Optimal control of treatment time in a diffuse interface model of tumor growth and related issues

E. Rocca

Università degli Studi di Pavia

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joint works with Harald Garcke (Regensburg)-Kei Fong Lam (Hong-Kong)
and Sergio Frigeri (Brescia)-Kei Fong Lam (Hong-Kong)-Giulio Schimperna (Pavia)

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Regione Lombardia

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Outline

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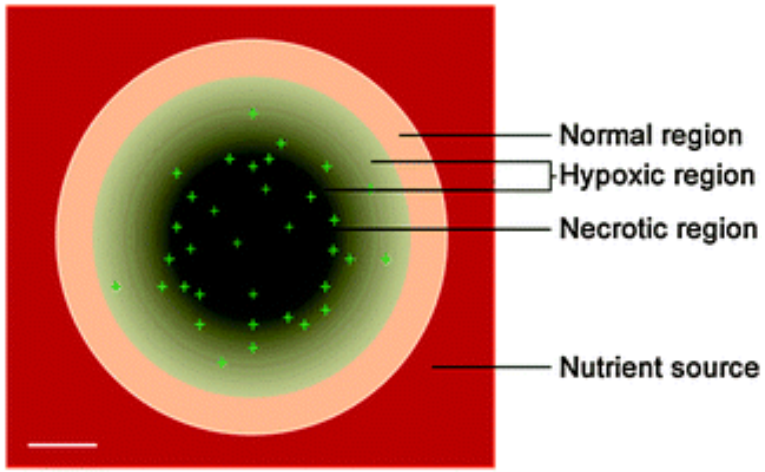
Setting

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



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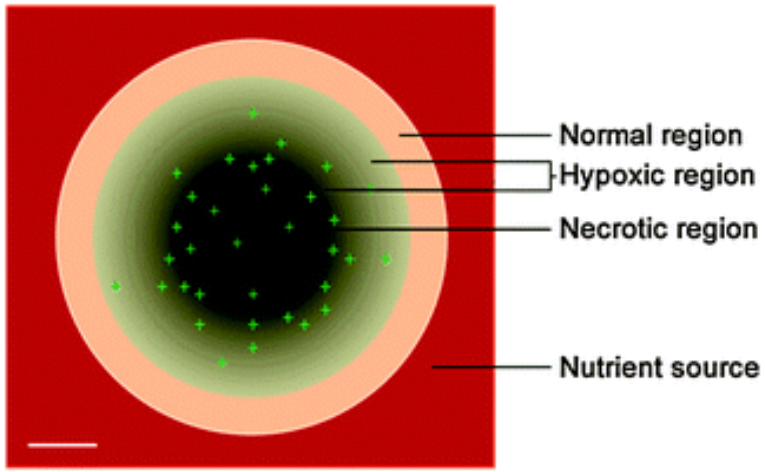

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A continuum thermodynamically consistent model is introduced with the ansatz:

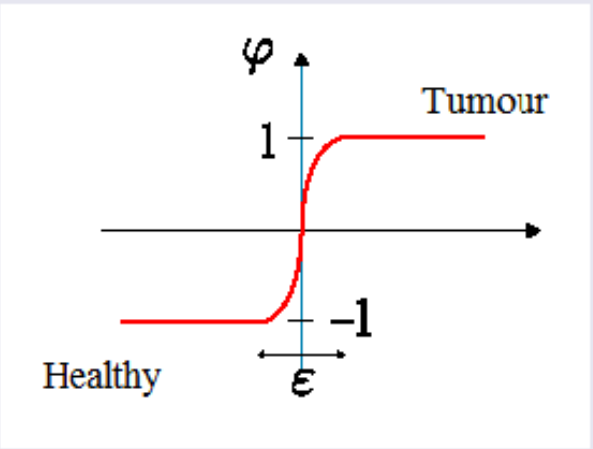
- sharp interfaces are replaced by narrow transition layers arising due to adhesive forces among the cell species: a diffuse interface separates tumor and healthy cell regions
- proliferating tumor cells surrounded by (healthy) host cells, and a nutrient (e.g. glucose)

Diffuse interfaces

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.,

- Ciarletta, Cristini, Frieboes, Garcke, Hawkins, Hilhorst, Lam, Lowengrub, Oden, Wise, also for their numerical simulations $\rightarrow$ complex changes in tumor morphologies due to the interactions with nutrients or toxic agents and also due to mechanical stresses

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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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- Chemotheraphy
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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., $\Psi(s) = 1/4(1 - s^2)^2$

Outline

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 $u : [0, T] \to [0, 1]$ 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

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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 - 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

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

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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

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

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

$$\varphi \in L^\infty(0,T;H^2) \cap L^2(0,T;H^3) \cap H^1(0,T;L^2) \cap C^0(\overline{Q}),$$
$$\mu \in L^2(0,T;H^2) \cap L^\infty(0,T;L^2),$$
$$\sigma \in L^\infty(0,T;H^1) \cap L^2(0,T;H^2) \cap H^1(0,T;L^2), \quad 0 \leq \sigma \leq 1 \text{ a.e. in } Q$$

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satisfying the state equations.

Key points:

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

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

  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

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

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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 $[0,T]$.

Existence of a minimiser

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

$$J_r(\varphi,u,\tau) \geq -\frac{\beta_S}{2r}\int_{\tau-r}^{\tau}\int_\Omega |\varphi| \geq -\frac{\beta_S}{2r}\|\varphi\|_{L^1(0,T;L^1)} \geq -C.$$

- 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

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

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

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

- 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:

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

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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

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

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

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

That is, (u_*, τ_*) is a minimiser.

Outline

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),
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with Neumann boundary conditions and zero initial conditions.

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\end{aligned}$$

with Neumann boundary conditions and zero initial conditions.

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 $\mathcal{U}_{\mathrm{ad}} \subset \mathcal{U}$. Then $\mathcal{S} : \mathcal{U} \subset L^2(Q) \to \mathcal{Y}$ is Fréchet differentiable, where

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

Fréchet differentiability with respect to the control

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

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

Fréchet differentiability with respect to time

For

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

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), \\
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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.
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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

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

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Issues: For the above expression to be well-defined, 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 $\mathcal{U}_{\mathrm{ad}} = \{u \in H^1(0, T; L^2) : 0 \le u \le 1, \|\partial_t u\|_{L^2(Q)} \le K\}$ 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 $\varrho\,\mathrm{sign}(\varphi - \varphi^*)$ 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

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

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

Outline

Simulations: Garcke, Lam, Sitka, Styles, 2016

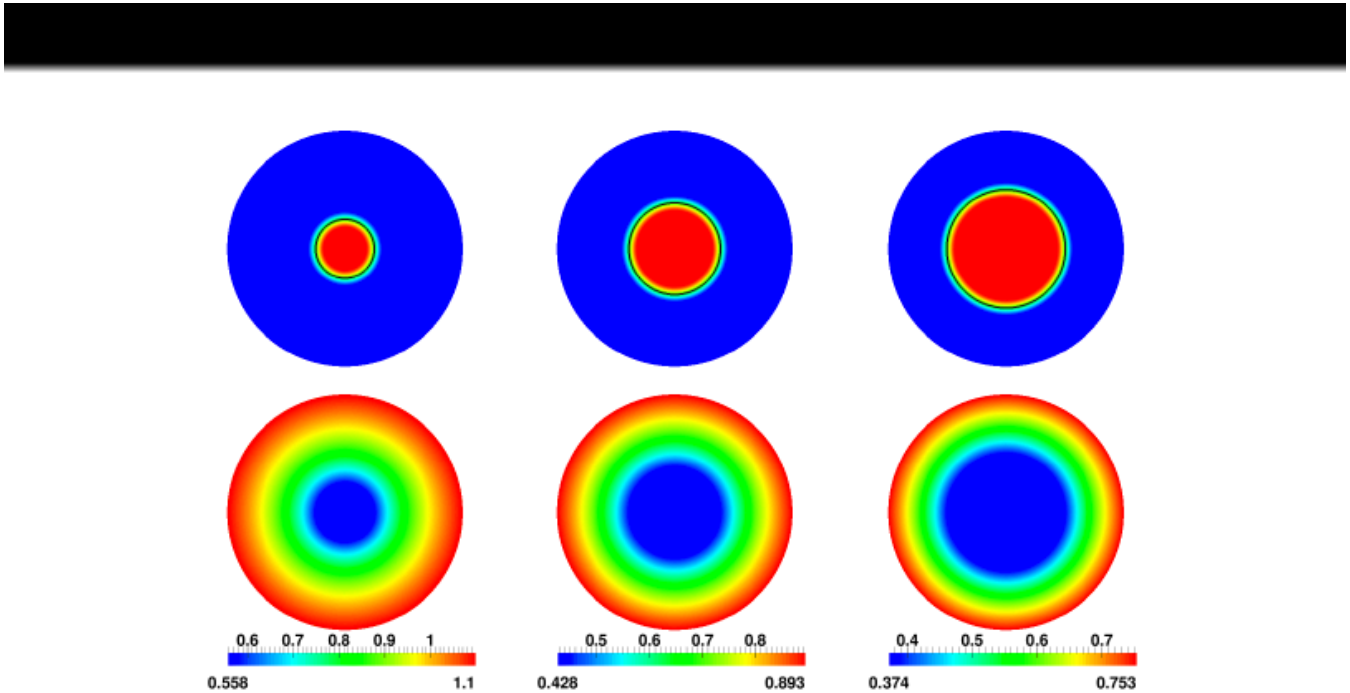

Abb.Evolution of tumour (above) and nutrient (below)

Stability of (no chemotaxis) growing circular tumour
Question from medicine: When does a compact growth changes to branched structures?

Simulations: Garcke, Lam, Sitka, Styles, 2016

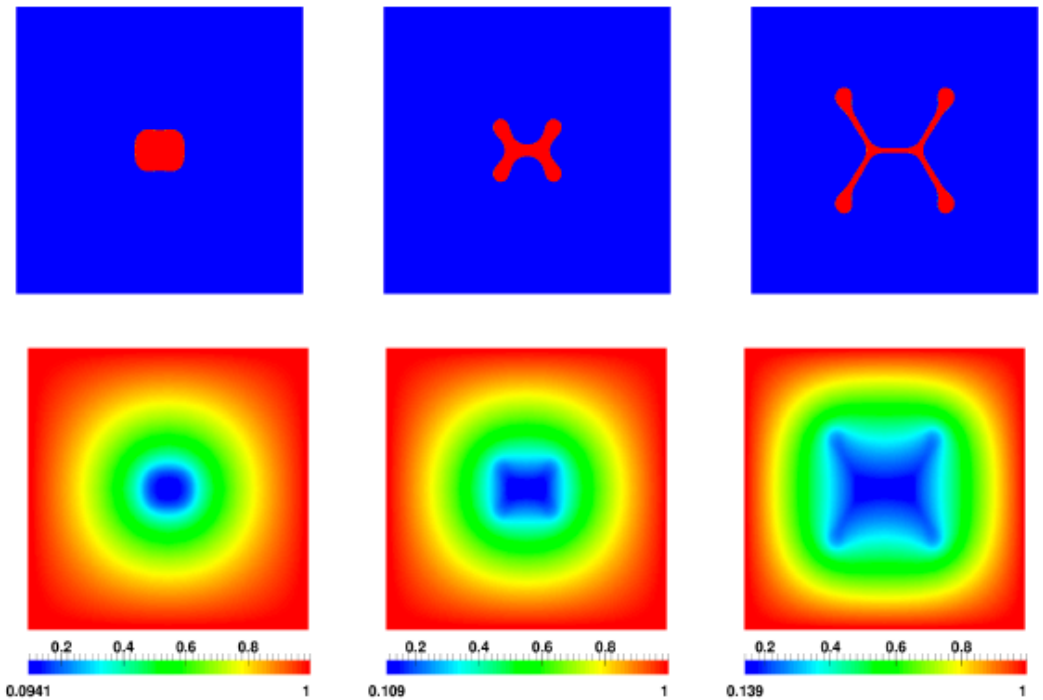

Abb.Solutions with chemotaxis at $t = 5, 10, 20$.

Outline

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

Typical structure of tumors grown in vitro:

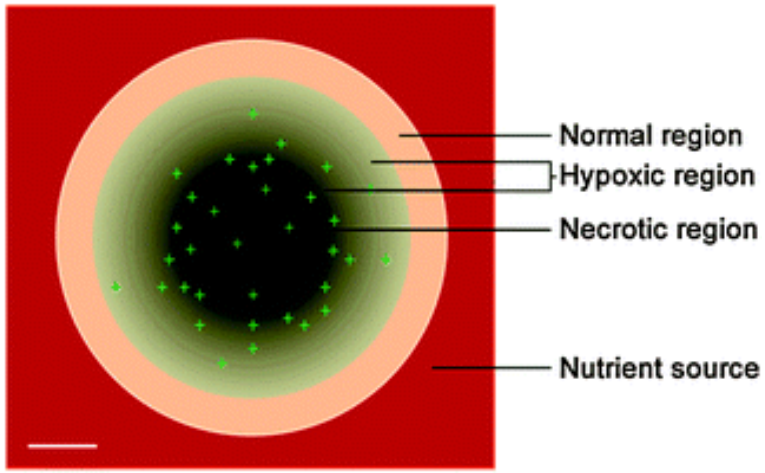

Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100μm $=$ 0:1mm

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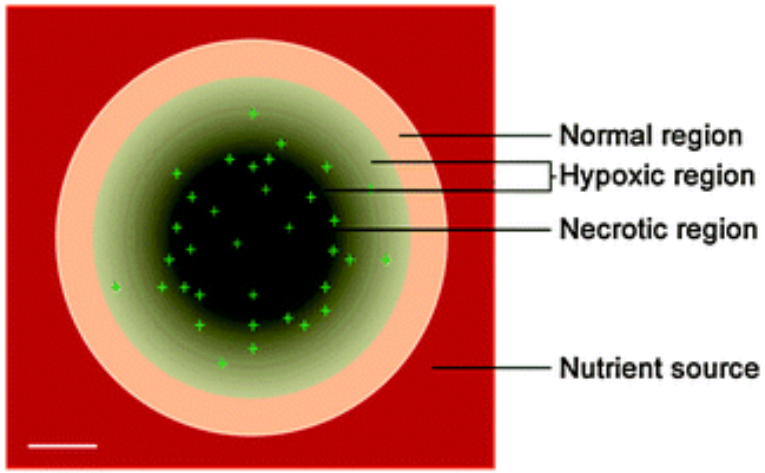

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A continuum thermodynamically consistent model is introduced with the ansatz:

- 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

S. Frigeri, K.-F. Lam, E. R., G. Schimperna, arXiv:1709.01469 (2017)

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The model is a variant of the one introduced in [Y. Chen, S.M. Wise, V.B. Shenoy and J.S. Lowengrub, Int. J. Numer. Meth. Biomed. Engng. (2014)]:

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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 $\boldsymbol{\varphi} := (\varphi_p, \varphi_d)^\top$ lies in the simplex $\Delta := \{\boldsymbol{y} \in \mathbb{R}^2 : \ 0 \leq y_1, y_2, \ y_1 + y_2 \leq 1\} \subset \mathbb{R}^2$

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- $\varphi_p, \varphi_d, \varphi_h \in [0,1]$: 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 $\boldsymbol{\varphi} := (\varphi_p, \varphi_d)^\top$ lies in the simplex $\Delta := \{\boldsymbol{y} \in \mathbb{R}^2 : \ 0 \leq y_1, y_2, \ y_1 + y_2 \leq 1\} \subset \mathbb{R}^2$
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- n: the nutrient concentration (it was σ before)
- $\boldsymbol{u} := \boldsymbol{u}_i, i = 1,2,3$: 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 $\boldsymbol{J}_i$, $i \in \{p, d, h\}$, denote the mass fluxes for the cells, then the general balance law for the volume fractions reads as

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

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

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Assume: the tumor growth process tends to evolve towards (local) minima of the free energy functional of Ginzburg–Landau type:

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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 $\boldsymbol{J}_i$ are defined as follows:

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

FLRS: the velocity and nutrient evolutions

We set $\boldsymbol{J}_h = -\boldsymbol{J}_p - \boldsymbol{J}_d$, 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:

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

The velocity field $\boldsymbol{u}$ 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

The goal and the main difficulties of FLRS

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- such a relation does not involve directly the singular part F_0. Hence, the evolution of y_p, y_d are not automatically compatible with the physical constraint and this has to be proved by assuming proper conditions on coefficients and making a careful choice of the boundary conditions
- the choice $(M_i \nabla \mu_i - \varphi_i \boldsymbol{u}) \cdot \boldsymbol{n} = 0$ seems essential

FLRS: The weak notion of solution

Definition. $(\varphi_p, \varphi_d, \boldsymbol{u}, q, n)$ 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:

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

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

$$\int_\Omega \boldsymbol{u} \cdot \nabla \xi \, dx = -\int_\Omega (S_p + S_d)\xi \, dx \quad \forall \xi \in H^1_0(\Omega),$$

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

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

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

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

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

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

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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 $\boldsymbol{x} = (x_p, x_d) \in [K_{p,-}, K_{p,+}] \times [K_{d,-}, K_{d,+}]$, there holds

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

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Assumptions on the initial data :

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

FLRS: Examples of mass sources

Examples of mass sources in $\partial_t \varphi_i - \operatorname{div}(M_i \nabla \mu_i - \varphi_i \boldsymbol{u}) = S_i$ 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, arXiv:1709.01469 (2017)

Theorem

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

$$\varphi_i \in H^1(0,T;H^1(\Omega)') \cap L^\infty(0,T;H^1(\Omega)) \cap L^2(0,T;H^2(\Omega)),$$

$$\text{with } 0 \le \varphi_i \le 1, \quad \varphi_p + \varphi_d \le 1 \text{ a.e. in } Q, \quad \text{for } i = p, d,$$

$$\mu_i \in L^2(0,T;H^1(\Omega)), \quad \eta_i \in L^2(Q),$$

$$\boldsymbol{u} \in L^2(Q) \text{ with } \operatorname{div} \boldsymbol{u} \in L^2(Q), \quad q \in L^2(0,T;H^1_0(\Omega)),$$

$$n \in (1 + L^2(0,T;H^2(\Omega) \cap H^1_0(\Omega))), \quad 0 \le n \le 1 \text{ a.e. in } Q.$$

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&\boldsymbol{u} \in L^2(Q) \text{ with } \operatorname{div} \boldsymbol{u} \in L^2(Q), \quad q \in L^2(0,T;H^1_0(\Omega)),\\
&n \in (1 + L^2(0,T;H^2(\Omega) \cap H^1_0(\Omega))), \quad 0 \le n \le 1 \text{ a.e. in } Q.
\end{aligned}$$

Notice that the boundary conditions:

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

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

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

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where $(S_p, S_d) = (\Sigma_p, \Sigma_d) + \underline{\underline{M}}(\varphi_p, \varphi_d)^T$, leads to the following system of ODE's:

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Using the assumption

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

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The bound of the mean values

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

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

where $(S_p, S_d) = (\Sigma_p, \Sigma_d) + \underline{\underline{M}}(\varphi_p, \varphi_d)^T$, leads to the following system of ODE's:

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

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

Outline

Perspectives and Open problems

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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

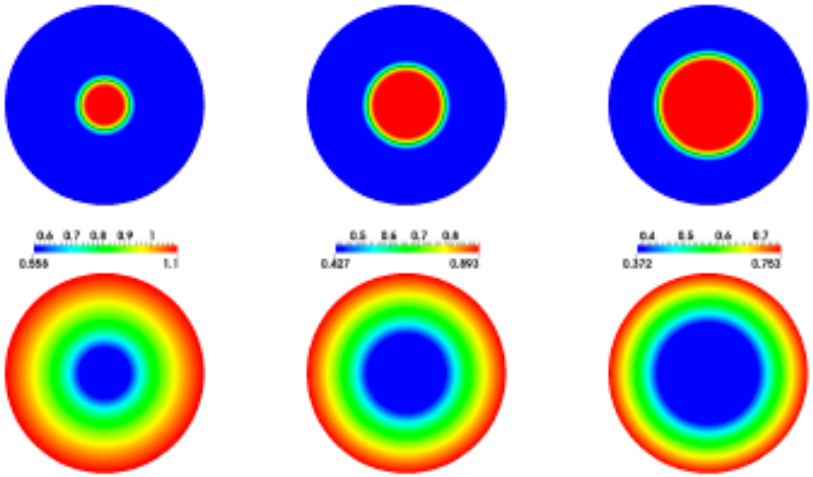
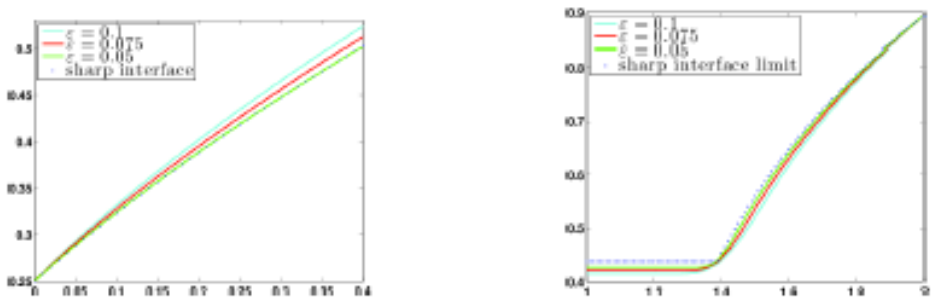


Figure 2: Approximate solutions of (5.2) at $t = 0$ (left), $t = 0.2$ (centre) and $t = 0.4$, φ (top row), σ bottom row. The black line in the φ solutions denotes the corresponding sharp interface solution.



(a) radius versus time

(b) σ versus arclength at $t = 0.2$

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

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

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We can estimate the right-hand side as

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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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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

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

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Then define the mapping

$$M_2 : L^2(Q) \to L^\infty(0,T;H^2) \cap L^2(0,T;H^3) \cap H^1(0,T;L^2),$$
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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.