On the long time behavior of a tumor growth model

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joint works with Cecilia Cavaterra (Milano), Hao Wu (Fudan), and Alain Miranville (Poitiers)-Giulio Schimperna (Pavia)

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Outline

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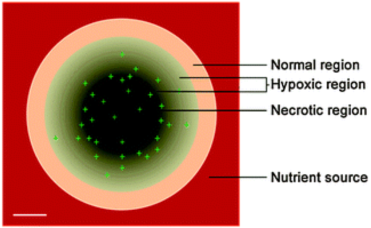
Setting

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



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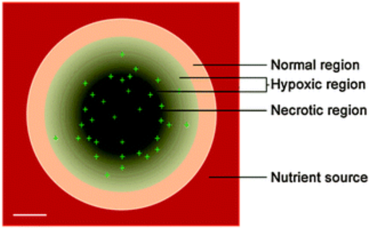

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- sharp interfaces are replaced by narrow transition layers arising due to adhesive forces among the cell species: a diffuse interface separates tumor and healthy cell regions
- proliferating tumor cells surrounded by (healthy) host cells, and a nutrient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

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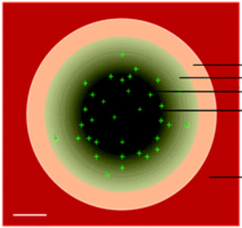

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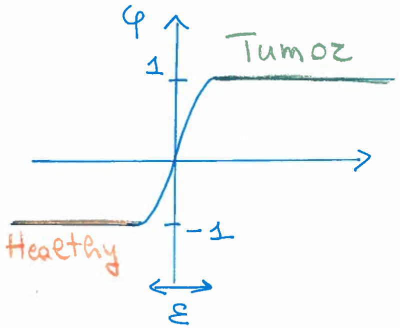
We investigate the long-time dynamics and optimal control problem of a two-phase diffuse interface model that describes the growth of a tumor in presence of a nutrient and surrounded by host tissues.

Diffuse interfaces



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

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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, 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.

Outline

Long-time dynamics and optimal control of a diffuse interface model for tumor growth: joint work with C. Cavaterra and H. Wu (preprint arXiv:1901.07500, 2019)

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- The state system consists of a Cahn-Hilliard type equation for the tumor cell fraction and a reaction-diffusion equation for the nutrient
- The possible medication that serves to eliminate tumor cells is in terms of drugs and is introduced into the system through the nutrient
- 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.

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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

The state system: Cahn–Hilliard + nutrient model with source terms

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The PDE system is an approximation of the model proposed in [HZO: A. Hawkins-Daarud, K.-G. van der Zee and J.-T. Oden (2011)] in $Q := \Omega \times (0, T)$:

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

subject to initial and boundary conditions

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

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- The state variables are:
  - the tumor cell fraction ϕ: $\phi \simeq 1$ (tumorous phase), $\phi \simeq -1$ (healthy tissue phase)
  - the nutrient concentration σ: $\sigma \simeq 1$ 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 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.

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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.

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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
- The first three terms of $\mathcal{J}$ are of standard tracking type and the fourth term of $\mathcal{J}$ 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 $\mathcal{J}$ 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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- 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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- 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

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  2. [GLR: Garcke, Lam, R. (2017)] where a different diffuse interface model is studied. There the distributed control appears in the ϕ equation, which is a Cahn-Hilliard type equation with a source of mass on the right hand side, but not depending on μ. 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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With our work we aim to provide a contribution to the theory of free terminal time optimal control in the context of diffuse interface tumor models, 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:

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(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

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

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

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

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:

$$\int_\Omega (\phi(t) + \sigma(t))\,\mathrm{d}x = \int_\Omega (\phi_0 + \sigma_0)\,\mathrm{d}x, \quad \forall\, t \geq 0.$$

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

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

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

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

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Theorem (4. Critical points)

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

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(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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Theorem (5. Lyapunov stability)

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

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

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

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

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

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 $\mathcal{S}(u)$. 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,* $\phi_* = \mathcal{S}_1(u_*)$, $\sigma_* = \mathcal{S}_3(u_*)$ *satisfy*

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

Differentiability of the control-to-state map

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

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$$
\begin{aligned}
&\partial_t \xi - \Delta \eta = P'(\phi_*)(\sigma_* - \mu_*)\,\xi + P(\phi_*)(\rho - \eta), \qquad \eta = -\Delta \xi + F''(\phi_*)\,\xi, \\
&\partial_t \rho - \Delta \rho = -P'(\phi_*)(\sigma_* - \mu_*)\,\xi - P(\phi_*)(\rho - \eta) + h \\
&\partial_{\mathrm{n}} \xi = \partial_{\mathrm{n}} \eta = \partial_{\mathrm{n}} \rho = 0, \qquad \xi(0) = \rho(0) = 0.
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$$\partial_{\mathrm{n}}\xi = \partial_{\mathrm{n}}\eta = \partial_{\mathrm{n}}\rho = 0, \qquad \xi(0) = \rho(0) = 0.$$

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

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$$\times \Big(H^1(0,T;L^2(\Omega)) \cap L^2(0,T;H^2(\Omega))\Big).$$

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 $\mathcal{U}_R$.

First order optimality conditions

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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

Necessary optimality conditions

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

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

Interpretation of the first condition

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

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

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

Long-time behavior for a different model – joint work with A. Miranville and G. Schimperna, arXiv:1810.12239v1 (2018)

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We consider here the long time dynamics for the following model for tumor growth:

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&\varphi_t - \Delta\mu = (\mathcal{P}\sigma - \mathcal{A})h(\varphi),\\
&\mu = -\Delta\varphi + \Psi'(\varphi),\\
&\sigma_t - \Delta\sigma = -\mathcal{C}\sigma h(\varphi) + B(\sigma_s - \sigma),
\end{aligned}
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settled in $\Omega \times (0, +\infty)$, and complemented with the Cauchy conditions and with no-flux (i.e., homogeneous Neumann) boundary conditions for all unknowns.

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settled in $\Omega \times (0, +\infty)$, and complemented with the Cauchy conditions and with no-flux (i.e., homogeneous Neumann) boundary conditions for all unknowns.

- 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
- The constant σ_s denotes the nutrient concentration in a pre-existing vasculature, and $B(\sigma_s - \sigma)$ models the supply of nutrient from the blood vessels if $\sigma_s > \sigma$ and the transport of nutrient away from the domain Ω if $\sigma_s < \sigma$.

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

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The model was introduced in [Chen, Wise, Shenoy, Lowengrub (2014)] and the in [Garcke, Lam, Sitka, Styles (2016)] in a more general framework.

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We prove that, under physically motivated assumptions on parameters and data,

- the corresponding initial-boundary value problem generates a dissipative dynamical system
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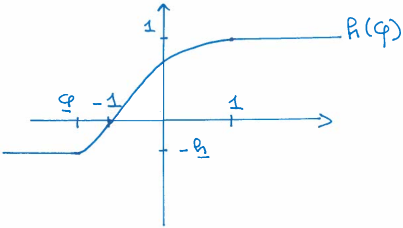
We prove that, under physically motivated assumptions on parameters and data,

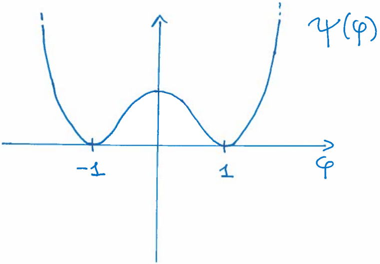
- the corresponding initial-boundary value problem generates a dissipative dynamical system
- that admits the global attractor in a proper phase space.

The main difference with respect to the previous model is that here we do not have the total energy baance we had before. Here we only have

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{1}{2}\|\nabla\varphi\|^2 + \int_\Omega \Psi(\varphi)\,\mathrm{d}x\right) + \|\nabla\mu\|^2 = \int_\Omega (\mathcal{P}\sigma - \mathcal{A})h(\varphi)\mu\,\mathrm{d}x.$$

Examples of functions h and Ψ





The basic assumptions on the potential

The configuration potential Ψ lies in $C^{1,1}_{\text{loc}}(\mathbb{R})$. Moreover its derivative is decomposed as a sum of a monotone part β and a linear perturbation:

$$\Psi'(r) = \beta(r) - \lambda r, \quad \lambda \geq 0, \; r \in \mathbb{R}.$$

We normalized so that $\beta(0) = 0$ and further β complies with the growth condition

$$\exists\, c_\beta > 0 : \; |\beta(r)| \leq c_\beta(1 + \Psi(r)) \; \forall r \in \mathbb{R},$$

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In order to prove uniqueness of solutions we also need that there exists $c > 0$ such that

$$|\beta(r) - \beta(s)| \leq c|r - s|\big(1 + |\beta(r)| + |\beta(s)|\big) \quad \forall r, s \in \mathbb{R}.$$

Note that this is still consistent with asking an at most exponential growth of β.

Assumptions on the function h and on the coefficients

The coefficients are assumed to satisfy $\mathcal{P}, \mathcal{A}, B, \mathcal{C} > 0$, $\sigma_c \in (0, 1)$.

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Remark

The function $h(\varphi)$ is assumed to satisfy $h(-1) = 0$ and $h(1) = 1$. The simplest situation when this occurs is the "symmetric" case when we have $\underline{h} = 0$ and $\underline{\varphi} = -1$. On the other hand we will see in what follows that dissipativity of trajectories may not hold in such a case. This motivates our choice to consider the possibility of having $\underline{h} > 0$.

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Remark

We could also take $h(\varphi) = k\varphi + h_0(\varphi)$, where $k > 0$ and h_0 is smooth and uniformly bounded. This situation is somehow simpler because, at least as long as we can guarantee that $\mathcal{P}\sigma - \mathcal{A} > 0$, the linear part of h drives some mass dissipation effect in the Cahn-Hilliard type equation $\varphi_t - \Delta\mu = (\mathcal{P}\sigma - \mathcal{A})h(\varphi)$.

Outline

We assume the initial data to satisfy

$$\sigma_0 \in L^\infty(\Omega), \qquad 0 \le \sigma_0 \le 1 \text{ a.e. in } \Omega,$$
$$\varphi_0 \in H^1(\Omega), \qquad \Psi(\varphi_0) \in L^1(\Omega).$$

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Theorem (Well-posedness)

Then the tumor-growth model

$$\varphi_t - \Delta\mu = (\mathcal{P}\sigma - \mathcal{A})h(\varphi), \quad \varphi(0) = \varphi_0, \quad \partial_n \varphi = 0 \text{ on } \partial\Omega,$$
$$\mu = -\Delta\varphi + \Psi'(\varphi), \quad \partial_n \mu = 0 \text{ on } \partial\Omega,$$
$$\sigma_t - \Delta\sigma = -\mathcal{C}\sigma h(\varphi) + B(\sigma_s - \sigma), \quad \sigma(0) = \sigma_0, \quad \partial_n \sigma = 0 \text{ on } \partial\Omega$$

admits one and only one global in time weak solution:

$$\varphi \in H^1(0,T;H^1(\Omega)') \cap C^0([0,T];H^1(\Omega)) \cap L^2(0,T;H^2(\Omega)),$$
$$\beta(\varphi) \in L^2(0,T;L^2(\Omega)), \quad \mu \in L^2(0,T;H^1(\Omega)),$$
$$\sigma \in H^1(0,T;H^1(\Omega)') \cap C^0([0,T];L^2(\Omega)) \cap L^2(0,T;H^1(\Omega)) \cap L^\infty(0,T;L^\infty(\Omega));$$

Moreover, for any $T > 0$ there exists $\overline{\sigma}_T \ge 1$ such that

$$0 \le \sigma(t,x) \le \overline{\sigma}_T, \quad \text{for a.e. } (t,x) \in (0,T) \times \Omega,$$

where we can take $\overline{\sigma}_T$ independent of time if $B - \mathcal{C}\underline{h} > 0$ and $\overline{\sigma}_T = 1$ if $\underline{h} = 0$.

Outline

Assumptions for dissipativity

Let the parameters in

$$\varphi_t - \Delta\mu = (\mathcal{P}\sigma - \mathcal{A})h(\varphi),$$
$$\mu = -\Delta\varphi + \Psi'(\varphi),$$
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satisfy (where $h(r) \equiv -\underline{h}$ for all $r \leq \underline{\varphi} \leq -1$)

$$(H1) \quad \underline{h} > 0, \qquad B - \mathcal{C}\underline{h} > 0,$$
$$(H2) \quad \frac{B\sigma_s}{B - \mathcal{C}\underline{h}} < 1,$$
$$(H3) \quad \mathcal{A} - \mathcal{P}\frac{B\sigma_s}{B - \mathcal{C}\underline{h}} > 0.$$

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$$(H3) \quad \mathcal{A} - \mathcal{P}\frac{B\sigma_s}{B - \mathcal{C}\underline{h}} > 0.$$

These conditions essentially prescribe $\underline{h}$ to be *strictly positive*, but *small*.

Assumptions for dissipativity

Let the parameters in

$$\varphi_t - \Delta\mu = (\mathcal{P}\sigma - \mathcal{A})h(\varphi),$$
$$\mu = -\Delta\varphi + \Psi'(\varphi),$$
$$\sigma_t - \Delta\sigma = -\mathcal{C}\sigma h(\varphi) + B(\sigma_s - \sigma),$$

satisfy (where $h(r) \equiv -\underline{h}$ for all $r \leq \underline{\varphi} \leq -1$)

$$(H1) \quad \underline{h} > 0, \qquad B - \mathcal{C}\underline{h} > 0,$$
$$(H2) \quad \frac{B\sigma_s}{B - \mathcal{C}\underline{h}} < 1,$$
$$(H3) \quad \mathcal{A} - \mathcal{P}\frac{B\sigma_s}{B - \mathcal{C}\underline{h}} > 0.$$

These conditions essentially prescribe $\underline{h}$ to be *strictly positive*, but *small*.

Let also β have a superquadratic behavior at infinity, namely

$$\exists\, \kappa_\beta > 0, C_\beta \geq 0, p_\beta > 2 : \ \beta(r)\,\mathrm{sign}\, r \geq \kappa_\beta |r|^{p_\beta} - C_\beta \ \forall r \in \mathbb{R}.$$

The spatially homogeneous case: (H1)

Starting from spatially homogeneous initial data we reduce to the following ODE system:

$$X' + (\mathcal{A} - \mathcal{P}S)h(X) = 0,$$
$$S' + \mathcal{C}Sh(X) + B(S - \sigma_s) = 0$$

where $X = X(t)$ and $S = S(t)$ are the spatial mean values of φ and σ.

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If $\mathcal{C}\underline{h} \geq B$, i.e. H1) ii) does not hold and $X(0) << 0$, $S(0) >> 0$ (in such a way that $\mathcal{P}S - \mathcal{A} > 0$), then it follows

$$X' = -(\mathcal{P}S - \mathcal{A})\underline{h} < 0,$$
$$S' = B\sigma_s + (\mathcal{C}\underline{h} - B)S > 0$$

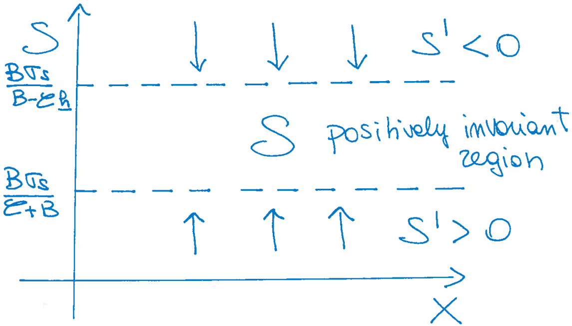
and both $|X|$ and S go increasing forever. Even if we restrict ourselves to $S(0) \leq 1$, if $X(0) < -1$ then the physical constraint $S(t) \in [0, 1]$ is not respected.

The spatially homogeneous case: (H2)

Assume $(H1)$: $\underline{h} > 0$, $B - \mathcal{C}\underline{h} > 0$. Then, the region

$\mathcal{S} := \left\{ (X, S) : \frac{B\sigma_s}{\mathcal{C} + B} \leq S \leq \frac{B\sigma_s}{B - \mathcal{C}\underline{h}} \right\}$ is positively invariant for the dynamical process

because $B\sigma_s - (\mathcal{C} + B)S \leq S' \leq B\sigma_s - (B - \mathcal{C}\underline{h})S$:



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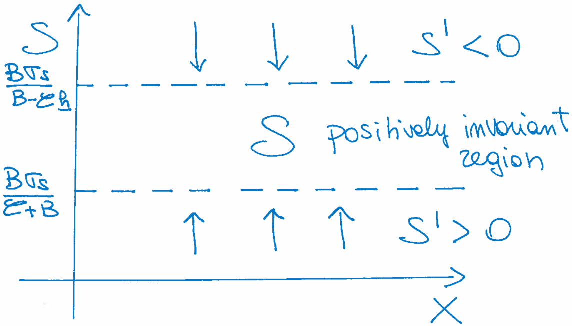


Now, if we want to keep the physical constraint $S(t) \in [0, 1]$, we need to assume

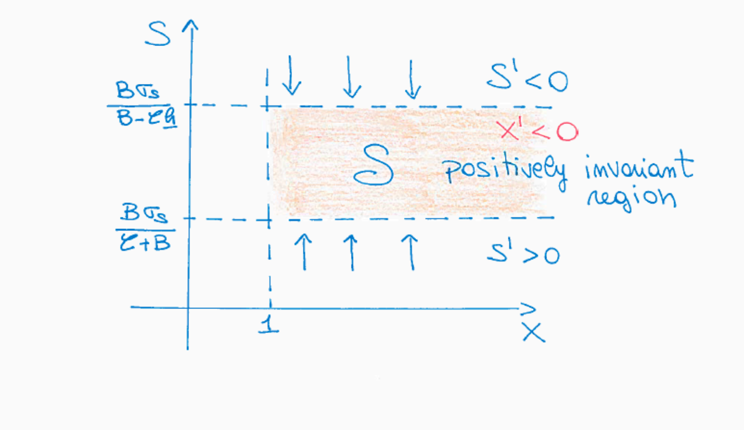
$$(H2) : \qquad \frac{B\sigma_s}{B - \mathcal{C}\underline{h}} < 1$$

The spatially homogeneous case: (H3)

Let us assume that $X(0) > 1$, which also implies $h(X) = 1$. Then, we have:

$$X' = (\mathcal{P}S - \mathcal{A})$$

and condition (H3): $\frac{\mathcal{A}}{\mathcal{P}} > \frac{B\sigma_s}{B-\mathcal{C}\underline{h}}$ prescribes that in $\mathcal{S} \cap \{X > 1\}$ we have $X' < 0$:



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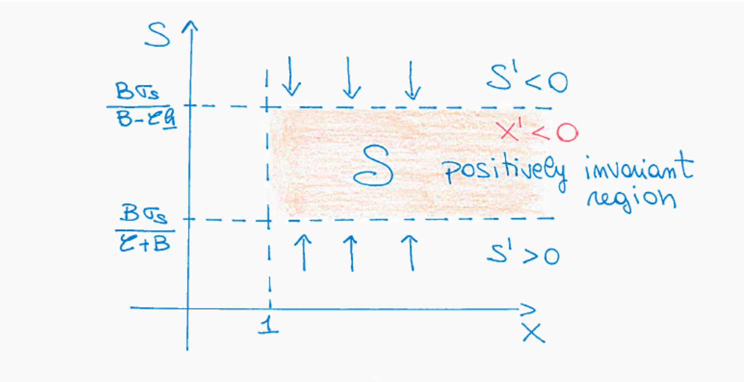

On the other hand when $\frac{\mathcal{A}}{\mathcal{P}} \leq \frac{B\sigma_s}{B+\mathcal{C}}$, dissipativity cannot hold. Indeed if $S(0) \in \left[\frac{B\sigma_s}{\mathcal{C}+B}, \frac{B\sigma_s}{B-\mathcal{C}\underline{h}}\right]$ and $X(0) \geq 1$, then $X(t)$ is forced to increase forever ($X' > 0$).

Dissipativity and Attractor

We can define the "energy space"

$$\mathcal{X} := \left\{(\varphi, \sigma) \in H^1(\Omega) \times L^\infty(\Omega) : \ \Psi(\varphi) \in L^1(\Omega)\right\}$$

and we correspondingly introduce the "magnitude" of an element $(\varphi, \sigma) \in \mathcal{X}$ as

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Theorem (Dissipativity)

Under the previous compatibility conditions, there exists a positive constant C_0 independent of the initial data and a time T_0 depending only on the $\mathcal{X}$-magnitude of the initial data such that any weak solution satisfies

$$\|(\varphi(t), \sigma(t))\|_{\mathcal{X}} \leq C_0 \quad \textit{for every } \ t \geq T_0.$$

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Theorem (Existence of the Attractor)

Under the previous compatibility conditions the dynamical system generated by weak trajectories on the phase space $\mathcal{X}$ admits the global attractor $\mathcal{A}$. More precisely, $\mathcal{A}$ is a relatively compact subset of $\mathcal{X}$ which is also bounded in $H^2(\Omega) \times H^1(\Omega)$ and uniformly attracts the trajectories emanating from any bounded set $\mathcal{B} \subset \mathcal{X}$.

Outline

Open problems and Perspectives

0. Open problem: 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: $|\phi(x,\tau) - \phi_\Omega| \leq \epsilon$ for a.e. $x \in \Omega$, which could be reduced to $\|\phi(x,\tau) - \phi_\Omega\|_{L^2(\Omega)} \leq \epsilon$ by using possible regularity of ϕ (if available). This leads to a more involved adjoint system...

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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 (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

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