A Gamma convergence approach to a phase transition problem, with application to a tumor growth model

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The talk is divided in three parts:

1. The diffuse tumor growth model

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Part 1

THE DIFFUSE TUMOR GROWTH MODEL

Part 1

Background. The analysis of models for cancer evolution is becoming more and more studied in the recent years (see the general monograph Cristini-Lowengrub 2010). The considered models are divided into two classes: *continuum models* and *discrete models*. The former are usually diffuse-interface models based on *continuum mixture theory*.

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We will consider a very simplified model where the cell velocities are neglected and the transport-reaction term has a very specific form.

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- The chemical potential v which is linked with the phase variable by the relation

$$v := \frac{1}{\epsilon} f(u) - \epsilon \Delta u,$$

  with ϵ a model parameter representing the regularization (the width of the narrow transition layer). The function f is the derivative of a double-well potential W with zeros at $\{\pm 1\}$.

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For $\epsilon \sim 0$ we will obtain a sharp interface model!

The tumor growth model

The equations of the model are

$$\begin{cases} u_t - \Delta v = R(u, v, \sigma) \\ \sigma_t - \Delta \sigma = -R(u, v, \sigma), \end{cases} \tag{1}$$

R denoting the reaction term containing the proliferation of the tumorous phase.

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$$\begin{cases} u_t - \Delta v = 2\sigma + u - v \\ \sigma_t - \Delta \sigma = -2\sigma - u + v \\ v = \frac{1}{\epsilon} f(u) - \epsilon \Delta u. \end{cases} \tag{2}$$

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Our aim is to study the behavior of the solutions to (2) as $\epsilon \to 0$. This would give rise to a sharp interface model!

The tumor growth model

Indeed, the system has the following *Lyapunov function*

$$\frac{1}{\epsilon}\int_\Omega W(u)dx + \epsilon\int_\Omega |\nabla u|^2 dx + \frac{3}{2}\|\sigma\|_{L^2}^2 + \frac{1}{2}\|\nabla\sigma\|_{L^2}^2 + \int_\Omega u\sigma dx. \qquad (3)$$

This means that $\frac{1}{\epsilon}\int_\Omega W(u)dx$ remains uniformly bounded in time and ϵ.

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When ϵ is close to zero then the finiteness of the energy $\frac{1}{\epsilon}\int_{\Omega} W(u)dx$ would force u to assume only values close to $+1$ and -1.

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When ϵ is close to zero then the finiteness of the energy $\frac{1}{\epsilon}\int_\Omega W(u)dx$ would force u to assume only values close to $+1$ and -1.
We expect that at the limit the functions u and v satisfy a free-boundary problem, where the boundary is an interface separating the phases $u = \pm 1$.

Part 2

GAMMA CONVERGENCE OF GRADIENT FLOWS

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Let $\epsilon \in (0,1)$ and let $X_\epsilon \subset Y$ Hilbert spaces. We assume that the functionals E_ϵ on X_ϵ are of class C^1 and we deal with the solutions $u^\epsilon : [0,T] \to X_\epsilon$ of the gradient flows

$$u_t^\epsilon = -\nabla_{X_\epsilon} E_\epsilon(u^\epsilon), \tag{4}$$

with energy balance

$$E_\epsilon(u^\epsilon(0)) - E_\epsilon(u^\epsilon(t)) = \int_0^t \|u_t^\epsilon\|_{X_\epsilon}^2 \, ds. \tag{5}$$

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We want to study the limit as $\epsilon \to 0$ of u^ϵ.

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(i) (Gamma liminf) There exists a C^1 functional F on a Hilbert space $X \subset Y$ such that for all sequences $v^\epsilon \xrightarrow{S} v$ it holds

$$\liminf_{\epsilon \to 0} E_\epsilon(v^\epsilon) \geq F(v).$$

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(ii) (Lower bound on the velocities) If $u^\epsilon(t) \xrightarrow{S} u(t)$ for all $t \in [0, T]$ then

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(iv) The initial data are well prepared, in the sense that $E_\epsilon(u^\epsilon(0)) \to F(u(0))$.

Gamma convergence of gradient flows

Theorem (Sandier-Serfaty)

If conditions (i)-(iv) are satisfied, then

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Then the Fatou Lemma implies

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$$\geq -\int_0^t \langle u_t(s), \nabla_X F(u(s))\rangle_X ds = -\int_0^t \frac{d}{dt} F(u(s)) ds = F(u(0)) - F(u(t)).$$

But, thanks to (i) and (iv) we have

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This implies that all the inequalities are equalities! In particular

$$\frac{1}{2}\int_0^t \|u_t(s)\|_X^2 ds + \|\nabla_X F(u(s))\|_X^2 = -\int_0^t \langle u_t(s), \nabla_X F(u(s))\rangle_X ds,$$

which entails

$$u_t(t) = -\nabla_X F(u(t)),$$

for a.e. $t \in [0, T]$.

Part 3

THE SHARP INTERFACE LIMIT

The sharp interface limit

We now want to write the system

$$\begin{cases} u_t - \Delta v = 2\sigma + u - v \\ \sigma_t - \Delta\sigma = -2\sigma - u + v \\ v = \frac{1}{\epsilon} f(u) - \epsilon\Delta u \end{cases} \tag{7}$$

as a gradient flow. With the change of variable $u = \varphi - \sigma$ we arrive at

$$\begin{cases} \varphi_t = \Delta\Big(\frac{1}{\epsilon} f(\varphi - \sigma) - \epsilon\Delta(\varphi - \sigma)\Big) + \Delta\sigma \\ \sigma_t = \Delta\sigma + \frac{1}{\epsilon} f(\varphi - \sigma) - \epsilon\Delta(\varphi - \sigma) - \sigma - \varphi. \end{cases} \tag{8}$$

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Let us introduce the space

$$H_n^{-1}(\Omega) := \{u \in (H^1(\Omega))' : \exists v \in H^1(\Omega) \text{ such that } \langle u, \varphi \rangle = \int_\Omega \nabla v \cdot \nabla \varphi dx \; \forall \varphi \in H^1(\Omega)\},$$

with scalar product

$$\langle u, v \rangle_{H_n^{-1}} := \langle \nabla \Delta^{-1} u, \nabla \Delta^{-1} v \rangle.$$

The sharp interface limit

The equations (8) are recognized as a gradient flow of the energy

$$E^{\epsilon}(\varphi,\sigma) := \frac{1}{\epsilon}\int_{\Omega} W(\varphi-\sigma)dx + \epsilon\int_{\Omega}|\nabla(\varphi-\sigma)|^2 dx + \frac{1}{2}\|\sigma\|_{L^2}^2 + \frac{1}{2}\|\nabla\sigma\|_{L^2}^2 + \int_{\Omega}\varphi\sigma dx.$$

with respect to the structure of $H_n^{-1}(\Omega)\times L^2(\Omega)$.

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Therefore we aim to apply the technique introduced so far (with few modifications).

Theorem

The functionals E^ϵ Γ-converge in $L^1 \times L^1$ to

$$2c_W\mathcal{H}^2(\partial\{\varphi-\sigma=1\}) + \frac{1}{2}\|\sigma\|_{L^2}^2 + \frac{1}{2}\|\nabla\sigma\|_{L^2}^2 + \int_\Omega \varphi\sigma dx, \tag{9}$$

when $\varphi-\sigma\in\{\pm1\}$ and where $\partial\{\varphi-\sigma=1\}$ denotes the interface between the phase 1 and -1.

This implies condition (i).

The sharp interface limit

It is easy to obtain the following a-priori estimates

$$\|\varphi^\epsilon\|_{H^1(0,T;H_n^{-1}(\Omega))} \leq M, \tag{10}$$

$$\|\sigma^\epsilon\|_{H^1(0,T;L^2(\Omega))} \leq M, \tag{11}$$

$$\|v^\epsilon\|_{L^2(0,T;H^1(\Omega))} \leq M, \tag{12}$$

$$\|\sigma^\epsilon\|_{L^2(0,T;H^2(\Omega))} \leq M, \tag{13}$$

$$\|u^\epsilon\|_{L^\infty(0,T;L^4(\Omega))} \leq M \tag{14}$$

from which follows condition (iii).

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from which follows condition (iii).

Lemma

For a subsequence, we have

$$u^\epsilon \rightharpoonup u \quad \text{weakly in } L^4(\Omega \times [0,T]). \tag{15}$$

Moreover, for all $t \in [0,T]$, $u(t) \in BV(\Omega; \{-1,1\})$ *and*

$$u^\epsilon(t) \rightharpoonup u(t) \quad \text{weakly in } L^4(\Omega), \tag{16}$$
$$u^\epsilon(t) \to u(t) \quad \text{strongly in } L^1(\Omega), \tag{17}$$
$$u^\epsilon(t) \rightharpoonup u(t) \quad \text{weakly* in } BV(\Omega). \tag{18}$$

If we assume that the limit interface $\partial\{u = 1\}$ is smooth (at least C^3), then we can write the time derivative of the limiting energy E.

Lemma

Let $\cup_{t\in[0,T^*]}\Gamma(t) \times \{t\} \subset \Omega \times [0, T^*]$ *be a* C^3 *hypersurface with* $\Gamma(t)$ *closed for all* $t \in [0, T^*]$. *Let* $u(t) := \chi_{\Omega^+(t)} - \chi_{\Omega^+(t)}$ *for all* $t \in [0, T^*]$, *and assume* $u \in H^1(0, T; H_n^{-1}(\Omega))$ *and* $\sigma \in L^\infty(0, T^*; H^1(\Omega)) \cap H^1(0, T^*; L^2(\Omega))$. *Then for all* $t \in [0, T^*]$

$$\frac{d}{dt} E^0(u(t) + \sigma(t), \sigma(t)) = -2c_W \langle V(t), k(t)\rangle_{L^2(\Gamma)} + 2\langle V(t), \sigma(t)\rangle_{L^2(\Gamma)} + \langle \sigma_t(t), -\Delta\sigma(t) + u(t) + 3\sigma(t)\rangle,$$

where $V(t)$ *is the normal velocity of the surface* $\Gamma(t)$, *and* $k(t)$ *is its mean curvature.*

We are now ready to prove the lower bound on the velocities, (ii):

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For all $t \in [0, T]$ there holds

$$\liminf_{\epsilon \to 0} \int_0^t \|\varphi_t^\epsilon(s)\|_{H_n^{-1}(\Omega)} ds \geq \int_0^t \|2\partial_t \Gamma(s) + \sigma_t(s)\|_{H_n^{-1}(\Omega)} ds. \tag{19}$$

In some sense this follows from the fact that $\varphi_t^\epsilon = u_t^\epsilon - \sigma_t^\epsilon$.

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In some sense this follows from the fact that $\varphi_t^\epsilon = u_t^\epsilon - \sigma_t^\epsilon$.
Finally we need the following lemma:

Lemma

The functions $v^\epsilon \rightharpoonup v$ weakly in $L^2(0, T; H^1(\Omega))$ and the limit function v satisfies for a.e. $t \in [0, T]$

$$v(t) = -c_W k(t) \quad \text{on } \Gamma(t), \tag{20}$$

where $k(t) \in H^{1/2}(\Gamma(t))$ is the mean curvature of the smooth surface $\Gamma(t)$ at time t.

following the proof of the convergence of gradient flows we find

$$
\begin{aligned}
& E^\epsilon(\varphi_0^\epsilon, \sigma_0^\epsilon) - E^\epsilon(\varphi(t)^\epsilon, \sigma(t)^\epsilon) \\
& = \int_0^t (\frac{1}{2}\|\varphi_t^\epsilon\|_{H_n^{-1}}^2 + \frac{1}{2}\|\sigma_t^\epsilon\|_{L^2}^2) + \int_0^t (\frac{1}{2}\|\Delta v^\epsilon + \Delta\sigma^\epsilon\|_{H_n^{-1}}^2 + \frac{1}{2}\|\Delta\sigma^\epsilon + v^\epsilon - \varphi^\epsilon - \sigma^\epsilon\|_{L^2}^2) \\
& \geq \int_0^t (\frac{1}{2}\|2\frac{d}{dt}\Gamma + \sigma_t\|_{H_n^{-1}}^2 + \frac{1}{2}\|\Delta v + \Delta\sigma\|_{H_n^{-1}}^2 + \frac{1}{2}\int_0^t (\|\sigma_t\|_{L^2}^2 + \|\Delta\sigma + v - \varphi - \sigma\|_{L^2}^2) \\
& \geq \int_0^t \langle (2\frac{d}{dt}\Gamma + \sigma_t), \Delta v + \Delta\sigma\rangle_{H_n^{-1}} + \langle \sigma_t, \Delta\sigma + v - \varphi - \sigma\rangle ds \\
& = \int_0^t -2\langle \frac{d}{dt}\Gamma, v + \sigma\rangle_{H_n^{-1}\times H^1} + \langle \sigma_t, \Delta\sigma - u - 3\sigma\rangle ds \\
& = \int_0^t -2\langle V, v + \sigma\rangle_{L^2(\Gamma)} + \langle \sigma_t, \Delta\sigma - u - 3\sigma\rangle ds \\
& = \int_0^t 2c_W\langle V, k\rangle_{L^2(\Gamma)} - 2\langle V, \sigma\rangle_{L^2(\Gamma)} + \langle \sigma_t, \Delta\sigma - u - 3\sigma\rangle ds \\
& = E(\varphi_0, \sigma_0) - E(\varphi(t), \sigma(t)). \qquad (21)
\end{aligned}
$$

Sharp interface limit

We then obtain the following statements:

Theorem

If the initial data are well prepared, i.e.,

$$E^{\epsilon}(\varphi^{\epsilon}(0), \sigma^{\epsilon}(0)) \to E(\varphi(0), \sigma(0)),$$

then it holds

$$-\Delta v = -u - 2\sigma - v \quad \text{on } \Omega^{+} \cup \Omega^{-} \tag{22}$$

$$\sigma_t = -\Delta\sigma + v - u - 2\sigma \quad \text{on } \Omega, \tag{23}$$

and

$$v = -c_W k \quad \text{and} \quad [\frac{\partial v}{\partial n}] = 2V \quad \text{a.e. on } \Gamma, \tag{24}$$

almost everywhere on $[0, T]$.

The last condition follows from the fact that

$$2\frac{d}{dt}\Gamma(t) = -\Delta v(t) + \varphi(t) + \sigma(t) + v(t) \tag{25}$$

Part 4

COMMENTS AND OPEN PROBLEMS

Remarks

We tacitly made some hypotheses:

- One is on the regularity of the limit interface. As a consequence there will be a death time T^* until the evolution is regular. After the death time the evolution is undetermined!
- Behind Lemma 5 there is a technical hypothesis on the convergence of the measures

$$\frac{\epsilon}{2}|\nabla u^\epsilon|^2 + \frac{W(u^\epsilon)}{\epsilon} \rightharpoonup 2c_W d\mathcal{H}^{d-1}\llcorner\Gamma. \tag{26}$$

  This is unknown in general, but is proved with higher regularity and then conjectured by Tonegawa to hold in the general case.
- To obtain higher regularity it is possible regularize the gradient flow by introduce a suitable power of the Laplacian replacing Δ. Unfortunately in such a case it is nontrivial (and out of reach) to prove the interface property $[\frac{\partial v}{\partial n}] = 2V$.

Remarks

To be precise, we introduce the space

$$H_n^{-s}(\Omega) := \{u \in (H^s(\Omega))' : \exists v \in H^s(\Omega) \text{ such that } \langle u, \varphi \rangle = \int_\Omega A^{s/2} v A^{s/2} \varphi dx \forall \varphi \in H^s(\Omega)\},$$

with scalar product

$$\langle u, v \rangle_{H_n^{-s}} := \langle A^{s/2} u, A^{s/2} v \rangle,$$

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$$E^\epsilon(\varphi, \sigma) := \frac{1}{\epsilon} \int_\Omega W(\varphi - \sigma) dx + \epsilon \int_\Omega |\nabla(\varphi - \sigma)| dx + \frac{1}{2} \|\sigma\|_{L^2}^2 + \frac{1}{2} \|A^{s/2} \sigma\|_{L^2}^2 + \int_\Omega \varphi \sigma dx.$$

with respect to the structure $H_n^{-s}(\Omega) \times L^2(\Omega)$ giving rise to

$$\begin{cases} \varphi_t = -A^s \left(\frac{1}{\epsilon} f(\varphi - \sigma) - \epsilon \Delta(\varphi - \sigma) \right) - A^s \sigma \\ \sigma_t = -A^s \sigma + \frac{1}{\epsilon} f(\varphi - \sigma) - \epsilon \Delta(\varphi - \sigma) - \sigma - \varphi. \end{cases} \tag{27}$$

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This leads to more regularity of the chemical potential! In particular the condition above is true!

Remarks

Theorem

If the initial data are well prepared, i.e.,

$$E^\epsilon(\varphi^\epsilon(0), \sigma^\epsilon(0)) \to E(\varphi(0), \sigma(0)),$$

then

$$A^s v = u + 2\sigma + v \quad \text{on } \Omega^+ \cup \Omega^- \tag{28}$$

$$\sigma_t = -A^s\sigma + v - u - 2\sigma \quad \text{on } \Omega, \tag{29}$$

and

$$v = -c_W k \quad \text{and} \tag{30}$$

almost everywhere on $[0, T]$.

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However, A^s being nonlocal, it seems out of reach the condition $[\frac{\partial v}{\partial n}] = 2V$!

$$2\frac{d}{dt}\Gamma(t) = A^s v(t) + \varphi(t) + \sigma(t) \tag{31}$$

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The end

THANK YOU FOR ATTENTION