Optimal Control in Diffuse Interface Models of Tumor Growth

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joint work with Harald Garcke and Kei Fong Lam (Regensburg)

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Outline

1. Phase field models for tumour growth
2. The optimal control problem
3. First order optimality conditions
4. Issues with the original functional
5. Ongoing projects and open problems

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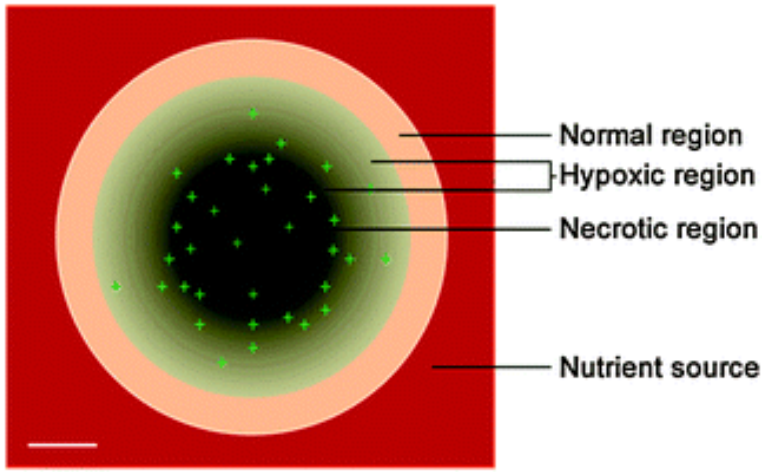
Setting

Tumours grown *in vitro* often exhibit "layered" structures:



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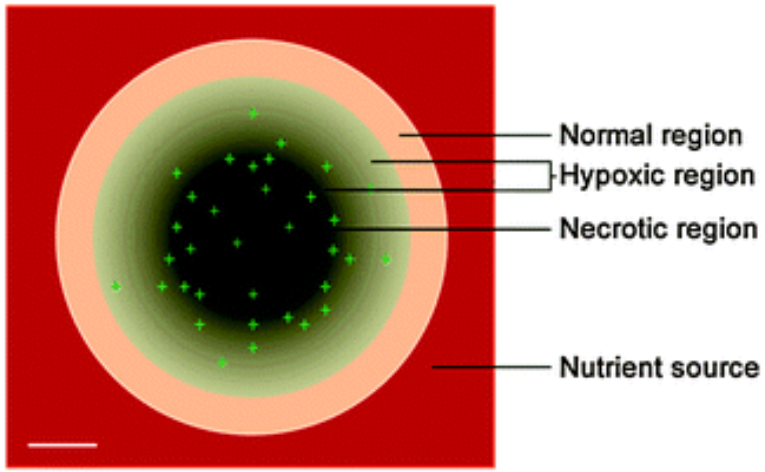

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A continuum thermodynamically consistent model is introduced with the ansatz:

- 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)

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The main *advantages of the diffuse interface* formulation are:

- 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;
- sharp interface models are no longer valid when the tumor undergoes metastasis $\Longrightarrow$ the interface has a topological change

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):

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

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where $\mathcal{S}$ models interaction with the tumour cells.

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- Linear kinetics [Chen, Wise, Shenoy, Lowengrub], [Garcke, Lam]

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

  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:

$$\begin{aligned}
\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 tumour cells,
- $h(\varphi)\alpha u$ - elimination of tumour cells by cytotoxic drugs at a constant rate α,
- u acts as a control here. In applications $u : [0, T] \to [0, 1]$ 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

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

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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

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

- A large value of $|\varphi - \varphi_Q|^2$ would mean that the patient suffers from the growth of the tumor, and a large value of $|u|^2$ would mean that the patient suffers from high toxicity of the drug;

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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 $f : \mathbb{R}^+ \to \mathbb{R}^+$ is continuously differentiable and increasing.

Relaxed objective functional

However, we will not study the functional

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but a relaxed version - for mathematical reasons (explained later on)!

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

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

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The optimal control problem is

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

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

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

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 $u \in \mathcal{U}_{\mathrm{ad}}$ there exists a unique triplet

$$\varphi \in L^\infty(0,T;H^2) \cap L^2(0,T;H^3) \cap H^1(0,T;L^2) \cap C^0(\overline{Q}),$$
$$\mu \in L^2(0,T;H^2) \cap L^\infty(0,T;L^2),$$
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Key points:

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

$$\partial_t \sigma = \Delta \sigma - \mathcal{C} h(\varphi) \sigma.$$

- 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:

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

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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

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

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

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

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

Existence of minimiser

To pass to the limit in:

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we make use of

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

to obtain

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

Existence of minimiser

To pass to the limit in:

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

we make use of

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

to obtain

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

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

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

That is, (u_*, τ_*) is a minimiser.

Outline

1. Phase field models for tumour growth
2. The optimal control problem
3. First order optimality conditions
4. Issues with the original functional
5. Ongoing projects and open problems

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

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

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

$$\begin{aligned}
&\Phi \in L^\infty(0, T; H^1) \cap L^2(0, T; H^3) \cap H^1(0, T; (H^1)^*) =: \mathbb{X}_1,\\
&\Xi \in L^2(0, T; H^1) =: \mathbb{X}_2,\\
&\Sigma \in L^\infty(0, T; H^1) \cap H^1(0, T; L^2) \cap L^2(0, T; H^2) =: \mathbb{X}_3,
\end{aligned}$$

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 $u \in \mathcal{U}_{\mathrm{ad}}$ in the direction w is

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

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Theorem

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

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

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

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

Fréchet differentiability with respect to time

Lemma

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

$$\mathrm{D}_\tau \left(\int_0^\tau \int_\Omega |f|^2 \right) = \int_\Omega |f(\tau)|^2 .$$

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

we have

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

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Note that the control u does not appear explicitly.

First order optimality conditions

Introducing the adjoint system

$$
\begin{aligned}
-\partial_t p &= \Delta q + \Psi''(\varphi_*)q - \mathcal{C}h'(\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 - \mathcal{C}h(\varphi_*)r + \mathcal{P}h(\varphi_*)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

$$
\begin{aligned}
&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*

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

and

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

Summary

1. We introduced an optimal control problem for optimising treatment time of a cancer therapy involving cytotoxic drugs:

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

2. The (relaxed) objective functional penalises long treatment times, and contains various tracking-type objectives:

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

3. Existence of an pair (u_*, τ_*) for the optimal drug distribution and treatment time is shown.
4. Two first order optimality conditions are derived.

Outline

1. Phase field models for tumour growth
2. The optimal control problem
3. First order optimality conditions
4. Issues with the original functional
5. Ongoing projects and open problems

Open related problem

1. 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

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

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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 $\mathcal{U}_{\mathrm{ad}} = \{u \in H^1(0, T; L^2) : 0 \leq u \leq 1, \|\partial_t u\|_{L^2(Q)} \leq K\}$ for fixed $K > 0$, and impose $\varphi_0 \in H^5$, $\sigma_0 \in H^3$, then it is possible to obtain $\varphi \in H^2(0, T; L^2) \cap W^{1,\infty}(0, T; H^1)$.

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2. To prove the convergence to stationary solutions by means of suitable Simon-Lojasiewicz techniques: the function φ_Ω is a stable configuration of the system, so that the tumor does not grow again once the treatment is completed (joint project with C. Cavaterra and H. Wu).

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 $\mathcal{S}$:

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- Linear phenomenological laws for chemical reactions [Hawkins–Daarud, Prudhomme, van der Zee, Oden], [Frigeri, Grasselli, E.R.], [Colli, Gilardi, E.R., Sprekels, Nonlinearity (2017): optimal control without time dependence and with the control in the nutrient equation]:

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- Simplified law for chemical reaction leading to a Gradient-Flow structure [E.R., R. Scala, A rigorous sharp interface limit of a diffuse interface model related to tumor growth, J. Nonlinear Sci. (2017)]:

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

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DFRSS: A multispecies model with velocities

Typical structure of tumors grown in vitro:

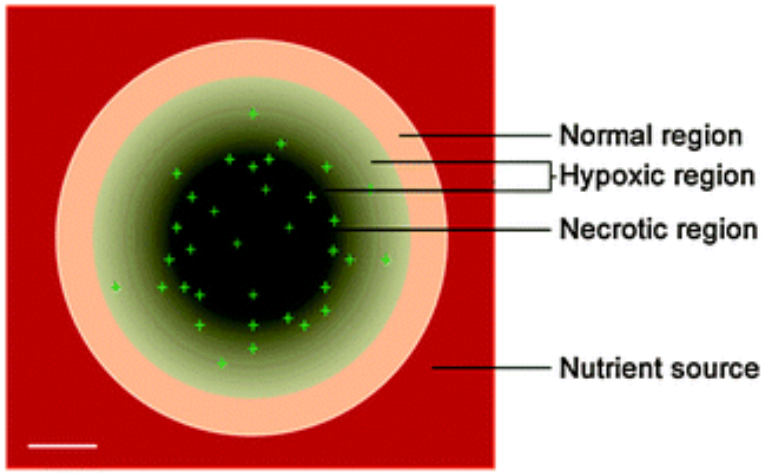

Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100μm = 0:1mm

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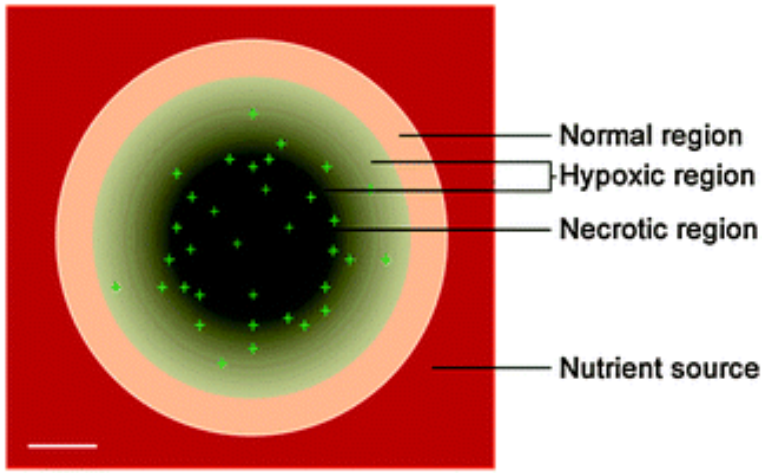

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A continuum thermodynamically consistent model is introduced with the ansatz:

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

- $\phi_i, i = 1, 2, 3$: 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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- $\phi_i, i = 1, 2, 3$: the volume fractions of the cells:
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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 (it was σ before)
- u:=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: The PDEs

In summary, let $\Omega \subset \mathbb{R}^3$ be a bounded domain and $T > 0$ the final time of the process.

DFRSS: The PDEs

In summary, let $\Omega \subset \mathbb{R}^3$ be a bounded domain and $T > 0$ the final time of the process. Then, in $\Omega \times (0, T)$, we have the following system of equations:

$$\begin{aligned}
&\text{(Cahn} - \text{Hilliard)} && \partial_t \Phi + \mathrm{div}_x(\mathrm{u}\Phi) - \mathrm{div}_x(\nabla_x \mu) = \Phi S_T, \ \mu = -\Delta \Phi + \mathcal{F}'(\Phi) \\
&\text{(Darcy)} && \mathrm{u} = -\nabla_x \Pi + \mu \nabla_x \Phi, \quad \mathrm{div}_x \mathrm{u} = S_T \\
&\text{(Transport)} && \partial_t P + \mathrm{div}_x(\mathrm{u}P) = \Phi(S_T - S_D) \\
&\text{(Reac} - \text{Diff)} && -\Delta n + nP = T_c(n, \Phi)
\end{aligned}$$

where

$$\begin{aligned}
&\text{(Source} - \text{Tumor)} && S_T(n, P, \Phi) = nP - \lambda_3(\Phi - P) \\
&\text{(Source} - \text{Dead)} && S_D(n, P, \Phi) = (\lambda_1 + \lambda_2 H(n_N - n))\, P - \lambda_3(\Phi - P) \\
&\text{(Nutrient} - \text{Capill)} && T_c(n, \Phi) = [\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)]\,(n_c - n)
\end{aligned}$$

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

Note: $P = 0$ in the inflow part of the boundary $\mathrm{u} \cdot \nu < 0$.

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

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

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

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

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

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

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:

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

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

DFRSS: Weak formulation

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

(i) these functions belong to the regularity class:

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

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

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

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

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

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

(ii) the following integral relations hold:

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

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

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

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

$$\int_0^T \int_\Omega [P\partial_t\varphi + P\mathrm{u}\cdot\nabla_x\varphi + \Phi(S_T - S_D)\varphi] \ \mathrm{d}x \ \mathrm{d}t \ge -\int_\Omega P_0\varphi(0,\cdot) \ \mathrm{d}x$$

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

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

DFRSS: Existence of weak solutions

The main result of [M. Dai, E. Feireisl, E.R., G. Schimperna, M. Schonbek, Analysis of a diffuse interface model of multispecies tumor growth, Nonlinearity, 2017]

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* $[0, T]$

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, Math. Models Methods Appl. (2016)]).
- However, a rigorous mathematical analysis of the resulting PDEs is still in its beginning and only for one species models with regular potentials (cf. [H. Garcke, K.F. Lam, E. Sitka, and V. Styles, Math. Models Methods Appl. (2016)]) and only very recently on multiphase models (cf. [H. Garcke, K.F. Lam, R. Nuernberg, and E. Sitka, arXiv:1701.06656, 2017])

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  - 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 - multispecies

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 $\Longrightarrow$ the main problems are:

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- we have two different Cahn-Hilliard equations with different mobilities M_i: $\partial_t \varphi_i = M_i \Delta \mu_i - \mathrm{div}(\varphi_i \boldsymbol{u}) + S_i$ 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 bareers $\Longrightarrow$ ad hoc estimate based on ODEs technique
- the choice of the right boundary conditions for $\boldsymbol{u}$ and μ_i: apparently $M_i \nabla \mu_i \cdot \nu + \phi_i \boldsymbol{u} \cdot \nu = 0$ on $\partial\Omega$ works!

Perspectives and Open problems - sharp interfaces

- To study the sharp interface limit as $\varepsilon \searrow 0$ in the coupled Cahn-Hilliard-Darcy system where

$$\partial_t \Phi + \mathrm{div}_x(\mathrm{u}\Phi) - \mathrm{div}_x(\nabla_x \mu) = 0, \ \ \mu = -\varepsilon^2 \Delta \Phi + \mathcal{F}'(\Phi)$$

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  - We assumed the regularity of the limit interface, hence there is a death time T^* until the evolution is regular. After the death time the evolution is undetermined!
  - We made a technical hypothesis on the convergence of the measures
$$\frac{\varepsilon}{2} |\nabla \varphi^\varepsilon|^2 + \frac{\Psi(\varphi^\varepsilon)}{\varepsilon} \rightharpoonup 2 c_\Psi \, d\mathcal{H}^2 \llcorner \Gamma$$
  This is unknown in general, but is proved under higher regularity of the chemical potential μ^ε and conjectured by Tonegawa to hold in the general case

Many thanks to all of you for the attention!

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

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

$$\frac{\mathrm{d}}{\mathrm{d}t} \underbrace{\int_\Omega \left(\Psi(\varphi) + \frac{1}{2}|\nabla\varphi|^2 + \frac{1}{2}|\sigma|^2\right)}_{=:\mathcal{E}} + \int_\Omega \left(|\nabla\mu|^2 + |\nabla\sigma|^2 + h(\varphi)\mathcal{C}|\sigma|^2\right)$$

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We can estimate the right-hand side as

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leading to

$$\begin{aligned}&\mathcal{E}(t) + \int_0^t \int_\Omega \left(|\nabla\mu|^2 + |\nabla\sigma|^2\right)\\ &\qquad \le \mathcal{E}(0) + \int_0^t \int_\Omega \left(\delta|\mu|^2 + \text{ other terms...}\right).\end{aligned}$$

Issues with the well-posedness

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$$\leq \mathcal{E}(0) + \int_0^t \int_\Omega \left(\delta \, |\mu|^2 + \text{ other terms...} \right).$$

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

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

But, to control $\|\varphi\|^{2p}_{L^{2p}(L^{2p})}$ 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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Then one obtains

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With an assumption like

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

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

The Schauder argument

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

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

where σ solves

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The solution to the fixed point problem

$$z = M_2(z)$$

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