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

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BILBAO WORKSHOP ON THEORETICAL FLUID DYNAMICS

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

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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)]


4. Well-posedness

5. Long-term dynamics

6. The optimal control problem

7. Open problems and Perspectives
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Setting

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

*Figure:* Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100µm = 0.1mm
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![Diagram of tumor structure](image)

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

A continuum 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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- \textit{proliferating} tumor cells surrounded by (healthy) \textit{host cells}, and a \textit{nutrient} (e.g. glucose).

We investigate the \textit{two-phase} case: growth of a \textit{tumor} in presence of a \textit{nutrient} and surrounded by \textit{host tissues}.
Advantages of diffuse interfaces in tumor growth models

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.

The mathematical description remains valid even when the tumor undergoes topological changes (e.g., metastasis).

Regarding modeling of diffuse interface tumor growth, we can quote, e.g., Ciarletta, Cristini, Frieboes, Garcke, Hawkins-Daarud, Hilhorst, Lam, Lowengrub, Oden, van der Zee, Wise, also for their numerical simulations and complex changes in tumor morphologies due to the interactions with nutrients or toxic agents and also due to mechanical stresses. Frieboes, Jin, Chuang, Wise, Lowengrub, Cristini, Garcke, Lam, Nürnberg, Sitka, for the interaction of multiple tumor cell species described by multiphase mixture models.
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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

\[
E = \int_{\Omega} \left( f(u) + \frac{\varepsilon^2}{2} |\nabla u|^2 + \chi(u, n) + \frac{1}{2\delta} n^2 \right) \, dx.
\] (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

\[ u_t = \nabla \cdot \left( M \nabla \mu u \right) + \gamma u, \quad \mu u = \partial u \]

\[ E = f'(u) + \partial u \chi(u, n) - \epsilon \Delta u, \quad n_t = \nabla \cdot \left( M \nabla \mu n \right) + \gamma n, \quad \mu n = \partial n \chi(u, n) + 1 \delta n \]

Question: how to define \( \gamma u \) and \( \gamma n \)?

In HZO they use the condition \( \sum_i \mu_i \gamma_i \leq 0 \) needed for Thermodynamical consistency.

More in particular, they choose:

\[ \gamma u = P(u)(\mu n - \mu u), \quad \gamma n = -\gamma u, \]

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

being \( \delta \) a small positive constant and \( P_0 \geq 0 \).

Then we get \( \gamma u = P_0 un + \delta P_0 u (\partial n \chi(u, n) - \mu u) \) and so the dominant term is \( P_0 un \).

Other choices are possible (see Giulio's talk).
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and so the dominant term is \( P_0 un \). Other choices are possible (see Giulio’s talk).
Simulations by HZO: the tumor starts growing increasingly more ellipsoidal at first and eventually begins forming buds growing toward the higher levels of nutrient.
Simulations by HZO: the influence of $\chi_0$ and $\delta$

- When the ratio $\chi_0/\Gamma$ is small, the tumor remains circular $u \sim 0, 1$
- When $\chi_0\sim \Gamma$ the tumor goes into an ellipse
- When $\chi_0/\Gamma$ and $\chi_0/\epsilon$ 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 $\chi_0$ is large the value of $\delta$ makes a difference in simulations
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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
Our notation for the tumor phase parameter \((u =) \phi \in [-1, 1]\)

The sharp interface \(S\) replaced by a thin transition layer:
- \(\phi = -1\) in the Healthy tissue phase
- \(\phi = 1\) in the Tumorz 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
  
  ▶ for models of Cahn-Hilliard-Darcy or Cahn-Hilliard-Brinkman type.
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In this talk we concentrate on two recent results on optimal control and long-time behavior of solution.
The state system consists of a Cahn-Hilliard type equation for the tumor cell fraction $\phi \in [-1,1]$ and a reaction-diffusion equation for the nutrient ($n = \sigma \in [0,1]$). The possible medication that serves to eliminate tumor cells is in terms of drugs and is introduced into the system through the nutrient $n$. In this setting, the control variable acts as an external source in the nutrient equation. 

1. First, we consider the problem of "long-time treatment" under a suitable given source and prove the convergence of any global solution to a single equilibrium as $t \to \infty$.

2. Then we consider the "finite-time treatment" of tumor, which corresponds to an optimal control problem. Here we also allow the objective cost functional to depend on a free time variable, which represents the unknown treatment time to be optimized. We prove the existence of an optimal control and obtain first order necessary optimality conditions for both the drug concentration and the treatment time.
Long-time dynamics and optimal control

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Our main idea

One of the main aim of the control problem is to realize in the best possible way a desired final distribution of the tumor cell, which is expressed by the target function $\phi_\Omega$. 
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By establishing the Lyapunov stability of certain equilibria of the state system (without external source), we see that $\phi_\Omega$ can be taken as a stable configuration, so that the tumor will not grow again once the finite-time treatment is completed.
The state system: Cahn–Hilliard + nutrient model with source terms
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The PDE system is a particular case ($\chi_0 \equiv 0$, $\Gamma = \epsilon = \delta = 1$) of the model proposed in [HZO: A. Hawkins-Daarud, K.-G. van der Zee and J.-T. Oden (2011)] in $Q := \Omega \times (0, T)$:

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\begin{align*}
\phi_t - \Delta \mu &= P(\phi)(\sigma - \mu), & \mu &= -\Delta \phi + F'(\phi) \\
\sigma_t - \Delta \sigma &= -P(\phi)(\sigma - \mu) + u
\end{align*}
\]

subject to initial and boundary conditions

\[
\phi|_{t=0} = \phi_0, \quad \sigma|_{t=0} = \sigma_0, \quad \text{in } \Omega, \quad \partial_\nu \phi = \partial_\nu \mu = \partial_\nu \sigma = 0, \quad \text{on } \partial \Omega \times (0, T)
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The state variables are:

▶ the tumor cell fraction $\phi$: $\phi \approx 1$ (tumorous phase), $\phi \approx -1$ (healthy tissue phase)

▶ the nutrient concentration $\sigma$: $\sigma \approx 1$ and $\sigma \approx 0$ indicate a nutrient-rich or nutrient-poor extracellular water phase

$F$ is typically a double-well potential with equal minima at $\phi = \pm 1$

$P \geq 0$ denotes a suitable regular proliferation function

The choice of reactive terms is motivated by the linear phenomenological constitutive laws

The control variable $u$ serves as an external source in the equation for $\sigma$ and can be interpreted as a medication.
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The state system: Cahn–Hilliard + nutrient model with source terms

The PDE system is a particular case ($\chi_0 \equiv 0$, $\Gamma = \epsilon = \delta = 1$) of the model proposed in [HZO: A. Hawkins-Daarud, K.-G. van der Zee and J.-T. Oden (2011)] in $Q := \Omega \times (0, T)$:

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

subject to initial and boundary conditions

$$\phi|_{t=0} = \phi_0, \quad \sigma|_{t=0} = \sigma_0, \quad \text{in } \Omega, \quad \partial_\nu \phi = \partial_\nu \mu = \partial_\nu \sigma = 0, \quad \text{on } \partial \Omega \times (0, T)$$

- The state variables are:
  - the tumor cell fraction $\phi$: $\phi \simeq 1$ (tumorous phase), $\phi \simeq -1$ (healthy tissue phase)
  - the nutrient concentration $\sigma$: $\sigma \simeq 1$ and $\sigma \simeq 0$ indicate a nutrient-rich or nutrient-poor extracellular water phase
- $F$ is typically a double-well potential with equal minima at $\phi = \pm 1$
- $P \geq 0$ 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 $\sigma$ 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 \((\phi, \sigma)\) is a dissipative gradient flow for the total free energy:

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

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

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

which motives the twofold aim of the present contribution.
Our results

1. We prove that any global weak solution will converge to a single equilibrium as $t \to +\infty$ and provide an estimate on the convergence rate.

Our result indicates that after certain medication (or even without medication, i.e., $u = 0$), the tumor will eventually grow to a steady state as time evolves. However, since the potential function $F$ is nonconvex (double-well), the problem may admit infinite many steady states so that for the moment one cannot identify which exactly the unique asymptotic limit as $t \to +\infty$ will be.

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)

$$
\text{Minimize the cost functional}
$$

$$
J(\phi, \sigma, u, \tau) = \beta Q_2 \int_0^\tau \int_\Omega |\phi - \phi_Q|^2 \, dx \, dt + \beta \Omega_2 \int_\Omega |\phi(\tau) - \phi_{\Omega_2}|^2 \, dx + \alpha Q_2 \int_0^\tau \int_\Omega |\sigma - \sigma_Q|^2 \, dx \, dt + \beta S_2 \int_\Omega (1 + \phi(\tau)) \, dx + \beta u_2 \int_0^T \int_\Omega |u|^2 \, dx \, dt + \beta T_\tau
$$

subject to the state system and the control constraint $u \in U_{ad} := \{ u \in L_\infty(Q) : u_{\min} \leq u \leq u_{\max} \text{ a.e. in } Q \}$.
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\begin{align*}
\minimize \text{ the cost functional} \\
J(\phi, \sigma, u, \tau) &= \frac{\beta Q}{2} \int_0^T \int_\Omega |\phi - \phi_Q|^2 \, dx \, dt + \frac{\beta \Omega}{2} \int_\Omega |\phi(\tau) - \phi_\Omega|^2 \, dx \\
&\quad + \frac{\alpha Q}{2} \int_0^T \int_\Omega |\sigma - \sigma_Q|^2 \, dx \, dt + \frac{\beta S}{2} \int_\Omega (1 + \phi(\tau)) \, dx + \frac{\beta u}{2} \int_0^T \int_\Omega |u|^2 \, dx \, dt + \beta T \tau
\end{align*}
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u \in \mathcal{U}_{\text{ad}} := \{u \in L^\infty(Q) : \ u_{\text{min}} \leq u \leq u_{\text{max}} \ \text{a.e. in} \ Q\}, \quad \tau \in (0, T)
\]
Comments on the cost functional

\[ J(\phi, \sigma, u, \tau) = \frac{\beta_Q}{2} \int_0^T \int_{\Omega} |\phi - \phi_Q|^2 \, dx \, dt + \frac{\beta_\Omega}{2} \int_{\Omega} |\phi(\tau) - \phi_\Omega|^2 \, dx \]

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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, \(\phi_Q\) and \(\sigma_Q\) represent a desired evolution for the tumor cells and for the nutrient, \(\phi_\Omega\) stands for desired final distribution of tumor cells.
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- The first three terms of \( J \) are of standard tracking type and the fourth term of \( J \) measures the size of the tumor at the end of the treatment.
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- The first three terms of \( J \) are of standard tracking type and the fourth term of \( J \) measures the size of the tumor at the end of the treatment
- The fifth term penalizes large concentrations of the cytotoxic drugs, and the sixth term of \( J \) penalizes long treatment times
The choice of $\phi_\Omega$

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 $\phi_\Omega$ in the above optimal control problem (CP).

- For the former case, one can simply take $\phi_\Omega$ 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 $\phi_\Omega$ as a “stable” configuration of the system, so that the tumor does not grow again once the treatment is complete.

For this purpose, we prove that any local minimizer of the total free energy $\mathcal{E}$ is Lyapunov stable provided that $u = 0$. 
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The mathematical difficulties

The study of long-time behavior is nontrivial, since the nonconvexity of the free energy $E$ indicates that the set of steady states may have a rather complicated structure. For the single Cahn-Hilliard equation this difficulty can be overcome by employing the Lojasiewicz-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.,

$$\int_{\Omega} \phi(t) \, dx = \int_{\Omega} \phi_0 \, dx \quad \text{for} \quad t \geq 0.$$ 

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 $\int_{\Omega} \phi(t) \, dx$ is not preserved due to possible reactions, here in our case it is not obvious how to control the mass changing rate:

$$\frac{d}{dt} \int_{\Omega} \phi \, dx = \int_{\Omega} P(\phi)(\sigma - \mu) \, dx.$$ 

Similar problem happens to the nutrient as well, that is

$$\frac{d}{dt} \int_{\Omega} \sigma \, dx = -\int_{\Omega} P(\phi)(\sigma - \mu) \, dx + \int_{\Omega} \mu \, dx.$$
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$$
The problem of mass conservation

The observation that the total mass can be determined by the initial data and the external source:

$$\int_{\Omega} (\phi(t) + \sigma(t)) \, dx = \int_{\Omega} (\phi_0 + \sigma_0) \, dx + \int_{t_0}^{t} \int_{\Omega} u \, dx \, d\tau,$$

allows us to derive a suitable version of the Lojasiewicz-Simon type inequality.

On the other hand, we can control the mass changing rates of $\phi$ and $\sigma$ by using the extra dissipation related to reactive terms in the basic energy law, i.e.,

$$\int_{\Omega} P(\phi)(\mu - \sigma)^2 \, dx.$$

Based on the above mentioned special structure of the system, by introducing a new version of Lojasiewicz-Simon inequality we are able to prove that every global weak solution $(\phi, \sigma)$ 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.

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

- Recently in [MRS: Miraville, R., Schimperna (2018)] we prove the existence of a global attractor for a different model (see Giulio’s talk).
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  2. [GLR: Garcke, Lam, R. (2017)] where a different model is studied. There the distributed control appears in the \( \phi \) equation, which is a Cahn-Hilliard type equation with a source of mass on the right hand side, but not depending on \( \mu \). Due to the presence of the control in the Cahn-Hilliard equation, in [GLR] only the case of a regularized objective cost functional can be analyzed for bounded controls.
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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

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
Well-posedness (cf, [CGRS, Theorem 2.1])
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Let \( \phi_0 \in H_N^2(\Omega) \cap H^3(\Omega) \) 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

\[
|F''_1(s)| \leq \alpha_2, \quad \alpha_3 (1 + |s|^{r-2}) \leq F''_0(s) \leq \alpha_4 (1 + |s|^{r-2}), \quad F(s) \geq \alpha_5 |s| - \alpha_6 \quad \forall s \in \mathbb{R}
\]

(U1) For any \( T > 0 \), \( u \in L^2(0, T; L^2(\Omega)) \).
Well-posedness (cf, [CGRS, Theorem 2.1])

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|F_1''(s)| \leq \alpha_2,
\alpha_3 (1 + |s|^{r-2}) \leq F_0''(s) \leq \alpha_4 (1 + |s|^{r-2}),
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(U1) For any \( T > 0 \), \( u \in L^2(0, T; L^2(\Omega)) \). Then

Theorem (Strong solutions)

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

\[
\| \phi \|_{L^\infty(0, T; H^3(\Omega))} \cap L^2(0, T; H^4(\Omega)) \cap H^1(0, T; H^1(\Omega)) + \| \mu \|_{L^\infty(0, T; H^1(\Omega))} \cap L^2(0, T; H^2(\Omega)) \\
+ \| \sigma \|_{C([0, T]; H^1(\Omega))} \cap L^2(0, T; H_N^2(\Omega)) \cap H^1(0, T; L^2(\Omega)) \leq K_1.
\]
Well-posedness (cf, [CGRS, Theorem 2.1])

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\]

**(U1)** For any \( T > 0 \), \( u \in L^2(0, T; L^2(\Omega)) \). Then

---

**Theorem (Strong solutions)**

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

\[
\begin{align*}
\|\phi\|_{L^\infty(0, T; H^3(\Omega))} + \|\mu\|_{L^\infty(0, T; H^1(\Omega))} + \|\sigma\|_{C([0, T]; H^1(\Omega))} &
\leq K_1.
\end{align*}
\]

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

\[
\begin{align*}
\|\phi_1 - \phi_2\|_{L^\infty(0, T; H^1)} + \|\mu_1 - \mu_2\|_{L^2(0, T; H^1)} + \|\sigma_1 - \sigma_2\|_{C([0, T]; H^1)} &
\leq K_2 \|u_1 - u_2\|_{L^2(0, T; L^2)}.
\end{align*}
\]
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)]
4. Well-posedness
5. Long-term dynamics
6. The optimal control problem
7. Open problems and Perspectives
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

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

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

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 $(\phi, \mu, \sigma)$: $\lim_{t \to +\infty} \left( \|\phi(t) - \phi_\infty\|_{H^2(\Omega)} + \|\sigma(t) - \sigma_\infty\|_{L^2(\Omega)} + \|\mu(t) - \mu_\infty\|_{L^2(\Omega)} \right) = 0$, where $(\phi_\infty, \mu_\infty, \sigma_\infty)$ satisfies the stationary problem

$$\begin{cases} 
-\Delta \phi_\infty + F'(\phi_\infty) = \mu_\infty, & \text{in } \Omega \\
\partial_\nu \phi_\infty = 0, & \text{on } \partial \Omega \\
\int_\Omega (\phi_\infty + \sigma_\infty) \, dx = \int_\Omega (\phi_0 + \sigma_0) \, dx + \int_0^{+\infty} \int_\Omega u \, dx \, dt 
\end{cases}$$

with $\mu_\infty$ and $\sigma_\infty$ 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

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

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

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 \( \Omega; \ \theta \in (0, \frac{1}{2}) \) is a constant depending on \( \phi_\infty \).
An idea of the proof

The proof consists of several steps:

1. We first derive some uniform-in-time a priori estimates on the solution \((φ,µ,σ)\).

2. Then we give a characterization on the \(ω\)-limit \(ω(φ_0,σ_0) = \{(φ_∞,σ_∞) ∈ (H_2(Ω) \cap H_3(Ω)) \times H_1(Ω) : \exists \{t_n\} \uparrow +∞ \text{ such that } (φ(t_n),σ(t_n)) \to (φ_∞,σ_∞) \text{ in } H_2(Ω) \times L_2(Ω)\}.

And we have the following result:

**Theorem (3. The \(ω\)-limit)**

Assume \((P1), (F1), (U2)\). For any initial datum \((φ_0,σ_0) ∈ H_1(Ω) \times L_2(Ω)\), the associated \(ω\)-limit set \(ω(φ_0,σ_0)\) is non-empty. For any element \((φ_∞,σ_∞) ∈ ω(φ_0,σ_0)\), \(σ_∞\) is a constant and \((φ_∞,σ_∞)\) satisfies the stationary problem. Besides, \(µ_∞\) is a constant given by \(|Ω| − 1∫_Ω F′(φ_∞) \, dx\) and the following relation holds \(P(φ_∞)(σ_∞ − µ_∞) = 0\), a.e. in \(Ω\).

And the positivity of \(P\) entails immediately also \(σ_∞ = µ_∞\).
An idea of the proof

The proof consists of several steps:

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An idea of the proof

The proof consists of several steps:

- We first derive some uniform-in-time a priori estimates on the solution \((\phi, \mu, \sigma)\)
- Then we give a characterization on the \(\omega\)-limit

\[
\omega(\phi_0, \sigma_0) = \{ (\phi_\infty, \sigma_\infty) \in (H^2_0(\Omega) \cap H^3(\Omega)) \times H^1(\Omega) : \exists \{t_n\} \searrow +\infty \text{ such that } (\phi(t_n), \sigma(t_n)) \rightarrow (\phi_\infty, \sigma_\infty) \text{ in } H^2(\Omega) \times L^2(\Omega) \}.
\]

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**Theorem (3. The \(\omega\)-limit)**

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

\[
P(\phi_\infty)(\sigma_\infty - \mu_\infty) = 0, \quad \text{a.e. in } \Omega.
\]

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:

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 

\[ m_\infty := |\Omega|^{-1} \left( \int_\Omega (\phi_0 + \sigma_0) \, dx + \int_0^\infty \int_\Omega u \, dx \, dt \right) \]

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 \(\phi_\infty, m_\infty,\) and \(\Omega\), such that for any 

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

\[ \int_\Omega (\phi + \sigma) \, dx + m_u |\Omega| = \int_\Omega (\phi_\infty + \sigma_\infty) \, dx = m_\infty |\Omega|, \]

where \(m_u\) is a certain constant fulfiling 

\[ |m_u| \leq |\Omega|^{-\frac{1}{2}} \|u\|_{L^1(0, +\infty; L^2(\Omega))}. \]

Then we have

\[ \|\mu - \mu_\infty\|_{(H^1(\Omega))'} + C \|\nabla \sigma\|_{L^2(\Omega)} + C \|\sqrt{P(\phi)(\mu - \sigma)}\|_{L^2(\Omega)} + C |m_u|^\frac{1}{2} \geq |E(\phi, \sigma) - E(\phi_\infty, \sigma_\infty)|^\frac{1}{1-\theta}, \]

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

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**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 $\phi_\infty$, $m_\infty$ and $\Omega$, such that for any $(\phi, \sigma) \in H^2_N(\Omega) \times H^1(\Omega)$ satisfying

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

$$\int_\Omega (\phi + \sigma) \, dx + m_u |\Omega| = \int_\Omega (\phi_\infty + \sigma_\infty) \, dx = m_\infty |\Omega|,$$

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

$$\|\mu - \mu_\infty\|_{(H^1(\Omega))'} + C \|\nabla \sigma\|_{L^2(\Omega)} + C \|\sqrt{P(\phi)}(\mu - \sigma)\|_{L^2(\Omega)} + C |m_u|^{\frac{1}{2}}$$

$$\geq |E(\phi, \sigma) - E(\phi_\infty, \sigma_\infty)|^{1-\theta}, \quad \text{where}$$

$$\mu = -\Delta \phi + F'(\phi) \quad \text{and} \quad C > 0 \quad \text{depends on} \quad \Omega, \, \phi_\infty, \, m_\infty, \, \|\phi\|_{H^2(\Omega)}, \, \|\sigma\|_{H^1(\Omega)}, \, \|u\|_{L^1(0, +\infty; L^2(\Omega))}.$$
Energy minimizers with $u = 0$
Let us now assume $u = 0$. Then it follows that the total mass of the system is now conserved:

$$\int_{\Omega} (\phi(t) + \sigma(t)) \, dx = \int_{\Omega} (\phi_0 + \sigma_0) \, dx, \quad \forall \ t \geq 0.$$
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\[
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\]

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

\[
Z_m = \left\{ (\phi, \sigma) \in H^1(\Omega) \times L^2(\Omega) : \int_\Omega (\phi + \sigma) \, dx = |\Omega| m \right\}.
\]
Energy minimizers with \( u = 0 \)

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

\[
\mathcal{Z}_m = \{ (\phi, \sigma) \in H^1(\Omega) \times L^2(\Omega) : \int_{\Omega} (\phi + \sigma) \, dx = |\Omega| m \}.
\]

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

- a **local energy minimizer** of the total energy

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

if there exists a constant \( \chi > 0 \) such that \( E(\phi^*, \sigma^*) \leq E(\phi, \sigma) \), 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 \((\phi^*, \sigma^*)\) is called a **global energy minimizer** of \( E(\phi, \sigma) \) in \( \mathcal{Z}_m \).
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 $(\phi, \mu, \sigma)$:

$$
\begin{cases}
-\Delta \phi + F'(\phi) = \mu, & \text{in } \Omega \\
\partial_{\nu} \phi = 0, & \text{on } \partial \Omega \\
\int_{\Omega} (\phi + \sigma) \, dx = |\Omega| m,
\end{cases}
$$

where $\mu$ and $\sigma$ are constants given by $\sigma = \mu = |\Omega| - 1 \int_{\Omega} F'(\phi) \, dx$.

Theorem (4. Critical points)

Let assumption $(F_1)$ be satisfied. Then we have:

1. If $(\phi^*, \sigma^*) \in H^2_0(\Omega) \times \mathbb{R}$ is a strong solution to the stationary problem above, then $(\phi^*, \sigma^*)$ is a critical point of $\mathcal{E}(\phi, \sigma)$ in $\mathcal{Z}_m$. Conversely, if $(\phi^*, \sigma^*)$ is a critical point of $\mathcal{E}(\phi, \sigma)$ in $\mathcal{Z}_m$, then $\phi^* \in H^2_0(\Omega)$, $\sigma^* \in \mathbb{R}$ satisfy the stationary problem above.

2. If $(\phi^*, \sigma^*)$ is a local energy minimizer of $\mathcal{E}(\phi, \sigma)$ in $\mathcal{Z}_m$, then $(\phi^*, \sigma^*)$ 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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We first derive some properties for the critical points of $E(\phi, \sigma)$ in $\mathcal{Z}_m$. For any given $m \in \mathbb{R}$, we consider the following stationary problem for $(\phi, \mu, \sigma)$

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-\Delta \phi + F'(\phi) = \mu, & \text{in } \Omega, \\
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\end{cases}
$$

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

Theorem (4. Critical points) Let assumption ($F_1$) 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 $(\phi^*, \sigma^*)$ is a critical point of $E(\phi, \sigma)$ in $\mathcal{Z}_m$. Conversely, if $(\phi^*, \sigma^*)$ is a critical point of $E(\phi, \sigma)$ in $\mathcal{Z}_m$, then $\phi^* \in H^2 N(\Omega)$, $\sigma^* \in \mathbb{R}$ satisfy the stationary problem above.

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

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

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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 $(\phi, \mu, \sigma)$

$$
\begin{align*}
-\Delta \phi + F'(\phi) &= \mu, &\text{in } \Omega, \\
\partial_\nu \phi &= 0, &\text{on } \partial\Omega, \\
\int_\Omega (\phi + \sigma) \, dx &= |\Omega| m,
\end{align*}
$$

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

**Theorem (4. Critical points)**

*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 $(\phi^*, \sigma^*)$ is a critical point of $\mathcal{E}(\phi, \sigma)$ in $\mathcal{Z}_m$. Conversely, if $(\phi^*, \sigma^*)$ 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.

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

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\begin{cases}
-\Delta \phi + F'(\phi) = \mu, & \text{in } \Omega, \\
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**Theorem (4. Critical points)**

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

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**Theorem (4. Critical points)**

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

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

$$
\mathcal{E}(\phi^*, \sigma^*) = \inf_{(\phi, \sigma) \in \mathcal{Z}_m} \mathcal{E}(\phi, \sigma)
$$
Lyapunov Stability with $u = 0$
Lyapunov Stability with $u = 0$

Then, we can get our main result on long-term dynamics:
Lyapunov Stability with $u = 0$

Then, we can get our main result on long-term dynamics:

**Theorem (5. Lyapunov stability)**

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

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

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

$$
\int_{\Omega} (\phi_0 + \sigma_0) \, dx = |\Omega| m \quad \text{and} \quad \|\phi_0 - \phi^*\|_{H^1(\Omega)} + \|\sigma_0 - \sigma^*\|_{L^2(\Omega)} \leq \eta,
$$

the state system admits a unique global strong solution $(\phi, \sigma)$ such that

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

Namely, any local energy minimizer of $\mathcal{E}(\phi, \sigma)$ in $\mathcal{Z}_m$ is locally Lyapunov stable.
Lyapunov Stability with $u = 0$

Then, we can get our main result on long-term dynamics:

**Theorem (5. Lyapunov stability)**

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

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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 $\int_{\Omega} (\phi_0 + \sigma_0) \, dx = |\Omega|m$ and $\|\phi_0 - \phi^*\|_{H^1(\Omega)} + \|\sigma_0 - \sigma^*\|_{L^2(\Omega)} \leq \eta$, the state system admits a unique global strong solution $(\phi, \sigma)$ such that

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

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 \((\phi^*, \sigma^*)\) is an isolated local energy minimizer then it is locally asymptotic stable.
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)]


4. Well-posedness

5. Long-term dynamics

6. The optimal control problem

7. Open problems and Perspectives
Assumptions for the optimal control problem

In this section we study the optimal control problem

(CP) \textit{Minimize the cost functional}

\[ J(\phi, \sigma, u, \tau) = \frac{\beta_Q}{2} \int_0^\tau \int_\Omega |\phi - \phi_Q|^2 \, dx \, dt + \frac{\beta_\Omega}{2} \int_\Omega |\phi(\tau) - \phi_\Omega|^2 \, dx \]
\[ + \frac{\alpha_Q}{2} \int_0^\tau \int_\Omega |\sigma - \sigma_Q|^2 \, dx \, dt + \frac{\beta_S}{2} \int_\Omega (1 + \phi(\tau)) \, dx + \frac{\beta_u}{2} \int_0^T \int_\Omega |u|^2 \, dx \, dt + \beta_T \tau \]

subject to the state system and the the control constraint

\[ u \in \mathcal{U}_{ad} := \{ u \in L^\infty(Q) : u_{\text{min}} \leq u \leq u_{\text{max}} \text{ a.e. in } Q \}, \quad \tau \in (0, T), \]
Assumptions for the optimal control problem

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\[(CP) \quad \text{Minimize the cost functional} \]

\[
\mathcal{J}(\phi, \sigma, u, \tau) = \frac{\beta_Q}{2} \int_0^\tau \int_\Omega |\phi - \phi_Q|^2 \, dx \, dt + \frac{\beta_\Omega}{2} \int_\Omega |\phi(\tau) - \phi_\Omega|^2 \, dx \\
+ \frac{\alpha_Q}{2} \int_0^\tau \int_\Omega |\sigma - \sigma_Q|^2 \, dx \, dt + \frac{\beta_S}{2} \int_\Omega (1 + \phi(\tau)) \, dx + \frac{\beta_u}{2} \int_0^T \int_\Omega |u|^2 \, dx \, dt + \beta_T \tau
\]

subject to the state system and the control constraint

\[u \in U_{\text{ad}} := \{u \in L^\infty(Q) : u_{\text{min}} \leq u \leq u_{\text{max}} \text{ a.e. in } Q\}, \quad \tau \in (0, T),\]

where \(T \in (0, +\infty)\) is a fixed maximal time. We assume:
Assumptions for the optimal control problem

In this section we study the optimal control problem

\[
\text{(CP) Minimize the cost functional}
\]

\[
\mathcal{J}(\varphi, \sigma, u, \tau) = \frac{\beta_Q}{2} \int_0^\tau \int_\Omega |\varphi - \varphi_Q|^2 \, dx \, dt + \frac{\beta_\Omega}{2} \int_\Omega |\varphi(\tau) - \varphi_\Omega|^2 \, dx
\]

\[
+ \frac{\alpha_Q}{2} \int_0^\tau \int_\Omega |\sigma - \sigma_Q|^2 \, dx \, dt + \frac{\beta_S}{2} \int_\Omega (1 + \varphi(\tau)) \, dx + \frac{\beta_u}{2} \int_0^\tau \int_\Omega |u|^2 \, dx \, dt + \beta_T \tau
\]

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

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

(C1) \(\beta_Q, \beta_\Omega, \beta_S, \beta_u, \beta_T, \alpha_Q\) are nonnegative constants but not all zero.

(C2) \(\varphi_Q, \sigma_Q \in L^2(Q), \varphi_\Omega, \sigma_\Omega \in L^2(\Omega), u_{\text{min}}, u_{\text{max}} \in L^\infty(Q),\) and \(u_{\text{min}} \leq u_{\text{max}}, \) a.e. in \(Q\).

(C3) Let \(\mathcal{U}_R\) be an open set in \(L^2(Q)\): \(\mathcal{U}_{\text{ad}} \subset \mathcal{U}_R\) and \(\|u\|_{L^2(Q)} \leq R,\) for all \(u \in \mathcal{U}_R.\)
Existence of an optimal control

From the well-posedness results it follows that the control-to-state operator
\[ S : u \mapsto (\phi, \mu, \sigma) := (\phi, \mu, \sigma) \]
\[ \text{is well-defined and Lipschitz continuous as a mapping from} \]
\[ U \subset L^2 \rightarrow \text{the following space} \]
\[ (L^\infty (0, T; (H^1(\Omega))) \cap L^2 (0, T; H^1(\Omega))) \times L^2 (0, T; (H^1(\Omega))) \times (L^\infty (0, T; (H^1(\Omega))) \cap L^2 (\Omega))) \].

The triplet \((\phi, \mu, \sigma)\) is the unique weak solution to the state system with data \((\phi_0, \sigma_0, u)\) over the time interval \([0, T]\). For convenience, we use the notations \(\phi = S_1(u)\) and \(\sigma = S_3(u)\) for the first and third component of \(S(u)\).

Then we prove the following result that implies the existence of a solution to problem \((CP)\).

**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,
\[ \phi^* = S_1(u^*), \sigma^* = S_3(u^*) \]
\[ s.t. \phi = S_1(w), \sigma = S_3(w) \]
\[ J(\phi, \sigma, w, s) = \inf_{(w, s) \in U_{ad} \times [0, T]} J(w, s). \]
Existence of an optimal control

From the well-posedness results it follows that the control-to-state operator $S$ 

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

is well-defined and Lipschitz continuous as a mapping from $U_R \subset L^2(Q)$ 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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Namely, $\phi_* = S_1(u_*)$, $\sigma_* = S_3(u_*)$ satisfy

$$J(\phi_*, \sigma_*, u_*, \tau_*) = \inf_{(w, s) \in U_{ad} \times [0, T]} J(\phi, \sigma, w, s).$$

s.t. $\phi = S_1(w), \sigma = S_3(w)$.
Differentiability of the control-to-state map

We establish then the Fréchet differentiability of the solution operator $S$ with respect to the control $u$.

For $u^* \in U$, let $(\phi^*, \mu^*, \sigma^*) = S(u^*)$. We consider for any $h \in L^2(Q)$ the linearized system

\begin{align*}
\partial_t \xi - \Delta \eta &= P'(\phi^*)(\sigma^* - \mu^*)\xi + P(\phi^*)(\rho - \eta), \\
\partial_t \rho - \Delta \rho &= -P'(\phi^*)(\sigma^* - \mu^*)\xi - P(\phi^*)(\rho - \eta) + h \partial_n \xi = \partial_n \eta = \partial_n \rho = 0, \\
\xi(0) = \rho(0) &= 0.
\end{align*}

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 $S$ with respect to $u$.

Assume $(P1), (F1), (U1), (C1)–(C3)$, let $\phi_0 \in H^2_N(\Omega) \cap H^3(\Omega)$ and $\sigma_0 \in H^1(\Omega)$. Then the control-to-state operator $S$ is Fréchet differentiable in $U$ as a mapping from $L^2(Q)$ into $Y := (H^1(0, T; (H^2_N(\Omega))') \cap L^\infty(0, T; L^2(\Omega)) \cap L^2(0, T; H^2_N(\Omega))) \times L^2(Q) \times (H^1(0, T; L^2(\Omega)) \cap L^2(0, T; H^2(\Omega)))$.

For any $u^* \in U$, the Fréchet derivative $D_S(u^*) \in L(L^2(Q), Y)$ is defined as follows: for any $h \in L^2(Q)$, $D_S(u^*)h = (\xi_h, \eta_h, \rho_h)$, where $(\xi_h, \eta_h, \rho_h)$ is the unique solution to the linearized system associated with $h$. 

E. Rocca (Università degli Studi di Pavia)

Diffuse interface models of tumor growth

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\[
\mathcal{Y} := \left( H^1(0, T; (H^2_N(\Omega))') \right) \cap \left( L^\infty(0, T; L^2(\Omega)) \cap L^2(0, T; H^2_N(\Omega)) \right) \times L^2(Q)
\]

\[
\times \left( H^1(0, T; L^2(\Omega)) \cap L^2(0, T; H^2(\Omega)) \right).
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\]

\[
\times \left( H^1(0, T; L^2(\Omega)) \cap L^2(0, T; H^2(\Omega)) \right).
\]

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

First order optimality conditions

Define a reduced functional

\[ \tilde{J}(u, \tau) := J(S_1(u), S_3(u), u, \tau). \]

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

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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

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

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

$$
\partial_n p = \partial_n q = \partial_n r = 0, \quad r(\tau_*) = 0, \quad p(\tau_*) = \beta_\Omega (\phi_* (\tau_*) - \phi_\Omega) + \frac{\beta s}{2}
$$

has a unique weak solution $(p, q, r)$ on $[0, \tau_*]$: $p \in H^1(0, \tau_*; (H^2_N(\Omega))') \cap C^0([0, \tau_*]; L^2(\Omega)) \cap L^2(0, \tau_*; H^2_N(\Omega))$, $q \in L^2(\Omega \times (0, \tau_*))$, $r \in H^1(0, \tau_*; L^2(\Omega)) \cap C^0([0, \tau_*]; H^1(\Omega)) \cap L^2(0, \tau_*; H^2_N(\Omega))$. 

E. Rocca (Università degli Studi di Pavia)
Theorem (Necessary optimality conditions)

Let \((u^\ast, \tau^\ast) \in U_{ad} \times [0, T]\) denote a minimizer to the optimal control problem \((CP)\) with corresponding state variables \((\phi^\ast, \mu^\ast, \sigma^\ast) = S(u^\ast)\) and associated adjoint variables \((p, q, r)\), then it holds:

\[
\beta u \int_0^T \int_\Omega u^\ast (u - u^\ast) \, dx \, dt + \int_0^{\tau^\ast} \int_\Omega r (u - u^\ast) \, dx \, dt \geq 0, \quad \forall u \in U_{ad}.
\]

Besides, setting

\[
L(\phi^\ast, \sigma^\ast, \tau^\ast) = \beta Q^2 \int_\Omega |\phi^\ast(\tau^\ast) - \phi Q(\tau^\ast)|^2 \, dx + \beta S^2 \int_\Omega \partial_t \phi^\ast(\tau^\ast) \, dx + \beta T
\]

we have

\[
L(\phi^\ast, \sigma^\ast, \tau^\ast) \begin{cases} 
\geq 0, & \text{if } \tau^\ast = 0, \\
= 0, & \text{if } \tau^\ast \in (0, T), \\
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Theorem (Necessary optimality conditions)

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

\[
\beta_u \int_0^T \int_{\Omega} u_*(u - u_*) \, dx \, dt + \int_0^{\tau_*} \int_{\Omega} r(u - u_*) \, dx \, dt \geq 0, \quad \forall u \in \mathcal{U}_{ad}.
\]

Besides, setting

\[
\mathcal{L}(\phi_*, \sigma_*, \tau_*) = \frac{\beta Q^2}{2} \int_{\Omega} |\phi_*(\tau_*) - \phi Q(\tau_*)|^2 \, dx + \beta \Omega \int_{\Omega} (\phi_*(\tau_*) - \phi \Omega) \partial_t \phi_*(\tau_*) \, dx + \frac{\alpha Q^2}{2} \int_{\Omega} |\sigma_*(\tau_*) - \sigma Q(\tau_*)|^2 \, dx + \frac{\beta S}{2} \int_{\Omega} \partial_t \phi_*(\tau_*) \, dx + \beta T
\]

we have

\[
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\geq 0, & \text{if } \tau_* = 0, \\
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\leq 0, & \text{if } \tau_* = T. 
\end{cases}
\]
Interpretation of the first condition

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

$$
\beta_u \int_0^T \int_\Omega u_*(u - u_*) \, dx \, dt + \int_0^{\tau_*} \int_\Omega r(u - u_*) \, dx \, dt \geq 0, \quad \forall u \in U_{ad}.
$$

as

$$
\int_0^T \int_\Omega (\beta_u u_* + r)(u - u_*) \, dx \, dt \geq 0, \quad \forall u \in U_{ad},
$$

which allows the interpretation that the optimal control $u_*$ is the $L^2(Q)$-projection of $-\beta_u^{-1} r$ onto the set $U_{ad}$ (provided that $\beta_u > 0$).
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)]
4. Well-posedness
5. Long-term dynamics
6. The optimal control problem
7. Open problems and Perspectives
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 $L^\infty$-sense rather than in the $L^2$-sense or to include a pointwise state constraint on $\phi$: $|\phi(x, \tau) - \phi_\Omega| \leq \epsilon$ for a.e. $x \in \Omega$. This leads to a more involved adjoint system.
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P1. To study the existence of attractors for different models:
   - with A. Miranville and G. Schimperna for a model proposed by Garcke at al. (cf. Giulio’s talk),
   - with A. Giorgini, K.-F. Lam, and G. Schimperna for a model proposed by Lowengrub et al. including velocities.

P2. The study of optimal control: for a prostate model introduced by H. Gomez et al. and proposed to us by G. Lorenzo and A. Reali (with P. Colli and G. Marinoschi).

P3. To add the mechanics in Lagrangean coordinates in a multiphase model: for example considering the tumor sample as a porous media (with P. Krejčí and J. Sprekels).

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).
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Many thanks to all of you for the attention!
Preliminaries

Def. $B_0$ is an absorbing set for a semigroup $S(t)$ on a metric space $(X, d_X)$ iff

- $B_0$ is bdd
- $\forall B \subset X$ bdd $\exists T_B \geq 0$ s.t. $S(t)B \subset B_0 \quad \forall t \geq T_B$.

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 $B_0$;
- $\forall B \subset X$ 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

$$\mathcal{A} = \bigcap_{\tau \geq 0} \bigcup_{t \geq \tau} S(t)B_0.$$