

Formal asymptotic limit of diffuse-interface tumor-growth models

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Diffuse and sharp interface models for tumor growth

When modeling interface motion, one can choose between diffuse and sharp interface models. In literature, there are a number of diffuse interface models describing tumor-growth, and there are also a number sharp interface models. A general goal would be to try to connect them, or in other words, to be able to say which smooth models correspond to which limiting moving boundary problems.

Our purpose today : formally find the singular limit of a diffuse interface model developed by Hawkins Daarub, van der Zee and Oden.

Before doing so, I will recall some known facts about the Cahn-Hilliard equation, a corresponding phase field model and their singular limits.

The Cahn-Hilliard equation as a model equation

The Cahn-Hilliard equation

$$\begin{cases} \partial_t u = \Delta \mu & \text{in } \Omega \times (0, T] \\ \mu = -\varepsilon \Delta u - \frac{1}{\varepsilon} f(u) & \text{in } \Omega \times (0, T]. \end{cases}$$

Typically $W(u) = \frac{1}{4}(1 - u^2)^2$ and $f(u) = u(1 - u^2)$.

This equation, which appears in many mathematical models, is the so-called **Cahn-Hilliard equation**. The function u is a phase function; if ε is small enough, u is either close to 1 or to -1 . The function μ is referred to as the chemical potential.

One may also view Cahn-Hilliard equation as a single 4th order equation. To that purpose we substitute the second into the first equation to obtain

$$\partial_t u = \Delta \left(-\varepsilon \Delta u - \frac{1}{\varepsilon} f(u) \right) \text{ in } \Omega \times (0, T].$$

The singular limit of the Cahn-Hilliard equation

It is often referred to as the two-phase Hele-Shaw model

$$\left\{ \begin{array}{l} u = 1 \text{ on } Q^+ \\ u = -1 \text{ on } Q^- \\ \Delta\mu = 0 \text{ on } Q^+ \\ \Delta\mu = 0 \text{ on } Q^- \\ -(N-1)\kappa - \frac{2\sqrt{2}}{3}\mu = 0 \text{ on } \Gamma \\ V_n = -\frac{1}{2} \left[\frac{\partial\mu}{\partial\nu} \right]_{\Gamma} \text{ on } \Gamma \\ \Gamma(0) = \Gamma_0. \end{array} \right.$$

Here we suppose that the initial function u_0 in the Cahn-Hilliard problem changes sign across Γ_0 .

It is rather difficult to guess how the two-phase Hele-Shaw problem can be obtained as the limit of the Cahn-Hilliard equation. Moreover if you are given some perturbation of the Cahn-Hilliard equation, it may be very complicated to find its limit, even in a formal way.

To that purpose, a possible idea is the following : we consider instead the most standard Caginalp type phase-field model

$$\begin{cases} \alpha \mu_t + \partial_t u = \Delta \mu & \text{in } \Omega \times (0, T] \\ -\alpha \varepsilon u_t + \mu = -\varepsilon \Delta u - \frac{1}{\varepsilon} f(u) & \text{in } \Omega \times (0, T], \end{cases}$$

Phase-field model

When $\alpha = 0$, we recover Cahn-Hilliard's equation.

$$\begin{cases} \alpha \mu_t + \partial_t u = \Delta \mu & \text{in } \Omega \times (0, T] \\ \alpha u_t = \Delta u + \frac{1}{\varepsilon^2}(f(u) + \varepsilon \mu) & \text{in } \Omega \times (0, T]. \end{cases}$$

If we set $\mu = T$, we recover the very standard phase field equations

$$\begin{cases} \alpha T_t + \partial_t u = \Delta T & \text{in } \Omega \times (0, T] \\ \alpha u_t = \Delta u + \frac{1}{\varepsilon^2}(f(u) + \varepsilon T) & \text{in } \Omega \times (0, T]. \end{cases}$$

for the order parameter u and the temperature T . The advantages : with some habit, we can visualize at once the singular limit of the Allen-Cahn equation for u (the second equation in the phase-field model). In order to obtain the limit of the Cahn-Hilliard equation, we just have to set $\alpha = 0$ in the singular limit of the phase field model.

The singular limit of the phase field model

$$\left\{ \begin{array}{l} u = 1 \text{ on } Q^+ \\ u = -1 \text{ on } Q^- \\ \alpha \mu_t = \Delta \mu \text{ on } Q^+ \\ \alpha \mu_t = \Delta \mu \text{ on } Q^- \\ \alpha V_n = -(N-1)\kappa - \frac{2\sqrt{2}}{3}\mu \text{ on } \Gamma \\ V_n = -\frac{1}{2} \left[\frac{\partial \mu}{\partial \nu} \right]_{\Gamma} \text{ on } \Gamma \\ \Gamma(0) = \Gamma_0. \end{array} \right. \quad (*)$$

Setting above $\alpha = 0$, we recover the limit of Cahn-Hilliard equation.

The tumor growth model

The basic equations involve a tumor cell concentration u , a chemical potential μ and a nutrient concentration σ . They are given by

$$u_t = \Delta \mu + \frac{1}{\varepsilon} p_0 \sigma u$$

$$\mu = -\varepsilon \Delta u - \frac{1}{\varepsilon} f(u)$$

$$0 = \Delta \sigma - \frac{1}{\varepsilon} \sigma u$$

where p_0 a proliferation parameter; Hawkins-Daarud, van der Zee and Oden have slightly modified this model in the following way:

Tumor-growth model

They obtain

$$\begin{aligned}u_t &= \Delta \mu + \frac{1}{\varepsilon} p(u)(\sigma - \delta \mu) \\ \mu &= -\varepsilon \Delta u - \frac{1}{\varepsilon} f(u) \\ \sigma_t &= \Delta \sigma - \frac{1}{\varepsilon} p(u)(\sigma - \delta \mu),\end{aligned}$$

where δ is a small regularization parameter. The growth function $p(u)$ is defined as

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

Note that $u \simeq 1$ and that $u \simeq -1$ correspond to the tumorous and healthy cell phases respectively. The function σ represents the density of an extra-cellular water phase.

The corresponding phase field model

We consider this model together with the natural boundary conditions

$$\frac{\partial u}{\partial \nu} = \frac{\partial \mu}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = 0,$$

where ν is the outer unit normal vector to $\partial\Omega$. Just as before, we associate to the Cahn-Hilliard type tumor-growth model a corresponding phase-field model

$$\begin{aligned}\alpha\mu_t^\varepsilon + u_t^\varepsilon &= \Delta\mu^\varepsilon + \frac{1}{\varepsilon}p(u^\varepsilon)(\sigma^\varepsilon - \gamma\mu^\varepsilon) && \text{in } \Omega \times (0, T], \\ \frac{1}{\varepsilon}\mu^\varepsilon - \alpha u_t^\varepsilon &= -\Delta u^\varepsilon - \frac{1}{\varepsilon^2}f(u^\varepsilon) && \text{in } \Omega \times (0, T], \\ \sigma_t^\varepsilon &= \Delta\sigma^\varepsilon - \frac{1}{\varepsilon}p(u^\varepsilon)(\sigma^\varepsilon - \gamma\mu^\varepsilon) && \text{in } \Omega \times (0, T].\end{aligned}$$

The corresponding phase field model

together with the boundary conditions

$$\frac{\partial \mu^\varepsilon}{\partial \nu} = \frac{\partial u^\varepsilon}{\partial \nu} = \frac{\partial \sigma}{\partial \nu} = 0 \quad \text{on } \partial\Omega \times (0, T],$$

and the initial conditions

$$\mu^\varepsilon(\cdot, 0) = \mu^0, \quad u^\varepsilon(\cdot, 0) = u^0, \quad \sigma^\varepsilon(\cdot, 0) = \sigma^0, \quad \text{on } \Omega.$$

A Lyapunov functional

This system is a reaction-diffusion system with a gradient structure

We define the functional

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

Theorem

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

Note that

- 1 if $\alpha = \sigma = 0$, E_ε is the Lyapunov functional corresponding to the Allen-Cahn equation;
- 2 if $\alpha = 0$, E_ε is the Lyapunov functional corresponding to the tumor-growth problem;
- 3 in the general case, E_ε is the Lyapunov functional corresponding to the phase-field tumor-growth problem.

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A Lyapunov functional

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

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

Idea for a rigorous proof?

Exploit the gradient structure?

Possible steps for proof could be

- 1 prove that the functional

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

Γ -converges to the functional

$$E_0(\mu, \sigma) := \int_\Omega \left(|\nabla u| + \frac{\alpha \mu^2}{2} + \frac{\sigma^2}{2\delta} \right) = E(\Gamma)$$

as $\varepsilon \rightarrow 0$, where Γ is the interface separating the phases of the function $u \in BV(\Omega, \{-1, 1\})$.

- 2 Prove the convergence of the corresponding semi-groups, following ideas of Sandier and Serfaty and of Nam Q. Le.

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The formal limit to a free boundary problem

In what follows, we will show that if

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

in a suitable sense, 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 for u^ε .

Singular limit for the cell concentration

For all $t \in (0, T)$, there exists two domains $\Omega^-(t)$ and $\Omega^+(t)$ and a closed smooth hyper-surface $\Gamma(t) \subset\subset \Omega$ such that

$$\Omega = \Omega^-(t) \cup \Gamma(t) \cup \Omega^+(t),$$

and that

$$u(x, t) = \begin{cases} -1 & \text{for } x \in \Omega^-(t), \\ 1 & \text{for } x \in \Omega^+(t). \end{cases}$$

Moreover, $\Gamma(t)$ is determined as the solution of the initial value problem

$$\alpha V_n = -(N-1)\kappa - \frac{2\sqrt{2}}{3}\mu \quad \text{on } \Gamma(t)$$

$$\Gamma(0) = \Gamma_0,$$

Singular limit for the cell concentration

Idea of proof

The equation

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

is the most standard Allen-Cahn equation. As ε tends to zero, u_ε converges to ± 1 on both sides of the interface Γ defined by the initial value problem

$$\alpha V_n = -(N-1)\kappa - \frac{2\sqrt{2}}{3}\mu \quad \text{on } \Gamma(t)$$

$$\Gamma(0) = \Gamma_0,$$

The limit equations for μ and σ

The limit equation for μ is given by

$$\alpha\mu_t + u_t = \Delta\mu + 2\sqrt{2} p_0 (\sigma - \delta\mu) \delta_0(x - \Gamma(t))$$

while the limit equation for σ is given by

$$\sigma_t = \Delta\sigma - 2\sqrt{2} p_0 (\sigma - \delta\mu) \delta_0(x - \Gamma(t)),$$

in the sense of distributions in $\Omega \times (0, T)$.

While parts of these equations consist of terms defined in $\Omega \times (0, T)$, some terms are given by Dirac distributions supported on the moving boundary explicitly in the case of the two last terms in the partial differential equations or implicitly in the case of the term u_t .

The corresponding weak formulation

We say that μ and σ are weak solutions of the equations above if they satisfy the integral equations

$$\begin{aligned} \int_0^T \int_{\Omega} (-\alpha\mu - u)\psi_t - \int_{\Omega} (\alpha\mu_0 + u_0)\psi(0) &= \int_0^T \int_{\Omega} \mu\Delta\psi \\ &+ 2\sqrt{2}\rho_0 \int_0^T \int_{\Gamma(t)} (\sigma - \delta\mu)\psi, \end{aligned}$$

and

$$\int_0^T \int_{\Omega} -\sigma\psi_t - \int_{\Omega} \sigma_0\psi(0) = \int_0^T \int_{\Omega} \sigma\Delta\psi - 2\sqrt{2}\rho_0 \int_0^T \int_{\Gamma(t)} (\sigma - \delta\mu)\psi,$$

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

The singular limit of the reaction terms

We obtain the following result : As $\varepsilon \rightarrow 0$,

$$\varepsilon^{-1} p(u^\varepsilon)(\sigma^\varepsilon - \gamma \mu^\varepsilon) \rightarrow 2\sqrt{2} p_0 (\sigma - \gamma \mu) \delta(x - \Gamma(t)).$$

The proof is based on a variant of a result due to Du, Liu, Ryham and Wang

Lemma

Let Γ be a smooth hypersurface without boundary such that $\Gamma \subset\subset \Omega$. Let $\phi \in C^0(\Omega)$ and assume that $g \in L^1(\mathbb{R})$ satisfies

$$\sup_{|\xi| > \eta} |g(\xi)\xi| \leq C/\eta^m, \quad m > 1.$$

Then

$$\lim_{\varepsilon \searrow 0} \frac{1}{\varepsilon} \int_{\Omega} g(d(x)/\varepsilon) \phi(x) dx = \int_{-\infty}^{\infty} g(\xi) d\xi \int_{\Gamma} \phi(s) ds,$$

where d is the distance to Γ .

A slightly different form of the singular limit equations

We can show that as $\varepsilon \rightarrow 0$,

$$u_t^\varepsilon \rightarrow -2 V_n \delta(x - \Gamma(t))$$

so that we can replace the term u_t by $2 V_n \delta(x - \Gamma(t))$ in the limit equation for μ . The limiting equations for μ and σ are then given by

$$\alpha \mu_t = \Delta \mu + (2 V_n + 2\sqrt{2} p_0 (\sigma - \gamma \mu)) \delta(x - \Gamma(t)),$$

$$\sigma_t = \Delta \sigma - 2\sqrt{2} p_0 (\sigma - \gamma \mu) \delta(x - \Gamma(t)),$$

in the sense of distributions in $\Omega \times (0, T)$.

The strong form of the limit equations for μ and σ

$$\alpha\mu_t = \Delta\mu \quad \text{in } Q_T^+ \cup Q_T^-,$$

$$\sigma_t = \Delta\sigma \quad \text{on } Q_T^+ \cup Q_T^-,$$

together with

$$[[\mu]] = [[\sigma]] = 0 \quad \text{on } \Gamma_T,$$

and

$$\left[\left[\frac{\partial\mu}{\partial n}\right]\right] = -2V_n - 2\sqrt{2}p_0(\sigma - \delta\mu) \quad \text{on } \Gamma_T,$$

$$\left[\left[\frac{\partial\sigma}{\partial n}\right]\right] = 2\sqrt{2}p_0(\sigma - \delta\mu) \quad \text{on } \Gamma_T$$

A tumor growth model

I thank you for your attention!