\varphi - \varphi_{1}|^2 \leq \frac{1}{4} \|\nabla\varphi\|^2 + c|\varphi - \varphi_{1}|^2_{V'}.
\]  

To control the remaining term, we need to use assumption (2.10) and then we derive

\[
\begin{align*}
\varphi_{1} \int_\Omega (\beta(\varphi_1) - \beta(\varphi_2)) \, dx &\leq c|\varphi_{1}| \int_\Omega |\varphi|(1 + |\beta(\varphi_1)| + |\beta(\varphi_2)|) \, dx \\
&\leq c|\varphi_{1}| |\varphi|(1 + \|\beta(\varphi_1)| + \|\beta(\varphi_2)|) \\
&\leq c|\varphi_{1}|^2 (1 + \|\beta(\varphi_1)|^2 + \|\beta(\varphi_2)|^2) + c|\varphi - \varphi_{1}|^2 + c|\varphi_{1}|^2 \\
&\leq c|\varphi_{1}|^2 (1 + \|\beta(\varphi_1)|^2 + \|\beta(\varphi_2)|^2) + c|\varphi - \varphi_{1}|^2_{V'} + \frac{1}{4} \|\nabla\varphi\|^2.
\end{align*}
\]  

(3.40)
Proof. We first recall that we get uniqueness whenever \((\varphi, \sigma)\) dependence estimate

\[
\frac{1}{2} \frac{d}{dt} (|\varphi|^2 + |\varphi - \varphi_0|^2 + |\sigma|^2) + \frac{1}{2} \|\nabla \varphi\|^2 + \|\nabla \sigma\|^2
\leq c|\varphi|^2 (1 + \|\beta(\varphi_1)\|^2) + \|\beta(\varphi_2)\|^2) + c(\|\varphi - \varphi_0\|^2 + |\sigma|^2).
\]

(3.41)

Then, using the regularity property (2.15) both for \(\varphi_1\) and for \(\varphi_2\) and applying Gronwall’s lemma, we get uniqueness whenever \((\varphi_{0,1}, \sigma_{0,1}) = (\varphi_{0,2}, \sigma_{0,2})\). In the general case, we obtain the continuous dependence estimate

\[
|\varphi_{1}(t) - (\varphi_{2})_{1}(t)| + \|\varphi_{1}(t) - (\varphi_{2})_{1}(t)\|_{V}^2 + \|\sigma_{1}(t) - \sigma_{2}(t)\|^2
\leq C_T \left(|\varphi_{0,1} - (\varphi_{0,2})_{1}| + \|\varphi_{0,1} - (\varphi_{0,2})_{1}\|_{V}^2 + \|\sigma_{0,1} - \sigma_{0,2}\|^2\right),
\]

(3.42)

for every \(T > 0\) and every \(t \in (0, T]\), the constant \(C_T > 0\) depending on the \(X\)-magnitude of the initial data and on \(T\).

3.2 Proof of Theorem 2.10: Dissipativity

As a first step, we consider some auxiliary ODE’s. Namely, we define \(S_+\) and \(S_-\) as the solutions to the following Cauchy problems:

\[
S_+(t) = -(B - C \sigma)_{1} S_+ + B \sigma_{1}, \quad S_+(0) = 1,
\]

(3.43)

and

\[
S_-(t) = -(B - C) S_+ + B \sigma_{1}, \quad S_-(0) = 0.
\]

(3.44)

Then we can readily compute

\[
S_+(t) = e^{-(B - C \sigma)_{1} t} + \frac{B \sigma_{1}}{B - C \sigma} (1 - e^{-(B - C \sigma)_{1} t})
\]

(3.45)

and

\[
S_-(t) = \frac{B \sigma_{1}}{B + C} (1 - e^{-(B - C \sigma)_{1} t}).
\]

(3.46)

Lemma 3.2. Let the assumptions of Theorem 2.10 hold. Let \((\varphi, \sigma)\) be any weak solution to (1.1)–(1.5). Then we have

\[
S_-(t) \leq \sigma(t, x) \leq S_+(t) \quad \text{for every } t \geq 0 \text{ and } x \in \Omega.
\]

(3.47)

Proof. We first recall that \(\sigma(t, x) \geq 0\) for a.e. \(t \geq 0\), \(x \in \Omega\) thanks to the minimum principle argument in the proof of Theorem 2.7 (cf. (3.1)). Then, we can prove that \(S_-\) is a subsolution, namely the first inequality in (3.49) holds. Taking the difference between (3.43) and (3.45) we actually obtain

\[
(\sigma - S_-)' - \Delta (\sigma - S_-) = -B(\sigma - S_-) - C(\sigma \varphi - S_-),
\]

(3.50)

whence testing by \(-(\sigma - S_-)\) and using the fact that \(h \leq 1\) we readily get the assert. Indeed, since \(\sigma \geq 0\), we notice that

\[
C(\sigma \varphi - S_-)(\sigma - S_-) \leq C(\sigma - S_-)(\sigma - S_-) \leq 0.
\]

(3.51)

Analogously, the difference between (3.43) and (3.45) gives

\[
(\sigma - S_+)' - \Delta (\sigma - S_+) = -B(\sigma - S_+) - C(\sigma \varphi + S_+ h).
\]

(3.52)

Testing by \((\sigma - S_+)^+\), noting that

\[
-C(\sigma \varphi + S_+ h)(\sigma - S_+) \leq -C(-\sigma h + S_+ h)(\sigma - S_+) \leq C h (\sigma - S_+)^2,
\]

(3.53)

and recalling (2.23), we easily obtain the second assertion.
Recalling (2.21) and (2.25), we can take \( \epsilon > 0 \) to be a small number satisfying
\[
2\epsilon \leq A - P \frac{B\sigma_{s}}{B - Ch} \quad \text{and} \quad \frac{B\sigma_{s}}{B - Ch} + \frac{\epsilon}{P} < 1.
\]
(3.54)
We can then prove the following.

**Lemma 3.3.** Let the assumptions of Theorem 2.10 hold. Let \((\varphi, \sigma)\) be any weak solution in the sense of Definition 2.6. Then there exist \( T_{1} > 0 \) and \( C_{1} > 0 \) independent of the initial data such that
\[
\frac{B\sigma_{s}}{C + B} - \frac{\epsilon}{P} \leq \sigma(t, x) \leq \frac{B\sigma_{s}}{B - Ch} + \frac{\epsilon}{P} \quad \text{for all} \quad t \geq T_{1}, \quad \text{a.e.} \quad x \in \Omega,
\]
(3.55)
\[\|((\varphi(T_{1}), \sigma(T_{1}))\|_{X} \leq C_{1}(1 + \|\varphi_{0}, \sigma_{0}\|_{X}).\]
(3.56)

**Proof.** Thanks to (3.49) the component \( \sigma \) evolves between the subsolution \( S_- \) and the supersolution \( S_+ \). Then, a simple computation based on (3.41), (3.43) shows that (3.55) holds provided that we choose
\[
T_{1} := \max \left\{ \frac{1}{B + C} \log \left( \frac{B\sigma_{s}P}{\epsilon(B + C)} \right), \frac{1}{B - Ch} \log \left( \frac{P(B - Ch - B\sigma_{s})}{\epsilon(B - Ch)} \right) \right\}.
\]
(3.57)
Notice in particular that the argument of the second logarithm is strictly positive thanks to assumption (2.24). Next, to prove (3.56), it suffices to repeat the a priori estimates of Subsec. 3.1. We may incidentally notice that the constant \( c_{T} \) in (3.13) can now be taken independent of \( T \) thanks to Lemma 3.2. Anyway, integrating (3.13) over the time interval \((0, T)\) and applying once more the Gronwall lemma, we readily obtain the assertion.

**Proof of Theorem 2.10.** We start again from relation (5.8), which we will now consider for \( t \geq T_{1} \). Hence, in particular we can take advantage of the second inequality in (3.55). As a consequence, we can observe that, thanks to (3.54),
\[
\sigma \leq \frac{B\sigma_{s}}{B - Ch} + \frac{\epsilon}{P} \Rightarrow P\sigma - A \leq P \frac{B\sigma_{s}}{B - Ch} + \epsilon - A \leq -\epsilon.
\]
(3.58)
Consequently, for \( t \geq T_{1} \), (5.8) implies the following inequality:
\[
\frac{d}{dt} \left( \frac{1}{2} \|\nabla \varphi\|^{2} + \int_{\Omega} \psi(\varphi) \, dx \right) + \|\nabla \mu\|^{2} + \epsilon \int_{\Omega} h'(\varphi)|\nabla \varphi|^{2} \, dx \\
+ \int_{\Omega} (A - P\sigma)h(\varphi)\beta(\varphi) \, dx \leq \int \lambda(A - P\sigma)h(\varphi) \, dx + P \int_{\Omega} h(\varphi) \nabla \sigma \cdot \nabla \varphi \, dx.
\]
(3.59)
Now, the terms on the right-hand side can be controlled as in (3.11). On the other hand, using Assumptions 2.1 and 2.3 (and in particular the facts that \( h \) is strictly positive and that \( \beta(\varphi) \) has the same sign as \( \varphi \)), it is not difficult to check that
\[
h(\varphi)\beta(\varphi) \geq \kappa|\beta(\varphi)| - c,
\]
(3.60)
whence the latter term on the left-hand side of (3.59) gives
\[
\int_{\Omega} (A - P\sigma)h(\varphi)\beta(\varphi) \, dx \geq \kappa\epsilon\|\beta(\varphi)\|_{L^{1}(\Omega)} - c,
\]
(3.61)
so that (3.59) implies the differential inequality
\[
\frac{d}{dt} \left( \frac{1}{2} \|\nabla \varphi\|^{2} + \int_{\Omega} \psi(\varphi) \, dx \right) + \|\nabla \mu\|^{2} + \kappa\epsilon\|\beta(\varphi)\|_{L^{1}(\Omega)} \leq \frac{1}{2} \|\nabla \sigma\|^{2} + c(1 + \|\varphi\|_{L^{1}(\Omega)} + \|\nabla \varphi\|^{2}).
\]
(3.62)
Adding (3.12) to the above relation, we arrive at
\[
\frac{d}{dt} \left( \frac{1}{2} \|\nabla \varphi\|^{2} + \int_{\Omega} \psi(\varphi) \, dx + \frac{1}{2} \|\sigma\|^{2} \right) + \frac{1}{2} \|\nabla \sigma\|^{2} + \|\nabla \mu\|^{2} \\
+ \kappa\epsilon\|\beta(\varphi)\|_{L^{1}(\Omega)} \leq c(1 + \|\varphi\|_{L^{1}(\Omega)} + \|\nabla \varphi\|^{2}),
\]
(3.63)
Now, using (2.26) again together with the continuous embedding where the norm of $\kappa, \epsilon$ has disappeared because we now know that $0 \leq \sigma \leq 1$ almost everywhere.

Next, let us multiply (1.2) by $-\Delta \varphi$. We deduce

$$\|\Delta \varphi\|^2 + \int_{\Omega} \beta'(\varphi)|\nabla \varphi|^2 \, dx \leq (\nabla \varphi, \nabla \mu) - \lambda(\varphi, \Delta \varphi) \leq (\nabla \varphi, \nabla \mu) + \frac{1}{2} \|\Delta \varphi\|^2 + \frac{\lambda^2}{2} \|\varphi\|^2. \tag{3.64}$$

Correspondingly, testing (1.1) by $\varphi$ we obtain

$$\frac{1}{2} \frac{d}{dt} \|\varphi\|^2 + (\nabla \varphi, \nabla \mu) + \int_{\Omega} (A - P\sigma)h(\varphi) \varphi \, dx = 0, \tag{3.65}$$

whence in particular

$$\frac{1}{2} \frac{d}{dt} \|\varphi\|^2 + (\nabla \varphi, \nabla \mu) \leq c(1 + \|\varphi\|^2). \tag{3.66}$$

Adding (3.64) and (3.66) to (3.63) and adding also the inequality $\frac{1}{2} \|\sigma\|^2 \leq c$, neglecting some positive term on the left-hand side, we obtain

$$\frac{d}{dt} \left( \frac{1}{2} \|\varphi\|^2 \right) + \int_{\Omega} \psi(\varphi) \, dx + \frac{1}{2} \|\sigma\|^2 + \frac{1}{2} \|\Delta \varphi\|^2 + \|\nabla \mu\|^2 + \kappa \|\beta(\varphi)\|_{L^1(\Omega)} + \frac{\lambda^2}{2} \|\varphi\|^2 \leq c(1 + \|\varphi\|^2 + \|\nabla \varphi\|^2). \tag{3.67}$$

Now, to control the right-hand side, we first observe that

$$c\|\nabla \varphi\|^2 = c(-\Delta \varphi, \varphi) \leq \frac{1}{4} \|\Delta \varphi\|^2 + c\|\varphi\|^2. \tag{3.68}$$

Then, by virtue of assumption (2.26), for $\kappa, \epsilon$ as in (3.67), we have

$$c\|\varphi\|^2 \leq \frac{\lambda^2}{2} \|\beta(\varphi)\|_{L^1(\Omega)} + c_{\kappa, \epsilon}. \tag{3.69}$$

**Remark 3.4.** We point out that it may be possible to allow $p_\beta = 2$ in (2.26) at least in the case when $\kappa_\beta$ is large enough. We leave the details to the reader.

Taking (3.68) and (3.69) into account, (3.67) gives

$$\frac{d}{dt} \left( \frac{1}{2} \|\varphi\|^2 \right) + \int_{\Omega} \psi(\varphi) \, dx + \frac{1}{2} \|\sigma\|^2 + \frac{1}{4} \|\Delta \varphi\|^2 + \|\nabla \mu\|^2 + \frac{\lambda^2}{2} \|\varphi\|^2 \leq c. \tag{3.70}$$

Now, using (2.26) again together with the continuous embedding $H^2(\Omega) \subset L^\infty(\Omega)$, we notice that

$$\frac{1}{4} \|\Delta \varphi\|^2 + \frac{\kappa \epsilon^2}{2} \|\beta(\varphi)\|_{L^1(\Omega)} \geq \kappa \|\varphi\|_{H^2(\Omega)} - c \geq \kappa_1 \|\varphi\|_{L^\infty(\Omega)} - c. \tag{3.71}$$

Let us then define

$$Z(r) := \hat{\beta}(r) + \hat{\beta}(-r), \quad \forall r \geq 0, \tag{3.72}$$

where $\hat{\beta}$ is the antiderivative of $\beta$ satisfying $\hat{\beta}(0) = 0$ (hence in particular $\hat{\beta}$ is convex and nonnegative due to Assumption (2.1)). Noting that $Z$ is monotone over $[0, \infty)$ with $Z(0) = 0$, we have

$$\int_{\Omega} \beta(\varphi) \, dx \leq \int_{\Omega} Z(|\varphi|) \, dx \leq \int_{\Omega} Z(|\varphi|_{L^\infty(\Omega)}) \, dx = Z\left(|\varphi|_{L^\infty(\Omega)}\right). \tag{3.73}$$

As a consequence,

$$\|\varphi\|_{L^\infty(\Omega)} \geq Z^{-1}\left(\int_{\Omega} \beta(\varphi) \, dx\right). \tag{3.74}$$
Hence, recalling also (3.71), relabelling some constants, and rearranging some terms, (3.70) implies
$$
\frac{d}{dt} \left[ \frac{1}{2} \| \varphi \|_V^2 + \frac{1}{2} \| \sigma \|^2 + \int_{\Omega} \psi(\varphi) \, dx \right] + \frac{\kappa_3}{2} (\| \varphi \|_V^2 + \| \sigma \|^2) \\
+ \kappa_1 Z^{-1} \left( \int_{\Omega} \beta(\varphi) \, dx \right) + \kappa_2 (\| \Delta \varphi \|^2 + \| \nabla \mu \|^2 + \| \nabla \sigma \|^2) \leq c,
$$
where the term $\frac{\kappa_3}{2} \| \varphi \|_V^2$ has been added to both hands sides. Then its occurrence on the right-hand side has been controlled essentially by repeating the procedure in (3.68)-(3.69). Now, for $K > 0$ as in Assumption 2.1, there holds
$$
\hat{\beta}(r) = \psi(r) + \frac{\lambda}{2} r^2 - K \geq \psi(r) \quad \forall r \geq \left( \frac{2K}{\lambda} \right)^{1/2}.
$$
As a consequence, for some $c > 0$ we have
$$
\kappa_1 Z^{-1} \left( \int_{\Omega} \hat{\beta}(\varphi) \, dx \right) \geq \kappa_1 Z^{-1} \left( \int_{\Omega} \psi(\varphi) \, dx \right) - c.
$$
Actually, to prove this relation it suffices to split the integration domain $\Omega$ into the sets where $|\varphi|$ is smaller and respectively larger than $\left( \frac{2K}{\lambda} \right)^{1/2}$ and to use (3.71). Thanks to the above relations, (3.76) takes now the form
$$
\frac{d}{dt}(\mathcal{E}_1 + \mathcal{E}_2) + \kappa_3 \mathcal{E}_1 + \kappa_1 Z^{-1}(\mathcal{E}_2) + \kappa_2 \mathcal{D} \leq c_1,
$$
where we have set
$$
\mathcal{E}_1 := \frac{1}{2} (\| \varphi \|_V^2 + \| \sigma \|^2), \quad \mathcal{E}_2 := \int_{\Omega} \psi(\varphi) \, dx,
$$
$$
\mathcal{D} := \| \Delta \varphi \|^2 + \| \nabla \mu \|^2 + \| \nabla \sigma \|^2
$$
and we can notice that the above quantities are nonnegative. In order to prove that the above differential inequality is dissipative, we first observe that, as a consequence of (2.8),
$$
\frac{\| \beta(r) \|}{\beta(r)} \leq c \quad \text{for sufficiently large } |r|.
$$
whence, recalling (3.72), it is easy to deduce, for some $c \geq 0$,
$$
Z(r) \leq c + c e^{c r} \quad \forall r \geq 0
$$
and, in turn, passing to inverse functions,
$$
Z^{-1}(r) \geq \kappa \ln(y - c) \quad \forall r \geq \bar{r},
$$
where $\bar{r}$ is some computable positive number. The above implies
$$
\kappa_1 Z^{-1}(r) \geq \kappa_4 \ln(y + 1) - c \quad \forall r \geq 0,
$$
so that inequality (3.78) takes the form
$$
\frac{d}{dt}(\mathcal{E}_1 + \mathcal{E}_2) + \kappa_3 \mathcal{E}_1 + \kappa_4 \ln(\mathcal{E}_2 + 1) \leq c_2,
$$
and, using subadditivity of the logarithm,
$$
\frac{d}{dt}(\mathcal{E}_1 + \mathcal{E}_2) + \kappa_5 \ln(\mathcal{E}_1 + \mathcal{E}_2 + 1) \leq c_3,
$$
which is a dissipative differential inequality and implies the desired condition (2.30). Actually, it can be easily checked that there exists a finite and computable time $T_0 \geq T_1$ depending only on the “energy” (in the sense of (2.29)) of the initial data such that for every $t \geq T_0$ there holds
$$
\kappa_5 \ln(\mathcal{E}_1 + \mathcal{E}_2 + 1) \leq 2c_3, \quad \text{i.e. } \mathcal{E}_1 + \mathcal{E}_2 \leq e^{\frac{2c_3}{\kappa_5}} - 1.
$$
Indeed, if condition (3.87) is violated, then the time derivative of $\mathcal{E}_1 + \mathcal{E}_2$ is less than $-c_3$, implying that $\mathcal{E}_1 + \mathcal{E}_2$ decreases at least linearly with time until (3.87) starts holding after some computable time $T_0$. Relation (2.30) is then an immediate consequence of (3.87).
3.3 Proof of Theorem 2.11: Attractor

Thanks to the dissipativity property of Theorem 2.10, we only need to show asymptotic compactness of solutions. To this aim, we prove a further regularity estimate. As above, we will directly work on system (1.1)-(1.3), being intended that this formal procedure may be justified within some approximation scheme. In what follows the various constants \( c \) will be allowed to depend on the \( \lambda \)-radius \( C_0 \) (cf. (2.3.1)) of the absorbing set.

That said, we first test (1.1) by \( \mu_t \). Then, integrating by parts in time the term on the right-hand side, we get

\[
\frac{d}{dt} \| \nabla \mu \|^2 + \frac{d}{dt} \int_{\Omega} (A - P\sigma) h(\varphi) \mu \, dx = \int_{\Omega} \mu((A - P\sigma) h(\varphi)) \, dx
\]

\[
= \int_{\Omega} (A - P\sigma) h'(\varphi) \varphi_t \mu \, dx - \int_{\Omega} P\sigma h(\varphi) \mu \, dx
\]

\[
\leq c(\| \varphi_t \| + \| \sigma_t \|) \| \mu \| \leq \frac{1}{2} \| \varphi_t \|^2 + \frac{1}{2} \| \sigma_t \|^2 + c\| \mu \|^2.
\]  

(3.88)

We used here the boundedness of \( h \) and \( h' \), and the fact that \( 0 \leq \sigma \leq 1 \). These conditions will be repeatedly used again below without further mentioning them. Next, we differentiate (1.2) in time \( \varphi_t \) to obtain

\[
(\mu_t, \varphi_t) = \| \nabla \varphi_t \|^2 + \int_{\Omega} \beta'(\varphi) \varphi_t^2 \, dx - \lambda \| \varphi_t \|^2.
\]  

(3.89)

Multiplying now (1.1) by \((1 + 2\lambda) \varphi_t\) we obtain

\[
(1 + 2\lambda) \| \varphi_t \|^2 = -(1 + 2\lambda)(\nabla \mu, \nabla \varphi_t) + (1 + 2\lambda) \int_{\Omega} (P\sigma - A) h(\varphi) \varphi_t \, dx
\]

\[
\leq \frac{1}{2} \| \nabla \varphi_t \|^2 + c_\lambda \| \nabla \mu \|^2 + \lambda \| \varphi_t \|^2 + c_\lambda.
\]  

(3.90)

Finally, multiplying (1.3) by \( 2\sigma_t \) and standardly controlling the right-hand side, it is not difficult to deduce

\[
\| \sigma_t \|^2 + \frac{d}{dt} \| \nabla \sigma \|^2 \leq c.
\]  

(3.91)

Taking the sum of relations (3.88), (3.90) and (3.91), and using (3.89), we arrive at

\[
\frac{d}{dt} \left[ \frac{1}{2} \| \nabla \mu \|^2 + \| \nabla \sigma \|^2 + \int_{\Omega} (A - P\sigma) h(\varphi) \mu \, dx \right] + \frac{1}{2} \| \nabla \varphi_t \|^2 + \int_{\Omega} \beta'(\varphi) \varphi_t^2 \, dx
\]

\[
+ \frac{1}{2} \| \sigma_t \|^2 + \frac{1}{2} \| \varphi_t \|^2 \leq c + c\| \nabla \mu \|^2 + c\| \mu \|^2.
\]  

(3.92)

Now, using the Poincaré-Wirtinger inequality (2.3) we have

\[
c\| \mu \|^2 = c\| \mu - \mu_0 \|^2 + c\| \mu_0 \|^2 \leq c\| \nabla \mu \|^2 + c\int_{\Omega} \psi'(\varphi) \, dx \leq c\| \nabla \mu \|^2 + c\int_{\Omega} \psi(\varphi) \, dx \leq c + c\| \nabla \mu \|^2,
\]  

(3.93)

where we have also used condition (2.58) and the uniform bound on the \( L^1 \)-norm of \( \psi(\varphi) \).

Then, noting as \( \mathcal{E}_3 \) the sum of the terms in square brackets on the left-hand side of (3.92), we can observe that

\[
\mathcal{E}_3 \geq \frac{1}{2} \| \nabla \mu \|^2 + \| \nabla \sigma \|^2 - c\| \mu \|_{L^1(\Omega)}
\]

\[
\geq \frac{1}{2} \| \nabla \mu \|^2 + \| \nabla \sigma \|^2 - c\| \mu - \mu_0 \|_{L^1(\Omega)} - c|\mu_0|
\]

\[
\geq \frac{1}{2} \| \nabla \mu \|^2 + \| \nabla \sigma \|^2 - c\| \nabla \mu \| - c - c\int_{\Omega} \psi(\varphi) \, dx
\]

\[
\geq \frac{1}{4} \| \nabla \mu \|^2 + \| \nabla \sigma \|^2 - c_0,
\]  

(3.94)
where $c_0$ depends only on the uniform bound on the $X$-magnitude of the solution (cf. (2.30)) holding for $t \geq T_0$.

Thanks to (3.93) and (3.94), (3.92) gives rise to the following inequality:
\[
\frac{d}{dt}(E_3 + c_0) + \frac{1}{2}\|\nabla \varphi_t\|^2 + \int_{\Omega} \beta'(\varphi)\varphi_t^2 \, dx + \frac{1}{2}\|\sigma_t\|^2 + \frac{1}{2}\|\varphi_t\|^2 \leq c + c\|\nabla \mu\|^2. \tag{3.95}
\]

Now, coming back to (3.78), integrating it over the generic time interval $(t, t+1)$, $t \geq T_1$, and recalling (3.80), we obtain
\[
\int_{t}^{t+1} (\|\nabla \mu_t\|^2 + \|\nabla \sigma_t\|^2) \, ds \leq c. \tag{3.96}
\]

Consequently, we can apply the uniform Gronwall lemma (see, e.g., [30]) to (3.95) to obtain
\[
\|\mu(t)\|_V + \|\sigma(t)\|_V \leq C_1, \quad \forall t \geq T_0 + 1, \tag{3.97}
\]
where $C_1 > 0$ is independent of the initial data. To get additional regularity on $\varphi$ it is then sufficient to go back to (1.2) and apply standard elliptic regularity results to obtain
\[
\|\varphi(t)\|_{H^2(\Omega)} \leq C_2, \quad \forall t \geq T_0 + 1, \tag{3.98}
\]
where $C_2 > 0$ is independent of the initial data. Properties (3.97) and (3.98), combined with the dissipativity proved in Theorem 2.10, provide existence of the global attractor $\mathcal{A}$ as well as its boundedness in $H^2(\Omega) \times H^1(\Omega)$, which concludes the proof.

### 3.4 Spatially homogeneous case

We give here some evidence of the fact that, if conditions (2.23), (2.25) do not hold, then dissipativity of the process may fail. To this aim we will analyze the behavior of spatially homogeneous solutions. Indeed, in view of the no-flux boundary conditions, these are particular solutions to system (1.1)-(1.3) starting from spatially homogeneous initial data. Then, let us denote by $X = X(t)$ and by $S = S(t)$ the spatially homogeneous versions of $\varphi$ and $\sigma$, respectively. In this setting, our problem reduces to the following ODE system for the vector variable $(X, S)$:

\[
X' + (A - PS)h(X) = 0, \tag{3.99}
\]
\[
S' + CSh(X) + B(S - \sigma_s) = 0. \tag{3.100}
\]

We can first observe that, if $\underline{h} = 0$ and $X(0) < -1$, equation (3.99) prescribes $X(t)$ to be conserved in time. In particular, there is no hope to prove that $X(t)$ eventually lies in some bounded absorbing set. Indeed, if $X$ is large negative at the initial time, then it remains like that forever.

Let us now assume $\underline{h} > 0$. Then we observe that
\[
B\sigma_s - (C + B)S \leq S' \leq B\sigma_s - (B - C\underline{h})S. \tag{3.101}
\]

The first inequality implies that
\[
S < \frac{B\sigma_s}{C + B} \Rightarrow S' > 0. \tag{3.102}
\]

For what concerns the second inequality, we have two cases. Let us first consider the situation when $C\underline{h} \geq B$, i.e., (2.22) does not hold. Let also the initial data be chosen in such a way that $X(0) < 0$ and $S(0) >> 0$ (in such a way that $PS - A > 0$). Then it follows

\[
X' = -(PS - A)\underline{h} < 0, \tag{3.103}
\]
\[
S' = B\sigma_s + (C\underline{h} - B)S > 0 \tag{3.104}
\]

and both $|X|$ and $S$ go increasing forever. Note that in this situation, even if we restrict ourselves to the “physical” case $S(0) \in [0, 1]$, if $X(0) < -1$ then due to (3.101) $S(t)$ eventually becomes larger than 1; hence, the physical constraint $S(t) \in [0, 1]$ is not respected.
In view of the above discussion, it looks reasonable to assume $h > 0$ and (2.23). Under these conditions, the second inequality in (3.101) implies

$$S > \frac{B\sigma_s}{B - C\hat{h}} \Rightarrow S' < 0.$$  

(3.105)

We can then define the region

$$S := \{(X, S) \in \mathbb{R}^2 : \frac{B\sigma_s}{C + B} \leq S \leq \frac{B\sigma_s}{B - C\hat{h}}\}$$  

(3.106)

and it follows from (3.102) and (3.105) that $S$ is positively invariant for the dynamical process generated by (3.99)-(3.100). Now, if we want to keep the physical constraint $S(t) \in [0, 1]$, we need to assume $\frac{B\sigma_s}{B - C\hat{h}} < 1$, i.e. (2.24) (otherwise basically our results still hold provided that we allow $S$ to take also values larger than 1). In such a situation, we need to emphasize the role of (2.25). To this purpose, let us assume that $X(0) > 1$, which also implies $h(X) = 1$. Then, (3.99) reduces to

$$X' = (PS - A)$$  

(3.107)

and in this sense condition (2.25) (which can be rewritten as $\frac{A}{P} > \frac{B\sigma_s}{B - C\hat{h}}$) prescribes that (if we reason in the $(X, S)$-plane with $X$ represented in the horizontal axis), in the intersection between $S$ and the semiplane $\{X > 1\}$, $X'$ stays negative (hence arbitrary growth of $X$ is prevented, because trajectories tend to eventually enter the region $S$).

On the other hand, we can see that, when $\frac{A}{P} \leq \frac{B\sigma_s}{B - C\hat{h}}$, dissipativity cannot hold. Indeed if $S(0) \in \left[\frac{B\sigma_s}{C + B}, \frac{B\sigma_s}{B - C\hat{h}}\right]$ and $X(0) \geq 1$, then $X(t)$ is forced to increase forever, because $(X, S)$ can never leave the positively invariant region $S$ where, now, $X' > 0$. On the other hand, the situation when $\frac{A}{P} \in \left(\frac{B\sigma_s}{C + B}, \frac{B\sigma_s}{B - C\hat{h}}\right)$ is unclear, in the sense that, when $X > 1$, in the “upper” part of the strip $S$, $X'$ is positive, whereas $X$' is negative in the “lower” part of $S$, so the evolution of $(X, S)$ may be more difficult to capture. Of course, the behavior may be even more complicated once one considers general (i.e., not necessarily spatially homogeneous) solutions to (1.1)-(1.3), because in that case also equation (1.2) plays an important role (whereas (1.2) “disappears” in the spatially homogeneous setting).

Acknowledgments. This research has been performed in the framework of the project Fondazione Cariplo-Regione Lombardia MEGAsTAR “Matematica d’Eccellenza in biologia ed ingegneria come acceleratore di una nuova strateGia per l’ATtriRattività dell’ateneo pavese”. The present paper also benefits from the support of the MIUR-PRIN Grant 2015PA5MP7 “Calculus of Variations” for GS, and of the GNAMPA (Gruppo Nazionale per l’Analisi Matematica, la Probabilità e le loro Applicazioni) of INdAM (Istituto Nazionale di Alta Matematica) for ER and GS.

References

[1] A. Agosti, P.F. Antonietti, P. Ciarletta, M. Grasselli, M. Verani, A Cahn-Hilliard-type equation with application to tumor growth dynamics, Math. Methods Appl. Sci., 40 (2017), 7598–7626.

[2] A.V. Babin, M.I. Vishik, Attractors of evolution equations, North-Holland, Amsterdam, 1992.

[3] S. Bosia, M. Conti, M. Grasselli, On the Cahn–Hilliard–Brinkman system, Commun. Math. Sci., 13, (2015), 1541–1567.

[4] J.W. Cahn and J.E. Hilliard, Free energy of a nonuniform system. I. Interfacial free energy, J. Chem. Phys., 28 (1958), 258–267.

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

[6] 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.
[7] P. Colli, G. Gilardi, E. Rocca, 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), 37–54.

[8] V. Cristini, J. Lowengrub, Multiscale modeling of cancer. An integrated experimental and mathematical modeling approach, Cambridge Univ. Press, 2010.

[9] V. Cristini, X. Li, J.S. Lowengrub, S.M. Wise, Nonlinear simulations of solid tumor growth using a mixture model: invasion and branching, J. Math. Biol., 58 (2009), 723–763.

[10] M. Dai, E. Feireisl, E. Rocca, G. Schimperna, M. Schonbek, Analysis of a diffuse interface model for multispecies tumor growth, Nonlinearity, 30 (2017), 1639–1658.

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

[12] S. Frigeri, K.F. Lam, E. Rocca, On a diffuse interface model for tumor growth with non-local interactions and degenerate mobilities. In: P. Colli, A. Favini, E. Rocca, G. Schimperna, J. Sprekels (eds.), Solvability, Regularity, Optimal Control of Boundary Value Problems for PDEs, pp. 217–254, Springer INdAM Series, Springer, Milan, 2017.

[13] S. Frigeri, K.F. Lam, E. Rocca, G. Schimperna, On a multi-species Cahn-Hilliard-Darcy tumor growth model with singular potentials, Commun. Math. Sci., 16 (2018), 821–856.

[14] H. Garcke, K.F. Lam, Global weak solutions and asymptotic limits of a Cahn–Hilliard–Darcy system modelling tumour growth, AIMS Mathematics, 1 (2016), 318–360.

[15] H. Garcke, K.F. Lam, Analysis of a Cahn–Hilliard system with non zero Dirichlet conditions modelling tumour growth with chemotaxis, Discrete Contin. Dyn. Syst., 37 (2017), 4277–4308.

[16] H. Garcke, K.F. Lam, Well-posedness of a Cahn–Hilliard system modelling tumour growth with chemotaxis and active transport, European J. Appl. Math., 28 (2017), 284–316.

[17] H. Garcke, K.F. Lam, R. Nünnberg, E. Sitka, A multiphase Cahn–Hilliard–Darcy model for tumour growth with necrosis, Math. Models Methods Appl. Sci., 28 (2018), 525–577.

[18] H. Garcke, K.F. Lam, E. Rocca, Optimal control of treatment time in a diffuse interface model for tumour growth, Appl Math Optim, 78 (2018), 495–544.

[19] H. Garcke, K.F. Lam, E. Sitka, V. Styles, A Cahn–Hilliard–Darcy model for tumour growth with chemotaxis and active transport, Math. Models Methods Appl. Sci., 26 (2016), 1095–1148.

[20] 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.

[21] A. Hawkins-Daarud, S. Prudhomme, K.G. van der Zee, J.T. Oden, Bayesian calibration, validation, and uncertainty quantification of diffuse interface models of tumor growth, J. Math. Biol., 67 (2013), 1457–1485.

[22] D. Hilhorst, J. Kampmann, T.N. Nguyen, K.G. van der Zee, Formal asymptotic limit of a diffuse-interface tumor-growth model, Math. Models Methods Appl. Sci., 25 (2015), 1011–1043.

[23] J. Jiang, H. Wu, S. Zheng, Well-posedness and long-time behavior of a non-autonomous Cahn–Hilliard–Darcy system with mass source modeling tumor growth, J. Differential Equations, 259 (2015), 3032–3077.

[24] J.S. Lowengrub, E. Titi, K.Zhao, Analysis of a mixture model of tumor growth, European J. Appl. Math., 24 (2013), 691–734.

[25] S. Melchionna, E. Rocca, Varifold solutions of a sharp interface limit of a diffuse interface model for tumor growth, Interfaces Free Bound., 19 (2018), 571–590.
[26] A. Miranville, The Cahn-Hilliard equation and some of its variants, AIMS Mathematics, 2 (2017), 479–544.

[27] A. Miranville, S. Zelik, Robust exponential attractors for Cahn-Hilliard type equations with singular potentials, Math. Methods Appl. Sci., 27 (2004), 545–582.

[28] A. Miranville, S. Zelik, Attractors for dissipative partial differential equations in bounded and unbounded domains, in “Handbook of Differential Equations: Evolutionary Equations, Vol. IV” (eds. C.M. Dafermos and M. Pokorny), Elsevier/North-Holland, 103–200, 2008.

[29] E. Rocca, R. Scala, A rigorous sharp interface limit of a diffuse interface model related to tumor growth, J. Nonlinear Sci., 27 (2017), 847–872.

[30] R. Temam, Infinite Dimensional Dynamical Systems in Mechanics and Physics, Springer, New York, 1997.

[31] 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.

[32] 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.