

On a multi-species Cahn-Hilliard-Darcy tumor growth model

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Asymptotic approach to spatial and dynamical organizations

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joint works with Harald Garcke (Regensburg)-Kei Fong Lam (Hong-Kong)
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Outline

- 1 Phase field models for tumor growth
- 2 The optimal control problem
- 3 First order optimality conditions
- 4 Some simulations
- 5 A multispecies model with velocity
- 6 Our contribution: analysis of a multiphase model with different mobilities
- 7 Comparison with other models
- 8 Perspectives and Open problems

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Setting

Tumors grown *in vitro* often exhibit “layered” structures:

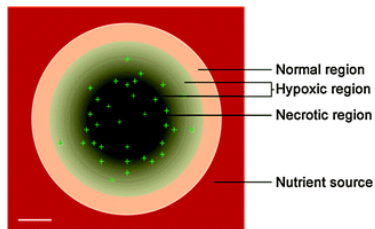


Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar $100\mu\text{m} = 0.1\text{mm}$

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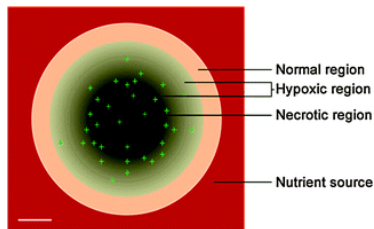


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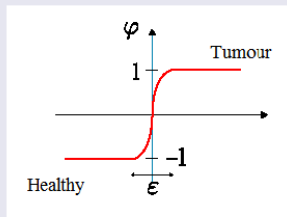
A continuum thermodynamically consistent model is introduced with the ansatz:

- 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** tumor cells surrounded by (healthy) **host cells**, and a **nutrient** (e.g. glucose)

Two possible modelling approaches

- Sharp interface / Free boundary models:
Interface Γ is modelled as idealised moving hypersurface
- Diffuse interface / Phase field models:
Interface Γ is modelled with thin transition layer

Diffuse interface



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Regarding **modeling** of diffuse interface tumor growth we can quote, e.g.,

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- Frieboes, Jin, Chuang, Wise, Lowengrub, Cristini, Garcke, Lam, Nürnberg, Sitka, for the interaction of multiple tumor cell species described by *multiphase mixture models*

Theoretical analysis: two-phase models

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- Analytical results related to well-posedness, asymptotic limits and long-time behavior, but also **optimal control** and sliding modes, have been established in a number of papers of a number of authors which include: Agosti, Ciarletta, Colli, Frigeri, Garcke, Gilardi, Grasselli, Hilhorst, Lam, Marinoschi, Melchionna, E.R., Scala, Sprekels Wu, etc...

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 - ▶ for tumor growth models based on the coupling of Cahn–Hilliard (for the tumor density) and reaction–diffusion (for the nutrient) equations, and
 - ▶ for models of Cahn–Hilliard–Darcy type.

Optimization over the treatment time: H. Garcke, K.F. Lam, E. Rocca, Applied Mathematics & Optimization, 2017

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

Cahn–Hilliard + nutrient models with source terms

The simplest phase field model is a Cahn–Hilliard system with source terms for φ : the difference in volume fractions ($\varphi = 1$: tumor phase, $\varphi = -1$: healthy tissue phase):

$$\partial_t \varphi = \Delta \mu + \mathcal{M}, \quad \mu = \Psi'(\varphi) - \Delta \varphi$$

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- In [Chen, Wise, Shenoy, Lowengrub (2014)], [Garcke, Lam, Sitka, Styles (2016)]:

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

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
- A regular double-well potential Ψ , e.g., $\Psi(s) = 1/4(1 - s^2)^2$

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State equations

We consider the Cahn–Hilliard + nutrient model with linear kinetics and Neumann boundary conditions:

$$\partial_t \varphi = \Delta \mu + h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u)$$

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- $h(\varphi)\mathcal{C}\sigma$ - consumption of nutrient by the tumor cells
- $h(\varphi)\alpha u$ - elimination of tumor cells by **cytotoxic drugs** at a constant rate α ,
- u acts as a **control** here. In applications $u : [0, T] \rightarrow [0, 1]$ is spatially constant, where $u = 1$ represents full dosage, $u = 0$ represents no dosage

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.

Regarding the terms appearing in the cost functional

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- The variable τ can be regarded as the **treatment time of one cycle**, i.e., the amount of time the drug is applied to the patient before the period of rest, or **the treatment time before surgery**;
- It is possible to replace $\beta_T \tau$ by a more general function $f(\tau)$ where $f : \mathbb{R}^+ \rightarrow \mathbb{R}^+$ is continuously differentiable and increasing.

Relaxed objective functional

However, we will not study the functional

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but a relaxed version - in order to keep a control u just bounded without requiring more regularity

Let $r > 0$ be fixed and let $T \in (0, \infty)$ denote a fixed maximal time in which the patient is allowed to undergo a treatment, we define

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

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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

$$\begin{aligned} \partial_t \varphi &= \Delta \mu + h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u) && \text{in } \Omega \times (0, T) = Q, \\ \mu &= \Psi'(\varphi) - \Delta \varphi && \text{in } Q, \\ \partial_t \sigma &= \Delta \sigma - \mathcal{C}h(\varphi)\sigma && \text{in } Q, \\ 0 &= \partial_n \varphi = \partial_n \sigma = \partial_n \mu && \text{on } \partial\Omega \times (0, T), \\ \varphi(0) &= \varphi_0, \quad \sigma(0) = \sigma_0 && \text{in } \Omega. \end{aligned}$$

Well-posedness of state equations

Theorem

Let $\varphi_0 \in H^3$, $\sigma_0 \in H^1$ with $0 \leq \sigma_0 \leq 1$, $h \in C^{0,1}(\mathbb{R}) \cap L^\infty(\mathbb{R})$ *non-negative*, and Ψ is a quartic potential, then for every $u \in \mathcal{U}_{\text{ad}}$ there exists a unique triplet

$$\varphi \in L^\infty(0, T; H^2) \cap L^2(0, T; H^3) \cap H^1(0, T; L^2) \cap C^0(\bar{Q}),$$

$$\mu \in L^2(0, T; H^2) \cap L^\infty(0, T; L^2),$$

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satisfying the state equations.

Key points:

- Boundedness of σ comes from a weak comparison principle applied to

$$\partial_t \sigma = \Delta \sigma - Ch(\varphi)\sigma$$

and it is an essential ingredient for the existence proof

- Proof utilises a Schauder fixed point argument

Existence of a minimiser

- Using that $\varphi \in L^1(0, T; L^1)$, J_r is bounded from below:

$$\begin{aligned} J_r(\varphi, u, \tau) &:= \int_0^\tau \int_\Omega \frac{\beta_Q}{2} |\varphi - \varphi_Q|^2 + \frac{1}{r} \int_{\tau-r}^\tau \int_\Omega \frac{\beta_\Omega}{2} |\varphi - \varphi_\Omega|^2 \\ &+ \frac{1}{r} \int_{\tau-r}^\tau \int_\Omega \frac{\beta_S}{2} (1 + \varphi) + \int_0^T \int_\Omega \frac{\beta_u}{2} |u|^2 + \beta_T \tau \\ &\geq -\frac{\beta_S}{2r} \int_{\tau-r}^\tau \int_\Omega |\varphi| \geq -\frac{\beta_S}{2r} \|\varphi\|_{L^1(0, T; L^1)} \geq -C. \end{aligned}$$

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- Minimising sequence $(u_n, \tau_n) \in \mathcal{U}_{\text{ad}} \times (0, T)$, with corresponding state variables $(\varphi_n, \mu_n, \sigma_n)$ such that

$$\lim_{n \rightarrow \infty} J_r(\varphi_n, u_n, \tau_n) = \inf_{(\phi, w, s)} J_r(\phi, w, s).$$

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- Minimising sequence $(u_n, \tau_n) \in \mathcal{U}_{\text{ad}} \times (0, T)$, with corresponding state variables $(\varphi_n, \mu_n, \sigma_n)$ such that

$$\lim_{n \rightarrow \infty} J_r(\varphi_n, u_n, \tau_n) = \inf_{(\phi, w, s)} J_r(\phi, w, s).$$

- We extract a convergent subsequence $u_n \rightharpoonup^* u_* \in L^\infty(Q)$ and limit functions $(\varphi_*, \mu_*, \sigma_*)$ satisfying the state equations and

$$\varphi_n \rightarrow \varphi_* \text{ in } C^0([0, T]; L^2) \cap L^2(Q).$$

Key point: All of the convergence are with respect to the interval $[0, T]$.

Existence of a minimiser

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- As $\{\tau_n\}_{n \in \mathbb{N}}$ is a bounded sequence, we extract a convergent subsequence $\tau_n \rightarrow \tau_* \in [0, T]$.

Existence of minimiser

To pass to the limit in:

$$\begin{aligned} J_r(\varphi_n, u_n, \tau_n) &:= \int_0^{\tau_n} \int_{\Omega} \frac{\beta_Q}{2} |\varphi_n - \varphi_Q|^2 + \frac{1}{r} \int_{\tau_n-r}^{\tau_n} \int_{\Omega} \frac{\beta_{\Omega}}{2} |\varphi_n - \varphi_{\Omega}|^2 \\ &+ \frac{1}{r} \int_{\tau_n-r}^{\tau_n} \int_{\Omega} \frac{\beta_S}{2} (1 + \varphi_n) + \int_0^T \int_{\Omega} \frac{\beta_u}{2} |u_n|^2 + \beta_T \tau_n, \end{aligned}$$

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we make use of

$$\chi_{[0, \tau_n]}(t) \rightarrow \chi_{[0, \tau_*]}(t), \quad \varphi_n - \varphi_Q \rightarrow \varphi_* - \varphi_Q \text{ strongly in } L^2(Q)$$

to obtain

$$\lim_{n \rightarrow \infty} \int_0^{\tau_n} \int_{\Omega} |\varphi_n - \varphi_Q|^2 = \lim_{n \rightarrow \infty} \int_Q |\varphi_n - \varphi_Q|^2 \chi_{[0, \tau_n]}(t) = \int_0^{\tau_*} \int_{\Omega} |\varphi_* - \varphi_Q|^2.$$

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Weak lower semi-continuity of the $L^2(Q)$ norm then yields

$$\inf_{(\phi, w, s)} J_r(\phi, w, s) \geq \liminf_{n \rightarrow \infty} J_r(\varphi_n, u_n, \tau_n) \geq J_r(\varphi_*, u_*, \tau_*).$$

That is, (u_*, τ_*) is a minimiser.

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- 2 The optimal control problem
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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

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

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

$$\partial_t \Sigma = \Delta \Sigma - \mathcal{C}(h(\varphi)\Sigma + h'(\varphi)\Phi\sigma),$$

with Neumann boundary conditions and zero initial conditions.

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Theorem

For any $w \in L^2(Q)$ there exists a unique triplet (Φ, Ξ, Σ) with

$$\Phi \in L^\infty(0, T; H^1) \cap L^2(0, T; H^3) \cap H^1(0, T; (H^1)^*) =: \mathbb{X}_1,$$

$$\Xi \in L^2(0, T; H^1) =: \mathbb{X}_2,$$

$$\Sigma \in L^\infty(0, T; H^1) \cap H^1(0, T; L^2) \cap L^2(0, T; H^2) =: \mathbb{X}_3,$$

and

$$\|\Phi\|_{\mathbb{X}_1} + \|\Xi\|_{\mathbb{X}_2} + \|\Sigma\|_{\mathbb{X}_3} \leq C \|w\|_{L^2(Q)}$$

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Expectation: The Fréchet derivative of \mathcal{S} at $u \in \mathcal{U}_{\text{ad}}$ in the direction w is

$$D_u \mathcal{S}(u)w = (\Phi^w, \Xi^w, \Sigma^w).$$

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Theorem

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

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

Fréchet differentiability with respect to the control

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

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

Fréchet differentiability with respect to time

For

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

we have

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

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Note that the control u does not appear explicitly.

First order optimality conditions

Introducing the adjoint system

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

$$q = \Delta p,$$

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

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Theorem

There exists a unique (p, q, r) to the adjoint system such that

$$p \in L^2(0, \tau_*; H^2) \cap H^1(0, \tau_*; (H^2)^*) \cap L^\infty(0, \tau_*; L^2) \cap C^0([0, \tau_*]; L^2),$$

$$q \in L^2(0, \tau_*; L^2),$$

$$r \in L^2(0, \tau_*; H^2) \cap L^\infty(0, \tau_*; H^1) \cap H^1(0, \tau_*; L^2) \cap C^0([0, \tau_*]; L^2).$$

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Theorem

The optimal control (u_*, τ_*) satisfy

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

and

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

Issues with the original functional

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

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

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

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 fixed $K > 0$, and impose $\varphi_0 \in H^5$, $\sigma_0 \in H^3$, then we get $\varphi \in H^2(0, T; L^2) \cap W^{1, \infty}(0, T; H^1)$.

However, to require the a-priori boundedness of $\partial_t u$ is difficult to verify in applications.

Other control-type results

- **SMC.** In [Colli, Gilardi, Marinoschi, E.R., Appl Math Optim, to appear] we introduce a sliding mode control (SMC) law $\varrho \operatorname{sign}(\varphi - \varphi^*)$ in the chemical potential which forces the system to **reach within finite time the sliding manifold** (that we chose in order that the tumor phase remains constant in time $\varphi \equiv \varphi^*$)

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- **Different sources.** In the phase field model we introduced

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

we can choose different form of \mathcal{M} and \mathcal{S} : **linear phenomenological laws** for chemical reactions cf. [Hawkins–Daarud, Prudhomme, van der Zee, Oden (2012)], [Frigeri, Grasselli, E.R. (2015)]:

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In [Colli, Gilardi, E.R., Sprekels, Nonlinearity (2017)]: the optimal control with respect to the drug distribution which acts as a control u in the nutrient equation

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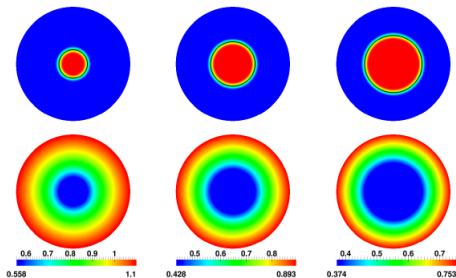


Abb. Evolution of tumour (above) and nutrient (below)

Stability of (no chemotaxis) growing circular tumour

Question from medicine: When does a compact growth changes to branched structures?

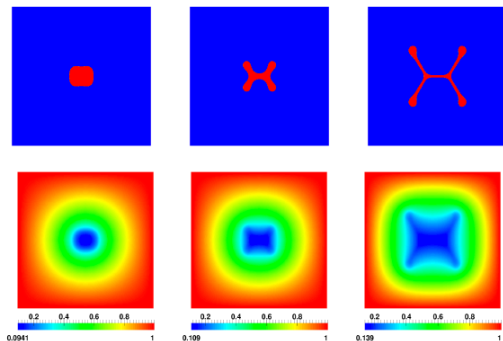


Abb.Solutions with chemotaxis at $t = 5, 10, 20$.

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FLRS: A multispecies model with velocities - with Frigeri, Lam, Schimperna

Typical structure of tumors grown in vitro:

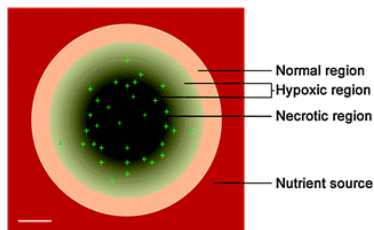


Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar $100\mu\text{m} = 0.1\text{mm}$

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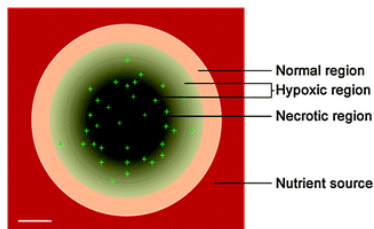


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A continuum thermodynamically consistent model is introduced with the ansatz:

- 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 oxygen)
- tumor cells are regarded as inertia-less fluids: include the **velocity** - satisfying a Darcy type law with Korteweg term

Theoretical analysis: multiphase models

Comparatively, there have been fewer analytical results for the **multi-phase variants**, which distinguish between the proliferating and necrotic tumor cells:

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- in [DFRSS: M. Dai, [Feireisl, E.R.](#), [G. Schimperna](#), M. Schonbek, Nonlinearity (2017)] we study a simplification of the tumor model introduced in [CWSL: Y. Chen, S.M. Wise, V.B. Shenoy, J.S. Lowengrub, Int. J. Numer. Meth. Biomed. Engng. (2014)]

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- the original model of [CWSL] consists of a **Cahn–Hilliard–Darcy** system with high order source terms, and the natural energy identity of the model appears not to provide sufficient a priori estimates

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- in [**Garcke, Lam**, Nürnberg, Sitka, M3AS (2018)], instead, a **vectorial Cahn–Hilliard–Darcy** model has been proposed. A new feature is the use of a **volume-average velocity** simplifying the equation for the mixture velocity. The corresponding natural energy identity yields better a priori estimates for existence

Outline

- 1 Phase field models for tumor growth
- 2 The optimal control problem
- 3 First order optimality conditions
- 4 Some simulations
- 5 A multispecies model with velocity
- 6 Our contribution: analysis of a multiphase model with different mobilities**
- 7 Comparison with other models
- 8 Perspectives and Open problems

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- $\varphi_p, \varphi_d, \varphi_h \in [0, 1]$: the volume fractions of the cells:
 - ▶ φ_p : proliferating tumor cell fraction
 - ▶ φ_d : dead tumor cell fraction
 - ▶ φ_h : healthy cell fraction
- The variables above are naturally constrained by the relation $\varphi_p + \varphi_d + \varphi_h = 1$ hence it suffices to track the evolution of φ_p and φ_d and the vector $\varphi := (\varphi_p, \varphi_d)^\top$ lies in the simplex $\Delta := \{\mathbf{y} \in \mathbb{R}^2 : 0 \leq y_1, y_2, y_1 + y_2 \leq 1\} \subset \mathbb{R}^2$

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- $\mathbf{u} := \mathbf{u}_i, i = 1, 2, 3$: 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
- q : the cell-to-cell pressure

FLRS: the balance law

Letting \mathbf{J}_i , $i \in \{p, d, h\}$, denote the mass fluxes for the cells, then the general **balance law for the volume fractions**, for matched densities of the components, reads as

$$\partial_t \varphi_i + \operatorname{div}(\varphi_i \mathbf{u}) = -\operatorname{div} \mathbf{J}_i + S_i \quad \text{for } i \in \{p, d, h\}$$

where we set $S_h = 0$, whereas S_p, S_d may depend on n , φ_p and φ_d

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$$E(\varphi_p, \varphi_d) := \int_{\Omega} F(\varphi_p, \varphi_d) + \frac{1}{2} |\nabla \varphi_p|^2 + \frac{1}{2} |\nabla \varphi_d|^2 dx$$

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where $F = F_0 + F_1$ is a **multi-well** configuration potential, e.g.

$$F_0(\varphi_p, \varphi_d) := \varphi_p \log \varphi_p + \varphi_d \log \varphi_d + (1 - \varphi_p - \varphi_d) \log(1 - \varphi_p - \varphi_d)$$

$$F_1(\varphi_p, \varphi_d) := \frac{\chi}{2} (\varphi_d(1 - \varphi_d) + \varphi_p(1 - \varphi_p) + (1 - \varphi_d - \varphi_p)(\varphi_d + \varphi_p))$$

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The fluxes \mathbf{J}_i are defined as follows (with **different mobilities** for each phase):

$$\mathbf{J}_i = -M_i \nabla \mu_i, \quad \mu_i := \frac{\delta E}{\delta \varphi_i} = -\Delta \varphi_i + F_{,\varphi_i} \quad \text{for } i = p, d$$

FLRS: the velocity and nutrient evolutions

We set $\mathbf{J}_h = -\mathbf{J}_p - \mathbf{J}_d$, then upon summing up the three mass balances for $i = p, d, h$, using the fact that $\varphi_p + \varphi_d + \varphi_h = 1$ and $S_h = 0$, we deduce the following relation:

$$\operatorname{div} \mathbf{u} = S_p + S_d =: S_t$$

The velocity field \mathbf{u} is assumed to fulfill **Darcy's law**:

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Since the time scale of nutrient diffusion is much faster (minutes) than the rate of cell proliferation (days), **the nutrient is assumed to evolve quasi-statically**:

$$0 = -\Delta n + \varphi_p n$$

where $\varphi_p n$ models consumption by the proliferating tumor cells

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 $\partial_t \varphi_i - \operatorname{div}(M_i \nabla \mu_i - \varphi_i \mathbf{u}) = S_i$ and if we do not choose the Dirichlet b.c.s on μ_i then we need to estimate the mean values of $\mu_i = -\Delta \varphi_i + F_{,\varphi_i}$ containing a **multiwell logarithmic type potential** F_0

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- the choice **$(M_i \nabla \mu_i - \varphi_i \mathbf{u}) \cdot \mathbf{n} = 0$** seems essential

FLRS: The weak notion of solution

Definition. $(\varphi_p, \varphi_d, \mathbf{u}, \mathbf{q}, n)$ is a weak solution to the problem in $(0, T) \times \Omega$ if the previous equations hold, for a.e. $t \in (0, T)$ and for $i = p, d$, in the following weak sense:

$$\langle \partial_t \varphi_i, \zeta \rangle + \int_{\Omega} M_i \nabla \mu_i \cdot \nabla \zeta - \varphi_i \mathbf{u} \cdot \nabla \zeta \, dx = \int_{\Omega} S_i \zeta \, dx \quad \forall \zeta \in H^1(\Omega),$$

$$\int_{\Omega} \mu_i \zeta \, dx = \int_{\Omega} \nabla \varphi_i \cdot \nabla \zeta + \eta_i \zeta + F_{1, \varphi_i}(\varphi_p, \varphi_d) \zeta \, dx \quad \forall \zeta \in H^1(\Omega),$$

$$\int_{\Omega} \mathbf{u} \cdot \nabla \xi \, dx = - \int_{\Omega} (S_p + S_d) \xi \, dx \quad \forall \xi \in H_0^1(\Omega),$$

$$\int_{\Omega} \mathbf{u} \cdot \zeta \, dx = \int_{\Omega} -\nabla \mathbf{q} \cdot \zeta - \varphi_p \nabla \mu_p \cdot \zeta - \varphi_d \nabla \mu_d \cdot \zeta \, dx \quad \forall \zeta \in (L^2(\Omega))^d,$$

$$0 = -\Delta n + \varphi_p n \quad \text{a.e. in } \Omega,$$

$$\eta_i = F_{0, \varphi_i}(\varphi_p, \varphi_d) \quad \text{a.e. in } \Omega,$$

$$S_p = \Sigma_p(n, \varphi_p, \varphi_d) + m_{pp} \varphi_p + m_{pd} \varphi_d \quad \text{a.e. in } \Omega,$$

$$S_d = \Sigma_d(n, \varphi_p, \varphi_d) + m_{dp} \varphi_p + m_{dd} \varphi_d \quad \text{a.e. in } \Omega.$$

Moreover, there hold the initial conditions

$$\varphi_p(x, 0) = \varphi_{p,0}(x), \quad \varphi_d(x, 0) = \varphi_{d,0}(x) \quad \text{a.e. in } \Omega,$$

where $\langle \cdot, \cdot \rangle$ denotes the duality pairing between $H^1(\Omega)$ and its dual $H^1(\Omega)'$.

FLRS: Assumptions on the mass sources and on the initial data

Set $\Sigma(n, \varphi_p, \varphi_d) := (\Sigma_p, \Sigma_d)$ and $\underline{M} = (m_{ij})$, $i, j \in \{p, d\}$, the matrix of the coefficients of the mass sources in the Cahn-Hilliard equations: $(S_p, S_d) = \Sigma + \underline{M}(\varphi_p, \varphi_d)^T$

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Assumption on the mass sources:

- Σ is globally Lipschitz and
- that there exist a closed and sufficiently regular subset Δ_0 contained in the open simplex Δ and constants $K_{p,-}, K_{p,+}, K_{d,-}, K_{d,+} \in \mathbb{R}$, with $K_{p,-} \leq K_{p,+}$ and $K_{d,-} \leq K_{d,+}$, such that $\Sigma(\mathbb{R}^3) \subset [K_{p,-}, K_{p,+}] \times [K_{d,-}, K_{d,+}]$
- for any $\mathbf{x} = (x_p, x_d) \in [K_{p,-}, K_{p,+}] \times [K_{d,-}, K_{d,+}]$, there holds

$$(\underline{M}\mathbf{y} + \mathbf{x}) \cdot \mathbf{n} < 0 \text{ for all } \mathbf{y} \in \partial\Delta_0,$$

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Assumptions on the initial data :

- $\varphi_{p,0}, \varphi_{d,0} \in H^1(\Omega)$ with $0 \leq \varphi_{p,0}, 0 \leq \varphi_{d,0}, \varphi_{p,0} + \varphi_{d,0} \leq 1$ a.e. in Ω ,
- the mean values satisfy $(\frac{1}{|\Omega|} \int_{\Omega} \varphi_{p,0}(x) dx, \frac{1}{|\Omega|} \int_{\Omega} \varphi_{d,0}(x) dx) \in \text{int } \Delta_0$ and $F_0(\varphi_{p,0}, \varphi_{d,0}) \in L^1(\Omega)$

FLRS: Examples of mass sources

Examples of **mass sources** in $\partial_t \varphi_i - \operatorname{div}(M_i \nabla \mu_i - \varphi_i \mathbf{u}) = S_i$ for $i \in \{p, d\}$ complying with the assumptions in the “logarithmic” case are:

$$S_p = \lambda_M g(n) - \lambda_A \varphi_p$$

$$S_d = \lambda_A \varphi_p - \lambda_L \varphi_d$$

for positive constants $\lambda_M, \lambda_A, \lambda_L$ (with $\lambda_M(\lambda_A + \lambda_L) < \lambda_A \lambda_L$, $\lambda_A < 2\lambda_L$) and a bounded positive function g such that $0 < g(s) \leq 1$, e.g., $g(s) = \max(n_c, \min(s, 1))$ for some constant $n_c \in (0, 1)$.

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- the **growth of the proliferating tumor cells** due to nutrient consumption **at a constant rate λ_M**
- the **death of proliferating tumor cells at a constant rate λ_A** , which leads to a source term for the necrotic cells
- the **lysing/disintegration of necrotic cells at a constant rate λ_L**

FLRS: Existence of weak solutions

The main result of S. Frigeri, K.-F. Lam, E. R., G. Schimperna, *Comm. Math. Sci.* (to appear)

Theorem

For every $T > 0$ here exists **at least one weak solution** $(\varphi_p, \mu_p, \eta_p, \varphi_d, \mu_d, \eta_d, \mathbf{u}, \mathbf{q}, n)$ to the multi-species tumor model on $[0, T]$ with the regularity

$$\begin{aligned} \varphi_i &\in H^1(0, T; H^1(\Omega)') \cap L^\infty(0, T; H^1(\Omega)) \cap L^2(0, T; H^2(\Omega)), \\ &\text{with } 0 \leq \varphi_i \leq 1, \quad \varphi_p + \varphi_d \leq 1 \text{ a.e. in } Q, \quad \text{for } i = p, d, \\ \mu_i &\in L^2(0, T; H^1(\Omega)), \quad \eta_i \in L^2(Q), \\ \mathbf{u} &\in L^2(Q) \text{ with } \operatorname{div} \mathbf{u} \in L^2(Q), \quad \mathbf{q} \in L^2(0, T; H_0^1(\Omega)), \\ n &\in (1 + L^2(0, T; H^2(\Omega) \cap H_0^1(\Omega))), \quad 0 \leq n \leq 1 \text{ a.e. in } Q. \end{aligned}$$

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Notice that the boundary conditions:

$$(M_i \nabla \mu_i - \varphi_i \mathbf{u}) \cdot \mathbf{n} = 0, \quad \partial_n \varphi_i = 0, \quad \mathbf{q} = 0, \quad n = 1 \text{ on } \Gamma$$

are incorporated in the definition of weak solutions

FLRS: an idea of the proof

- 1 consider a regularized version of this problem by replacing the singular potential F_0 by its Moreau–Yosida approximation F_ε , and by introducing some suitable **truncation functions**. The latter choice is due to the fact that F_ε is no longer a singular function, and consequently the **uniform boundedness properties** $0 \leq \varphi_p$, $0 \leq \varphi_d$, $\varphi_p + \varphi_d \leq 1$ are not expected to hold in the approximation level.

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- 2 to prove existence of a solution to the regularized system a further regularization and a Schauder fixed point argument: only exploits elementary existence and uniqueness results methods for PDEs
- 3 derive the bounds - independent of the regularization parameters - in order to pass to the limit in the approximation scheme via compactness tools: the main problem is to **bound the mean values of φ_i away from the potential bareers**

The bound of the mean values

Denoting $\mathbf{y}(t) := ((\varphi_p)_\Omega(t), (\varphi_d)_\Omega(t))$, $(\boldsymbol{\Sigma})_\Omega = ((\boldsymbol{\Sigma}_p)_\Omega, (\boldsymbol{\Sigma}_d)_\Omega)$, then by testing by 1 the mass balances

$$\langle \partial_t \varphi_i, \zeta \rangle + \int_{\Omega} M_i \nabla \mu_i \cdot \nabla \zeta - \varphi_i \mathbf{u} \cdot \nabla \zeta \, dx = \int_{\Omega} S_i \zeta \, dx,$$

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$$(\underline{\underline{M}} \mathbf{y} + \mathbf{x}) \cdot \mathbf{n} < 0 \text{ for all } \mathbf{y} \in \partial \Delta_0$$

we infer that the vector $\mathbf{y}(t) = ((\varphi_p)_\Omega(t), (\varphi_d)_\Omega(t)) \in \text{int } \Delta_0$ for all $t \in [0, T]$.

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Taking $t = t_*$ in the ODE, multiplying with \mathbf{n} , we get

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Hence $\mathbf{y}(t)$ cannot leave Δ_0 and so there exist positive constants $0 < c_1 < c_2 < 1$:

$$c_1 \leq (\varphi_p)_\Omega(t), (\varphi_d)_\Omega(t) \leq c_2, \quad c_1 \leq (\varphi_p + \varphi_d)_\Omega(t) \leq c_2 \quad \forall t \in [0, T].$$

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- 2 The optimal control problem
- 3 First order optimality conditions
- 4 Some simulations
- 5 A multispecies model with velocity
- 6 Our contribution: analysis of a multiphase model with different mobilities
- 7 Comparison with other models**
- 8 Perspectives and Open problems

Comparison with the original Chen-model and with [DFRSS]

- In [CWSL], the effect of a basement membrane on the growing tumor is also considered \rightarrow additional coupling with a Cahn–Hilliard equation transported by \mathbf{u} .
- The **key distinction** is that in our choice of a multi-well potential E we included **interfacial energy for the proliferating-necrotic tumor interface and also for the tumor-host interfaces**: in [CWLS] the free energy depends **only on the total tumor volume fraction** $\varphi_T = \varphi_p + \varphi_d$, i.e., $E(\varphi_T) = \int_{\Omega} f(\varphi_T) + \frac{1}{2} |\nabla \varphi_T|^2 dx$ for **scalar double-well potential** f with minima at 0 and 1.

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- **Different boundary conditions** with respect to [CWSL] and [DFRSS], where a zero Dirichlet boundary datum was taken for the chemical potentials. Here we consider **$(M_i \nabla \mu_i - \varphi_i \mathbf{u}) \cdot \mathbf{n} = 0$** (more reasonable from the modeling point of view). The (easier) case of Dirichlet or Robin boundary conditions for μ_i could also be treated, while the case of no-flux conditions for μ_i (which would also be meaningful) seems not easy to be treated mathematically.

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- We can have here **different mobility coefficients**, which would have given rise to a number of mathematical complications in the case of [DFRSS].

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Perspectives and Open problems

1. To study the **long-time behavior of solutions in terms of attractors and/or trajectories**: in case of **two-phase** models: we have three projects going on: with C. Cavaterra and H. Wu (on a model by Oden et al.), with A. Miranville and G. Schimperna (on a model proposed by H. Garcke et. al.), with A. Giorgini, K.-F. Lam, and G. Schimperna (on the reduction of this model to the two-phase variant).

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4. **Include a stochastic** term in phase-field models for tumor growth representing for example uncertainty of a therapy or random oscillations of the tumor phase (ongoing project with C. Orrieri and L. Scarpa).

Many thanks to all of you for the attention!

<http://matematica.unipv.it/rocca/>

Simulations: Garcke, Lam, Sitka, Styles, 2016

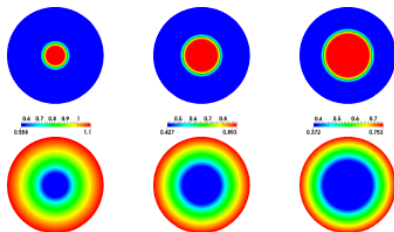


Figure 2: Approximate solutions of (5.2) at $t = 0$ (left), $t = 0.2$ (centre) and $t = 0.4$, φ (top row), σ bottom row. The black line in the φ solutions denotes the corresponding sharp interface solution.

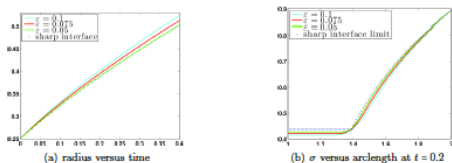


Figure 3: Comparison of diffuse interface model (5.2) with the sharp interface solution

Issues with the well-posedness

The state equations

$$\begin{aligned}\partial_t \varphi &= \Delta \mu + h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u), \\ \mu &= \Psi'(\varphi) - \Delta \varphi, \\ \partial_t \sigma &= \Delta \sigma - \mathcal{C}h(\varphi)\sigma.\end{aligned}$$

satisfies the energy identity

$$\begin{aligned}\frac{d}{dt} \int_{\Omega} \underbrace{\left(\Psi(\varphi) + \frac{1}{2} |\nabla \varphi|^2 + \frac{1}{2} |\sigma|^2 \right)}_{=: \mathcal{E}} + \int_{\Omega} \left(|\nabla \mu|^2 + |\nabla \sigma|^2 + h(\varphi)\mathcal{C}|\sigma|^2 \right) \\ = \int_{\Omega} h(\varphi) (\mathcal{P}\sigma - \mathcal{A} - \alpha u) \mu.\end{aligned}$$

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We can estimate the right-hand side as

$$\delta \|\mu\|_{L^2}^2 + \frac{\mathcal{C}}{\delta} (\mathcal{P}^2 \|\sigma\|_{L^2}^2 + \dots) \quad \text{for some } \delta > 0,$$

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To apply Poincaré inequality to the $\|\mu\|_{L^2(L^2)}$ on the RHS, we need to estimate the **square of the mean** of μ using

$$\mu = \Psi'(\varphi) - \Delta \varphi.$$

If $|\Psi'(s)| \leq C(1 + |s|^p)$ for some p , then we have

$$\left\| \frac{1}{|\Omega|} \int_{\Omega} \mu \right\|_{L^2(L^2)}^2 \leq C(1 + \|\varphi\|_{L^{2p}(L^{2p})}^{2p}) + \text{other terms ...}$$

But, to control $\|\varphi\|_{L^{2p}(L^{2p})}^{2p}$ **in the absence of any a priori estimate**, we need $p = 1$! I.e., Ψ can only be a quadratic potential [Garcke, L.].

Issues with the well-posedness

If σ is bounded in Q , then

$$\left| \int_{\Omega} h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u)\mu \right| \leq C\|\mu\|_{L^1}$$

and by the Poincaré inequality, we have

$$\|\mu\|_{L^1} \leq C\|\nabla\mu\|_{L^1} + C\left| \frac{1}{|\Omega|} \int_{\Omega} \mu \right|.$$

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With an assumption like

$$|\Psi'(s)| \leq C_1 \Psi(s) + C_2,$$

we obtain a priori estimates for potentials with higher polynomial growth.

The Schauder argument

Given $\phi \in L^2(Q)$, consider the mapping

$$M_1 : L^2(Q) \rightarrow L^\infty(0, T; H^1) \cap L^2(0, T; H^2) \cap H^1(0, T; L^2) \cap L^\infty(Q),$$
$$\phi \mapsto \sigma,$$

where σ solves

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Then define the mapping

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The solution to the fixed point problem

$$z = M_2(z)$$

yields a triplet (φ, μ, σ) which solves the state equations.