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FORMAL ASYMPTOTIC LIMIT OF A DIFFUSE-INTERFACE TUMOR-GROWTH MODEL

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Abstract We consider a diffuse-interface tumor-growth model, which has the form of a phase-field system. We discuss the singular limit of this problem. More precisely, we formally prove that as the reaction coefficient tends to zero, the solution converges to the solution of a free boundary problem.

Keywords Reaction-diffusion system, singular perturbation, interface motion, matched asymptotic expansion, tumor-growth model.

1 Introduction

Diffuse-interface tumor-growth models have been modeled and studied in several articles [33, 49, 20, 8, 37, 36]. We also refer to the overviews in [19, 38, 21, 42]. The basic model is composed of a fourth order parabolic

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equation for the tumor cell concentration $u : \Omega \rightarrow \mathbb{R}$ coupled to an elliptic equation for the nutrient concentration $\sigma : \Omega \rightarrow \mathbb{R}$:

$$u_t = \Delta(-\varepsilon^{-1}f(u) - \varepsilon\Delta u) + \varepsilon^{-1}p_0\sigma u \quad (1a)$$

$$-\Delta\sigma + \varepsilon^{-1}p_0\sigma u = 0, \quad (1b)$$

where ε^2 is the diffusivity corresponding to the surface energy, the positive constant p_0 is a proliferation growth parameter, and f is a bistable function.

Introducing the chemical potential $\mu : \Omega \rightarrow \mathbb{R}$, given by

$$\mu := -\varepsilon^{-1}f(u) - \varepsilon\Delta u,$$

(1a)-(1b) becomes

$$u_t = \Delta\mu + \varepsilon^{-1}p_0\sigma u, \quad (2a)$$

$$\mu = -\varepsilon^{-1}f(u) - \varepsilon\Delta u, \quad (2b)$$

$$0 = \Delta\sigma - \varepsilon^{-1}p_0\sigma u. \quad (2c)$$

The above system models the evolution of the first stage of a growing tumor [44]. In this stage a tumor grows because of the consumption of nutrients that diffuse through the surrounding tissue. This stage is referred to as avascular growth, as the tumor has not yet acquired its own blood supply to nurture itself. Consumption of nutrients is modeled in (2a) and (2c) via the reactive terms. To describe the evolution of the tumor boundary a diffuse-interface description is employed. This is classically modeled in (2a) with a diffusion via the chemical potential μ which depends in a nonlinear manner on u and contains the higher-order regularization $\varepsilon\Delta u$, see (2b).

Diffuse-interface tumor-growth models fall within the broader class of multiconstituent tumor-growth models based on continuum mixture theory, such as presented in [5, 4, 12, 34, 7]. The derivation of diffuse-interface models within continuum mixture theory has been reviewed in [42], and requires the set up of balance laws for each constituent as well as the specification of constraints on the constitutive choices imposed by the second law of thermodynamics. Typically, only the cellular and fluidic constituents of a tumor are modeled as parts of a mixture, while nutrients are considered separately. Recently however, a diffuse-interface tumor growth model has been proposed that incorporates all constituents within the mixture and is proven to be thermodynamically consistent, see [37]. In fact, the model is of gradient-flow type.

The model from [37] is a modification of (2) and has a natural four-constituent interpretation: a tumorous phase $u \approx 1$, a healthy cell phase $u \approx -1$, a nutrient-rich extracellular water phase $\sigma \approx 1$ and a nutrient-poor extracellular water phase $\sigma \approx 0$. It is given by

$$u_t = \Delta\mu + \varepsilon^{-1}p(u)(\sigma - \delta\mu) \quad (3a)$$

$$\mu = -\varepsilon^{-1}f(u) - \varepsilon\Delta u \quad (3b)$$

$$\sigma_t = \Delta\sigma - \varepsilon^{-1}p(u)(\sigma - \delta\mu) \quad (3c)$$

where $\delta > 0$ is a small regularization parameter, and the growth function $p(u)$ is defined by

$$p(u) := \begin{cases} 2p_0\sqrt{W(u)} & u \in [-1, 1] \\ 0 & \text{elsewhere.} \end{cases}$$

Here $W(u) := -\int_{-1}^u f(s) ds$ is the classical Cahn–Hilliard double well free-energy density. We assume that the bistable function $f(u)$ has two stable roots ± 1 , an unstable root 0 and mean zero: $\int_{-1}^1 f(s) ds = 0$. Note that, compared to (2a)-(2c), the reactive terms have been modified to be thermodynamically consistent. They include a regularization part $\delta\mu$ and they have been localized to the interface (since $p(u)$ is nonzero if $u \in (-1, 1)$); see [37] for more details.

In this work, we shall be interested in the singular limit $\varepsilon \downarrow 0$ of (3a)-(3c) together with homogeneous Neumann boundary conditions. For articles involving singular limits we refer to [3, 13, 17, 14, 46, 43, 9, 39, 26, 2, 23, 48, 15, 1]; we should also mention the overviews [18, 32, 41, 40], and the numerical studies [28, 27, 29, 30, 31, 16].

The unknown pair (u, σ) is a dissipative gradient flow for the energy functional

$$\mathcal{E}(u, \sigma) := \int_{\Omega} \left(\frac{\varepsilon}{2} |\nabla u|^2 + \varepsilon W(u) + \frac{\sigma^2}{2\delta} \right).$$

We refer to Theorem 1.1 for the proof of this property in a slightly more general context.

1.1 The main results

In order to study the singular limit of Problem (3a)-(3c) as $\varepsilon \downarrow 0$, we introduce the following phase-field model

$$\begin{aligned} \alpha\mu_t^\varepsilon + u_t^\varepsilon &= \Delta\mu^\varepsilon + \varepsilon^{-1}p(u^\varepsilon)(\sigma^\varepsilon - \delta\mu^\varepsilon) & \text{in } \Omega \times (0, +\infty), & (4a) \\ \varepsilon^{-1}\mu^\varepsilon - \alpha u_t^\varepsilon &= -\varepsilon^{-2}f(u^\varepsilon) - \Delta u^\varepsilon & \text{in } \Omega \times (0, +\infty), & (4b) \\ \sigma_t^\varepsilon &= \Delta\sigma^\varepsilon - \varepsilon^{-1}p(u^\varepsilon)(\sigma^\varepsilon - \delta\mu^\varepsilon) & \text{in } \Omega \times (0, +\infty), & (4c) \end{aligned}$$

together with the boundary and initial conditions

$$\begin{aligned} \frac{\partial\mu^\varepsilon}{\partial\nu} = \frac{\partial u^\varepsilon}{\partial\nu} = \frac{\partial\sigma^\varepsilon}{\partial\nu} &= 0 & \text{on } \partial\Omega \times (0, +\infty), & (4d) \\ \alpha\mu^\varepsilon(\cdot, 0) = \alpha\mu_0^\varepsilon, \quad u^\varepsilon(\cdot, 0) = u_0^\varepsilon, \quad \sigma^\varepsilon(\cdot, 0) = \sigma_0^\varepsilon, & \text{on } \Omega. & (4e) \end{aligned}$$

Here, Ω is a smooth bounded domain of \mathbb{R}^N ($N \geq 2$), ν is the outer unit normal vector to $\partial\Omega$ and α is a positive constant. We denote by (P_ε) the problem (4a)-(4e). Setting $\alpha = 0$ in the singular limit of Problem (P_ε) , we will obtain the singular limit of Problem (3a)-(3c). Problem (P_ε) possesses the Lyapunov functional

$$E_\varepsilon(u, \mu, \sigma) := \int_\Omega \left(\frac{\varepsilon}{2} |\nabla u|^2 + \frac{1}{\varepsilon} W(u) + \frac{\alpha\mu^2}{2} + \frac{\sigma^2}{2\delta} \right).$$

We will prove in section 2 that Problem (P_ε) is a gradient flow associated to the functional $E_\varepsilon(u, \mu, \sigma)$.

Theorem 1.1. *Let $(u^\varepsilon, \mu^\varepsilon, \sigma^\varepsilon)$ be a smooth solution of Problem (P_ε) . Then $E_\varepsilon(u^\varepsilon, \mu^\varepsilon, \sigma^\varepsilon)$ is decreasing along solution orbits.*

We will show in the following that, if in some sense

$$\mu^\varepsilon \longrightarrow \mu, \quad u^\varepsilon \longrightarrow u, \quad \sigma^\varepsilon \longrightarrow \sigma,$$

then the triple (μ, u, σ) is characterized by a limit free boundary problem, where the interface motion equation appears as the limit of the equation (4b). A rigorous proof of the convergence of the solution of the equation (4b) may for instance be found in [1]. According to [1], the function u only takes the two values -1 or 1 and the interface which separates the regions where $\{u = -1\}$ and $\{u = 1\}$ partially moves according to its mean curvature.

Assumption on initial conditions: We assume that as $\varepsilon \downarrow 0$,

$$\mu_0^\varepsilon \longrightarrow \mu_0, \quad u_0^\varepsilon \longrightarrow u_0, \quad \sigma_0^\varepsilon \longrightarrow \sigma_0,$$

in some sense and that there exists a closed smooth hypersurface without boundary $\Gamma_0 \subset\subset \Omega$ which divides Ω into two subdomains $\Omega^+(0)$ and $\Omega^-(0)$ such that

$$u_0 = \begin{cases} -1 & \text{in } \Omega^-(0), \\ 1 & \text{in } \Omega^+(0). \end{cases} \quad (5)$$

We also assume that $\Omega^+(0)$ is the region enclosed by Γ_0 and that $\Omega^-(0)$ is the region enclosed between $\partial\Omega$ and Γ_0 .

Now, we are ready to introduce a free boundary problem namely the singular limit of Problem (P_ε) as $\varepsilon \downarrow 0$:

$$u(x, t) = \begin{cases} 1 & \text{in } \Omega^+(t), t \in (0, T) \\ -1 & \text{in } \Omega^-(t), t \in (0, T) \end{cases} \quad (6a)$$

$$\alpha V_n = -(N-1)\kappa + \mathcal{C}\mu \quad \text{on } \Gamma(t), t \in (0, T) \quad (6b)$$

$$\alpha\mu_t + u_t = \Delta\mu + 2\sqrt{2}p_0(\sigma - \delta\mu)\delta_0(x - \Gamma(t)) \quad \text{in } \Omega \times (0, T), \quad (6c)$$

$$\sigma_t = \Delta\sigma - 2\sqrt{2}p_0(\sigma - \delta\mu)\delta_0(x - \Gamma(t)) \quad \text{in } \Omega \times (0, T), \quad (6d)$$

together with the boundary and initial conditions

$$\frac{\partial\mu}{\partial\nu} = \frac{\partial\sigma}{\partial\nu} = 0 \quad \text{on } \partial\Omega \times (0, T), \quad (6e)$$

$$\alpha\mu(\cdot, 0) = \alpha\mu_0, \quad \sigma(\cdot, 0) = \sigma_0, \quad \text{on } \Omega, \quad (6f)$$

$$\Gamma(0) = \Gamma_0, \quad (6g)$$

Here, $\Gamma(t) \subset\subset \Omega$ is a closed hypersurface; $\Omega^+(t)$ is the region enclosed by $\Gamma(t)$; $\Omega^-(t) = \Omega \setminus (\Omega^+(t) \cup \Gamma(t))$; δ_0 is the Dirac distribution; $V_n : \Gamma(t) \rightarrow \mathbb{R}^N$ is the normal velocity of the evolving interface $\Gamma(t)$, κ is the mean curvature at each point of $\Gamma(t)$ and

$$\mathcal{C} = \left[\int_{-1}^1 \sqrt{W(s)/2} \, ds \right]^{-1}.$$

We denote by (P_0) the problem (6a)-(6g) and define

$$\Gamma_T := \bigcup_{t \in (0, T)} \Gamma(t) \times \{t\}.$$

Definition 1.2. *We say that the triple (Γ_T, μ, σ) is a solution of Problem (P_0) if*

(i) Γ_T is smooth,

(ii) for all test functions

$$\psi \in \mathcal{F}_T := \{\psi \in C^{2,1}(\bar{\Omega} \times [0, T]) \text{ such that } \frac{\partial \psi}{\partial \nu} = 0 \text{ on } \partial\Omega \times [0, T] \text{ and } \psi(T) = 0\},$$

we have

$$\int_0^T \int_{\Omega} (-\alpha\mu - u)\psi_t - \int_{\Omega} (\alpha\mu_0 + u_0)\psi(0) = \int_0^T \int_{\Omega} \mu\Delta\psi + 2\sqrt{2}p_0 \int_0^T \int_{\Gamma(t)} (\sigma - \delta\mu)\psi,$$

and

$$\int_0^T \int_{\Omega} -\sigma\psi_t - \int_{\Omega} \sigma_0\psi(0) = \int_0^T \int_{\Omega} \sigma\Delta\psi - 2\sqrt{2}p_0 \int_0^T \int_{\Gamma(t)} (\sigma - \delta\mu)\psi.$$

Now, in order to state the next result, we need some notations. Let $n^+(t), n^-(t)$ be the outer unit normal vectors to $\partial\Omega^+(t)$ and $\partial\Omega^-(t)$, respectively. Note that $n^+ = -n^-$ on Γ_T , so we may define $n := n^+ = -n^-$ on Γ_T . We define $[[\cdot]]$ the jump across $\Gamma(t)$, by $[[\phi]] := \phi^+ - \phi^-$, where ϕ^{\pm} should be understood as the following limit

$$\phi^{\pm}(\cdot) := \lim_{\rho \rightarrow 0^-} \phi(\cdot + \rho n^{\pm}(t)) \text{ on } \Gamma(t).$$

We also define

$$Q_T^+ := \bigcup_{t \in (0, T)} \Omega^+(t) \times \{t\}, \quad \text{and} \quad Q_T^- := \bigcup_{t \in (0, T)} \Omega^-(t) \times \{t\}.$$

Theorem 1.3. *Assume that Problem (P_0) possesses a solution (Γ_T, μ, σ) such that Γ_T is smooth on the time interval $(0, T)$ and that μ and σ are smooth up to Γ_T on both sides of Γ_T . Then the triple (Γ_T, μ, σ) satisfies:*

$\alpha\mu_t = \Delta\mu$	<i>in $Q_T^+ \cup Q_T^-$,</i>	(7a)
$\sigma_t = \Delta\sigma$	<i>on $Q_T^+ \cup Q_T^-$,</i>	(7b)
$[[\mu]] = [[\sigma]] = 0$	<i>on Γ_T,</i>	(7c)
$[[\frac{\partial\mu}{\partial n}]] = -2V_n + 2\sqrt{2}p_0(\sigma - \delta\mu)$	<i>on Γ_T,</i>	(7d)
$[[\frac{\partial\sigma}{\partial n}]] = -2\sqrt{2}p_0(\sigma - \delta\mu)$	<i>on Γ_T,</i>	(7e)
$\alpha V_n = -(N - 1)\kappa + \mathcal{C}\mu$	<i>on Γ_T,</i>	(7f)

together with the boundary and initial conditions

$\frac{\partial\mu}{\partial\nu} = \frac{\partial\sigma}{\partial\nu} = 0$	<i>on $\partial\Omega \times (0, T)$,</i>	(7g)
$\mu(\cdot, 0) = \mu_0, \quad \sigma(\cdot, 0) = \sigma_0,$	<i>on Ω,</i>	(7h)
$\Gamma(0) = \Gamma_0.$		(7i)

In this case, we say that (Γ_T, μ, σ) is a classical solution of Problem (P_0) on the time interval $[0, T]$.

Problem (P_0) possesses the Lyapunov functional

$$E(\Gamma, \mu, \sigma) := \frac{2}{\mathcal{C}} \int_{\Gamma} 1 \, d\Gamma + \int_{\Omega} \left(\frac{\alpha\mu^2}{2} + \frac{\sigma^2}{2\delta} \right),$$

which is analogous to the Lyapunov functional satisfied by Problem (P_ε) .

Theorem 1.4. *Let (Γ_T, μ, σ) be a classical solution of Problem (P_0) . Then $E(\Gamma, \mu, \sigma)$ is decreasing along solution orbits.*

Finally, we will formally prove the following result.

Theorem 1.5. *Let $(\mu^\varepsilon, u^\varepsilon, \sigma^\varepsilon)$ be solution of Problem (P_ε) . We suppose that Problem (P_0) possesses a unique classical solution on the interval $[0, T]$. If $\varepsilon \rightarrow 0$,*

$$\mu^\varepsilon \longrightarrow \mu, \quad u^\varepsilon \longrightarrow u, \quad \sigma^\varepsilon \longrightarrow \sigma \text{ in a strong enough sense,}$$

then (Γ_T, μ, σ) coincide with the classical solution of Problem (P_0) and u is given by (6a).

We note that the singular limit corresponds to a moving boundary problem which is similar to other sharp-interface tumor-growth models [35, 22, 10, 11].

The remainder of the paper is organized as follows: in section 2 we prove Theorem 1.1 and Theorem 1.3; in section 3, we formally justify Theorem 1.5.

2 Proof of the main results

2.1 Proof of Theorem 1.1

It is sufficient to prove that

$$\frac{d}{dt}E_\varepsilon(u^\varepsilon, \mu^\varepsilon, \sigma^\varepsilon) \leq 0. \quad (8)$$

For simplicity, we write u, μ, σ instead of $u^\varepsilon, \mu^\varepsilon, \sigma^\varepsilon$. Now, the inequality (8) follows from the following computations:

$$\begin{aligned} \frac{d}{dt}E_\varepsilon(u, \mu, \sigma) &= \int_{\Omega} \left(\varepsilon \nabla u \nabla u_t + \varepsilon^{-1} W'(u) u_t + \alpha \mu \mu_t + \frac{\sigma \sigma_t}{\delta} \right) \\ &= \int_{\Omega} \left([-\varepsilon^{-1} f(u) - \varepsilon \Delta u] u_t + \alpha \mu \mu_t + \frac{\sigma \sigma_t}{\delta} \right) \\ &= \int_{\Omega} \left((\mu - \alpha \varepsilon u_t) u_t + \alpha \mu \mu_t \right) + \int_{\Omega} \frac{\sigma}{\delta} \left(\Delta \sigma - \varepsilon^{-1} p(u) (\sigma - \delta \mu) \right) \\ &= - \int_{\Omega} \alpha \varepsilon u_t^2 + \int_{\Omega} \mu (u_t + \alpha \mu_t) + \int_{\Omega} \frac{\sigma}{\delta} \left(\Delta \sigma - \varepsilon^{-1} p(u) (\sigma - \delta \mu) \right) \\ &= - \int_{\Omega} \alpha \varepsilon u_t^2 + \int_{\Omega} \mu \left(\Delta \mu + \varepsilon^{-1} p(u) (\sigma - \delta \mu) \right) + \int_{\Omega} \frac{\sigma}{\delta} \left(\Delta \sigma - \varepsilon^{-1} p(u) (\sigma - \delta \mu) \right) \\ &= - \int_{\Omega} \alpha \varepsilon u_t^2 - \int_{\Omega} |\nabla \mu|^2 - \int_{\Omega} \frac{|\nabla \sigma|^2}{\delta} + \varepsilon^{-1} \int_{\Omega} p(u) \left(\mu (\sigma - \delta \mu) - \frac{\sigma}{\delta} (\sigma - \delta \mu) \right) \\ &= - \int_{\Omega} \alpha \varepsilon u_t^2 - \int_{\Omega} |\nabla \mu|^2 - \int_{\Omega} \frac{|\nabla \sigma|^2}{\delta} - \varepsilon^{-1} \int_{\Omega} p(u) \left(\sqrt{\delta} \mu - \frac{\sigma}{\sqrt{\delta}} \right)^2 \leq 0. \end{aligned}$$

2.2 Proof of Theorem 1.3

First, we recall that $n^+(t), n^-(t)$ are the outer unit normal vectors to $\partial\Omega^+(t)$ and $\partial\Omega^-(t)$, respectively and $n := n^+ = -n^-$ on Γ_T . We define $V_n = V \cdot n_+$, where V is the velocity of displacement of the interface Γ_T .

2.2.1 Equations for μ

We recall that u, μ satisfy

$$\int_0^T \int_{\Omega} (-\alpha\mu - u)\psi_t - \int_{\Omega} (\alpha\mu_0 + u_0)\psi(0) = \int_0^T \int_{\Omega} \mu\Delta\psi + 2\sqrt{2}p_0 \int_0^T \int_{\Gamma(t)} (\sigma - \delta\mu)\psi, \quad (9)$$

for all $\psi \in \mathcal{F}_T$. We define the terms A_1, A_2 and the diffusion term B by

$$A_1 := \int_0^T \int_{\Omega} -\alpha\mu\psi_t, \quad A_2 := \int_0^T \int_{\Omega} -u\psi_t, \quad \text{and} \quad B := \int_0^T \int_{\Omega} \mu\Delta\psi.$$

Analysis of the terms A_1 and A_2 : Our analysis of the terms A_1 and A_2 relies on the Reynolds transport theorem, by which we have

$$\frac{d}{dt} \int_{\Omega^{\pm}(t)} \phi\psi = \int_{\Omega^{\pm}(t)} (\phi_t\psi + \phi\psi_t) \pm \int_{\Gamma(t)} V_n\phi^{\pm}\psi,$$

for all smooth function ψ and for function ϕ . These equations for the integrals over $\Omega^{\pm}(t)$ yield

$$\frac{d}{dt} \int_{\Omega^{+}(t) \cup \Omega^{-}(t)} \phi\psi = \int_{\Omega^{+}(t) \cup \Omega^{-}(t)} (\phi_t\psi + \phi\psi_t) + \int_{\Gamma(t)} V_n[\phi]\psi.$$

Hence we have

$$\int_{\Omega^{+}(t) \cup \Omega^{-}(t)} -\phi\psi_t = \int_{\Omega^{+}(t) \cup \Omega^{-}(t)} \phi_t\psi + \int_{\Gamma(t)} V_n[\phi]\psi - \frac{d}{dt} \int_{\Omega^{+}(t) \cup \Omega^{-}(t)} \phi\psi. \quad (10)$$

In our case, we chose $\phi := \alpha\mu$ in (10) and integrate from 0 to T . This yields

$$\begin{aligned} A_1 &= \int_0^T \int_{\Omega^{+}(t) \cup \Omega^{-}(t)} \alpha\mu_t\psi + \int_0^T \int_{\Gamma(t)} V_n[\alpha\mu]\psi - \int_0^T \frac{d}{dt} \int_{\Omega^{+}(t) \cup \Omega^{-}(t)} \alpha\mu\psi \\ &= \int_0^T \int_{\Omega^{+}(t) \cup \Omega^{-}(t)} \alpha\mu_t\psi + \int_0^T \int_{\Gamma(t)} \alpha V_n[\mu]\psi + \int_{\Omega^{+}(0) \cup \Omega^{-}(0)} \alpha\mu(0)\psi(0). \end{aligned} \quad (11)$$

Similarly, we apply the formula (10) for $\phi := u$ to obtain

$$\begin{aligned} A_2 &= \int_0^T \int_{\Omega^+(t) \cup \Omega^-(t)} u_t \psi + \int_0^T \int_{\Gamma(t)} V_n \llbracket u \rrbracket \psi + \int_{\Omega^+(0) \cup \Omega^-(0)} u(0) \psi(0) \\ &= 2 \int_0^T \int_{\Gamma(t)} V_n \psi + \int_{\Omega^+(0) \cup \Omega^-(0)} u(0) \psi(0). \end{aligned} \quad (12)$$

Analysis of the term B: We write B as the sum

$$B = \int_0^T \left(\int_{\Omega^+(t)} \mu \Delta \psi + \int_{\Omega^-(t)} \mu \Delta \psi \right).$$

Integration by parts yields

$$\begin{aligned} \int_{\Omega^-(t)} \mu \Delta \psi &= - \int_{\Omega^-(t)} \nabla \mu \nabla \psi + \int_{\Gamma(t)} \frac{\partial \psi}{\partial n^-} \mu^- \\ &= \int_{\Omega^-(t)} \Delta \mu \psi - \int_{\Gamma(t)} \frac{\partial \mu^-}{\partial n^-} \psi - \int_{\partial \Omega} \frac{\partial \mu}{\partial \nu} \psi + \int_{\Gamma(t)} \frac{\partial \psi}{\partial n^-} \mu^- \\ &= \int_{\Omega^-(t)} \Delta \mu \psi + \int_{\Gamma(t)} \frac{\partial \mu^-}{\partial n} \psi - \int_{\partial \Omega} \frac{\partial \mu}{\partial \nu} \psi - \int_{\Gamma(t)} \frac{\partial \psi}{\partial n} \mu^- \end{aligned}$$

and

$$\int_{\Omega^+(t)} \mu \Delta \psi = \int_{\Omega^+(t)} \Delta \mu \psi - \int_{\Gamma(t)} \frac{\partial \mu^+}{\partial n} \psi + \int_{\Gamma(t)} \frac{\partial \psi}{\partial n} \mu^+$$

which implies that

$$\int_{\Omega^+(t) \cup \Omega^-(t)} \mu \Delta \psi = \int_{\Omega^+(t) \cup \Omega^-(t)} \Delta \mu \psi - \int_{\Gamma(t)} \llbracket \frac{\partial \mu}{\partial n} \rrbracket \psi + \int_{\Gamma(t)} \frac{\partial \psi}{\partial n} \llbracket \mu \rrbracket - \int_{\partial \Omega} \frac{\partial \mu}{\partial \nu} \psi.$$

Integrating this identity from 0 to T , we obtain

$$B = \int_0^T \int_{\Omega^+(t) \cup \Omega^-(t)} \Delta \mu \psi - \int_0^T \int_{\Gamma(t)} \llbracket \frac{\partial \mu}{\partial n} \rrbracket \psi + \int_0^T \int_{\Gamma(t)} \frac{\partial \psi}{\partial n} \llbracket \mu \rrbracket - \int_0^T \int_{\partial \Omega} \frac{\partial \mu}{\partial \nu} \psi. \quad (13)$$

Conclusion: Combining (9), (11) (12) and (13), we then have for all $\psi \in \mathcal{F}_T$,

$$\begin{aligned}
& \int_0^T \int_{\Omega^+(t) \cup \Omega^-(t)} \alpha \mu_t \psi + \int_0^T \int_{\Gamma(t)} V_n(\alpha \llbracket \mu \rrbracket + 2) \psi \\
& \quad + \int_{\Omega^+(t) \cup \Omega^-(t)} \alpha(\mu(0) - \mu_0) \psi(0) + \int_{\Omega^+(t) \cup \Omega^-(t)} (u(0) - u_0) \psi(0) \\
& = \int_0^T \int_{\Omega^+(t) \cup \Omega^-(t)} \Delta \mu \psi - \int_0^T \int_{\Gamma(t)} \llbracket \frac{\partial \mu}{\partial n} \rrbracket \psi + \int_0^T \int_{\Gamma(t)} \frac{\partial \psi}{\partial n} \llbracket \mu \rrbracket - \int_0^T \int_{\partial \Omega} \frac{\partial \mu}{\partial \nu} \psi \\
& \quad + \int_0^T \int_{\Gamma(t)} 2\sqrt{2} p_0 (\sigma - \delta \mu) \psi.
\end{aligned} \tag{14}$$

By using test functions with suitable supports, namely $\psi \in C_0^\infty(Q_T^+)$ and $\psi \in C_0^\infty(Q_T^-)$, we obtain

$$\alpha \mu_t = \Delta \mu \text{ in } Q_T^+ \cup Q_T^-. \tag{5b}$$

Similarly, by using $\psi \in C_0^\infty(Q_T)$ such that $\frac{\partial \psi}{\partial n} = 0$ on Γ_T , we obtain

$$V_n(2 + \alpha \llbracket \mu \rrbracket) = -\llbracket \frac{\partial \mu}{\partial n} \rrbracket + 2\sqrt{2} p_0 (\sigma - \delta \mu) \text{ on } \Gamma_T. \tag{15}$$

Now, we use $\psi \in C_0^\infty(Q_T)$, to deduce that

$$\int_0^T \int_{\Gamma(t)} \frac{\partial \psi}{\partial n} \llbracket \mu \rrbracket = 0 \text{ for all } \psi \in C_0^\infty(Q_T). \tag{16}$$

Therefore,

$$\llbracket \mu \rrbracket = 0 \text{ on } \Gamma_T. \tag{17}$$

It follows from (15) and (17) that

$$2V_n = -\llbracket \frac{\partial \mu}{\partial n} \rrbracket + 2\sqrt{2} p_0 (\sigma - \delta \mu) \text{ on } \Gamma_T.$$

Now, for the initial conditions, we use the test function $\psi \in \mathcal{F}_T$ such that $\psi = 0$ on $\partial \Omega \times (0, T)$ to obtain

$$u(0) + \alpha \mu(0) = u_0 + \alpha \mu_0,$$

which in view of (5) implies that

$$\mu(0) = \mu_0, \quad u(0) = u_0$$

Finally, the remaining term in (14) allows us to conclude that

$$\frac{\partial \mu}{\partial \nu} = 0.$$

Therefore, μ satisfies the equations:

$$\begin{aligned} \alpha \mu_t &= \Delta \mu && \text{in } Q_T^+ \cup Q_T^-, \\ 2V_n &= -\llbracket \frac{\partial \mu}{\partial n} \rrbracket + 2\sqrt{2}p_0(\sigma - \delta \mu) && \text{on } \Gamma_T, \\ \llbracket \mu \rrbracket &= 0 && \text{on } \Gamma_T, \end{aligned}$$

together with the boundary condition and the initial condition:

$$\frac{\partial \mu}{\partial \nu} = 0, \quad \mu(0) = \mu_0.$$

2.2.2 Equations for σ

Since the computations in this section are similar to the previous ones, we will only give a sketch of the necessary steps. For $\psi \in C_0^\infty(Q_T)$, we have

$$\int_0^T \int_\Omega -\sigma \psi_t = \int_0^T \int_\Omega \sigma \Delta \psi - 2\sqrt{2}p_0 \int_0^T \int_{\Gamma(t)} (\sigma - \delta \mu) \psi. \quad (18)$$

We define two terms

$$C := \int_0^T \int_\Omega -\sigma \psi_t \quad \text{and} \quad D := \int_0^T \int_\Omega \sigma \Delta \psi.$$

One can easily deduce that

$$C = \int_0^T \int_{\Omega^+(t) \cup \Omega^-(t)} \sigma_t \psi + \int_0^T \int_{\Gamma(t)} V_n \llbracket \sigma \rrbracket \psi,$$

and

$$D = \int_0^T \int_{\Omega^+(t) \cup \Omega^-(t)} \Delta \sigma \psi - \int_0^T \int_{\Gamma(t)} \llbracket \frac{\partial \sigma}{\partial n} \rrbracket \psi + \int_0^T \int_{\Gamma(t)} \frac{\partial \psi}{\partial n} \llbracket \sigma \rrbracket.$$

It follows that

$$\begin{aligned} \int_0^T \int_{\Omega^+(t) \cup \Omega^-(t)} \sigma_t \psi + \int_0^T \int_{\Gamma(t)} V_n \llbracket \sigma \rrbracket \psi &= \int_0^T \int_{\Omega^+(t) \cup \Omega^-(t)} \Delta \sigma \psi \\ &- \int_0^T \int_{\Gamma(t)} \llbracket \frac{\partial \sigma}{\partial n} \rrbracket \psi + \int_0^T \int_{\Gamma(t)} \frac{\partial \psi}{\partial n} \llbracket \sigma \rrbracket - 2\sqrt{2}p_0 \int_0^T \int_{\Gamma(t)} (\sigma - \delta\mu) \psi. \end{aligned}$$

and hence we have

$$\begin{aligned} \sigma_t &= \Delta \sigma && \text{in } Q_T^+ \cup Q_T^-, \\ \llbracket \frac{\partial \sigma}{\partial n} \rrbracket &= -2\sqrt{2}p_0(\sigma - \delta\mu) && \text{on } \Gamma_T, \\ \llbracket \sigma \rrbracket &= 0 && \text{on } \Gamma_T, \end{aligned}$$

This concludes the proof of Theorem 1.3

2.3 Proof of Theorem 1.4

We prove below that

$$\frac{d}{dt} E(\Gamma, \mu, \sigma) \leq 0. \quad (19)$$

The inequality (19) follows from the following computations and [24, Theorem 4.3 p.355 and formula 4.12 p.356]):

$$\begin{aligned} &\frac{d}{dt} E(\Gamma, \mu, \sigma) \\ &= \frac{2}{\mathcal{C}} \int_{\Gamma} (N-1)\kappa V_n + \int_{\Omega^+ \cup \Omega^-} (\alpha\mu\mu_t + \delta^{-1}\sigma\sigma_t) \\ &= \frac{2}{\mathcal{C}} \int_{\Gamma} [\mathcal{C}\mu - \alpha V_n] V_n + \int_{\Omega^+ \cup \Omega^-} (\alpha\mu\mu_t + \delta^{-1}\sigma\sigma_t) \\ &= \int_{\Gamma} 2\mu V_n - \int_{\Gamma} \frac{2\alpha}{\mathcal{C}} V_n^2 + \int_{\Omega^+ \cup \Omega^-} (\mu\Delta\mu + \delta^{-1}\sigma\Delta\sigma) \\ &= \int_{\Gamma} \mu \left(-\llbracket \frac{\partial \mu}{\partial n} \rrbracket + 2\sqrt{2}p_0(\sigma - \delta\mu) \right) - \int_{\Gamma} \frac{2\alpha}{\mathcal{C}} V_n^2 + \int_{\Omega^+ \cup \Omega^-} (\mu\Delta\mu + \delta^{-1}\sigma\Delta\sigma) \\ &= \int_{\Gamma} 2\sqrt{2}p_0\mu(\sigma - \delta\mu) - \int_{\Gamma} \frac{2\alpha}{\mathcal{C}} V_n^2 - \int_{\Omega^+ \cup \Omega^-} |\nabla\mu|^2 + \int_{\Omega^+ \cup \Omega^-} \delta^{-1}\sigma\Delta\sigma \\ &= \int_{\Gamma} 2\sqrt{2}p_0\mu(\sigma - \delta\mu) - \int_{\Gamma} \frac{2\alpha}{\mathcal{C}} V_n^2 - \int_{\Omega^+ \cup \Omega^-} |\nabla\mu|^2 - \int_{\Omega^+ \cup \Omega^-} \frac{|\nabla\sigma|^2}{\delta} + \int_{\Gamma} \delta^{-1}\sigma \llbracket \frac{\partial \sigma}{\partial n} \rrbracket \end{aligned}$$

which in turn implies that

$$\begin{aligned}
& \frac{d}{dt} E(\Gamma, \mu, \sigma) \\
&= \int_{\Gamma} 2\sqrt{2}p_0 \left(\mu(\sigma - \delta\mu) - \delta^{-1}\sigma(\sigma - \delta\mu) \right) - \int_{\Gamma} \frac{2\alpha}{\mathcal{C}} V_n^2 - \int_{\Omega \cup \Omega^-} |\nabla \mu|^2 - \int_{\Omega \cup \Omega^-} \frac{|\nabla \sigma|^2}{\delta} \\
&= - \int_{\Gamma} \frac{2\alpha}{\mathcal{C}} V_n^2 - \int_{\Omega \cup \Omega^-} |\nabla \mu|^2 - \int_{\Omega \cup \Omega^-} \frac{|\nabla \sigma|^2}{\delta} - \int_{\Gamma} 2\sqrt{2}p_0 \left(\sqrt{\delta}\mu - \frac{\sigma}{\sqrt{\delta}} \right)^2 \leq 0.
\end{aligned}$$

3 Formal derivation of Theorem 1.5

This section is devoted to prove formally theorem 1.5. We shall derive in turn equations for $u, \Gamma(t), \mu, \sigma$.

3.1 Equation for u

First, we formally show that u only takes two values ± 1 . To that purpose, we rewrite Equation (4b) in the form

$$\alpha u_t^\varepsilon = \Delta u^\varepsilon + \varepsilon^{-2} f(u^\varepsilon) + \varepsilon^{-1} \mu^\varepsilon.$$

By setting $\tau := t/\varepsilon^2$, we obtain

$$\alpha u_\tau^\varepsilon = \varepsilon^2 \Delta u^\varepsilon + f(u^\varepsilon) + \varepsilon \mu^\varepsilon.$$

When ε is small, we neglect the effect of diffusion term $\varepsilon^2 \Delta u^\varepsilon$ and of the term $\varepsilon \mu^\varepsilon$ with respect to the term $f(u^\varepsilon)$, which yields the ordinary differential equation

$$\alpha \frac{du^\varepsilon}{d\tau} \cong f(u^\varepsilon). \quad (20)$$

Note that $\tau \rightarrow \infty$ as $\varepsilon \rightarrow 0$. Remembering that ± 1 are two stable zeros of this equation. We formally deduce that as $\varepsilon \downarrow 0$

$$\begin{cases} u^\varepsilon(x, t) \text{ approaches } -1 & \text{if } u^\varepsilon(x, 0) < 0 \\ u^\varepsilon(x, t) \text{ approaches } 1 & \text{if } u^\varepsilon(x, 0) > 0. \end{cases} \quad (21)$$

3.2 Formal derivation of the interface equation

We define

$$\Omega^-(t) = \{x \in \Omega : u(x, t) = -1\}, \quad \Omega^+(t) = \{x \in \Omega : u(x, t) = 1\},$$

and

$$\Gamma(t) := \Omega \setminus (\Omega^-(t) \cup \Omega^+(t)).$$

Since roughly speaking, the regions $\{u = -1\}$ and $\{u = 1\}$ are the "limit" of the regions $\{u^\varepsilon \approx -1\}$ and $\{u^\varepsilon \approx 1\}$ as $\varepsilon \rightarrow 0$, $\Gamma(t)$ can be considered as the limit as $\varepsilon \rightarrow 0$ of $\Gamma^\varepsilon(t)$ which is the interface between the two regions

$$\{x \in \Omega : u^\varepsilon(x, t) \approx -1\} \quad \text{and} \quad \{x \in \Omega : u^\varepsilon(x, t) \approx 1\}.$$

We recall that 0 is an unstable equilibria of Equation (20), and define

$$\Gamma^\varepsilon(t) = \{x \in \Omega : u^\varepsilon(x, t) = 0\} \quad \text{for each } t \geq 0.$$

In what follows, we will use an formal asymptotic expansion to derive the equation describing $\Gamma(t)$. We need some preparations.

1. Signed distance function: We assume that the interface $\Gamma(t)$ is a smooth, closed hypersurface without boundary of \mathbb{R}^N . Further, we suppose that $\Omega^+(t)$ is the region enclosed by $\Gamma(t)$ and that $\Omega^-(t)$ is the region enclosed between $\partial\Omega$ and $\Gamma(t)$. Let $\tilde{d}(x, t)$ be the signed distance function to $\Gamma(t)$ defined by

$$\tilde{d}(x, t) = \begin{cases} \text{dist}(x, \Gamma(t)) & \text{for } x \in \Omega^-(t), \\ -\text{dist}(x, \Gamma(t)) & \text{elsewhere.} \end{cases}$$

Note that $\tilde{d} = 0$ on Γ_T and $|\nabla \tilde{d}| = 1$ in a neighborhood of Γ_T .

2. Outer expansion: It is reasonable to assume that outside a neighbourhood of Γ_T , u^ε has the expansion

$$u^\varepsilon(x, t) = \pm 1 + \varepsilon u_1^\pm(x, t) + \varepsilon^2 u_2^\pm(x, t) + \dots \quad (22)$$

3. Inner expansion: Near Γ_T , we assume that u^ε has form

$$u^\varepsilon(x, t) = U_0(x, t, \xi) + \varepsilon U_1(x, t, \xi) + \varepsilon^2 U_2(x, t, \xi) + \dots \quad (23)$$

Here $U_j(x, t, z), j \geq 0$ are defined for $x \in \Omega, t \geq 0, z \in \mathbb{R}$ and $\xi := \tilde{d}(x, t)/\varepsilon$.

4. Normalization conditions: The stretched space variable ξ gives exactly the right spatial scaling to describe the rapid transition between the regions $\{u^\varepsilon \approx -1\}$ and $\{u^\varepsilon \approx 1\}$. We normalize U_0 in such a way that

$$U_0(x, t, 0) = 0.$$

5. Matching conditions: For $\xi \rightarrow \pm\infty$, we require two expansions (22) and (23) to be consistent, i.e.

$$U_0(x, t, -\infty) = 1, \quad U_0(x, t, +\infty) = -1;$$

and

$$U_k(x, t, -\infty) = u_k^+(x, t), \quad U_k(x, t, +\infty) = u_k^-(x, t)$$

for all $k \geq 1$.

Formal interface motion equation We will substitute the inner expansion (23) into (4b). We will then compare the terms of the same order to determine equations of U_0 and U_1 . To that purpose, we start by some computations.

$$\begin{aligned} u_t^\varepsilon &= U_{0t} + U_{0z} \frac{\tilde{d}_t}{\varepsilon} + \varepsilon U_{1t} + U_{1z} \tilde{d}_t + \dots, \\ \nabla u^\varepsilon &= \nabla U_0 + U_{0z} \frac{\nabla \tilde{d}}{\varepsilon} + \varepsilon \nabla U_1 + U_{1z} \nabla \tilde{d} + \dots, \\ \Delta u^\varepsilon &= \Delta U_0 + 2 \frac{\nabla \tilde{d}}{\varepsilon} \cdot \nabla U_{0z} + U_{0z} \frac{\Delta \tilde{d}}{\varepsilon} + U_{0zz} \frac{|\nabla \tilde{d}|}{\varepsilon^2} + \varepsilon \Delta U_1 \\ &\quad + 2 \nabla \tilde{d} \cdot \nabla U_{1z} + U_{1z} \Delta \tilde{d} + U_{1zz} \frac{|\nabla \tilde{d}|}{\varepsilon} + \dots, \\ f(u^\varepsilon) &= f(U_0) + \varepsilon f'(U_0) U_1 + O(\varepsilon^2), \\ \mu^\varepsilon &= \mu + O(\varepsilon). \end{aligned}$$

Substituting $u_t^\varepsilon, \Delta u^\varepsilon, f(u^\varepsilon), \mu^\varepsilon$ in (4b), collecting all terms of order ε^{-2} then yields

$$\begin{cases} U_{0zz} + f(U_0) = 0 \\ U_0(-\infty) = 1, \quad U_0(0) = 0, \quad U_0(+\infty) = -1. \end{cases} \quad (24)$$

Because of $\int_{-1}^1 f(s) ds = 0$, this problem has a unique solution U_0 . Furthermore, U_0 is independent of (x, t) , i.e. $U_0(x, t, z) = U_0(z)$ and thus, we write U'_0, U''_0 instead of U_{0z}, U_{0zz} . We have the following lemma.

Lemma 3.1. *The solution U_0 of equation (24) also fulfills the differential equation*

$$U'_0 = -\sqrt{2W(U_0)}.$$

As a consequence, $\int_{\mathbb{R}} (U'_0(z))^2 dz$ can be written in the form:

$$\int_{\mathbb{R}} (U'_0(z))^2 dz = \sqrt{2} \int_{-1}^1 \sqrt{W(s)} ds.$$

Proof. Multiplying the above mentioned differential equation (24) for U_0 by U'_0 , we get

$$U''_0 U'_0 + f(U_0) U'_0 = 0. \quad (25)$$

Keeping in mind that $W'(u) = -f(u)$, (25) can be read as

$$\left(\frac{(U'_0)^2}{2} \right)' - (W(U_0))' = 0. \quad (26)$$

Integrating this equation from $-\infty$ to z , we obtain

$$\frac{(U'_0(z))^2}{2} = W(U_0(z)). \quad (27)$$

Moreover, U_0 is non increasing, therefore, we deduce that

$$U'_0(z) = -\sqrt{2W(U_0(z))}.$$

Consequently, we have

$$\int_{\mathbb{R}} (U'_0(z))^2 dz = - \int_{\mathbb{R}} U'_0(z) \sqrt{2W(U_0(z))} dz = \sqrt{2} \int_{-1}^1 \sqrt{W(s)} ds.$$

This completes the proof of Lemma 3.1. \square

We now collect the terms of order ε^{-1} in the substituted equation (4b). Because we have $|\nabla \tilde{d}| = 1$ in a neighbourhood of $\Gamma(t)$, we obtain

$$U_{1zz} + f'(U_0)U_1 = U'_0(\alpha \tilde{d}_t - \Delta \tilde{d}) - \mu. \quad (28)$$

A solvability condition for this equation is given by the following lemma.

Lemma 3.2 (see [1, Lemma 2.2]). *Let $A(z)$ be a bounded function for $z \in \mathbb{R}$. Then the existence of a solution ϕ for the problem*

$$\begin{cases} \phi_{zz} + f'(U_0(z))\phi = A(z) , & z \in \mathbb{R} \\ \phi(0) = 0, \phi \in L^\infty(\mathbb{R}) \end{cases} \quad (29)$$

is equivalent to

$$\int_{\mathbb{R}} A(z)U_0'(z) dz = 0. \quad (30)$$

Therefore, the existence of a solution U_1 of (28) is equivalent to

$$\int_{\mathbb{R}} \left[(U_0')^2(z)(\alpha\tilde{d}_t - \Delta\tilde{d})(x, t) - \mu(x, t)U_0'(z) \right] dz = 0 \quad (31)$$

for all (x, t) in a neighbourhood of the interface Γ_T . Thus,

$$(\alpha\tilde{d}_t - \Delta\tilde{d})(x, t) = \frac{\mu(x, t) \int_{\mathbb{R}} U_0'(z) dz}{\int_{\mathbb{R}} (U_0'(z))^2 dz} = -\frac{2\mu(x, t)}{\int_{\mathbb{R}} (U_0'(z))^2 dz}. \quad (32)$$

It follows from Lemma 3.1 that

$$(\alpha\tilde{d}_t - \Delta\tilde{d})(x, t) = -\frac{\sqrt{2}\mu(x, t)}{\int_{-1}^1 \sqrt{W(s)} ds}. \quad (33)$$

Note that, on $\Gamma(t)$ we have $n = n^+|_{\Gamma} = \nabla\tilde{d}$, $\kappa = \frac{\operatorname{div}(n)}{N-1} = \frac{\Delta\tilde{d}}{N-1}$, and $\tilde{d}_t = -V_n$. Therefore, we deduce that $\Gamma(t)$ satisfies indeed the interface motion equation (6b):

$$\boxed{\alpha V_n = -(N-1)\kappa + \frac{\sqrt{2}\mu}{\int_{-1}^1 \sqrt{W(s)} ds} = -(N-1)\kappa + \mathcal{C}\mu \quad \text{on } \Gamma_T,}$$

where $\mathcal{C} := \left[\int_{-1}^1 \sqrt{W(s)}/2 ds \right]^{-1}$.

3.3 Equations for μ, σ

We will suppose that the following convergence holds in a strong enough sense:

$$\mu^\varepsilon \longrightarrow \mu, \quad \sigma^\varepsilon \longrightarrow \sigma$$

as $\varepsilon \downarrow 0$ and derive the limit of the reaction term in (4a) and (4c). To that purpose, we first prove a stronger version of Lemma 2.1 by Du et al. [25] (see also [6, 39]).

Lemma 3.3. *Let $\gamma \subset\subset \Omega$ be a smooth hypersurface without boundary, d be the signed distance to γ , and let $g \in L^1(\mathbb{R})$. Furthermore, let $\phi^\varepsilon \in L^\infty(\Omega)$ and $V \subset \Omega$ be a neighborhood γ such that*

$$\begin{aligned} \|\phi^\varepsilon\|_{L^\infty(\Omega)} &\leq C, \\ \phi^\varepsilon &\text{ is continuous on } V, \\ \phi^\varepsilon &\longrightarrow \phi \quad \text{uniformly in } V. \end{aligned}$$

We then have

$$\lim_{\varepsilon \downarrow 0} \frac{1}{\varepsilon} \int_U g(d(x)/\varepsilon) \phi^\varepsilon(x) \, dx = \int_{-\infty}^{\infty} g(\tau) \, d\tau \int_\gamma \phi \, d\gamma,$$

for a small enough neighborhood $U \subset V$ of γ .

Proof. For simplicity, we prove this lemma in three-dimensional space and assume that γ has a parametrization α . More precisely, we assume that there exists an open set W of \mathbb{R}^2 such that the mapping α from \overline{W} onto γ is smooth and that α^{-1} is also a smooth mapping. We write the function α as

$$\alpha(z_1, z_2) = (\alpha_1(z_1, z_2), \alpha_2(z_1, z_2), \alpha_3(z_1, z_2)) \text{ for all } (z_1, z_2) \in \overline{W}.$$

For $\delta > 0$ small enough, we consider η from $\overline{W} \times [-\delta, \delta]$ to \mathbb{R}^3 , which satisfies

$$\begin{cases} \eta_\tau(z_1, z_2, \tau) = \nabla d(\eta(z_1, z_2, \tau)), \\ \eta(z_1, z_2, 0) = \alpha(z_1, z_2). \end{cases}$$

We write

$$\eta(z_1, z_2, \tau) = (\eta_1(z_1, z_2, \tau), \eta_2(z_1, z_2, \tau), \eta_3(z_1, z_2, \tau))$$

with $\eta_i : \overline{W} \times [-\delta, \delta] \rightarrow \mathbb{R}$. We define $U := \eta(\{\overline{W} \times [-\delta, \delta]\})$ and choose δ small enough so that $U \subset V$. Note that

$$\frac{d}{d\tau} d(\eta(z_1, z_2, \tau)) = \nabla d(\eta(z_1, z_2, \tau)) \eta_\tau(z_1, z_2, \tau) = |\nabla d(\eta(z_1, z_2, \tau))|^2 = 1,$$

and that $d(\eta(z_1, z_2, 0)) = d(\alpha(z_1, z_2)) = 0$. Thus we conclude that $d(\eta(z_1, z_2, \tau)) = \tau$. We define $J(z_1, z_2, \tau)$ as the determinant of the Jacobian matrix of η at (z_1, z_2, τ) and perform the change of coordinates $\eta(z_1, z_2, \tau) = x$ to obtain

$$\begin{aligned} \int_U g\left(\frac{d(x)}{\varepsilon}\right) \phi^\varepsilon(x) dx &= \int_{-\delta}^{\delta} d\tau \int_W g\left(\frac{d(\eta(z_1, z_2, \tau))}{\varepsilon}\right) \phi^\varepsilon(\eta(z_1, z_2, \tau)) |J(z_1, z_2, \tau)| dudv \\ &= \int_{-\delta}^{\delta} d\tau \int_W g\left(\frac{\tau}{\varepsilon}\right) \phi^\varepsilon(\eta(z_1, z_2, \tau)) |J(z_1, z_2, \tau)| dudv. \end{aligned}$$

By applying the change of coordinates $\tau = \varepsilon \tilde{\tau}$, we have

$$\begin{aligned} \int_U g\left(\frac{d(x)}{\varepsilon}\right) \phi^\varepsilon(x) dx &= \varepsilon \int_{-\frac{\delta}{\varepsilon}}^{\frac{\delta}{\varepsilon}} d\tilde{\tau} \int_W g(\tilde{\tau}) \phi^\varepsilon(\eta(z_1, z_2, \varepsilon \tilde{\tau})) |J(z_1, z_2, \varepsilon \tilde{\tau})| dz_1 dz_2. \end{aligned}$$

Therefore,

$$\begin{aligned} A_\varepsilon &:= \frac{1}{\varepsilon} \int_U g\left(\frac{d(x)}{\varepsilon}\right) \phi^\varepsilon(x) dx \\ &= \int_{-\infty}^{\infty} \int_W \mathbf{1}_{(-\frac{\delta}{\varepsilon}, \frac{\delta}{\varepsilon})}(\tilde{\tau}) g(\tilde{\tau}) \phi^\varepsilon(\eta(z_1, z_2, \varepsilon \tilde{\tau})) |J(z_1, z_2, \varepsilon \tilde{\tau})| d\tilde{\tau} dz_1 dz_2. \end{aligned}$$

In the following, we will apply the dominated convergence theorem to deduce the limit of A_ε as $\varepsilon \downarrow 0$. Set

$$H_\varepsilon(z_1, z_2, \tilde{\tau}) := \mathbf{1}_{(-\frac{\delta}{\varepsilon}, \frac{\delta}{\varepsilon})}(\tilde{\tau}) g(\tilde{\tau}) \phi^\varepsilon(\eta(z_1, z_2, \varepsilon \tilde{\tau})) |J(z_1, z_2, \varepsilon \tilde{\tau})|.$$

For $-\frac{\delta}{\varepsilon} \leq \tilde{\tau} \leq \frac{\delta}{\varepsilon}$, we have $-\delta \leq \varepsilon \tilde{\tau} \leq \delta$, so that for all $\varepsilon > 0$

$$\left| \mathbf{1}_{(-\frac{\delta}{\varepsilon}, \frac{\delta}{\varepsilon})}(\tilde{\tau}) |J(z_1, z_2, \varepsilon \tilde{\tau})| \right| \leq \sup_{z_1, z_2 \in \overline{W}, -\delta \leq \tau \leq \delta} |J(z_1, z_2, \tau)| =: C_1.$$

Moreover, $\|\phi^\varepsilon\|_{L^\infty(\Omega)} \leq C$ for all $\varepsilon > 0$, therefore,

$$|H_\varepsilon(z_1, z_2, \tilde{\tau})| \leq C|g(\tilde{\tau})| \quad \text{on } \overline{W} \times \mathbb{R}. \quad (34)$$

Next, since ϕ^ε converges uniformly to ϕ on U and since J is continuous, we have for all $\tau \in \mathbb{R}$, $(z_1, z_2) \in W$,

$$\begin{aligned} \mathbf{1}_{(-\frac{\delta}{\varepsilon}, \frac{\delta}{\varepsilon})}(\tilde{\tau}) \phi^\varepsilon(\eta(z_1, z_2, \varepsilon\tilde{\tau})) &\rightarrow \phi(\eta(z_1, z_2, 0)) = \phi(\alpha(z_1, z_2)), \\ J(z_1, z_2, \varepsilon\tilde{\tau}) &\rightarrow J(z_1, z_2, 0), \end{aligned}$$

as $\varepsilon \downarrow 0$. It follows that as $\varepsilon \downarrow 0$,

$$H_\varepsilon(z_1, z_2, \tilde{\tau}) \rightarrow g(\tilde{\tau})\phi(\eta(z_1, z_2, 0))|J(z_1, z_2, 0)| \quad \text{for all } \tilde{\tau} \in \mathbb{R}, (z_1, z_2) \in W. \quad (35)$$

Combining (34) and (35), we have

$$\lim_{\varepsilon \downarrow 0} A_\varepsilon = \int_{-\infty}^{\infty} g(\tilde{\tau}) d\tilde{\tau} \int_W \phi(\alpha(z_1, z_2)) |J(z_1, z_2, 0)| dz_1 dz_2. \quad (36)$$

Next, we compute $|J(z_1, z_2, 0)|$. For this purpose, we write

$$\begin{aligned} \frac{\partial \eta}{\partial z_1} &= \left(\frac{\partial \eta_1}{\partial z_1}, \frac{\partial \eta_2}{\partial z_1}, \frac{\partial \eta_3}{\partial z_1} \right), \\ \frac{\partial \eta}{\partial z_2} &= \left(\frac{\partial \eta_1}{\partial z_2}, \frac{\partial \eta_2}{\partial z_2}, \frac{\partial \eta_3}{\partial z_2} \right), \\ \frac{\partial \eta}{\partial \tau} &= \left(\frac{\partial \eta_1}{\partial \tau}, \frac{\partial \eta_2}{\partial \tau}, \frac{\partial \eta_3}{\partial \tau} \right). \end{aligned}$$

Note that $\frac{\partial \eta}{\partial \tau}(z_1, z_2, 0)$ is the outer normal vector to γ at the point $\eta(z_1, z_2, 0) = \alpha(z_1, z_2)$ and that $\left\{ \frac{\partial \eta}{\partial u}(z_1, z_2, 0), \frac{\partial \eta}{\partial v}(z_1, z_2, 0) \right\}$ is a basis of the tangent space of γ at point $\eta(z_1, z_2, 0) = \alpha(z_1, z_2)$. Therefore,

$$\begin{aligned} |J(z_1, z_2, 0)| &= \left| \left(\frac{\partial \eta}{\partial z_1} \wedge \frac{\partial \eta}{\partial z_2} \right) \cdot \frac{\partial \eta}{\partial \tau} \right| = \left| \frac{\partial \eta}{\partial z_1} \wedge \frac{\partial \eta}{\partial z_2} \right| \left| \frac{\partial \eta}{\partial \tau} \right| \\ &= \left| \frac{\partial \eta}{\partial z_1} \wedge \frac{\partial \eta}{\partial z_2} \right| |\nabla d(\eta(z_1, z_2, 0))| = \left| \frac{\partial \eta}{\partial z_1} \wedge \frac{\partial \eta}{\partial z_2} \right| (z_1, z_2, 0) \\ &= \left| \frac{\partial \alpha}{\partial u} \wedge \frac{\partial \alpha}{\partial v} \right| (z_1, z_2) \end{aligned}$$

where \wedge is the vector product. This together with (36) implies that

$$\lim_{\varepsilon \downarrow 0} A_\varepsilon = \int_{-\infty}^{\infty} g(\tilde{\tau}) d\tilde{\tau} \int_W \phi(\alpha(z_1, z_2)) \left| \frac{\partial \alpha}{\partial u} \wedge \frac{\partial \alpha}{\partial v} \right| dz_1 dz_2.$$

On the other hand, in view of the definition of the integral of surface (see [47, Formula (131), p. 283]), we have

$$\int_\gamma \phi d\gamma = \int_W \phi(\alpha(z_1, z_2)) \left| \frac{\partial \alpha}{\partial z_1} \wedge \frac{\partial \alpha}{\partial z_2} \right| dz_1 dz_2.$$

Therefore,

$$\lim_{\varepsilon \downarrow 0} A_\varepsilon = \int_{-\infty}^{\infty} g(\tilde{\tau}) d\tilde{\tau} \int_\gamma \phi d\gamma$$

which completes the proof of the lemma. \square

Application to reaction term: Now we apply Lemma 3.3 to formally compute the limit as $\varepsilon \downarrow 0$ of

$$\frac{1}{\varepsilon} \int_0^T \int_\Omega p(u^\varepsilon)(\sigma^\varepsilon - \delta\mu^\varepsilon)\psi, \quad \text{for } \psi \in \mathcal{F}_T.$$

Because of the outer and inner expression of u^ε in (22) and (23), we deduce that for ε small enough

$$u^\varepsilon(x, t) \approx \begin{cases} \pm 1 & \text{if } (x, t) \text{ is far from } \Gamma_T \\ U_0\left(\frac{\tilde{d}(x, t)}{\varepsilon}\right) & \text{if } (x, t) \text{ is closed to } \Gamma_T. \end{cases}$$

Therefore

$$p(u^\varepsilon(x, t)) \approx \begin{cases} 0 & \text{if } (x, t) \text{ is far from } \Gamma_T \\ p\left(U_0\left(\frac{\tilde{d}(x, t)}{\varepsilon}\right)\right) & \text{if } (x, t) \text{ is closed to } \Gamma_T. \end{cases}$$

Thus we can apply Lemma 3.3 by setting

$$g(\xi) := p(U_0(\xi)) \quad \text{and} \quad \phi^\varepsilon := (\sigma^\varepsilon - \delta\mu^\varepsilon)\psi,$$

where $\psi \in \mathcal{F}_T$. This yields

$$\begin{aligned} P^0(\psi(t)) &:= \lim_{\varepsilon \downarrow 0} \frac{1}{\varepsilon} \int_{\Omega} p(u^\varepsilon)(\sigma^\varepsilon - \delta\mu^\varepsilon)\psi = \lim_{\varepsilon \downarrow 0} \frac{1}{\varepsilon} \int_U p(u^\varepsilon)(\sigma^\varepsilon - \delta\mu^\varepsilon)\psi \\ &= \int_{-\infty}^{\infty} p(U_0(\xi)) \, d\xi \int_{\Gamma(t)} (\sigma(t) - \delta\mu(t))\psi(t) \, d\Gamma(t), \end{aligned}$$

where U is a small enough neighborhood of $\Gamma(t)$. Recalling that in view of the definition of p and of Lemma 3.1

$$p(U_0) = 2p_0\sqrt{W(U_0)} = -\sqrt{2}p_0 U'_0,$$

we get

$$\begin{aligned} P^0(\psi(t)) &= -\sqrt{2}p_0 \int_{-\infty}^{\infty} U'_0(\xi) \, d\xi \int_{\Gamma(t)} (\sigma(t) - \delta\mu(t))\psi(t) \, d\Gamma(t) \\ &= 2\sqrt{2}p_0 \int_{\Gamma(t)} (\sigma(t) - \delta\mu(t))\psi(t) \, d\Gamma(t). \end{aligned}$$

Hence, we formally conclude that, for all $\psi \in \mathcal{F}_T$

$$\lim_{\varepsilon \downarrow 0} \frac{1}{\varepsilon} \int_0^T \int_{\Omega} p(u^\varepsilon)(\sigma^\varepsilon - \delta\mu^\varepsilon)\psi = 2\sqrt{2}p_0 \int_0^T dt \int_{\Gamma(t)} (\sigma(t) - \delta\mu(t))\psi(t) \, d\Gamma(t). \quad (37)$$

Conclusion: Now, we recall the definition of a weak solution of the equation for μ^ε :

$$\int_0^T \int_{\Omega} (-\alpha\mu^\varepsilon - u^\varepsilon)\psi_t - \int_{\Omega} (\alpha\mu_0^\varepsilon + u_0^\varepsilon)\psi(0) = \int_0^T \int_{\Omega} (\mu^\varepsilon \Delta\psi + \varepsilon^{-1}p(u^\varepsilon)(\sigma^\varepsilon - \delta\mu^\varepsilon)\psi)$$

for ψ in \mathcal{F}_T and take the limit $\varepsilon \rightarrow 0$ on both sides, to obtain in view of (37)

$$\int_0^T \int_{\Omega} (-\alpha\mu - u)\psi_t - \int_{\Omega} (\alpha\mu_0 + u_0)\psi(0) = \int_0^T \int_{\Omega} \mu \Delta\psi + 2\sqrt{2}p_0 \int_0^T dt \int_{\Gamma(t)} (\sigma - \delta\mu)(t)\psi(t) \, d\Gamma(t).$$

This together a similar argument for the equation for σ completes the proof of Theorem 1.5.

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References

- [1] M. ALFARO, D. HILHORST, AND H. MATANO, *The singular limit of the Allen–Cahn equation and the FitzHugh–Nagumo system*, J. Differential Equations, 245 (2008), pp. 505–565.
- [2] N. D. ALIKAKOS, P. W. BATES, AND X. CHEN, *Convergence of the Cahn–Hilliard equation to the Hele–Shaw model*, Arch. Ration. Mech. Anal., 128 (1994), pp. 165–205.
- [3] S. M. ALLEN AND J. W. CAHN, *A microscopic theory for antiphase boundary motion and its application to antiphase domain coarsening*, Acta Metall., 27 (1979), pp. 1085–1095.
- [4] D. AMBROSI AND F. MOLLIKA, *Mechanical models in tumour growth*, in Cancer Modelling and Simulation, L. Preziosi, ed., vol. 3 of Mathematical Biology and Medicine Series, Chapman & Hall/CRC, 2003, ch. 5.
- [5] D. AMBROSI AND L. PREZIOSI, *On the closure of mass balance models for tumor growth*, Math. Models Methods Appl. Sci., 12 (2002), pp. 737–754.
- [6] D. M. ANDERSON, G. B. MCFADDEN, AND A. A. WHEELER, *Diffuse-interface methods in fluid mechanics*, Annu. Rev. Fluid Mech., 30 (1998), pp. 139–165.
- [7] S. ASTANIN AND L. PREZIOSI, *Multiphase models of tumour growth*, in Selected Topics in Cancer Modeling: Genesis, Evolution, Immune Competition, and Therapy, N. Bellomo, M. Chaplain, and E. De Angelis, eds., Modeling and Simulation in Science, Engineering and Technology, Birkhäuser, 2008, ch. 9, pp. 223–253.
- [8] E. L. BEARER, J. S. LOWENGRUB, H. B. FRIEBOES, Y.-L. CHUANG, F. JIN, S. M. WISE, M. FERRARI, D. B. AGUS, AND V. CRISTINI, *Multiparameter computational modeling of tumor invasion*, Cancer Res., 69 (2009), pp. 4493–4501.
- [9] L. BRONSARD AND R. V. KOHN, *Motion by mean curvature as the singular limit of Ginzburg–Landau dynamics*, J. Differential Equations, 90 (1991), pp. 211–237.

- [10] H. BYRNE, *Modelling avascular tumour growth*. In L. Preziosi, editor, *Cancer Modelling and Simulation*, volume 3 of *Mathematical Biology and Medicine Series*, chapter 4. Chapman & Hall/CRC, 2003.
- [11] H. M. BYRNE AND J. R. KING AND D. L. S. MCELWAIN, *A two-phase model of solid tumour growth*, *Applied Mathematics Letters*, 16, (2003), pp. 567–573.
- [12] H. BYRNE AND L. PREZIOSI, *Modelling solid tumour growth using the theory of mixtures*, *Math. Med. Biol.*, 20 (2003), pp. 341–366.
- [13] G. CAGINALP, *An analysis of a phase field model of a free boundary*, *Arch. Ration. Mech. Anal.*, 92 (1986), pp. 205–245.
- [14] —, *Stefan and Hele–Shaw type models as asymptotic limits of the phase-field equations*, 39 (1989), pp. 5887–5896.
- [15] G. CAGINALP AND X. CHEN, *Convergence of the phase field model to its sharp interface limits*, *European J. Appl. Math.*, 9 (1998), pp. 417–445.
- [16] G. CAGINALP, X. CHEN, AND C. ECK, *Numerical tests of a phase field model with second order accuracy*, 68 (2008), pp. 1518–1534.
- [17] G. CAGINALP AND P. C. FIFE, *Dynamics of layered interfaces arising from phase boundaries*, 48 (1988), pp. 506–518.
- [18] X. CHEN, *Global asymptotic limit of solutions of the Cahn–Hilliard equation*, *J. Differential Geom.*, 44 (1996), pp. 262–311.
- [19] V. CRISTINI, H. B. FRIEBOES, X. LI, J. S. LOWENGRUB, P. MACKLIN, S. SANGA, S. M. WISE, AND X. ZHENG, *Nonlinear modeling and simulation of tumor growth*, in *Selected Topics in Cancer Modeling: Genesis, Evolution, Immune Competition, and Therapy*, N. Bellomo, M. Chaplain, and E. De Angelis, eds., *Modeling and Simulation in Science, Engineering and Technology*, Birkhäuser, 2008, ch. 6, pp. 113–181.
- [20] V. CRISTINI, X. LI, J. S. LOWENGRUB, AND S. M. WISE, *Nonlinear simulations of solid tumor growth using a mixture model: invasion and branching*, *J. Math. Biol.*, 58 (2009), pp. 723–763.

- [21] V. CRISTINI AND J. S. LOWENGRUB, *Multiscale Modeling of Cancer: An Integrated Experimental and Mathematical Modeling Approach*, Cambridge University Press, Cambridge, 2010.
- [22] V. CRISTINI, J. S. LOWENGRUB, AND Q. NIE, *Nonlinear simulation of tumor growth*, J. Math. Biol., 46 (2003), pp. 191–224.
- [23] P. DE MOTTONI AND M. SCHATZMAN, *Geometrical evolution of developed interfaces*, Trans. Amer. Math. Soc., 347 (1995), pp. 1533–1589.
- [24] M. C. DELFOUR MOTTONI AND Z. -P. ZOLÉZIO, *Shapes and geometries, analysis, differential calculus and optimization*, Advances in design and control, (2001).
- [25] Q. DU, C. LIU, R. RYHAM, AND X. WANG, *A phase field formulation of the Willmore problem*, Nonlinearity, 18 (2005), pp. 1249–1267.
- [26] L. C. EVANS, H. M. SONER, AND P. E. SOUGANIDIS, *Phase transitions and generalized motion by mean curvature*, Comm. Pure Appl. Math., 45 (1992), pp. 1097–1123.
- [27] X. FENG AND A. PROHL, *Analysis of a fully discrete finite element method for the phase field model and approximation of its sharp interface limits*, Math. Comp., 73 (2003), pp. 541–567.
- [28] ———, *Numerical analysis of the Allen–Cahn equation and approximation for mean curvature flows*, Numer. Math., 94 (2003), pp. 33–65.
- [29] ———, *Numerical analysis of the Cahn–Hilliard equation and approximation for the Hele–Shaw problem*, Interfaces Free Bound., 7 (2005), pp. 1–28.
- [30] X. FENG AND H.-J. WU, *A posteriori error estimates and an adaptive finite element method for the Allen–Cahn equation and the mean curvature flow*, J. Sci. Comput., 24 (2005), pp. 121–146.
- [31] ———, *A posteriori error estimates for finite element approximations of the Cahn–Hilliard equation and the Hele–Shaw flow*, J. Comput. Math., 26 (2008), pp. 767–796.

- [32] P. C. FIFE, *Dynamics of Internal Layers and Diffusive Interfaces*, vol. 53 of CBMS-NSF Regional Conference Series in Applied Mathematics, Society of Industrial and Applied Mathematics (SIAM), Philadelphia, Pennsylvania, 1988.
- [33] H. B. FRIEBOES, J. S. LOWENGRUB, S. WISE, X. ZHENG, P. MACKLIN, E. BEARER, AND V. CRISTINI, *Computer simulation of glioma growth and morphology*, *Neuroimage*, 37 (2007), pp. S59–S70.
- [34] L. GRAZIANO AND L. PREZIOSI, *Mechanics in tumor growth*, in *Modeling of Biological Materials*, F. Mollica, L. Preziosi, and K. Rajagopal, eds., *Modeling and Simulation in Science, Engineering and Technology*, Birkhäuser, 2007, ch. 7, pp. 263–322.
- [35] H. P. GREENSPAN, *On the growth and stability of cell cultures and solid tumors*, *J. Theoret. Biol.*, 56 (1976), pp. 229–242.
- [36] A. HAWKINS-DAARUD AND S. PRUDHOMME AND K. G. VAN DER ZEE AND J. T. ODEN, *Bayesian calibration, validation, and uncertainty quantification of diffuse interface models of tumor growth*, *J. Math. Biol.*, (2012), DOI 10.1007/s00285-012-0595-9.
- [37] A. HAWKINS-DAARUD AND K. G. VAN DER ZEE AND J. T. ODEN, *Numerical simulation of a thermodynamically consistent four-species tumor growth model*, *Int. J. Numer. Meth. Biomed. Engng.*, 28 (2011), pp. 3–24.
- [38] J. S. LOWENGRUB, H. B. FRIEBOES, F. JIN, Y.-L. CHUANG, X. LI, P. MACKLIN, S. M. WISE, AND V. CRISTINI, *Nonlinear modeling of cancer: Bridging the gap between cells and tumors*, *Nonlinearity*, 23 (2010), pp. R1–R91.
- [39] J. S. LOWENGRUB AND L. TRUSKINOVSKY, *Quasi-incompressible Cahn–Hilliard fluids and topological transitions*, *Proc. R. Soc. Lond. Ser. A Math. Phys. Eng. Sci.*, 454 (1998), pp. 2617–2654.
- [40] M. MIMURA, *Reaction-diffusion systems arising in biological and chemical systems: Application of singular limit procedures*, in *Mathematical Aspects of Evolving Interfaces*, P. Colli and J. F. Rodrigues, eds., vol. 1812 of *Lecture Notes in Mathematics*, Springer, Berlin, 2003, ch. 3,

pp. 89–121. Lectures given at the C.I.M.-C.I.M.E. joint Euro-Summer School held in Madeira, Funchal, Portugal, July 3–9, 2000.

- [41] Y. NISHIURA, *Far-From-Equilibrium Dynamics*, vol. 209 of Translations of Mathematical Monographs, Iwanami Series in Modern Mathematics, American Mathematical Society (AMS), 2002.
- [42] J. T. ODEN, A. HAWKINS, AND S. PRUDHOMME, *General diffuse-interface theories and an approach to predictive tumor growth modeling*, *Math. Models Methods Appl. Sci.*, 20 (2010), pp. 477–517.
- [43] R. L. PEGO, *Front migration in the nonlinear Cahn–Hilliard equation*, *Proc. R. Soc. Lond. Ser. A Math. Phys. Eng. Sci.*, 422 (1989), pp. 261–278.
- [44] T. ROOSE AND S. J. CHAPMAN AND P. K. MAINI, *Mathematical models of avascular tumor growth*, *SIAM Rev.*, 49-2 (2007), pp. 179–208.
- [45] J. RUBINSTEIN, P. STERNBERG, *Nonlocal reaction-diffusion equations and nucleation*, *IMA. J. App. Math*, 48 (1992), pp. 249–264.
- [46] J. RUBINSTEIN, P. STERNBERG, AND J. B. KELLER, *Fast reaction, slow diffusion, and curve shortening*, 49 (1989), pp. 116–133.
- [47] W. RUDIN, *Principles of Mathematical Analysis*, 3ed (1976).
- [48] B. E. E. STOTH, *Convergence of the Cahn–Hilliard equation to the Mullins–Sekerka problem in spherical symmetry*, *J. Differential Equations*, 125 (1996), pp. 154–183.
- [49] S. M. WISE, J. S. LOWENGRUB, H. B. FRIEBOES, AND V. CRISTINI, *Three-dimensional multispecies nonlinear tumor growth—I Model and numerical method*, *J. Theoret. Biol.*, 253 (2008), pp. 524–543.