On the long time behavior and optimal control of a tumor growth model

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February 27, 2019, Bilbao
BILBAO WORKSHOP ON THEORETICAL FLUID DYNAMICS

joint work with Cecilia Cavaterra (Milano), Hao Wu (Fudan)

fondazione cariplo

Cariplo-Regione Lombardia Grant MEGAsTaR 2016-2020

Regione Lombardia

UNIVERSITÀ DI PAVIA

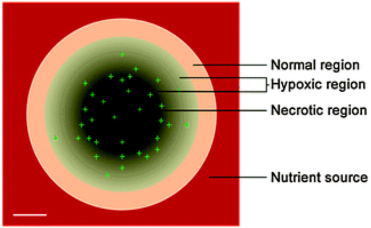
Outline

1. Phase field models for tumor growth
2. The model HZO by [A. Hawkins-Daarud, K.-G. van der Zee and J.-T. Oden (2011)]
3. Content of the joint work with C. Cavaterra and H. Wu, arXiv:1901.07500, 2019
4. Well-posedness
5. Long-term dynamics
6. The optimal control problem
7. Open problems and Perspectives

Outline

Setting

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



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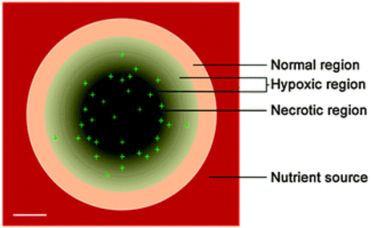

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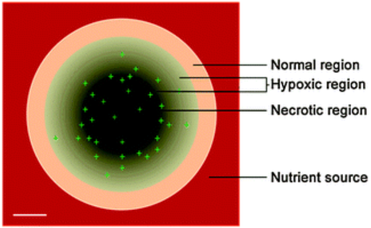

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We investigate the two-phase case: growth of a tumor in presence of a nutrient and surrounded by host tissues.

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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*

Outline

HZO: the free energy

- $u =$ tumor cell volume fraction $u \in [0,1]$
- $n =$ nutrient-rich extracellular water volume fraction $n \in [0,1]$
- $f(u) = \Gamma u^2(1-u)^2$: a double well
- $\chi(u,n) = -\chi_0 un$: chemotaxis driving the tumor cells toward the oxygen supply

$$E = \int_\Omega \left(f(u) + \frac{\epsilon^2}{2} |\nabla u|^2 + \chi(u,n) + \frac{1}{2\delta} n^2 \right) \mathrm{d}x. \quad (4)$$

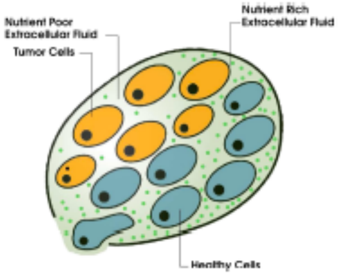

Figure 1. Four-species model: illustration of the four-species mixture. The tumor and healthy cell populations are assumed to have a thin diffuse interface, whereas the nutrient-rich and nutrient-poor extracellular water are segregated by a wide smooth interface.

The plot of the summand $f(u) + \chi(u, n)$

The lowest energy state is when $u = 1$ and $n = 1$, when there is a full interaction between the tumor species and the nutrient-rich extracellular water.

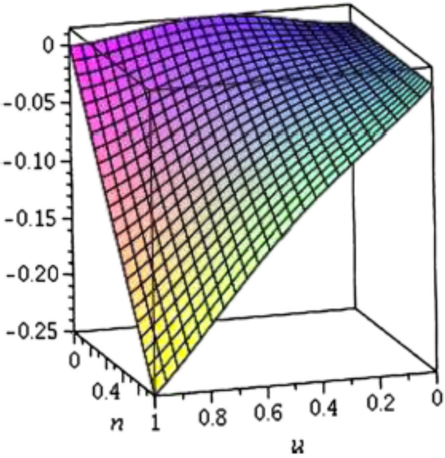

Figure 2. Graph of homogeneous free energy: $f(u) + \chi(u, n)$. ($\Gamma = \chi_0 = 0.25$).

The mass balance equations

The mass balance equations

$$u_t = \nabla \cdot (M_u \nabla \mu_u) + \gamma_u, \quad \mu_u = \partial_u E = f'(u) + \partial_u \chi(u, n) - \epsilon \Delta u$$

$$n_t = \nabla \cdot (M_n \nabla \mu_n) + \gamma_n, \quad \mu_n = \partial_n E = \partial_n \chi(u, n) + \frac{1}{\delta} n$$

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More in particular, they choose:

$$\gamma_u = P(u)(\mu_n - \mu_u), \quad \gamma_n = -\gamma_u, \quad \text{where}$$

$$P(u) = \begin{cases} \delta P_0 u & \text{if } u \geq 0 \\ 0 & \text{elsewhere} \end{cases}$$

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Simulations by HZO: the tumor starts growing increasingly more ellipsoidal at first and eventually begins forming buds growing toward the higher levels of nutrient

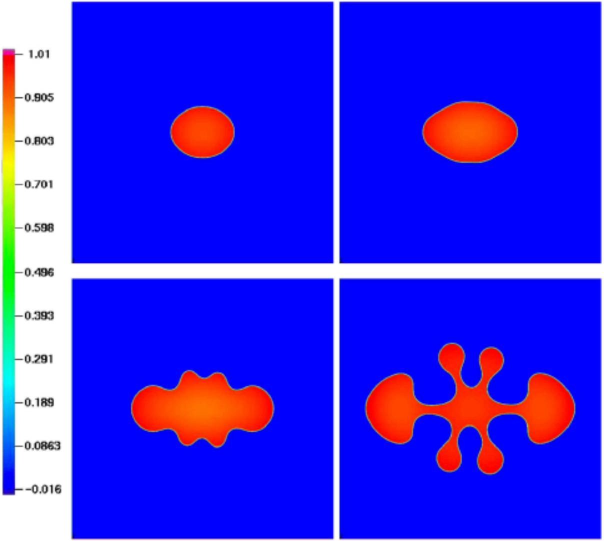


Figure 7. Example simulation: snapshots are shown at $t = 20, 40, 60$, and 80 of a simulation with $\Gamma = 0.045$, $\epsilon = 0.005$, $\chi_0 = 0.05$, $\delta = 0.01$, $P_0 = 0.1$, $\hat{M} = 200$, and $\hat{D} = 1$.

Simulations by HZO: the influence of χ_0 and δ

- When the ratio χ_0/Γ is small, the tumor remains circular $u \sim 0, 1$
- When $\chi_0 \sim \Gamma$ the tumor goes into an ellipse
- When χ_0/Γ and χ_0/ϵ are big, u no longer takes on values close to 0 and 1: it begins moving quickly toward the regions with higher nutrients
- Only when χ_0 is large the value of δ makes a difference in simulations

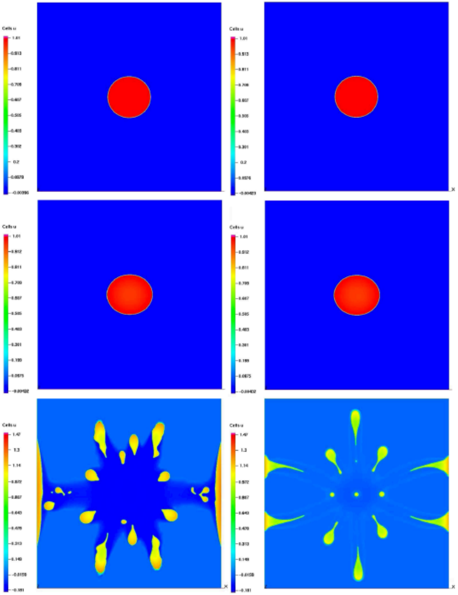
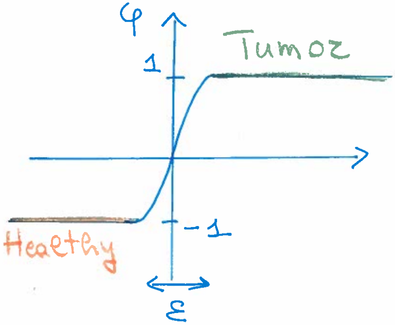


Figure 10. Effects of parameter χ_0: illustrated here are the effects of different values of χ_0 when $\Gamma = 0.045$ and $\epsilon = 0.005$ are held constant. In the first row, $\chi_0 = 0.005$; in the second row, $\chi_0 = 0.05$; and in the third row, $\chi_0 = 0.5$. In the first column, $\delta = 0.1$; and in the second column, $\delta = 0.01$.

Outline

Our notation for the tumor phase parameter $(u =)\phi \in [-1, 1]$



The sharp interface S replaced by a (thickness ε) thin transition layer

$\varphi \equiv -1$ in the Healthy tissue phase

$\varphi \equiv 1$ in the Tumor phase

Theoretical analysis: two-phase models

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- Analytical results related to well-posedness, asymptotic limits, but also optimal control and long-time behavior of solution, 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
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In this talk we concentrate on two recent results on optimal control and long-time behavior of solution.

Long-time dynamics and optimal control

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By establishing the Lyapunov stability of certain equilibria of the state system (without external source), we see that ϕ_Ω can be taken as a stable configuration, so that the tumor will not grow again once the finite-time treatment is completed

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$$\phi_t - \Delta\mu = P(\phi)(\sigma - \mu), \qquad \mu = -\Delta\phi + F'(\phi)$$

$$\sigma_t - \Delta\sigma = -P(\phi)(\sigma - \mu) + u$$

subject to initial and boundary conditions

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- $P \geq 0$ denotes a suitable regular proliferation function
- The choice of reactive terms is motivated by the linear phenomenological constitutive laws for chemical reactions
- The control variable u serves as an external source in the equation for σ and can be interpreted as a medication

Energy identity

The system turns out to be thermodynamically consistent. In particular, when $u = 0$ the unknown pair (ϕ, σ) is a dissipative gradient flow for the total free energy:

$$\mathcal{E}(\phi,\sigma) = \int_\Omega \left[\frac{1}{2}|\nabla\phi|^2 + F(\phi)\right] \mathrm{d}x + \frac{1}{2}\int_\Omega \sigma^2 \, \mathrm{d}x.$$

Moreover generally, under the presence of the external source u, we observe that any smooth solution (ϕ, σ) to the problem satisfies the following energy identity:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathcal{E}(\phi,\sigma) + \int_\Omega \left[|\nabla\mu|^2 + |\nabla\sigma|^2 + P(\phi)(\mu-\sigma)^2\right] \mathrm{d}x = \int_\Omega u\sigma \, \mathrm{d}x,$$

which motives the twofold aim of the present contribution.

Our results

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2. Denoting by $T \in (0, +\infty)$ a fixed maximal time in which the patient is allowed to undergo a medical treatment, we derive necessary optimality conditions for

   (CP) *Minimize the cost functional*

$$\mathcal{J}(\phi, \sigma, u, \tau) = \frac{\beta_Q}{2} \int_0^\tau \int_\Omega |\phi - \phi_Q|^2 \,\mathrm{d}x\,\mathrm{d}t + \frac{\beta_\Omega}{2} \int_\Omega |\phi(\tau) - \phi_\Omega|^2 \,\mathrm{d}x$$
$$+ \frac{\alpha_Q}{2} \int_0^\tau \int_\Omega |\sigma - \sigma_Q|^2 \,\mathrm{d}x\,\mathrm{d}t + \frac{\beta_S}{2} \int_\Omega (1 + \phi(\tau)) \,\mathrm{d}x + \frac{\beta_u}{2} \int_0^T \int_\Omega |u|^2 \,\mathrm{d}x\,\mathrm{d}t + \beta_T \tau$$

   subject to the state system and the the control constraint

$$u \in \mathcal{U}_{\mathrm{ad}} := \{u \in L^\infty(Q) : \ u_{\min} \le u \le u_{\max} \ \text{a.e. in } Q\}, \quad \tau \in (0, T)$$

Comments on the cost functional

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- $\tau \in (0, T]$ represents 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, ϕ_Q and σ_Q represent a desired evolution for the tumor cells and for the nutrient, ϕ_Ω stands for desired final distribution of tumor cells

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- The fifth term penalizes large concentrations of the cytotoxic drugs, and the sixth term of $\mathcal{J}$ penalizes long treatment times

The choice of ϕ_Ω

After the treatment, the ideal situation will be either the tumor is ready for surgery or the tumor will be stable for all time without further medication (i.e., $u = 0$) . This goal can be realized by making different choices of the target function ϕ_Ω in the above optimal control problem (CP).

- For the former case, one can simply take ϕ_Ω to be a configuration that is suitable for surgery.
- While for the later case, which is of more interest to us, we want to choose ϕ_Ω as a "stable" configuration of the system, so that the tumor does not grow again once the treatment is complete.

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For this purpose, we prove that any local minimizer of the total free energy $\mathcal{E}$ is Lyapunov stable provided that $u = 0$. As a consequence, these local energy minimizers serve as possible candidates for the target function ϕ_Ω. Then after completing a successful medication, the tumor will remain close to the chosen stable configuration for all time.

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- For the single Cahn-Hilliard equation this difficulty can be overcome by employing the Łojasiewicz-Simon approach: a key property that plays an important role in the analysis of the Cahn-Hilliard equation is the conservation of mass, i.e.,

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  However, for our coupled system this property no longer holds, which brings us new difficulties in analysis.

- Besides, quite different from the Cahn-Hilliard-Oono system considered in which the mass $\int_\Omega \phi(t)\,\mathrm{d}x$ is not preserved due to possible reactions, here in our case it is not obvious how to control the mass changing rate:

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \phi\,\mathrm{d}x = \int_\Omega P(\phi)(\sigma-\mu)\,\mathrm{d}x.$$

  Similar problem happens to the nutrient as well, that is

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \sigma\,\mathrm{d}x = -\int_\Omega P(\phi)(\sigma-\mu)\,\mathrm{d}x + \int_\Omega u\,\mathrm{d}x.$$

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- Based on the above mentioned special structure of the system, by introducing a new version of Łojasiewicz-Simon inequality we are able to prove that every global weak solution (ϕ, σ) of the problem will converge to a certain single equilibrium $(\phi_\infty, \sigma_\infty)$ as $t \to +\infty$ and, moreover, we obtain a polynomial decay of the solution.

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- Besides, a nontrivial application of the Łojasiewicz-Simon approach further leads to the Lyapunov stability of local minimizers of the free energy $\mathcal{E}$ (we only consider the case $u = 0$ for the sake of simplicity).

Comparison with other results in the literature

- To the best of our knowledge, the only contribution in the study of long-time behavior for this problem is given in [FGR: Frigeri, Grasselli, R. (2015)] with $u = 0$, where, however, the main focus is the existence of a global attractor .
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Here we aim to provide a contribution to the theory of free terminal time optimal control where the control is applied in the nutrient equation.

Outline

Well-posedness (cf, [CGRS, Theorem 2.1])

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Let $\phi_0 \in H^2_N(\Omega) \cap H^3(\Omega)$ and $\sigma_0 \in H^1(\Omega)$ and assume that

(P1) $P \in C^2(\mathbb{R})$ is nonnegative. There exist $\alpha_1 > 0$ and some $q \in [1, 4]$ such that, for all $s \in \mathbb{R}$, $|P'(s)| \leq \alpha_1(1 + |s|^{q-1})$

(F1) $F = F_0 + F_1$, with $F_0, F_1 \in C^5(\mathbb{R})$. There exist $\alpha_i > 0$ and $r \in [2, 6)$ such that

$$|F_1''(s)| \leq \alpha_2, \quad \alpha_3(1+|s|^{r-2}) \leq F_0''(s) \leq \alpha_4(1+|s|^{r-2}), \quad F(s) \geq \alpha_5|s|-\alpha_6 \quad \forall s \in \mathbb{R}$$

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Theorem (Strong solutions)

(1) For every $T > 0$, the state system admits a unique strong solution:

$$\|\phi\|_{L^\infty(0,T;H^3(\Omega))\cap L^2(0,T;H^4(\Omega))\cap H^1(0,T;H^1(\Omega))} + \|\mu\|_{L^\infty(0,T;H^1(\Omega))\cap L^2(0,T;H^2(\Omega))}$$
$$+ \|\sigma\|_{C([0,T];H^1(\Omega))\cap L^2(0,T;H^2_N(\Omega))\cap H^1(0,T;L^2(\Omega))} \leq K_1.$$

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$$+ \|\sigma\|_{C([0,T];H^1(\Omega))\cap L^2(0,T;H^2_N(\Omega))\cap H^1(0,T;L^2(\Omega))} \leq K_1.$$

(2) Let (ϕ_i, σ_i) be two strong solutions. Then there exists a constant $K_2 > 0$, depending on $\|u_i\|_{L^2(0,T;L^2)}$, Ω, T, $\|\phi_0\|_{H^3}$ and $\|\sigma_0\|_{H^1}$, such that

$$\|\phi_1 - \phi_2\|_{L^\infty(0,T;H^1)\cap L^2(0,T;H^3)\cap H^1(0,T;(H^1)')} + \|\mu_1 - \mu_2\|_{L^2(0,T;H^1)}$$
$$+ \|\sigma_1 - \sigma_2\|_{C([0,T];H^1)\cap L^2(0,T;H^2)\cap H^1(0,T;L^2)} \leq K_2\|u_1 - u_2\|_{L^2(0,T;L^2)}.$$

Outline

Long-term dynamics

We make the following additional assumptions:

(P2) $P(s) > 0$, for all $s \in \mathbb{R}$

(F2) $F(s)$ is real analytic on $\mathbb{R}$

(U2) $u \in L^1(0, +\infty; L^2(\Omega)) \cap L^2(0, +\infty; L^2(\Omega))$ and satisfies the decay condition

$$\sup_{t \geq 0} (1+t)^{3+\rho} \|u(t)\|_{L^2(\Omega)} < +\infty, \quad \text{for some } \rho > 0.$$

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Theorem (1. The stationary problem)

For any $\phi_0 \in H^1(\Omega)$, $\sigma_0 \in L^2(\Omega)$, the state system admits a unique global weak solution (ϕ, μ, σ): $\lim_{t \to +\infty} \left(\|\phi(t) - \phi_\infty\|_{H^2(\Omega)} + \|\sigma(t) - \sigma_\infty\|_{L^2(\Omega)} + \|\mu(t) - \mu_\infty\|_{L^2(\Omega)} \right) = 0$, *where $(\phi_\infty, \mu_\infty, \sigma_\infty)$ satisfies the stationary problem*

$$\begin{cases} -\Delta \phi_\infty + F'(\phi_\infty) = \mu_\infty, & \text{in } \Omega \\ \partial_\nu \phi_\infty = 0, & \text{on } \partial\Omega \\ \displaystyle\int_\Omega (\phi_\infty + \sigma_\infty)\,\mathrm{d}x = \int_\Omega (\phi_0 + \sigma_0)\,\mathrm{d}x + \int_0^{+\infty} \int_\Omega u\,\mathrm{d}x\,\mathrm{d}t \end{cases}$$

with μ_∞ and σ_∞ being two constants given by $\sigma_\infty = \mu_\infty = |\Omega|^{-1} \int_\Omega F'(\phi_\infty) dx$.

The convergence rate

Theorem (2. Convergence rate)

Moreover, under the same assumptions, the following estimates on convergence rate hold

$$\|\phi(t)-\phi_\infty\|_{H^1(\Omega)} + \|\sigma(t)-\sigma_\infty\|_{L^2(\Omega)} \le C(1+t)^{-\min\left\{\frac{\theta}{1-2\theta},\,\frac{\rho}{2}\right\}}, \quad \forall\, t \ge 0,$$

$$\|\mu(t)-\mu_\infty\|_{L^2(\Omega)} \le C(1+t)^{-\frac{1}{2}\min\left\{\frac{\theta}{1-2\theta},\,\frac{\rho}{2}\right\}}, \quad \forall\, t \ge 0,$$

where $C>0$ is a constant depending on $\|\phi_0\|_{H^1(\Omega)}$, $\|\sigma_0\|_{L^2(\Omega)}$, $\|\phi_\infty\|_{H^1(\Omega)}$, $\|u\|_{L^1(0,+\infty;L^2(\Omega))}$, $\|u\|_{L^2(0,+\infty;L^2(\Omega))}$ and Ω; $\theta \in (0,\frac{1}{2})$ is a constant depending on ϕ_∞.

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- We first derive some uniform-in-time a priori estimates on the solution (ϕ, μ, σ)
- Then we give a characterization on the ω-limit

$$\omega(\phi_0, \sigma_0) = \{(\phi_\infty, \sigma_\infty) \in (H^2_N(\Omega) \cap H^3(\Omega)) \times H^1(\Omega) \ : \ \exists \{t_n\} \nearrow +\infty \text{ such that } (\phi(t_n), \sigma(t_n)) \to (\phi_\infty, \sigma_\infty) \text{ in } H^2(\Omega) \times L^2(\Omega)\}.$$

And we have the following result

Theorem (3. The ω-limit)

Assume (P1), (F1), (U2). *For any initial datum* $(\phi_0, \sigma_0) \in H^1(\Omega) \times L^2(\Omega)$, *the associated ω-limit set* $\omega(\phi_0, \sigma_0)$ *is non-empty. For any element* $(\phi_\infty, \sigma_\infty) \in \omega(\phi_0, \sigma_0)$, σ_∞ *is a constant and* $(\phi_\infty, \sigma_\infty)$ *satisfies the stationary problem. Besides,* μ_∞ *is a constant given by* $|\Omega|^{-1} \int_\Omega F'(\phi_\infty) dx$ *and the following relation holds*

$$P(\phi_\infty)(\sigma_\infty - \mu_\infty) = 0, \quad a.e. \ in \ \Omega.$$

And the positivity of P entails immediately also $\sigma_\infty = \mu_\infty$.

- Finally, we prove the convergence of the trajectories and polynomial decay by means of a proper Łojasiewicz–Simon inequality:

- Finally, we prove the convergence of the trajectories and polynomial decay by means of a proper Łojasiewicz–Simon inequality: Given any initial datum $(\phi_0, \sigma_0) \in H^1(\Omega) \times L^2(\Omega)$ and source term u satisfying (U2), we denote by

$$m_\infty := |\Omega|^{-1} \left(\int_\Omega (\phi_0 + \sigma_0)\, \mathrm{d}x + \int_0^{+\infty} \int_\Omega u \, \mathrm{d}x \, \mathrm{d}t \right)$$

the total mass at infinity time. Then we are able to derive the following

Theorem (Łojasiewicz–Simon Inequality)

Let (F1), (F2), (P1), (P2) and (U2) be satisfied. Suppose that $(\phi_\infty, \mu_\infty, \sigma_\infty)$ is a solution to the elliptic stationary problem. Then there exist constants $\theta \in (0, \frac{1}{2})$ and $\beta > 0$, depending on ϕ_∞, m_∞ and Ω, such that for any $(\phi, \sigma) \in H^2_N(\Omega) \times H^1(\Omega)$ satisfying

$$\|\phi - \phi_\infty\|_{H^1(\Omega)} < \beta,$$

$$\int_\Omega (\phi + \sigma)\, \mathrm{d}x + m_u |\Omega| = \int_\Omega (\phi_\infty + \sigma_\infty)\, \mathrm{d}x = m_\infty |\Omega|,$$

where m_u is a certain constant fulfiling $|m_u| \le |\Omega|^{-\frac{1}{2}} \|u\|_{L^1(0,+\infty;L^2(\Omega))}$, then we have

$$\begin{aligned} &\|\mu - \overline{\mu}\|_{(H^1(\Omega))'} + C\|\nabla \sigma\|_{L^2(\Omega)} + C\|\sqrt{P(\phi)}(\mu - \sigma)\|_{L^2(\Omega)} + C|m_u|^{\frac{1}{2}} \\ &\quad \ge \ |\mathcal{E}(\phi, \sigma) - \mathcal{E}(\phi_\infty, \sigma_\infty)|^{1-\theta}, \quad \textit{where} \end{aligned}$$

$\mu = -\Delta\phi + F'(\phi)$ and $C > 0$ depends on Ω, ϕ_∞, m_∞, $\|\phi\|_{H^2(\Omega)}$, $\|\sigma\|_{H^1(\Omega)}$, $\|u\|_{L^1(0,+\infty;L^2(\Omega))}$.

Energy minimizers with $u = 0$

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Let us now assume $u = 0$. Then it follows that the total mass of the system is now conserved:

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Let $m \in \mathbb{R}$ be an arbitrary given constant. Set

$$\mathcal{Z}_m = \Big\{(\phi, \sigma) \in H^1(\Omega) \times L^2(\Omega) : \int_\Omega (\phi + \sigma)\,\mathrm{d}x = |\Omega| m\Big\}.$$

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Any $(\phi^*, \sigma^*) \in \mathcal{Z}_m$ is called

- a *local energy minimizer* of the total energy

  $$\mathcal{E}(\phi, \sigma) = \int_\Omega \left[\frac{1}{2}|\nabla\phi|^2 + F(\phi)\right]\,\mathrm{d}x + \frac{1}{2}\int_\Omega \sigma^2\,\mathrm{d}x$$

  if there exists a constant $\chi > 0$ such that $\mathcal{E}(\phi^*, \sigma^*) \leq \mathcal{E}(\phi, \sigma)$, for all $(\phi, \sigma) \in \mathcal{Z}_m$ satisfying $\|(\phi - \phi^*, \sigma - \sigma^*)\|_{H^1(\Omega)\times L^2(\Omega)} < \chi$
- If $\chi = +\infty$, then (ϕ^*, σ^*) is called a *global energy minimizer* of $\mathcal{E}(\phi, \sigma)$ in $\mathcal{Z}_m$.

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where μ and σ are constants given by $\sigma = \mu = |\Omega|^{-1} \int_\Omega F'(\phi)\,\mathrm{d}x$.

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Let assumption (F1) be satisfied. Then we have:

(1) *If $(\phi^*, \sigma^*) \in H^2_N(\Omega) \times \mathbb{R}$ is a strong solution to the stationary problem above, then (ϕ^*, σ^*) is a critical point of $\mathcal{E}(\phi, \sigma)$ in $\mathcal{Z}_m$. Conversely, if (ϕ^*, σ^*) is a critical point of $\mathcal{E}(\phi, \sigma)$ in $\mathcal{Z}_m$, then $\phi^* \in H^2_N(\Omega)$, $\sigma^* \in \mathbb{R}$ satisfy the stationary problem above*

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We first derive some properties for the critical points of $\mathcal{E}(\phi,\sigma)$ in $\mathcal{Z}_m$. For any given $m \in \mathbb{R}$, we consider the following stationary problem for (ϕ,μ,σ)

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(2) *If (ϕ^*,σ^*) is a local energy minimizer of $\mathcal{E}(\phi,\sigma)$ in $\mathcal{Z}_m$, then (ϕ^*,σ^*) is a critical point of $\mathcal{E}(\phi,\sigma)$.*

(3) *The functional $\mathcal{E}(\phi,\sigma)$ has at least one minimizer $(\phi^*,\sigma^*) \in \mathcal{Z}_m$ such that*

$$\mathcal{E}(\phi^*,\sigma^*) = \inf_{(\phi,\sigma)\in\mathcal{Z}_m} \mathcal{E}(\phi,\sigma)$$

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Assume that (F1), (F2), (P1), (P2) *are satisfied and* $u = 0$. *Given* $m \in \mathbb{R}$, *let* (ϕ^*, σ^*) *be a local energy minimizer in* $\mathcal{Z}_m$ *of*

$$\mathcal{E}(\phi, \sigma) = \int_\Omega \left[\frac{1}{2} |\nabla \phi|^2 + F(\phi) \right] \mathrm{d}x + \frac{1}{2} \int_\Omega \sigma^2 \, \mathrm{d}x.$$

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Then, for any $\epsilon > 0$, *there exists a constant* $\eta \in (0,1)$ *such that for arbitrary initial datum* $(\phi_0, \sigma_0) \in (H^2_N(\Omega) \cap H^3(\Omega)) \times H^1(\Omega)$ *satisfying* $\int_\Omega (\phi_0 + \sigma_0)\, \mathrm{d}x = |\Omega| m$ *and* $\|\phi_0 - \phi^*\|_{H^1(\Omega)} + \|\sigma_0 - \sigma^*\|_{L^2(\Omega)} \le \eta$, *the state system admits a unique global strong solution* (ϕ, σ) *such that*

$$\|\phi(t) - \phi^*\|_{H^1(\Omega)} + \|\sigma(t) - \sigma^*\|_{L^2(\Omega)} \le \epsilon, \quad \forall\, t \ge 0.$$

Namely, any local energy minimizer of $\mathcal{E}(\phi, \sigma)$ in $\mathcal{Z}_m$ is locally Lyapunov stable.

Conclusions on long-term dynamics

- The result on long-time behavior derived in Theorem 1 and 2 can be applied to the global strong solution obtained in Theorem 5
- Although it is still not obvious to identify the asymptotic limit $(\phi_\infty, \sigma_\infty)$, we are able to conclude that $(\phi_\infty, \sigma_\infty)$ also satisfies

$$\|\phi_\infty - \phi^*\|_{H^1(\Omega)} + \|\sigma_\infty - \sigma^*\|_{L^2(\Omega)} \leq \epsilon$$

- In particular, if (ϕ^*, σ^*) is an isolated local energy minimizer then it is locally asymptotic stable

Outline

Assumptions for the optimal control problem

In this section we study the optimal control problem

(CP) *Minimize the cost functional*

$$\mathcal{J}(\phi,\sigma,u,\tau) = \frac{\beta_Q}{2}\int_0^\tau\int_\Omega |\phi-\phi_Q|^2\,\mathrm{d}x\,\mathrm{d}t + \frac{\beta_\Omega}{2}\int_\Omega |\phi(\tau)-\phi_\Omega|^2\,\mathrm{d}x$$
$$+ \frac{\alpha_Q}{2}\int_0^\tau\int_\Omega |\sigma-\sigma_Q|^2\,\mathrm{d}x\,\mathrm{d}t + \frac{\beta_S}{2}\int_\Omega (1+\phi(\tau))\,\mathrm{d}x + \frac{\beta_u}{2}\int_0^T\int_\Omega |u|^2\,\mathrm{d}x\,\mathrm{d}t + \beta_T\tau$$

subject to the state system and the the control constraint

$$u \in \mathcal{U}_{\mathrm{ad}} := \{u \in L^\infty(Q) : \ u_{\min} \le u \le u_{\max} \ \text{ a.e. in } \ Q\}, \quad \tau \in (0,T)\,,$$

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where $T\in(0,+\infty)$ is a fixed maximal time. We assume:

(C1) β_Q, β_Ω, β_S, β_u, β_T, α_Q are nonnegative constants but not all zero.

(C2) ϕ_Q, $\sigma_Q\in L^2(Q)$, ϕ_Ω, $\sigma_\Omega\in L^2(\Omega)$, $u_{\min}$, $u_{\max}\in L^\infty(Q)$, and $u_{\min}\le u_{\max}$, a.e. in Q.

(C3) Let $\mathcal{U}_R$ be an open set in $L^2(Q)$: $\mathcal{U}_{\mathrm{ad}}\subset\mathcal{U}_R$ and $\|u\|_{L^2(Q)}\le R$, for all $u\in\mathcal{U}_R$.

Existence of an optimal control

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From the well-posedness results it follows that the *control-to-state operator* $\mathcal{S}$

$$u \mapsto \mathcal{S}(u) := (\phi, \mu, \sigma)$$

is well-defined and Lipschitz continuous as a mapping from $\mathcal{U}_R \subset L^2(Q)$ into the following space

$$(L^\infty(0,T;(H^1(\Omega))') \cap L^2(0,T;H^1(\Omega))) \times L^2(0,T;(H^1(\Omega))') \times (L^\infty(0,T;(H^1(\Omega))') \cap L^2(Q)).$$

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The triplet (ϕ, μ, σ) is the unique weak solution to the state system with data (ϕ_0, σ_0, u) over the time interval $[0, T]$. For convenience, we use the notations $\phi = \mathcal{S}_1(u)$ and $\sigma = \mathcal{S}_3(u)$ for the first and third component of $\mathcal{S}(u)$.

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Theorem (Existence of the optimal control)

Assume that (P1), (F1), (U1) *and* (C1)–(C3) *are satisfied. Let* $\phi_0 \in H^2_N(\Omega) \cap H^3(\Omega)$ *and* $\sigma_0 \in H^1(\Omega)$. *Then there exists at least one minimizer* $(\phi_*, \sigma_*, u_*, \tau_*)$ *to problem* (CP). *Namely,* $\phi_* = \mathcal{S}_1(u_*)$, $\sigma_* = \mathcal{S}_3(u_*)$ *satisfy*

$$\mathcal{J}(\phi_*, \sigma_*, u_*, \tau_*) = \inf_{\substack{(w,s)\in \mathcal{U}_{\rm ad}\times[0,T] \\ \text{s.t. } \phi = \mathcal{S}_1(w),\, \sigma = \mathcal{S}_3(w)}} \mathcal{J}(\phi, \sigma, w, s).$$

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\begin{aligned}
&\partial_t \xi - \Delta \eta = P'(\phi_*)(\sigma_* - \mu_*)\,\xi + P(\phi_*)(\rho - \eta), \qquad \eta = -\Delta \xi + F''(\phi_*)\,\xi, \\
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We can apply [Theorems 3.1, 3.2, CGRS] for the well-posedness of the linearized system and the Fréchet differentiability of the control-to-state operator $\mathcal{S}$ with respect to u.

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$$\mathcal{Y} := \Big(H^1(0,T;(H^2_N(\Omega))') \cap L^\infty(0,T;L^2(\Omega)) \cap L^2(0,T;H^2_N(\Omega)) \Big) \times L^2(Q)$$
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&\times \Big(H^1(0,T;L^2(\Omega)) \cap L^2(0,T;H^2(\Omega))\Big).
\end{aligned}$$

For any $u_* \in \mathcal{U}_R$, the Fréchet derivative $D\mathcal{S}(u_*) \in \mathcal{L}(L^2(Q), \mathcal{Y})$ is defined as follows: for any $h \in L^2(Q)$, $D\mathcal{S}(u_*)h = (\xi^h, \eta^h, \rho^h)$, where (ξ^h, η^h, ρ^h) is the unique solution to the linearized system associated with h.

First order optimality conditions

Define a reduced functional

$$\widetilde{\mathcal{J}}(u,\tau) := \mathcal{J}(S_1(u), S_3(u), u, \tau).$$

Since the control-to-state mapping $\mathcal{S}$ is also Fréchet differentiable into $C^0([0,T]; L^2(\Omega))$ with respect to u, then the reduced cost functional $\widetilde{\mathcal{J}}$ is Fréchet differentiable in $\mathcal{U}_R$.

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Theorem (Existence of solutions to the adjoint system)

Assume (P1), (F1), (U1), (C1)–(C3), $\phi_0 \in H^2_N(\Omega) \cap H^3(\Omega)$, *and* $\sigma_0 \in H^1(\Omega)$. *Then the adjoint system*

$$-\partial_t p + \Delta q - F''(\phi_*)\, q + P'(\phi_*)(\sigma_* - \mu_*)(r - p) = \beta_Q\,(\phi_* - \phi_Q)$$

$$q - \Delta p + P(\phi_*)(p - r) = 0, \qquad -\partial_t r - \Delta r + P(\phi_*)(r - p) = \alpha_Q(\sigma_* - \sigma_Q)$$

$$\partial_{\mathrm{n}} p = \partial_{\mathrm{n}} q = \partial_{\mathrm{n}} r = 0, \qquad r(\tau_*) = 0, \quad p(\tau_*) = \beta_\Omega\,(\phi_*(\tau_*) - \phi_\Omega) + \frac{\beta_S}{2}$$

has a unique weak solution (p, q, r) *on* $[0, \tau_*]$*:*

$$p \in H^1(0,\tau_*; (H^2_N(\Omega))') \cap C^0([0,\tau_*]; L^2(\Omega)) \cap L^2(0,\tau_*; H^2_N(\Omega)),$$
$$q \in L^2(\Omega \times (0,\tau_*)), \qquad r \in H^1(0,\tau_*; L^2(\Omega)) \cap C^0([0,\tau_*]; H^1(\Omega)) \cap L^2(0,\tau_*; H^2_N(\Omega)).$$

Necessary optimality conditions

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Theorem (Necessary optimality conditions)

Let $(u_*, \tau_*) \in \mathcal{U}_{\rm ad} \times [0, T]$ *denote a minimizer to the optimal control problem* (CP) *with corresponding state variables* $(\phi_*, \mu_*, \sigma_*) = \mathcal{S}(u_*)$ *and associated adjoint variables* (p, q, r)*, then it holds:*

$$\beta_u \int_0^T \int_\Omega u_*(u - u_*)\,\mathrm{d}x\,\mathrm{d}t + \int_0^{\tau_*} \int_\Omega r(u - u_*)\,\mathrm{d}x\,\mathrm{d}t \geq 0, \quad \forall\, u \in \mathcal{U}_{\rm ad}.$$

Besides, setting

$$\mathcal{L}(\phi_*, \sigma_*, \tau_*) = \frac{\beta_Q}{2} \int_\Omega |\phi_*(\tau_*) - \phi_Q(\tau_*)|^2\,\mathrm{d}x + \beta_\Omega \int_\Omega (\phi_*(\tau_*) - \phi_\Omega)\,\partial_t \phi_*(\tau_*)\,\mathrm{d}x$$
$$+ \frac{\alpha_Q}{2} \int_\Omega |\sigma_*(\tau_*) - \sigma_Q(\tau_*)|^2\,\mathrm{d}x + \frac{\beta_S}{2} \int_\Omega \partial_t \phi_*(\tau_*)\,\mathrm{d}x + \beta_T$$

we have

$$\mathcal{L}(\phi_*, \sigma_*, \tau_*) \begin{cases} \geq 0, & \textit{if } \tau_* = 0, \\ = 0, & \textit{if } \tau_* \in (0, T), \\ \leq 0, & \textit{if } \tau_* = T. \end{cases}$$

Interpretation of the first condition

Besides, if we extend r by zero to $(\tau_*, T]$, then we can express the variational inequality

$$\beta_u \int_0^T \int_\Omega u_*(u - u_*)\,\mathrm{d}x\,\mathrm{d}t + \int_0^{\tau_*} \int_\Omega r(u - u_*)\,\mathrm{d}x\,\mathrm{d}t \geq 0, \quad \forall\, u \in \mathcal{U}_{\mathrm{ad}}.$$

as

$$\int_0^T \int_\Omega (\beta_u u_* + r)(u - u_*)\,\mathrm{d}x\,\mathrm{d}t \geq 0, \quad \forall\, u \in \mathcal{U}_{\mathrm{ad}},$$

which allows the interpretation that the optimal control u_* is the $L^2(Q)$-projection of $-\beta_u^{-1} r$ onto the set $\mathcal{U}_{\mathrm{ad}}$ (provided that $\beta_u > 0$).

Outline

Open problems and Perspectives

O1. In practice it would be safer for the patient (and thus more desirable) to approximate the target functions in the L^∞-sense rather than in the L^2-sense or to include a pointwise state constraint on ϕ: $|\phi(x,\tau) - \phi_\Omega| \le \epsilon$ for a.e. $x \in \Omega$. This leads to a more involved adjoint system.

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P4. 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 (with C. Orrieri and L. Scarpa).

Many thanks to all of you for the attention!

Preliminaries

- Def. $\mathcal{B}_0$ is an *absorbing set* for a semigroup $S(t)$ on a metric space (X, d_X) iff
  - $\mathcal{B}_0$ is bdd
  - $\forall B \subset X$ bdd $\exists\, T_B \geq 0$ s.t. $S(t)B \subset \mathcal{B}_0 \quad \forall t \geq T_B$.

- Theorem. Let $S(t)$ be a strongly continuous semigroup on a c.m.s. (X, d_X). Moreover, if
  - $S(t)$ admits an absorbing set $\mathcal{B}_0$;
  - $\forall B \subset X$ bdd $\exists\, t_B > 0$ s.t. $\bigcup_{t \geq t_B} S(t)B$ is compact in X,

  then $S(t)$ admits a *universal attractor* $\mathcal{A}$ that is

$$\mathcal{A} = \bigcap_{\tau \geq 0} \overline{\bigcup_{t \geq \tau} S(t)\mathcal{B}_0}.$$