

Diffuse interface models in Biology and Mechanics

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Plan of the Lecture

- Diffuse interface models in **Biology: tumor growth models**

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- ▶ it eliminates the need to enforce complicated boundary conditions across the tumor/host tissue and other species/species interfaces;
- ▶ it eliminates the need to explicitly track the position of interfaces, as is required in the sharp interface framework

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- Possible relations with different diffuse interface models \implies **Liquid Crystals**
- Ongoing projects and open problems

Part 1 - Diffuse Interfaces in Biology - Multispecies Model

DFRSS: The model

Typical structure of tumors grown in vitro:

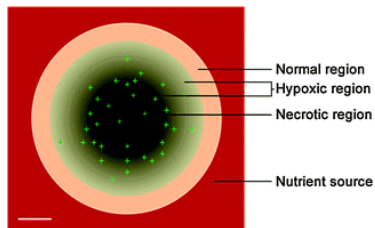


Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar $100\mu\text{m} = 0.1\text{mm}$

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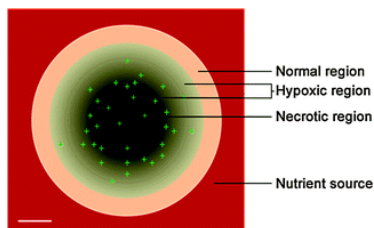


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A continuum thermodynamically consistent model is introduced with the ansatz:

- sharp interfaces are replaced by narrow transition layers arising due to adhesive forces among the cell species: a **diffuse interface** separates tumor and healthy cell regions
- **proliferating** and **dead tumor cells** and healthy cells are present, along with a **nutrient** (e.g. glucose or oxigene)

DFRSS: The state variables

- $\phi_i, i = 1, 2, 3$: the volume fractions of the cells:
 - ▶ $\phi_1 = P$: **proliferating tumor cell fraction**
 - ▶ $\phi_2 = \phi_D$: **dead tumor cell fraction**
 - ▶ $\phi_3 = \phi_H$: healthy cell fraction

The variables above are naturally constrained by the relation $\sum_{i=1}^3 \phi_i = \phi_H + \Phi = 1$

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- n : **the nutrient concentration**

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- $\Phi = \phi_D + P$: **the volume fraction of the tumor cells** split into the sum of the dead tumor cells and of the proliferating cells
- n : **the nutrient concentration**
- $\mathbf{u} = \mathbf{u}_i, i = 1, 2, 3$: **the tissue velocity field**. We treat the tumor and host cells as inertial-less fluids and assume that the cells are tightly packed and they march together
- Π : the cell-to-cell **pressure**

DFRSS: Mass conservation and choice of the energy

The volume fractions obey the mass conservation (advection-reaction-diffusion) equations:

$$\partial_t \phi_i + \operatorname{div}_x(\mathbf{u}\phi_i) = -\operatorname{div}_x \mathbf{J}_i + \Phi S_i$$

We have assumed that the densities of the components are matched

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

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The fluxes \mathbf{J}_{Φ} and \mathbf{J}_H that account for mechanical interactions among the species are as follows:

$$\mathbf{J}_{\Phi} = \mathbf{J}_1 + \mathbf{J}_2 := -\nabla_x \left(\frac{\delta E}{\delta \Phi} \right) = -\nabla_x (\mathcal{F}'(\Phi) - \Delta \Phi) := -\nabla_x \mu$$

$$\mathbf{J}_H = \mathbf{J}_3 := -\nabla_x \left(\frac{\delta E}{\delta \phi_H} \right) = \nabla_x \left(\frac{\delta E}{\delta \Phi} \right)$$

where we have used in the last equality the fact that $\phi_H = 1 - \Phi$ and where μ is the chemical potential of the system

DFRSS: The convective Cahn-Hilliard equation for the tumor cells fraction

For the source of mass in the host tissue, accounting for gains due to proliferation of cells and loss due to cell death, we have the following relations:

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

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Assuming the mobility of the system to be constant, then the tumor volume fraction Φ and the host tissue volume fraction ϕ_H obey the following mass conservation equations

$$\partial_t \Phi + \operatorname{div}_x(\mathbf{u}\Phi) = -\operatorname{div}_x \mathbf{J}_\Phi + \Phi(S_2 + S_1)$$

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Using now the fact that $S_T = S_1 + S_2$ and recalling that $\phi_H + \Phi = 1$, $\mathbf{J}_\Phi = -\nabla_x \mu$, we can forget of the equation for ϕ_H and we recover the equation for Φ in the form

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

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Suppose the net source of tumor cells S_T to be given by

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

where $\lambda_M \geq 0$ is the mitotic rate and $\lambda_L \geq 0$ is the lysing rate of dead cells

DFRSS: The transport equation for the proliferating cells fraction

The volume fraction of dead tumor cells ϕ_D would satisfy an equation similar to the one of Φ . However, we prefer to couple the equation for Φ with the one for $P = \Phi - \phi_D$ which then reads

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

where the source of dead cells is taken as

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

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Here

- $\lambda_A P$ describes the death of cells due to apoptosis with rate $\lambda_A \geq 0$ and the term $\lambda_N H(n_N - n)P$ models the death of cells due to necrosis with rate $\lambda_N \geq 0$
- for mathematical reasons, we choose H to be a regular and nonnegative function of n
- the term n_N represents the necrotic limit, at which the tumor tissue dies due to lack of nutrients

DFRSS: The Darcy law for the velocity field

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

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

where, for simplicity, the motility has been taken constant and equal to 1

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Summing up the mass balance equations

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$$\partial_t \phi_H + \operatorname{div}_x(\mathbf{u}\phi_H) = -\operatorname{div}_x \mathbf{J}_H + (1 - \Phi)S_T$$

and using $\Phi + \phi_H = 1$ and $\mathbf{J}_H = -\mathbf{J}_\Phi$, we end up with the following constraint for the velocity field:

$$\operatorname{div}_x \mathbf{u} = S_T = \lambda_M n P - \lambda_L (\Phi - P)$$

DFRSS: The quasistatic reaction diffusion equation for the nutrient

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

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

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

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Here

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

DFRSS: The boundary conditions

- We chose the b.c.s of [CWSL: Y. Chen, S.M. Wise, V.B Shenoy, J.S. Lowengrub, Int. J. Numer. Methods Biomed. Eng., 2014] for μ , Π , n , and Φ (ν is the outer normal unit vector to $\partial\Omega$):

$$\mu = \Pi = 0, \quad n = 1, \quad \nabla_x \Phi \cdot \nu = 0$$

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$$Pu \cdot \nu \geq 0$$

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- The proliferation function at the boundary has to be nonnegative on the set where the velocity \mathbf{u} satisfies $\mathbf{u} \cdot \nu > 0$. By maximum principle, then $P \geq 0$ in Ω

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- The proliferation function at the boundary has to be nonnegative on the set where the velocity \mathbf{u} satisfies $\mathbf{u} \cdot \nu > 0$. By maximum principle, then $P \geq 0$ in Ω
- As $P \geq 0$, the boundary condition $P\mathbf{u} \cdot \nu \geq 0$ means $P = 0$ whenever $\mathbf{u} \cdot \nu < 0$ i.e. on the part of the inflow part of the boundary

DFRSS: The PDEs

In summary, let $\Omega \subset \mathbb{R}^3$ be a bounded domain and $T > 0$ the final time of the process. For simplicity, choose $\lambda_M = \nu_U = 1$, $\lambda_A = \lambda_1$, $\lambda_N = \lambda_2$, $\lambda_L = \lambda_3$.

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Then, in $\Omega \times (0, T)$, we have the following system of equations:

$$\text{(Cahn - Hilliard)} \quad \partial_t \Phi + \operatorname{div}_x(\mathbf{u}\Phi) - \operatorname{div}_x(\nabla_x \mu) = \Phi S_T, \quad \mu = -\Delta \Phi + \mathcal{F}'(\Phi)$$

$$\text{(Darcy)} \quad \mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi, \quad \operatorname{div}_x \mathbf{u} = S_T$$

$$\text{(Transport)} \quad \partial_t P + \operatorname{div}_x(\mathbf{u}P) = \Phi(S_T - S_D)$$

$$\text{(Reac - Diff)} \quad -\Delta n + nP = T_c(n, \Phi)$$

where

$$\text{(Source - Tumor)} \quad S_T(n, P, \Phi) = nP - \lambda_3(\Phi - P)$$

$$\text{(Source - Dead)} \quad S_D(n, P, \Phi) = (\lambda_1 + \lambda_2 H(n_N - n))P - \lambda_3(\Phi - P)$$

$$\text{(Nutrient - Capill)} \quad T_c(n, \Phi) = [\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)](n_c - n)$$

coupled with the boundary conditions on $\partial\Omega \times (0, T)$: $\mu = \Pi = 0$, $n = 1$, $\nabla_x \Phi \cdot \nu = 0$, $P\mathbf{u} \cdot \nu \geq 0$ and with the initial conditions $\Phi(0) = \Phi_0$, $P(0) = P_0$ in Ω

DFRSS: Assumptions on the potential \mathcal{F}

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

$$0 \leq \Phi(t, x) \leq 1$$

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

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

Moreover, we ask that

$$\mathcal{C} \in C^1(0, 1), \quad \lim_{\Phi \rightarrow 0^+} \mathcal{C}'(\Phi) = \lim_{\Phi \rightarrow 1^-} \mathcal{C}'(\Phi) = \infty$$

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

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

DFRSS: Assumptions on the other data

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

$$\lambda_i \geq 0 \text{ for } i = 1, 2, 3, \quad H \geq 0$$

$$[\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)] \geq 0, \quad 0 < n_c < 1$$

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

$$\Phi_0 \in H^1(\Omega), \quad 0 \leq \Phi_0 \leq 1, \quad C(\Phi_0) \in L^1(\Omega)$$

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

DFRSS: Weak formulation

(Φ, \mathbf{u}, P, n) is a weak solution to the problem in $(0, T) \times \Omega$ if

(i) these functions belong to the regularity class:

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

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

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

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

$$P \in L^\infty((0, T) \times \Omega), \quad 0 \leq P \leq 1 \quad \text{a.a. in } (0, T) \times \Omega$$

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

(ii) the following integral relations hold:

$$\int_0^T \int_\Omega [\Phi \partial_t \varphi + \Phi \mathbf{u} \cdot \nabla_x \varphi + \mu \Delta \varphi + \Phi S_T \varphi] \, dx \, dt = - \int_\Omega \Phi_0 \varphi(0, \cdot) \, dx$$

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

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

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

$$\int_0^T \int_\Omega [P \partial_t \varphi + P \mathbf{u} \cdot \nabla_x \varphi + \Phi (S_T - S_D) \varphi] \, dx \, dt \geq - \int_\Omega P_0 \varphi(0, \cdot) \, dx$$

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

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

Now, we are able to state the main result of [M. Dai, E. Feireisl, E.R., G. Schimperna, M. Schonbek, **Analysis of a diffuse interface model of multispecies tumor growth**, preprint [arXiv:1507.07683](https://arxiv.org/abs/1507.07683) (2015)]

Theorem

*Let $T > 0$ be given. Under the previous assumptions the variational formulation of our initial-boundary value problem admits **at least one solution** on the time interval $[0, T]$*

DFRSS: Idea of the proof

- Approximation: regularize the equations
- Perform uniform a priori estimates
- Use compactness arguments in order to pass to the limit

DFRSS: The maximum principle

- The transport equation for the density function P is

$$\partial_t P + \mathbf{u} \cdot \nabla_x P = -PS_T + \Phi(S_T - S_D) = P[-S_T + \Phi(n - (\lambda_1 + \lambda_2 H(n_N - n)))]$$

Thus, provided

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

we can deduce by maximum principle arguments that

$$P \geq 0$$

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- In order to obtain positivity of n we need

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

to be positive (non-negative) whenever $n < 0$. Then we assume

$$[\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)] \geq 0, \quad 0 < n_c < 1$$

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

$$0 \leq n(t, x) \leq 1$$

DFRSS: The upper bound for P

Hence, using $\Phi, n \in [0, 1]$, and evaluating the expression on the right-hand side of

$$\partial_t P + \mathbf{u} \cdot \nabla_x P = -PS_T + \Phi(S_T - S_D) = P[-S_T + \Phi(n - (\lambda_1 + \lambda_2 H(n_N - n)))]$$

for $P = 1$, due to $-\Phi(\lambda_1 + \lambda_2 H(n_N - n)) \leq 0$, yields

$$P[\lambda_3(\Phi - P) - nP + \Phi(n - (\lambda_1 + \lambda_2 H(n_N - n)))] \leq \lambda_3(\Phi - 1) + n(\Phi - 1)$$

Consequently, provided

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

it follows that

$$0 \leq P(t, x) \leq 1$$

DFRSS: Main estimates on Φ

Testing by μ the Cahn-Hilliard equation

$$\text{(Cahn - Hilliard)} \quad \partial_t \Phi + \operatorname{div}_x(\mathbf{u}\Phi) - \operatorname{div}_x(\nabla_x \mu) = \Phi S_T, \quad \mu = -\Delta \Phi + \mathcal{F}'(\Phi)$$

and by \mathbf{u} the **(Darcy - law)**: $\mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi$, gives

$$\frac{d}{dt} \int_{\Omega} \left[\frac{1}{2} |\nabla_x \Phi|^2 + \mathcal{F}(\Phi) \right] dx + \int_{\Omega} \left[|\nabla_x \mu|^2 + |\mathbf{u}|^2 \right] dx = \int_{\Omega} \Pi S_T dx \leq \|S_T\|_{L^\infty(\Omega)} \|\Pi\|_{L^1(\Omega)}$$

Seeing that Π solves the Dirichlet problem

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

we deduce that

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

where, by means of Gagliardo-Nirenberg interpolation inequality,

$$\|\mu \nabla_x \Phi\|_{L^2(\Omega; \mathbb{R}^3)} \leq c \|\mu(t, \cdot)\|_{L^4(\Omega)} \left(\|\Phi(t, \cdot)\|_{L^\infty(\Omega)}^{1/2} \left(\|\mu\|_{L^2(\Omega)}^{1/2} + \|\nabla \Phi\|_{L^2(\Omega)}^{1/2} \right) + c \right)$$

Thus, and applying a standard Grönwall's lemma and by comparison arguments, we deduce

$$\sup_{t \in (0, T)} \|\Phi\|_{H^1(\Omega)} + \int_0^T \left[\|\nabla_x \mu\|_{L^2(\Omega; \mathbb{R}^3)}^2 + |\mathbf{u}|^2 + \|\Phi\|_{W^{2,6}(\Omega)}^2 \right] dt \leq c$$

DFRSS: Main estimates on \mathbf{u}

Note that we already know

$$\operatorname{div}_x \mathbf{u} = S_T \text{ bounded in } L^\infty((0, T) \times \Omega) \quad \text{and } \mathbf{u} \text{ bounded in } L^2((0, T) \times \Omega; \mathbb{R}^3)$$

Next, we compute from the **(Darcy – law)** : $\mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi$ the

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

Hence, in view of the fact that $\operatorname{div}_x(\varphi \mathbf{u})$ and $\mathbf{curl}(\varphi \mathbf{u})$ for any test function $\varphi \in C^\infty(\mathbb{R}^3)$ are bounded in $L^1(0, T; L^2(\mathbb{R}^3))$, we then obtain that $\varphi \mathbf{u}$ is bounded in $L^1(0, T; H^1(\mathbb{R}^3))$ and so \mathbf{u} satisfies

$$\int_0^T \|\mathbf{u}\|_{H_{loc}^1(\Omega; \mathbb{R}^3)} dt \leq c$$

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These estimates are sufficient in order to pass to the limit in the regularized system and to obtain our weak solutions

Comparison with some other models including velocities

- **Numerical simulations** of diffuse-interface models for tumor growth have been carried out in several papers (cf., e.g., [Cristini, Lowengrub, Cambridge Univ. Press, 2010] and more recently [Garcke, Lam, Sitka, Styles, arXiv:1508.00437, 2015]). However, a **rigorous mathematical analysis** of the resulting PDEs is still in its beginning and only for **one species models with regular potentials** (cf. [Garcke, Lam, J. Appl. Math and arXiv:1604.00287, 2016])

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- To the best of our knowledge, the first related mathematical papers study simplified models:
 - ▶ the so-called **Cahn-Hilliard-Hele-Shaw system** ([J. Lowengrub, E. Titi, K. Zhao, European J. Appl. Math., 2013], [X. Wang, H. Wu, Asymptot. Anal., 2012], [X. Wang, Z. Zhang, Ann. Inst. H. Poincaré Anal. Nonlinéaire, 2013]) in which the nutrient n , the source of tumor S_T and the fraction S_D of the dead cells are neglected or

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 - ▶ [J. Jang, H. Wu, S. Zheng, J. Differential Equations, 2015] where S_T is not 0 but it's not depending on the other variables but just on time and space

Perspectives and Open problems

- An ongoing project with S. Frigeri, K.-F. Lam, G. Schimperna: To study the **multispecies model** introduced in [CWSL] including **different mobilities** and non-Dirichlet b.c.s on the chemical potential \implies the main problems are:

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$$\partial_t \varphi_i = M_i \Delta \mu_i - \operatorname{div}(\varphi_i u) + S_i$$
 and if we do not choose the Dirichlet b.c.s on μ then we need to estimate the means of μ_i (containing a multiwell logarithmic type potential)
 - ▶ we need the mean values of φ_i (the proliferating and dead cells phases) in the two Cahn-Hilliard equations to be away from the potential barriers \implies ad hoc estimate based on ODEs technique
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- ▶ Very partial result in [DFRSS] assuming **strict convexity of \mathcal{F}** and $S_T = S_D = 0$
- ▶ An ongoing project with S. Melchionna: **Varifold solutions** at the limit as $\varepsilon \searrow 0$ in case we just consider the Cahn-Hilliard-Darcy system coupling the Φ equation to the u equation (neglecting the nutrient)

Part 2 - Diffuse Interfaces in Biology - One Species Model: Optimal Control

One Species Diffuse Interface Model

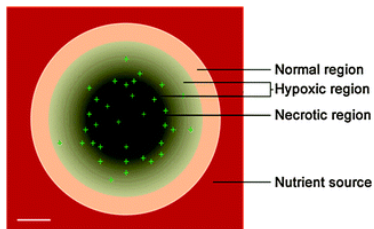


Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar $100\mu\text{m} = 0.1\text{mm}$

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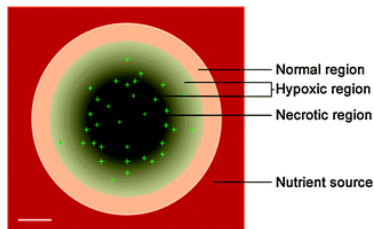


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In [GLR] H. Garcke, K.-F. Lam, E.R., **Optimal control of treatment time in a diffuse interface model of tumor growth, manuscript (2016)** we study the case where there are only **proliferating** tumor cells surrounded by (healthy) **host cells**, and a **nutrient** (e.g. glucose) is present and we neglect velocities

GLR: Optimization over the treatment time

Common treatment for tumors are

- Cytotoxic drugs - target and damage rapidly dividing cells.
- Cytostatic drugs - blocks proliferation.
- Radiation therapy.
- Surgery.

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Thus, aside from optimising the drug distribution, we should also consider **optimising the treatment time**.

The state equations: Cahn-Hilliard + nutrient models with sources

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We consider

- Linear kinetics (as in Part 1) [Chen, Wise, Shenoy, Lowengrub], [Garcke, L.]

$$\mathcal{M} = h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u), \quad \mathcal{S} = h(\varphi)\mathcal{C}\sigma$$

Here $h(s)$ is an interpolation function such that $h(-1) = 0$ and $h(1) = 1$, and

- ▶ $h(\varphi)\mathcal{P}\sigma$ - proliferation of tumor cells proportional to nutrient concentration,
 - ▶ $h(\varphi)\mathcal{A}$ - apoptosis of tumor cells,
 - ▶ $h(\varphi)\mathcal{C}\sigma$ - consumption of nutrient by the tumor cells,
 - ▶ $h(\varphi)\alpha u$ - elimination of tumor cells by **cytotoxic drugs** at a constant rate α .
- A regular double-well potential Ψ
 - Reaction-diffusion equation for the nutrient (here σ , while it was n in Part 1)

GLR: Objective functional

For positive β_T, β_u and non-negative $\beta_Q, \beta_\Omega, \beta_S$, we consider

$$\begin{aligned} J(\varphi, u, \tau) := & \int_0^\tau \int_\Omega \frac{\beta_Q}{2} |\varphi - \varphi_Q|^2 + \int_\Omega \frac{\beta_\Omega}{2} |\varphi(\tau) - \varphi_\Omega|^2 \\ & + \int_\Omega \frac{\beta_S}{2} (1 + \varphi(\tau)) + \int_0^\tau \int_\Omega \frac{\beta_u}{2} |u|^2 + \beta_T \tau \end{aligned}$$

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- the variable τ denotes the unknown treatment time to be optimised,
- φ_Q is a desired evolution of the tumor over the treatment,
- φ_Ω is a desired final state of the tumor (stable equilibrium of the system),
- the term $\frac{1+\varphi(\tau)}{2}$ measures the size of the tumor at the end of the treatment,
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Expectation: An optimal control will be a pair (u_*, τ_*) and we will obtain two optimality conditions.

However, we will not study this functional, but a relaxed version! Let $r > 0$ be fixed and let $T \in (0, \infty)$ denote a maximal time, we define

$$J_r(\varphi, u, \tau) := \int_0^\tau \int_\Omega \frac{\beta_Q}{2} |\varphi - \varphi_Q|^2 + \frac{1}{r} \int_{\tau-r}^\tau \int_\Omega \frac{\beta_\Omega}{2} |\varphi - \varphi_\Omega|^2 \\ + \frac{1}{r} \int_{\tau-r}^\tau \int_\Omega \frac{\beta_S}{2} (1 + \varphi) + \int_0^\tau \int_\Omega \frac{\beta_u}{2} |u|^2 + \beta_T \tau$$

GLR: Relaxed objective functional

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The optimal control problem is

$$\min_{(\varphi, u, \tau)} J_r(\varphi, u, \tau)$$

subject to $\tau \in (0, T)$, $u \in \mathcal{U}_{\text{ad}} = \{f \in L^\infty(\Omega \times (0, T)) : 0 \leq f \leq 1\}$, and

$$\partial_t \varphi = \Delta \mu + h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u) \quad \text{in } \Omega \times (0, T) = Q,$$

$$\mu = \Psi'(\varphi) - \Delta \varphi \quad \text{in } Q,$$

$$\partial_t \sigma = \Delta \sigma - \mathcal{C}h(\varphi)\sigma \quad \text{in } Q,$$

$$0 = \partial_\nu \varphi = \partial_\nu \sigma = \partial_\nu \mu \quad \text{on } \partial\Omega \times (0, T),$$

$$\varphi(0) = \varphi_0, \quad \sigma(0) = \sigma_0 \quad \text{in } \Omega.$$

Fréchet differentiability with respect to the control

We set $\mathcal{S}(u) = (\varphi, \mu, \sigma)$ as the solution operator on the interval $[0, T]$, and introduce the linearized state variables $(\Phi^w, \Xi^w, \Sigma^w)$ corresponding to w as solutions to

$$\partial_t \Phi = \Delta \Xi + h(\varphi)(\mathcal{P}\Sigma - \alpha w) + h'(\varphi)\Phi(\mathcal{P}\sigma - \mathcal{A} - \alpha u),$$

$$\Xi = \Psi''(\varphi)\Phi - \Delta \Phi,$$

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Theorem

Let $\mathcal{U} \subset L^2(Q)$ be open such that $\mathcal{U}_{\text{ad}} \subset \mathcal{U}$. Then $S : \mathcal{U} \subset L^2(Q) \rightarrow \mathcal{Y}$ is Fréchet differentiable, where

$$\mathcal{Y} = [L^2(0, T; H^2) \cap H^1(0, T; (H^2)^*) \cap C^0([0, T]; L^2)] \times L^2(Q) \times [L^\infty(0, T; H^1) \cap H^1(0, T; L^2)]$$

and $D_u S(u)w = (\Phi^w, \Xi^w, \Sigma^w)$

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and $D_u S(u)w = (\Phi^w, \Xi^w, \Sigma^w)$

Consequence: For the reduced functional $\mathcal{J}_r(u, \tau) := J_r(\varphi, u, \tau)$,

$$\begin{aligned}D_u \mathcal{J}_r(u_*, \tau)[w] &= \beta_Q \int_0^\tau \int_\Omega (\varphi_* - \varphi_Q)\Phi^w + \int_Q \beta_u u_* w \\ &\quad + \frac{1}{2r} \int_{\tau-r}^\tau \int_\Omega (\beta_\Omega (\varphi_* - \varphi_\Omega)\Phi^w + \beta_S \Phi^w).\end{aligned}$$

GLR: Fréchet differentiability with respect to time

Lemma

For $f \in H^1(0, T; L^2) \subset C^0([0, T]; L^2)$,

$$D_\tau \left(\int_0^\tau \int_\Omega |f|^2 \right) = \int_\Omega |f(\tau)|^2.$$

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we have

$$\begin{aligned} D_\tau \mathcal{J}_r(u, \tau_*) &= \beta_T + \frac{\beta_Q}{2} \|\varphi(\tau_*) - \varphi_Q(\tau_*)\|_{L^2}^2 \\ &\quad + \frac{\beta_\Omega}{2r} (\|(\varphi - \varphi_\Omega)(\tau_*)\|_{L^2}^2 - \|(\varphi - \varphi_\Omega)(\tau_* - r)\|_{L^2}^2) \\ &\quad + \int_\Omega \frac{\beta_S}{2r} (\varphi(\tau_*) - \varphi(\tau_* - r)). \end{aligned}$$

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Note that the control u does not appear explicitly.

GLR: First order optimality conditions

Introducing the adjoint system

$$\begin{aligned} -\partial_t p &= \Delta q + \Psi''(\varphi_*)q - Ch'(\varphi_*)\sigma_* r + h'(\varphi_*)(\mathcal{P}\sigma_* - \mathcal{A} - \alpha u_*)p \\ &\quad + \beta_Q(\varphi_* - \varphi_Q) + \frac{1}{2r}\chi_{(\tau_*-r, \tau_*)}(t)(2\beta_\Omega(\varphi_* - \varphi_\Omega) + \beta_S), \\ q &= \Delta p, \\ -\partial_t r &= \Delta r - Ch(\varphi_*)r + \mathcal{P}h(\varphi_*)p \end{aligned}$$

with Neumann boundary conditions and final time condition $r(\tau_*) = p(\tau_*) = 0$. We have

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with Neumann boundary conditions and final time condition $r(\tau_*) = p(\tau_*) = 0$. We have

Theorem

The optimal control (u_*, τ_*) satisfy

$$\int_0^T \int_\Omega \beta_U u_*(v - u_*) - \int_0^{\tau_*} \int_\Omega h(\varphi_*) \alpha p (v - u_*) \geq 0 \quad \forall v \in \mathcal{U}_{\text{ad}},$$

and

$$\begin{aligned} \beta_T + \frac{\beta_Q}{2} \|(\varphi_* - \varphi_Q)(\tau_*)\|_{L^2}^2 + \frac{\beta_S}{2r} \int_\Omega \varphi_*(\tau_*) - \varphi(\tau_* - r) \, dx \\ + \frac{\beta_\Omega}{2r} (\|(\varphi_* - \varphi_\Omega)(\tau_*)\|_{L^2}^2 - \|(\varphi - \varphi_\Omega)(\tau_* - r)\|_{L^2}^2) = 0. \end{aligned}$$

Open related problem

To deal with the original functional:

$$J(\varphi, u, \tau) = \int_0^\tau \int_\Omega \frac{\beta_Q}{2} |\varphi - \varphi_Q|^2 + \int_\Omega \frac{\beta_\Omega}{2} |\varphi(\tau) - \varphi_\Omega|^2 + \int_0^\tau \int_\Omega \frac{\beta_u}{2} |u|^2 + \beta_T \tau.$$

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Then, the optimality condition for τ_* is

$$0 = D_\tau \mathcal{J}|_{(u_*, \tau_*)} = \int_\Omega \frac{\beta_Q}{2} |(\varphi_* - \varphi_Q)(\tau_*)|^2 + \frac{\beta_\Omega}{2} (\varphi_*(\tau_*) - \varphi_\Omega) \partial_t \varphi_*(\tau_*) + \frac{\beta_u}{2} |u_*(\tau_*)|^2 dx + \beta_T.$$

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Issues: For the above expression to be well-defined and to apply the lemma, we need

$$\partial_{tt} \varphi_* \in L^2(0, T; L^2), \quad u_* \in H^1(0, T; L^2).$$

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If we define $\mathcal{U}_{\text{ad}} = \{u \in H^1(0, T; L^2) : 0 \leq u \leq 1, \|\partial_t u\|_{L^2(Q)} \leq K\}$ for some fixed $K > 0$, and impose $\varphi_0 \in H^5$, $\sigma_0 \in H^3$, then it is possible to obtain

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$$\varphi \in H^2(0, T; L^2) \cap W^{1, \infty}(0, T; H^1).$$

However, to require the a-priori boundedness of $\partial_t u$ is not meaningful (difficult to verify in applications).

Comparison with some other models

In the phase field model we introduced

$$\begin{aligned}\partial_t \varphi &= \Delta \mu + \mathcal{M}, \\ \mu &= \Psi'(\varphi) - \Delta \varphi \\ \partial_t \sigma &= \Delta \sigma - \mathcal{S},\end{aligned}$$

where \mathcal{M} accounts for biological mechanisms related to proliferation and death and \mathcal{S} models interaction with the tumor cells, we could choose different form of \mathcal{M} and \mathcal{S} :

- Linear phenomenological laws for chemical reactions [Hawkins–Daarud, Prudhomme, van der Zee, Oden], [Frigeri, Grasselli, E.R.], [Colli, Gilardi, E.R., Sprekels: [optimal control without time dependence and with the control in the nutrient equation](#)]:

$$\mathcal{M} = \mathcal{S} = h(\varphi)(\sigma - \mu).$$

- Simplified law for chemical reaction leading to a Gradient-Flow structure [RS: E.R., R. Scala, A rigorous sharp interface limit of a diffuse interface model related to tumor growth, preprint [arXiv:1606.04663 \(2016\)](#)]:

$$\mathcal{M} = \mathcal{S} = 2\sigma + \varphi - \mu$$

Part 3 - From Diffuse to Sharp Interfaces in a simplified tumor model

RS: The tumor growth model

The coupled Cahn-Hilliard-Reaction-Diffusion system is

$$\begin{cases} \varphi_t - \Delta\mu = 2\sigma + \varphi - \mu \\ \sigma_t - \Delta\sigma = -2\sigma - \varphi + \mu \\ \mu = \frac{1}{\varepsilon}\Psi'(\varphi) - \varepsilon\Delta\varphi \end{cases}$$

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The variables of the system are:

- The tumorous phase variable φ :

$$\varphi(x) \simeq 1 \Rightarrow \text{tumor cell at } x$$

$$\varphi(x) \simeq -1 \Rightarrow \text{sane cell at } x$$

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with ε a model parameter representing the **width of the narrow transition layer** and Ψ is a double-well potential with zeros at $\{\pm 1\}$

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

RS: The Gradient Flow system

We now want to write the system

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Then we recognize as a **gradient flow** of the energy

$$E^\varepsilon(u, \sigma) := \frac{1}{\varepsilon} \int_{\Omega} \Psi(u - \sigma) dx + \varepsilon \int_{\Omega} |\nabla(u - \sigma)|^2 dx + \frac{1}{2} \|\sigma\|_{H^1}^2 + \int_{\Omega} u\sigma dx$$

with respect to the space $\mathcal{V}' \times L^2(\Omega)$, where $\mathcal{V}' := \{\zeta \in H^1(\Omega)' : \frac{1}{|\Omega|} \langle \zeta, 1 \rangle = 0\}$

Gamma convergence of gradient flows

$X_\varepsilon \subset Y$ Hilbert spaces, E_ε C^1 -functionals on X_ε , $u^\varepsilon : [0, T] \rightarrow X_\varepsilon$ solutions of

$$u_t^\varepsilon = -\nabla_{X_\varepsilon} E_\varepsilon(u^\varepsilon) \text{ with energy balance } E_\varepsilon(u^\varepsilon(0)) - E_\varepsilon(u^\varepsilon(t)) = \int_0^t \|u_s^\varepsilon\|_{X_\varepsilon}^2 ds.$$

Assume that $u^\varepsilon \xrightarrow{S} u$ in some sense (to be specified from case to case) and

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

$$\liminf_{\varepsilon \rightarrow 0} E_\varepsilon(v^\varepsilon) \geq F(v).$$

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

$$\liminf_{\varepsilon \rightarrow 0} \int_0^S \|u_t^\varepsilon(t)\|_{X_\varepsilon}^2 dt \geq \int_0^S \|u_t(t)\|_X^2 dt.$$

- (iii) (Lower bound on the slopes) If $v^\varepsilon \xrightarrow{S} v$ then $\liminf_{\varepsilon \rightarrow 0} \|\nabla_{X_\varepsilon} E_\varepsilon(v^\varepsilon)\|_{X_\varepsilon} \geq \|\nabla_X F(v)\|_X$.
- (iv) The initial data are well prepared, in the sense that $E_\varepsilon(u^\varepsilon(0)) \rightarrow F(u(0))$.

Theorem (Sandier-Serfaty)

Then $u_t = -\nabla_X F(u)$

RS: The sharp interface limit (i)

We aim to apply the Sandier-Serfaty technique introduced so far (with few modifications) to the **gradient flow** of the energy

$$E^\varepsilon(u, \sigma) := \frac{1}{\varepsilon} \int_{\Omega} \Psi(u - \sigma) dx + \varepsilon \int_{\Omega} |\nabla(u - \sigma)|^2 dx + \frac{1}{2} \|\sigma\|_{H^1}^2 + \int_{\Omega} u \sigma dx$$

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First, we have by the well-known Modica-Mortola Theorem

Theorem

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

$$E^0(u, \sigma) = c_\Psi \mathcal{H}^2(\Gamma) + \frac{1}{2} \|\sigma\|_{H^1}^2 + \int_{\Omega} u \sigma dx$$

when $u - \sigma \in \{\pm 1\}$ and where Γ denotes the interface between the two open sets Ω^+ and Ω^- where φ takes values ± 1 , and $c_\Psi = \int_{-1}^1 \Psi(s) ds$

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This implies condition (i) with $F = E^0$ (Gamma liminf).

RS: The sharp interface limit (iii)

It is easy to obtain the following a-priori estimates

$$\begin{aligned}\|\mathbf{u}^\varepsilon\|_{H^1(0,T;V') \cap L^\infty(0,T;L^4(\Omega))} &\leq M \\ \|\sigma^\varepsilon\|_{H^1(0,T;L^2(\Omega)) \cap L^\infty(0,T;H^1(\Omega))} &\leq M \\ \|\mu^\varepsilon\|_{L^2(0,T;H^1(\Omega))} &\leq M \\ \|\sigma^\varepsilon\|_{L^2(0,T;H^2(\Omega))} &\leq M \\ \|\varphi^\varepsilon\|_{L^\infty(0,T;L^4(\Omega))} &\leq M\end{aligned}$$

from which follows condition (iii) (Lower bound on the slope).

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from which follows condition (iii) (Lower bound on the slope).

Lemma

For a subsequence, we have

$$\varphi^\varepsilon \rightharpoonup \varphi \quad \text{weakly in } L^4(\Omega \times [0, T]).$$

Moreover, following [N.Q. Le, *Calc. Var.* (2008)], we have:

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

$$\begin{aligned}\varphi^\varepsilon(t) &\rightharpoonup \varphi(t) \quad \text{weakly in } L^4(\Omega) \\ \varphi^\varepsilon(t) &\rightarrow \varphi(t) \quad \text{strongly in } L^1(\Omega) \\ \varphi^\varepsilon(t) &\rightharpoonup \varphi(t) \quad \text{weakly* in } BV(\Omega).\end{aligned}$$

The sharp interface limit (ii)

If we assume that the limit interface Γ is smooth (at least C^3), then we have:

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 $\varphi(t) := \chi_{\Omega^+(t)} - \chi_{\Omega^-(t)}$ for all $t \in [0, T]$, and assume $\varphi \in L^\infty(0, T; L^2(\Omega)) \cap H^1(0, T; \mathcal{V}')$ and $\sigma \in L^\infty(0, T; H^1(\Omega)) \cap L^2(0, T; H^2(\Omega)) \cap H^1(0, T; L^2(\Omega))$. Then for all $t \in [0, T]$

$$\begin{aligned} \frac{d}{dt} E^0(\varphi(t) + \sigma(t), \sigma(t)) &= -2c_\Psi \langle V(t), k(t) \rangle_{L^2(\Gamma)} + 2 \langle V(t), \sigma(t) \rangle_{L^2(\Gamma)} \\ &\quad + \langle \sigma_t(t), -\Delta \sigma(t) + \varphi(t) + 3\sigma(t) \rangle, \end{aligned}$$

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

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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):

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

$$\liminf_{\varepsilon \rightarrow 0} \int_0^t \|u_t^\varepsilon(s)\|_{H_n^{-1}(\Omega)} ds \geq \int_0^t \|2\partial_t \Gamma(s) + \sigma_t(s)\|_{H_n^{-1}(\Omega)} ds.$$

This follows from the fact that $u_t^\varepsilon = \varphi_t^\varepsilon + \sigma_t^\varepsilon$ and from the Gradient Flow structure of the problem.

RS: The main result

Finally we need the following lemma:

Lemma (Equipartition of Energy)

The functions $\mu^\varepsilon \rightharpoonup \mu$ weakly in $L^2(0, T; H^1(\Omega))$ and μ satisfies for a.e. $t \in [0, T]$

$$\mu(t) = -c_\Psi k(t) \quad \text{on } \Gamma(t),$$

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We then obtain the following statements:

Theorem

If the initial data are well prepared, i.e., $E^\varepsilon(\varphi^\varepsilon(0), \sigma^\varepsilon(0)) \rightarrow E(\varphi(0), \sigma(0))$, then it holds

$$-\Delta\mu = u + \sigma - \mu \quad \text{on } \Omega^+ \cup \Omega^-$$

$$\sigma_t = -\Delta\sigma + \mu - u - \sigma \quad \text{on } \Omega$$

$$\mu = -c_\Psi k \quad \text{and} \quad \left[\frac{\partial\mu}{\partial n} \right] = -2V \quad \text{a.e. on } \Gamma$$

almost everywhere on $[0, T]$.

Remark and Open Problems

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!

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- Behind the lemma on the Equipartition of Energy there is a technical hypothesis on the convergence of the measures

$$\frac{\varepsilon}{2} |\nabla u^\varepsilon|^2 + \frac{W(u^\varepsilon)}{\varepsilon} \rightarrow 2c_\Psi d\mathcal{H}^2 \llcorner \Gamma$$

This is unknown in general, but is proved under higher regularity of the chemical potential μ^ε in [M. Roger, Y. Tonegawa, Calc. Var. Partial Differ. Equat. (2008)] and then conjectured by Tonegawa to hold in the general case

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- To obtain higher regularity it is possible regularize the gradient flow by introduce a suitable s -power of the Laplacian replacing Δ both in the ϕ and the σ equations. Unfortunately in such a case it is nontrivial (and out of reach) to prove the analogous of the interface property $[\frac{\partial \mu}{\partial n}] = -2V$ unless $s = 2$

Diffuse Interface models in other applications: Liquid Crystals

Consider the following 2D hydrodynamical model for the flow of nematic liquid crystals (cf. [F.-H. Lin, Nonlinear theory of defects in nematic liquid crystals: Phase transitions and flow phenomena, Comm. Pure Appl. Math. (1989)]):

$$\partial_t \mathbf{v} + \mathbf{v} \cdot \nabla \mathbf{v} - \nu \Delta \mathbf{v} + \nabla P = -\lambda \nabla \cdot (\nabla \mathbf{d} \odot \nabla \mathbf{d})$$

$$\nabla \cdot \mathbf{v} = 0$$

$$\partial_t \mathbf{d} + \mathbf{v} \cdot \nabla \mathbf{d} = \Delta \mathbf{d} - \frac{1}{\epsilon^2} (|\mathbf{d}|^2 - 1) \mathbf{d}$$

where \mathbf{v} is the velocity field of the flow and \mathbf{d} represents the averaged macroscopic/continuum molecular orientations.

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where \mathbf{v} is the velocity field of the flow and \mathbf{d} represents the averaged macroscopic/continuum molecular orientations.

Possible applications of the results we have seen in the biological models are:

- **The Optimal Control in 2D:** on the boundary $\mathbf{d}(x, t) = \mathbf{h}(x, t)$. This is related to the well-known anchoring condition for liquid crystals (Ongoing work with C. Cavaterra and H. Wu)
- **The sharp interface limit as $\epsilon \searrow 0$:** the potential $F(\mathbf{d}) = \frac{1}{4\epsilon^2} (|\mathbf{d}|^2 - 1)^2$ was introduced to relax the nonlinear constraint $|\mathbf{d}| = 1$ on molecule length. Can the Gamma-Convergence technique be applied at least for the \mathbf{d} -equation without velocities? This is - up to my knowledge - a very open problem!

Many thanks to all of you for the attention!

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