Diffuse interface models of tumor growth: optimal control and other issues

E. Rocca

Università degli Studi di Pavia

4-6 décembre 2017 – Laboratoire Jacques-Louis Lions

First meeting of the French-German-Italian LIA COPDESC on Applied Analysis

joint works with Harald Garcke (Regensburg)-Kei Fong Lam (Hong-Kong)

and Sergio Frigeri (Brescia)-Kei Fong Lam (Hong-Kong)-Giulio Schimperna (Pavia)

fondazione cariplo

Regione Lombardia

Fondazione Cariplo and Regione Lombardia Grant MEGAsTaR 2016-2019

Outline

Outline

Setting

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

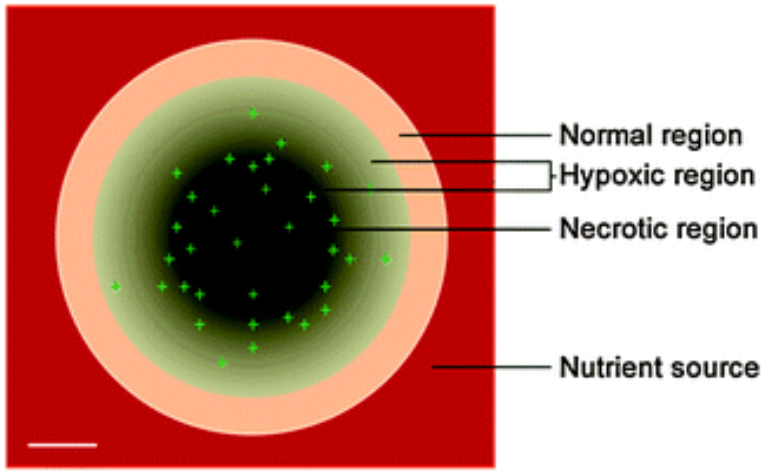

Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100μm = 0:1mm

Setting

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

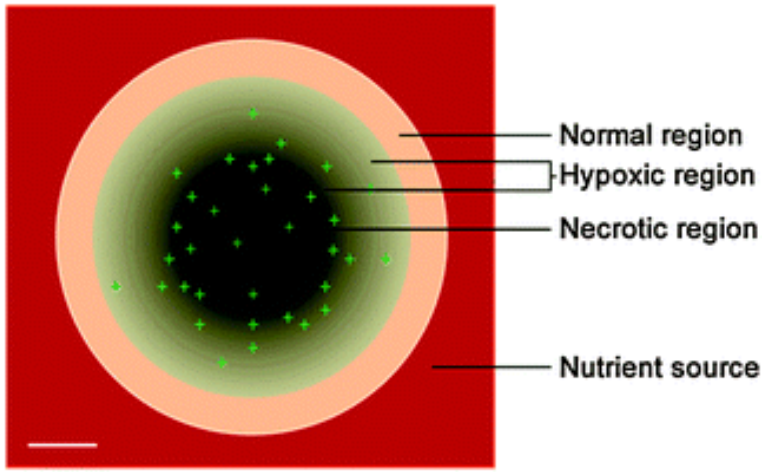

Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100μm = 0:1mm

A continuum thermodynamically consistent model is introduced with the ansatz:

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

Advantages of diffuse interfaces in tumor growth models

Sharp interfaces $\Longrightarrow$ narrow transition layers in which tumor and healthy cells are mixed

Advantages of diffuse interfaces in tumor growth models

Sharp interfaces $\Longrightarrow$ narrow transition layers in which tumor and healthy cells are mixed

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

Advantages of diffuse interfaces in tumor growth models

Sharp interfaces $\Longrightarrow$ narrow transition layers in which tumor and healthy cells are mixed

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

- it eliminates the need to enforce complicated boundary conditions across the tumor/host tissue and other species/species interfaces;
- it eliminates the need to explicitly track the position of interfaces, as is required in the sharp interface framework;
- the mathematical description remains valid even when the tumor undergoes toplogical changes (e.g. metastasis)

Optimization over the treatment time: H. Garcke, K.F. Lam, E. Rocca, Applied Mathematics & Optimization, 2017

Optimization over the treatment time: H. Garcke, K.F. Lam, E. Rocca, Applied Mathematics & Optimization, 2017

Common treatment for tumors are

- Chemotheraphy
- Radiation therapy
- Surgery

Optimization over the treatment time: H. Garcke, K.F. Lam, E. Rocca, Applied Mathematics & Optimization, 2017

Common treatment for tumors are

- Chemotheraphy
- Radiation therapy
- Surgery

For treatment involving drugs, the patient is given several doses of drugs over a few days, followed by a rest period of 3 - 4 weeks, and the cycle is repeated. Goal is to shrink the tumor into a more manageable size for which surgery can be applied.

Optimization over the treatment time: H. Garcke, K.F. Lam, E. Rocca, Applied Mathematics & Optimization, 2017

Common treatment for tumors are

- Chemotheraphy
- Radiation therapy
- Surgery

For treatment involving drugs, the patient is given several doses of drugs over a few days, followed by a rest period of 3 - 4 weeks, and the cycle is repeated. Goal is to shrink the tumor into a more manageable size for which surgery can be applied.

Unfortunately, cytotoxic drugs also harms the healthy host tissues, and can accumulate in the body. Furthermore, drug clearance may also cause damage to various vital organs (e.g. kidneys and liver).

Optimization over the treatment time: H. Garcke, K.F. Lam, E. Rocca, Applied Mathematics & Optimization, 2017

Common treatment for tumors are

- Chemotheraphy
- Radiation therapy
- Surgery

For treatment involving drugs, the patient is given several doses of drugs over a few days, followed by a rest period of 3 - 4 weeks, and the cycle is repeated. Goal is to shrink the tumor into a more manageable size for which surgery can be applied.

Unfortunately, cytotoxic drugs also harms the healthy host tissues, and can accumulate in the body. Furthermore, drug clearance may also cause damage to various vital organs (e.g. kidneys and liver).

Worst case scenario: Cytotoxins may have cancer-causing effects, and tumor cells can mutate to become resistant to the drug.

Optimization over the treatment time: H. Garcke, K.F. Lam, E. Rocca, Applied Mathematics & Optimization, 2017

Common treatment for tumors are

- Chemotheraphy
- Radiation therapy
- Surgery

For treatment involving drugs, the patient is given several doses of drugs over a few days, followed by a rest period of 3 - 4 weeks, and the cycle is repeated. Goal is to shrink the tumor into a more manageable size for which surgery can be applied.

Unfortunately, cytotoxic drugs also harms the healthy host tissues, and can accumulate in the body. Furthermore, drug clearance may also cause damage to various vital organs (e.g. kidneys and liver).

Worst case scenario: Cytotoxins may have cancer-causing effects, and tumor cells can mutate to become resistant to the drug.

Thus, aside from optimising the drug distribution, we should also consider optimising the treatment time.

Cahn–Hilliard + nutrient models with source terms

The simplest phase field model is a Cahn–Hilliard system with source terms for φ: the difference in volume fractions ($\varphi = 1$: tumor phase, $\varphi = -1$: healthy tissue phase):

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

Cahn–Hilliard + nutrient models with source terms

The simplest phase field model is a Cahn–Hilliard system with source terms for φ: the difference in volume fractions ($\varphi = 1$: tumor phase, $\varphi = -1$: healthy tissue phase):

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

The source term $\mathcal{M}$ accounts for biological mechanisms related to proliferation and death.

Cahn–Hilliard + nutrient models with source terms

The simplest phase field model is a Cahn–Hilliard system with source terms for φ: the difference in volume fractions ($\varphi = 1$: tumor phase, $\varphi = -1$: healthy tissue phase):

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

The source term $\mathcal{M}$ accounts for biological mechanisms related to proliferation and death. Introduce a Reaction-diffusion equation for the nutrient proportion σ:

$$\partial_t \sigma = \Delta \sigma - \mathcal{S}$$

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

Cahn–Hilliard + nutrient models with source terms

The simplest phase field model is a Cahn–Hilliard system with source terms for φ: the difference in volume fractions ($\varphi = 1$: tumor phase, $\varphi = -1$: healthy tissue phase):

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

The source term $\mathcal{M}$ accounts for biological mechanisms related to proliferation and death. Introduce a Reaction-diffusion equation for the nutrient proportion σ:

$$\partial_t \sigma = \Delta \sigma - \mathcal{S}$$

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

- In [Chen, Wise, Shenoy, Lowengrub (2014)], [Garcke, Lam, Sitka, Styles (2016)]:

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

  Here $h(s)$ is an interpolation function such that $h(-1) = 0$ and $h(1) = 1$, and
  - $h(\varphi)\mathcal{P}\sigma$ - proliferation of tumor cells proportional to nutrient concentration
  - $h(\varphi)\mathcal{A}$ - apoptosis of tumor cells
  - $h(\varphi)\mathcal{C}\sigma$ - consumption of nutrient by the tumor cells
- A regular double-well potential Ψ, e.g., $\Psi(s) = 1/4(1 - s^2)^2$

Outline

State equations

We consider the Cahn–Hilliard + nutrient model with linear kinetics and Neumann boundary conditions:

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

State equations

We consider the Cahn–Hilliard + nutrient model with linear kinetics and Neumann boundary conditions:

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

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

State equations

We consider the Cahn–Hilliard + nutrient model with linear kinetics and Neumann boundary conditions:

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

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
- $h(\varphi)\alpha u$ - elimination of tumor cells by cytotoxic drugs at a constant rate α,
- u acts as a control here. In applications $u : [0, T] \to [0, 1]$ is spatially constant, where $u = 1$ represents full dosage, $u = 0$ represents no dosage

Objective functional

For positive β_T, β_u and non-negative $\beta_Q, \beta_\Omega, \beta_S$, we consider

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

Objective functional

For positive β_T, β_u and non-negative $\beta_Q, \beta_\Omega, \beta_S$, we consider

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

- the variable τ denotes the unknown treatment time to be optimised,
- φ_Q is a desired evolution of the tumor over the treatment,
- φ_Ω is a desired final state of the tumor (stable equilibrium of the system),
- the term $\frac{1+\varphi(\tau)}{2}$ measures the size of the tumor at the end of the treatment,
- the constant β_T penalizes long treatment times.

Objective functional

For positive β_T, β_u and non-negative $\beta_Q, \beta_\Omega, \beta_S$, we consider

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

- the variable τ denotes the unknown treatment time to be optimised,
- φ_Q is a desired evolution of the tumor over the treatment,
- φ_Ω is a desired final state of the tumor (stable equilibrium of the system),
- the term $\frac{1+\varphi(\tau)}{2}$ measures the size of the tumor at the end of the treatment,
- the constant β_T penalizes long treatment times.

Expectation: An optimal control will be a pair (u_*, τ_*) and we will obtain two optimality conditions.

Regarding the terms appearing in the cost functional

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

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

Regarding the terms appearing in the cost functional

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

- A large value of $|\varphi - \varphi_Q|^2$ would mean that the patient suffers from the growth of the tumor, and a large value of $|u|^2$ would mean that the patient suffers from high toxicity of the drug;
- The function φ_Ω can be a stable configuration of the system, so that the tumor does not grow again once the treatment is completed or a configuration which is suitable for surgery;

Regarding the terms appearing in the cost functional

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

- A large value of $|\varphi - \varphi_Q|^2$ would mean that the patient suffers from the growth of the tumor, and a large value of $|u|^2$ would mean that the patient suffers from high toxicity of the drug;
- The function φ_Ω can be a stable configuration of the system, so that the tumor does not grow again once the treatment is completed or a configuration which is suitable for surgery;
- The variable τ can be regarded as the treatment time of one cycle, i.e., the amount of time the drug is applied to the patient before the period of rest, or the treatment time before surgery;

Regarding the terms appearing in the cost functional

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

- A large value of $|\varphi - \varphi_Q|^2$ would mean that the patient suffers from the growth of the tumor, and a large value of $|u|^2$ would mean that the patient suffers from high toxicity of the drug;
- The function φ_Ω can be a stable configuration of the system, so that the tumor does not grow again once the treatment is completed or a configuration which is suitable for surgery;
- The variable τ can be regarded as the treatment time of one cycle, i.e., the amount of time the drug is applied to the patient before the period of rest, or the treatment time before surgery;
- It is possible to replace $\beta_T \tau$ by a more general function $f(\tau)$ where $f : \mathbb{R}^+ \to \mathbb{R}^+$ is continuously differentiable and increasing.

Relaxed objective functional

However, we will not study the functional

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

but a relaxed version - in order to keep a control u just bounded without requiring more regularity

Relaxed objective functional

However, we will not study the functional

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

but a relaxed version - in order to keep a control u just bounded without requiring more regularity

Let $r > 0$ be fixed and let $T \in (0, \infty)$ denote a fixed maximal time in which the patient is allowed to undergo a treatment, we define

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

Relaxed objective functional

Let $r > 0$ be fixed and let $T \in (0, \infty)$ denote a maximal time, we define

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

Relaxed objective functional

Let $r > 0$ be fixed and let $T \in (0, \infty)$ denote a maximal time, we define

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

The optimal control problem is

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

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

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

Well-posedness of state equations

Theorem

Let $\varphi_0 \in H^3, \sigma_0 \in H^1$ with $0 \leq \sigma_0 \leq 1$, $h \in C^{0,1}(\mathbb{R}) \cap L^\infty(\mathbb{R})$ non-negative, and Ψ is a quartic potential, then for every $u \in \mathcal{U}_{\rm ad}$ there exists a unique triplet

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

satisfying the state equations.

Well-posedness of state equations

Theorem

Let $\varphi_0 \in H^3, \sigma_0 \in H^1$ with $0 \leq \sigma_0 \leq 1$, $h \in C^{0,1}(\mathbb{R}) \cap L^\infty(\mathbb{R})$ non-negative, and Ψ is a quartic potential, then for every $u \in \mathcal{U}_{\rm ad}$ there exists a unique triplet

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

satisfying the state equations.

Key points:

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

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

  and it is an essential ingredient for the existence proof
- Proof utilises a Schauder fixed point argument

Existence of a minimiser

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

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

Existence of a minimiser

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

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

- Minimising sequence $(u_n,\tau_n) \in \mathcal{U}_{\text{ad}} \times (0,T)$, with corresponding state variables $(\varphi_n,\mu_n,\sigma_n)$ such that

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

Existence of a minimiser

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

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

- Minimising sequence $(u_n,\tau_n) \in \mathcal{U}_{\rm ad}\times(0,T)$, with corresponding state variables $(\varphi_n,\mu_n,\sigma_n)$ such that

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

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

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

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

Existence of a minimiser

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

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

- Minimising sequence $(u_n,\tau_n) \in \mathcal{U}_{\mathrm{ad}} \times (0,T)$, with corresponding state variables $(\varphi_n,\mu_n,\sigma_n)$ such that

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

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

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

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

Existence of minimiser

To pass to the limit in:

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

Existence of minimiser

To pass to the limit in:

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

we make use of

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

to obtain

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

Existence of minimiser

To pass to the limit in:

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

we make use of

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

to obtain

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

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

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

That is, (u_*, τ_*) is a minimiser.

Outline

Fréchet differentiability with respect to the control

We set $\mathcal{S}(u) = (\varphi, \mu, \sigma)$ as the solution operator on the interval $[0, T]$, and introduce the linearized state variables $(\Phi^w, \Xi^w, \Sigma^w)$ corresponding to w as solutions to

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

with Neumann boundary conditions and zero initial conditions.

Fréchet differentiability with respect to the control

We set $\mathcal{S}(u) = (\varphi, \mu, \sigma)$ as the solution operator on the interval $[0, T]$, and introduce the linearized state variables $(\Phi^w, \Xi^w, \Sigma^w)$ corresponding to w as solutions to

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

with Neumann boundary conditions and zero initial conditions.

Theorem

For any $w \in L^2(Q)$ there exists a unique triplet (Φ, Ξ, Σ) with

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

and

$$\|\Phi\|_{\mathbb{X}_1} + \|\Xi\|_{\mathbb{X}_2} + \|\Sigma\|_{\mathbb{X}_3} \leq C\|w\|_{L^2(Q)}$$

Fréchet differentiability with respect to the control

We set $\mathcal{S}(u) = (\varphi, \mu, \sigma)$ as the solution operator on the interval $[0, T]$, and introduce the linearized state variables $(\Phi^w, \Xi^w, \Sigma^w)$ corresponding to w as solutions to

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

with Neumann boundary conditions and zero initial conditions.

Expectation: The Fréchet derivative of $\mathcal{S}$ at $u \in \mathcal{U}_{\mathrm{ad}}$ in the direction w is

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

Fréchet differentiability with respect to the control

We set $\mathcal{S}(u) = (\varphi, \mu, \sigma)$ as the solution operator on the interval $[0, T]$, and introduce the linearized state variables $(\Phi^w, \Xi^w, \Sigma^w)$ corresponding to w as solutions to

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

with Neumann boundary conditions and zero initial conditions.

Expectation: The Fréchet derivative of $\mathcal{S}$ at $u \in \mathcal{U}_{\mathrm{ad}}$ in the direction w is

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

Theorem

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

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

Fréchet differentiability with respect to the control

We set $\mathcal{S}(u) = (\varphi, \mu, \sigma)$ as the solution operator on the interval $[0, T]$, and introduce the linearized state variables $(\Phi^w, \Xi^w, \Sigma^w)$ corresponding to w as solutions to

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

with Neumann boundary conditions and zero initial conditions.

Expectation: The Fréchet derivative of $\mathcal{S}$ at $u \in \mathcal{U}_{\mathrm{ad}}$ in the direction w is

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

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

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

Fréchet differentiability with respect to time

For

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

we have

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

Fréchet differentiability with respect to time

For

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

we have

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

Note that the control u does not appear explicitly.

First order optimality conditions

Introducing the adjoint system

$$
\begin{aligned}
-\partial_t p &= \Delta q + \Psi''(\varphi_*)q - \mathcal{C}h'(\varphi_*)\sigma_* r + h'(\varphi_*)(\mathcal{P}\sigma_* - \mathcal{A} - \alpha u_*)p \\
&\quad + \beta_Q(\varphi_* - \varphi_Q) + \frac{1}{2r}\chi_{(\tau_* - r, \tau_*)}(t)(2\beta_\Omega(\varphi_* - \varphi_\Omega) + \beta_S), \\
q &= \Delta p, \\
-\partial_t r &= \Delta r - \mathcal{C}h(\varphi_*)r + \mathcal{P}h(\varphi_*)p
\end{aligned}
$$

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

First order optimality conditions

Introducing the adjoint system

$$
\begin{aligned}
-\partial_t p &= \Delta q + \Psi''(\varphi_*)q - \mathcal{C}h'(\varphi_*)\sigma_* r + h'(\varphi_*)(\mathcal{P}\sigma_* - \mathcal{A} - \alpha u_*)p \\
&\quad + \beta_Q(\varphi_* - \varphi_Q) + \frac{1}{2r}\chi_{(\tau_* - r, \tau_*)}(t)(2\beta_\Omega(\varphi_* - \varphi_\Omega) + \beta_S), \\
q &= \Delta p, \\
-\partial_t r &= \Delta r - \mathcal{C}h(\varphi_*)r + \mathcal{P}h(\varphi_*)p
\end{aligned}
$$

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

Theorem

There exists a unique (p, q, r) to the adjoint system such that

$$
\begin{aligned}
&p \in L^2(0, \tau_*; H^2) \cap H^1(0, \tau_*; (H^2)^*) \cap L^\infty(0, \tau_*; L^2) \cap C^0([0, \tau_*]; L^2), \\
&q \in L^2(0, \tau_*; L^2), \\
&r \in L^2(0, \tau_*; H^2) \cap L^\infty(0, \tau_*; H^1) \cap H^1(0, \tau_*; L^2) \cap C^0([0, \tau_*]; L^2).
\end{aligned}
$$

First order optimality conditions

Introducing the adjoint system

$$
\begin{aligned}
-\partial_t p &= \Delta q + \Psi''(\varphi_*)q - \mathcal{C}h'(\varphi_*)\sigma_* r + h'(\varphi_*)(\mathcal{P}\sigma_* - \mathcal{A} - \alpha u_*)p \\
&\quad + \beta_Q(\varphi_* - \varphi_Q) + \frac{1}{2r}\chi_{(\tau_*-r,\tau_*)}(t)(2\beta_\Omega(\varphi_* - \varphi_\Omega) + \beta_S), \\
q &= \Delta p, \\
-\partial_t r &= \Delta r - \mathcal{C}h(\varphi_*)r + \mathcal{P}h(\varphi_*)p
\end{aligned}
$$

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

Theorem

The optimal control (u_*, τ_*) *satisfy*

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

and

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

Issues with the original functional

To deal with the original functional:

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

Issues with the original functional

To deal with the original functional:

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

Then, the optimality condition for τ_* is

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

Issues with the original functional

To deal with the original functional:

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

Then, the optimality condition for τ_* is

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

Issues: For the above expression to be well-defined, we need

$$\partial_{tt} \varphi_* \in L^2(0, T; L^2), \quad u_* \in H^1(0, T; L^2).$$

Issues with the original functional

To deal with the original functional:

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

Then, the optimality condition for τ_* is

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

Issues: For the above expression to be well-defined, we need

$$\partial_{tt} \varphi_* \in L^2(0, T; L^2), \quad u_* \in H^1(0, T; L^2).$$

If we define $\mathcal{U}_{\mathrm{ad}} = \{u \in H^1(0, T; L^2) : 0 \le u \le 1, \|\partial_t u\|_{L^2(Q)} \le K\}$ for fixed $K > 0$, and impose $\varphi_0 \in H^5$, $\sigma_0 \in H^3$, then we get $\varphi \in H^2(0, T; L^2) \cap W^{1,\infty}(0, T; H^1)$.

However, to require the a-priori boundedness of $\partial_t u$ is difficult to verify in applications.

Other control-type results

- SMC. In [Colli, Gilardi, Marinoschi, E.R., Appl Math Optim, to appear] we introduce a sliding mode control (SMC) law $\varrho\,\mathrm{sign}(\varphi - \varphi^*)$ in the chemical potential which forces the system to reach within finite time the sliding manifold (that we chose in order that the tumor phase remains constant in time $\varphi \equiv \varphi^*$)

Other control-type results

- SMC. In [Colli, Gilardi, Marinoschi, E.R., Appl Math Optim, to appear] we introduce a sliding mode control (SMC) law $\varrho\,\mathrm{sign}(\varphi - \varphi^*)$ in the chemical potential which forces the system to reach within finite time the sliding manifold (that we chose in order that the tumor phase remains constant in time $\varphi \equiv \varphi^*$)
- Different sources. In the phase field model we introduced

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

we can choose different form of $\mathcal{M}$ and $\mathcal{S}$: linear phenomenological laws for chemical reactions cf. [Hawkins–Daarud, Prudhomme, van der Zee, Oden (2012)], [Frigeri, Grasselli, E.R. (2015)]:

$$\mathcal{M} = \mathcal{S} = h(\varphi)(\sigma - \mu)$$

Other control-type results

- SMC. In [Colli, Gilardi, Marinoschi, E.R., Appl Math Optim, to appear] we introduce a sliding mode control (SMC) law $\varrho\,\mathrm{sign}(\varphi - \varphi^*)$ in the chemical potential which forces the system to reach within finite time the sliding manifold (that we chose in order that the tumor phase remains constant in time $\varphi \equiv \varphi^*$)
- Different sources. In the phase field model we introduced

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

we can choose different form of $\mathcal{M}$ and $\mathcal{S}$: linear phenomenological laws for chemical reactions cf. [Hawkins–Daarud, Prudhomme, van der Zee, Oden (2012)], [Frigeri, Grasselli, E.R. (2015)]:

$$\mathcal{M} = \mathcal{S} = h(\varphi)(\sigma - \mu)$$

In [Colli, Gilardi, E.R., Sprekels, Nonlinearity (2017)]: the optimal control with respect to the drug distribution which acts as a control in the nutrient equation

Outline

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

Typical structure of tumors grown in vitro:

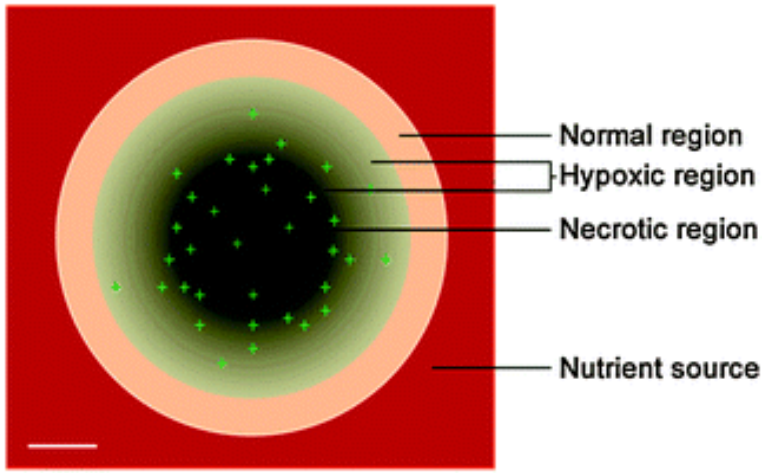

Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100μm $=$ 0:1mm

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

Typical structure of tumors grown in vitro:

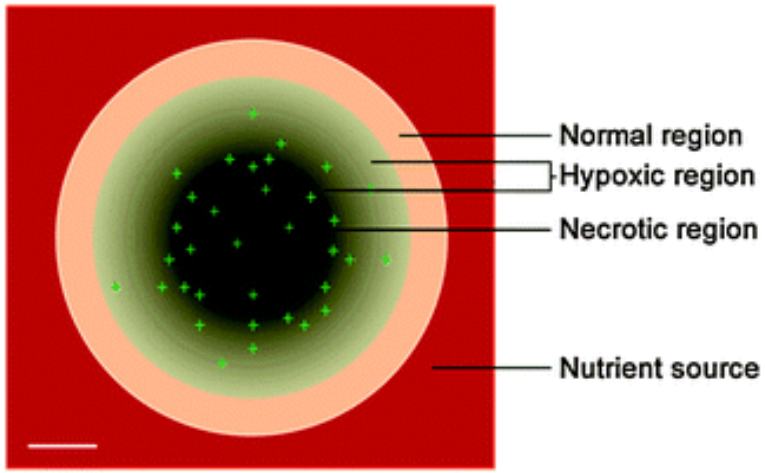

Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100μm = 0:1mm

A continuum thermodynamically consistent model is introduced with the ansatz:

- sharp interfaces are replaced by narrow transition layers arising due to adhesive forces among the cell species: a diffuse interface separates tumor and healthy cell regions
- proliferating and dead tumor cells and healthy cells are present, along with a nutrient (e.g. glucose or oxigene)
- tumor cells are regarded as inertia-less fluids: include the velocity - satisfying a Darcy type law with Korteveg term

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

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

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

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

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

- $\varphi_p, \varphi_d, \varphi_h \in [0,1]$: the volume fractions of the cells:
  - φ_p: proliferating tumor cell fraction
  - φ_d: dead tumor cell fraction
  - φ_h: healthy cell fraction
- The variables above are naturally constrained by the relation $\varphi_p + \varphi_d + \varphi_h = 1$ hence it suffices to track the evolution of φ_p and φ_d and the vector $\boldsymbol{\varphi} := (\varphi_p, \varphi_d)^\top$ lies in the simplex $\Delta := \{\boldsymbol{y} \in \mathbb{R}^2 : \ 0 \leq y_1, y_2, \ y_1 + y_2 \leq 1\} \subset \mathbb{R}^2$

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

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

- $\varphi_p, \varphi_d, \varphi_h \in [0,1]$: the volume fractions of the cells:
  - φ_p: proliferating tumor cell fraction
  - φ_d: dead tumor cell fraction
  - φ_h: healthy cell fraction
- The variables above are naturally constrained by the relation $\varphi_p + \varphi_d + \varphi_h = 1$ hence it suffices to track the evolution of φ_p and φ_d and the vector $\boldsymbol{\varphi} := (\varphi_p, \varphi_d)^\top$ lies in the simplex $\Delta := \{\boldsymbol{y} \in \mathbb{R}^2 : \ 0 \leq y_1, y_2, \ y_1 + y_2 \leq 1\} \subset \mathbb{R}^2$
- n: the nutrient concentration (it was σ before)

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

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

- $\varphi_p, \varphi_d, \varphi_h \in [0,1]$: the volume fractions of the cells:
  - φ_p: proliferating tumor cell fraction
  - φ_d: dead tumor cell fraction
  - φ_h: healthy cell fraction
- The variables above are naturally constrained by the relation $\varphi_p + \varphi_d + \varphi_h = 1$ hence it suffices to track the evolution of φ_p and φ_d and the vector $\boldsymbol{\varphi} := (\varphi_p, \varphi_d)^\top$ lies in the simplex $\Delta := \{\boldsymbol{y} \in \mathbb{R}^2 : \ 0 \leq y_1, y_2, \ y_1 + y_2 \leq 1\} \subset \mathbb{R}^2$
- n: the nutrient concentration (it was σ before)
- $\boldsymbol{u} := \boldsymbol{u}_i, i = 1,2,3$: the tissue velocity field. We treat the tumor and host cells as inertial-less fluids and assume that the cells are tightly packed and they march together
- q: the cell-to-cell pressure

FLRS: the balance law

Letting $\boldsymbol{J}_i$, $i \in \{p, d, h\}$, denote the mass fluxes for the cells, then the general balance law for the volume fractions reads as

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

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

FLRS: the balance law

Letting $\boldsymbol{J}_i$, $i \in \{p, d, h\}$, denote the mass fluxes for the cells, then the general balance law for the volume fractions reads as

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

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

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

$$E(\varphi_p, \varphi_d) := \int_\Omega F(\varphi_p, \varphi_d) + \frac{1}{2} |\nabla \varphi_p|^2 + \frac{1}{2} |\nabla \varphi_d|^2 \, dx$$

FLRS: the balance law

Letting $\boldsymbol{J}_i$, $i \in \{p, d, h\}$, denote the mass fluxes for the cells, then the general balance law for the volume fractions reads as

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

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

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

$$E(\varphi_p, \varphi_d) := \int_\Omega F(\varphi_p, \varphi_d) + \frac{1}{2} |\nabla \varphi_p|^2 + \frac{1}{2} |\nabla \varphi_d|^2 \, dx$$

where $F = F_0 + F_1$ is a multi-well configuration potential, e.g.

$$F_0(\varphi_p, \varphi_d) := \varphi_p \log \varphi_p + \varphi_d \log \varphi_d + (1 - \varphi_p - \varphi_d) \log(1 - \varphi_p - \varphi_d)$$

$$F_1(\varphi_p, \varphi_d) := \frac{\chi}{2} (\varphi_d(1 - \varphi_d) + \varphi_p(1 - \varphi_p) + (1 - \varphi_d - \varphi_p)(\varphi_d + \varphi_p))$$

FLRS: the balance law

Letting $\boldsymbol{J}_i$, $i \in \{p, d, h\}$, denote the mass fluxes for the cells, then the general balance law for the volume fractions reads as

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

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

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

$$E(\varphi_p, \varphi_d) := \int_\Omega F(\varphi_p, \varphi_d) + \frac{1}{2} |\nabla \varphi_p|^2 + \frac{1}{2} |\nabla \varphi_d|^2 \, dx$$

where $F = F_0 + F_1$ is a multi-well configuration potential, e.g.

$$F_0(\varphi_p, \varphi_d) := \varphi_p \log \varphi_p + \varphi_d \log \varphi_d + (1 - \varphi_p - \varphi_d) \log(1 - \varphi_p - \varphi_d)$$

$$F_1(\varphi_p, \varphi_d) := \frac{\chi}{2} (\varphi_d(1 - \varphi_d) + \varphi_p(1 - \varphi_p) + (1 - \varphi_d - \varphi_p)(\varphi_d + \varphi_p))$$

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

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

FLRS: the velocity and nutrient evolutions

We set $\boldsymbol{J}_h = -\boldsymbol{J}_p - \boldsymbol{J}_d$, then upon summing up the three mass balances for $i = p, d, h$, using the fact that $\varphi_p + \varphi_d + \varphi_h = 1$ and $S_h = 0$, we deduce the following relation:

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

The velocity field $\boldsymbol{u}$ is assumed to fulfill Darcy's law:

$$\boldsymbol{u} = -\nabla q - \varphi_p \nabla \mu_p - \varphi_d \nabla \mu_d$$

where q denotes the cell-to-cell pressure and the subsequent two terms have the meaning of Korteweg forces

FLRS: the velocity and nutrient evolutions

We set $\boldsymbol{J}_h = -\boldsymbol{J}_p - \boldsymbol{J}_d$, then upon summing up the three mass balances for $i = p, d, h$, using the fact that $\varphi_p + \varphi_d + \varphi_h = 1$ and $S_h = 0$, we deduce the following relation:

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

The velocity field $\boldsymbol{u}$ is assumed to fulfill Darcy's law:

$$\boldsymbol{u} = -\nabla q - \varphi_p \nabla \mu_p - \varphi_d \nabla \mu_d$$

where q denotes the cell-to-cell pressure and the subsequent two terms have the meaning of Korteweg forces

Since the time scale of nutrient diffusion is much faster (minutes) than the rate of cell proliferation (days), the nutrient is assumed to evolve quasi-statically:

$$0 = -\Delta n + \varphi_p n$$

where $\varphi_p n$ models consumption by the proliferating tumor cells

The goal and the main difficulties of FLRS

Goal: to study this multispecies model including different mobilities, singular potential and non-Dirichlet b.c.s on the chemical potential. The main problems are:

The goal and the main difficulties of FLRS

Goal: to study this multispecies model including different mobilities, singular potential and non-Dirichlet b.c.s on the chemical potential. The main problems are:

- we have two different Cahn-Hilliard equations with non-zero right hand sides: $\partial_t \varphi_i - \mathrm{div}(M_i \nabla \mu_i - \varphi_i \boldsymbol{u}) = S_i$ and if we do not choose the Dirichlet b.c.s on μ_i then we need to estimate the mean values of $\mu_i = -\Delta \varphi_i + F_{,\varphi_i}$ containing a multiwell logarithmic type potential F_0

The goal and the main difficulties of FLRS

Goal: to study this multispecies model including different mobilities, singular potential and non-Dirichlet b.c.s on the chemical potential. The main problems are:

- we have two different Cahn-Hilliard equations with non-zero right hand sides: $\partial_t \varphi_i - \mathrm{div}(M_i \nabla \mu_i - \varphi_i \boldsymbol{u}) = S_i$ and if we do not choose the Dirichlet b.c.s on μ_i then we need to estimate the mean values of $\mu_i = -\Delta \varphi_i + F_{,\varphi_i}$ containing a multiwell logarithmic type potential F_0
- we need the mean values of φ_i (the proliferating and dead cells phases) to be away from the potential bareers $\Longrightarrow$ ad hoc estimate based on ODEs technique

The goal and the main difficulties of FLRS

Goal: to study this multispecies model including different mobilities, singular potential and non-Dirichlet b.c.s on the chemical potential. The main problems are:

- we have two different Cahn-Hilliard equations with non-zero right hand sides: $\partial_t \varphi_i - \mathrm{div}(M_i \nabla \mu_i - \varphi_i \boldsymbol{u}) = S_i$ and if we do not choose the Dirichlet b.c.s on μ_i then we need to estimate the mean values of $\mu_i = -\Delta \varphi_i + F_{,\varphi_i}$ containing a multiwell logarithmic type potential F_0
- we need the mean values of φ_i (the proliferating and dead cells phases) to be away from the potential bareers $\Longrightarrow$ ad hoc estimate based on ODEs technique
- indeed, integrating the equations for φ_p and φ_d we obtain an evolution law for the mean values $y_i := \frac{1}{|\Omega|} \int_\Omega \varphi_i \, dx$ for $i = p, d$

The goal and the main difficulties of FLRS

Goal: to study this multispecies model including different mobilities, singular potential and non-Dirichlet b.c.s on the chemical potential. The main problems are:

- we have two different Cahn-Hilliard equations with non-zero right hand sides: $\partial_t \varphi_i - \mathrm{div}(M_i \nabla \mu_i - \varphi_i \boldsymbol{u}) = S_i$ and if we do not choose the Dirichlet b.c.s on μ_i then we need to estimate the mean values of $\mu_i = -\Delta \varphi_i + F_{,\varphi_i}$ containing a multiwell logarithmic type potential F_0
- we need the mean values of φ_i (the proliferating and dead cells phases) to be away from the potential bareers $\Longrightarrow$ ad hoc estimate based on ODEs technique
- indeed, integrating the equations for φ_p and φ_d we obtain an evolution law for the mean values $y_i := \frac{1}{|\Omega|} \int_\Omega \varphi_i \, dx$ for $i = p, d$
- such a relation does not involve directly the singular part F_0. Hence, the evolution of y_p, y_d are not automatically compatible with the physical constraint and this has to be proved by assuming proper conditions on coefficients and making a careful choice of the boundary conditions

The goal and the main difficulties of FLRS

Goal: to study this multispecies model including different mobilities, singular potential and non-Dirichlet b.c.s on the chemical potential. The main problems are:

- we have two different Cahn-Hilliard equations with non-zero right hand sides: $\partial_t \varphi_i - \mathrm{div}(M_i \nabla \mu_i - \varphi_i \boldsymbol{u}) = S_i$ and if we do not choose the Dirichlet b.c.s on μ_i then we need to estimate the mean values of $\mu_i = -\Delta \varphi_i + F_{,\varphi_i}$ containing a multiwell logarithmic type potential F_0
- we need the mean values of φ_i (the proliferating and dead cells phases) to be away from the potential bareers $\Longrightarrow$ ad hoc estimate based on ODEs technique
- indeed, integrating the equations for φ_p and φ_d we obtain an evolution law for the mean values $y_i := \frac{1}{|\Omega|} \int_\Omega \varphi_i \, dx$ for $i = p, d$
- such a relation does not involve directly the singular part F_0. Hence, the evolution of y_p, y_d are not automatically compatible with the physical constraint and this has to be proved by assuming proper conditions on coefficients and making a careful choice of the boundary conditions
- the choice $(M_i \nabla \mu_i - \varphi_i \boldsymbol{u}) \cdot \boldsymbol{n} = 0$ seems essential

FLRS: The weak notion of solution

Definition. $(\varphi_p, \varphi_d, \boldsymbol{u}, q, n)$ is a weak solution to the problem in $(0,T)\times\Omega$ if the previous equations hold, for a.e. $t \in (0,T)$ and for $i = p, d$, in the following weak sense:

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

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

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

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

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

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

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

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

Moreover, there hold the initial conditions

$$\varphi_p(x,0) = \varphi_{p,0}(x), \quad \varphi_d(x,0) = \varphi_{d,0}(x) \quad \text{a.e. in } \Omega,$$

where $\langle \cdot, \cdot \rangle$ denotes the duality pairing between $H^1(\Omega)$ and its dual $H^1(\Omega)'$.

FLRS: Assumptions on the mass sources and on the initial data

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

FLRS: Assumptions on the mass sources and on the initial data

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

Assumption on the mass sources:

- Σ is globally Lipschitz and

FLRS: Assumptions on the mass sources and on the initial data

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

Assumption on the mass sources:

- Σ is globally Lipschitz and
- that there exist a closed and sufficiently regular subset Δ_0 contained in the open simplex Δ and constants $K_{p,-}, K_{p,+}, K_{d,-}, K_{d,+} \in \mathbb{R}$, with $K_{p,-} \leq K_{p,+}$ and $K_{d,-} \leq K_{d,+}$, such that $\Sigma(\mathbb{R}^3) \subset [K_{p,-}, K_{p,+}] \times [K_{d,-}, K_{d,+}]$
- for any $\boldsymbol{x} = (x_p, x_d) \in [K_{p,-}, K_{p,+}] \times [K_{d,-}, K_{d,+}]$, there holds

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

where $\boldsymbol{n}$ denotes the outer unit normal vector to Δ_0

FLRS: Assumptions on the mass sources and on the initial data

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

Assumption on the mass sources:

- Σ is globally Lipschitz and
- that there exist a closed and sufficiently regular subset Δ_0 contained in the open simplex Δ and constants $K_{p,-}, K_{p,+}, K_{d,-}, K_{d,+} \in \mathbb{R}$, with $K_{p,-} \leq K_{p,+}$ and $K_{d,-} \leq K_{d,+}$, such that $\Sigma(\mathbb{R}^3) \subset [K_{p,-}, K_{p,+}] \times [K_{d,-}, K_{d,+}]$
- for any $\boldsymbol{x} = (x_p, x_d) \in [K_{p,-}, K_{p,+}] \times [K_{d,-}, K_{d,+}]$, there holds

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

  where $\boldsymbol{n}$ denotes the outer unit normal vector to Δ_0

Assumptions on the initial data :

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

FLRS: Examples of mass sources

Examples of mass sources in $\partial_t \varphi_i - \operatorname{div}(M_i \nabla \mu_i - \varphi_i \boldsymbol{u}) = S_i$ for $i \in \{p, d\}$ complying with the assumptions in the "logarithmic" case are:

$$S_p = \lambda_M g(n) - \lambda_A \varphi_p$$

$$S_d = \lambda_A \varphi_p - \lambda_L \varphi_d$$

for positive constants $\lambda_M, \lambda_A, \lambda_L$ (with $\lambda_M(\lambda_A + \lambda_L) < \lambda_A \lambda_L$, $\lambda_A < 2\lambda_L$) and a bounded positive function g such that $0 < g(s) \leq 1$, e.g., $g(s) = \max(n_c, \min(s, 1))$ for some constant $n_c \in (0, 1)$.

FLRS: Examples of mass sources

Examples of mass sources in $\partial_t \varphi_i - \mathrm{div}(M_i \nabla \mu_i - \varphi_i \boldsymbol{u}) = S_i$ for $i \in \{p, d\}$ complying with the assumptions in the "logarithmic" case are:

$$S_p = \lambda_M g(n) - \lambda_A \varphi_p$$
$$S_d = \lambda_A \varphi_p - \lambda_L \varphi_d$$

for positive constants $\lambda_M, \lambda_A, \lambda_L$ (with $\lambda_M(\lambda_A + \lambda_L) < \lambda_A \lambda_L$, $\lambda_A < 2\lambda_L$) and a bounded positive function g such that $0 < g(s) \leq 1$, e.g., $g(s) = \max(n_c, \min(s, 1))$ for some constant $n_c \in (0, 1)$. The biological effects we want to model are:

- the growth of the proliferating tumor cells due to nutrient consumption at a constant rate λ_M
- the death of proliferating tumor cells at a constant rate λ_A, which leads to a source term for the necrotic cells
- the lysing/disintegration of necrotic cells at a constant rate λ_L

FLRS: Existence of weak solutions

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

Theorem

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

$$\varphi_i \in H^1(0,T;H^1(\Omega)') \cap L^\infty(0,T;H^1(\Omega)) \cap L^2(0,T;H^2(\Omega)),$$
$$\text{with } 0 \le \varphi_i \le 1, \quad \varphi_p + \varphi_d \le 1 \text{ a.e. in } Q, \quad \text{for } i = p, d,$$
$$\mu_i \in L^2(0,T;H^1(\Omega)), \quad \eta_i \in L^2(Q),$$
$$\boldsymbol{u} \in L^2(Q) \text{ with } \operatorname{div} \boldsymbol{u} \in L^2(Q), \quad q \in L^2(0,T;H^1_0(\Omega)),$$
$$n \in (1 + L^2(0,T;H^2(\Omega) \cap H^1_0(\Omega))), \quad 0 \le n \le 1 \text{ a.e. in } Q.$$

FLRS: Existence of weak solutions

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

Theorem

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

$$\begin{aligned}
&\varphi_i \in H^1(0,T;H^1(\Omega)') \cap L^\infty(0,T;H^1(\Omega)) \cap L^2(0,T;H^2(\Omega)),\\
&\qquad \text{with } 0 \le \varphi_i \le 1, \quad \varphi_p + \varphi_d \le 1 \text{ a.e. in } Q, \quad \text{for } i = p, d,\\
&\mu_i \in L^2(0,T;H^1(\Omega)), \quad \eta_i \in L^2(Q),\\
&\boldsymbol{u} \in L^2(Q) \text{ with } \operatorname{div} \boldsymbol{u} \in L^2(Q), \quad q \in L^2(0,T;H^1_0(\Omega)),\\
&n \in (1 + L^2(0,T;H^2(\Omega) \cap H^1_0(\Omega))), \quad 0 \le n \le 1 \text{ a.e. in } Q.
\end{aligned}$$

Notice that the boundary conditions:

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

are incorporated in the definition of weak solutions

FLRS: an idea of the proof

1. consider a regularized version of this problem by replacing the singular potential F_0 by a regular one F_ε, and by introducing some suitable truncation functions

FLRS: an idea of the proof

1. consider a regularized version of this problem by replacing the singular potential F_0 by a regular one F_ε, and by introducing some suitable truncation functions
2. present two independent methods to prove existence of a solution to the regularized system:
   - 2.1 a further regularization and a Schauder fixed point argument: only exploits elementary existence and uniqueness results methods for PDEs
   - 2.2 a Faedo-Galerkin scheme: more direct (no further regularizing terms are introduced), and constructive (hence, it may be used for a numerical approximation of the problem)

FLRS: an idea of the proof

1. consider a regularized version of this problem by replacing the singular potential F_0 by a regular one F_ε, and by introducing some suitable truncation functions
2. present two independent methods to prove existence of a solution to the regularized system:
   - 2.1 a further regularization and a Schauder fixed point argument: only exploits elementary existence and uniqueness results methods for PDEs
   - 2.2 a Faedo-Galerkin scheme: more direct (no further regularizing terms are introduced), and constructive (hence, it may be used for a numerical approximation of the problem)
3. derive the bounds - independent of the regularization parameters - in order to pass to the limit in the approximation scheme via compactness tools: the main problem is to bound the mean values of φ_i away from the potential bareers

The bound of the mean values

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

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

The bound of the mean values

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

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

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

$$\frac{d}{dt}\boldsymbol{y}(t) = (\boldsymbol{\Sigma})_\Omega(t) + \underline{\underline{M}}\boldsymbol{y}(t) \quad \forall t \in [0, T].$$

The bound of the mean values

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

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

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

$$\frac{d}{dt}\boldsymbol{y}(t) = (\boldsymbol{\Sigma})_\Omega(t) + \underline{\underline{M}}\boldsymbol{y}(t) \quad \forall t \in [0, T].$$

Using the assumption

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

we infer that the vector $\boldsymbol{y}(t) = ((\varphi_p)_\Omega(t), (\varphi_d)_\Omega(t)) \in \operatorname{int}\Delta_0$ for all $t \in [0, T]$.

The bound of the mean values

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

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

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

$$\frac{d}{dt}\boldsymbol{y}(t) = (\boldsymbol{\Sigma})_\Omega(t) + \underline{\underline{M}}\boldsymbol{y}(t) \quad \forall t \in [0, T].$$

Using the assumption

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

we infer that the vector $\boldsymbol{y}(t) = ((\varphi_p)_\Omega(t), (\varphi_d)_\Omega(t)) \in \operatorname{int}\Delta_0$ for all $t \in [0, T]$. Indeed, at the time $t = 0$, $\boldsymbol{y}(0) \in \operatorname{int}\Delta_0$ by assumption. Suppose that $\exists\, t_*$ such that $\boldsymbol{y}(t_*) \in \partial\Delta_0$. Taking $t = t_*$ in the ODE, multiplying with $\boldsymbol{n}$, we get

$$\frac{d}{dt}\boldsymbol{y}(t_*) \cdot \boldsymbol{n} < 0.$$

The bound of the mean values

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

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

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

$$\frac{d}{dt}\boldsymbol{y}(t) = (\boldsymbol{\Sigma})_\Omega(t) + \underline{\underline{M}}\boldsymbol{y}(t) \quad \forall t \in [0, T].$$

Using the assumption

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

we infer that the vector $\boldsymbol{y}(t) = ((\varphi_p)_\Omega(t), (\varphi_d)_\Omega(t)) \in \operatorname{int}\Delta_0$ for all $t \in [0, T]$. Indeed, at the time $t = 0$, $\boldsymbol{y}(0) \in \operatorname{int}\Delta_0$ by assumption. Suppose that $\exists\, t_*$ such that $\boldsymbol{y}(t_*) \in \partial\Delta_0$. Taking $t = t_*$ in the ODE, multiplying with $\boldsymbol{n}$, we get

$$\frac{d}{dt}\boldsymbol{y}(t_*) \cdot \boldsymbol{n} < 0.$$

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

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

Comparison with some other models including velocities

- Numerical simulations of diffuse-interface models for tumor growth have been carried out in several papers (cf., e.g., [Cristini, Lowengrub, Cambridge Univ. Press, 2010] and more recently [H. Garcke, K.-F. Lam, E. Sitka, V. Styles, Math. Models Methods Appl. (2016)], [H. Garcke, K.F. Lam, R. Nuernberg, and E. Sitka, preprint (2017)])
- However, a rigorous mathematical analysis of the resulting PDEs is still in its beginning and mostly for one species models with regular potentials (cf. the model introduced in [H. Garcke, K.F. Lam, E. Sitka, and V. Styles, Math. Models Methods Appl. (2016)] and the subsequent analytical results) :

Comparison with some other models including velocities

- Numerical simulations of diffuse-interface models for tumor growth have been carried out in several papers (cf., e.g., [Cristini, Lowengrub, Cambridge Univ. Press, 2010] and more recently [H. Garcke, K.-F. Lam, E. Sitka, V. Styles, Math. Models Methods Appl. (2016)], [H. Garcke, K.F. Lam, R. Nuernberg, and E. Sitka, preprint (2017)])
- However, a rigorous mathematical analysis of the resulting PDEs is still in its beginning and mostly for one species models with regular potentials (cf. the model introduced in [H. Garcke, K.F. Lam, E. Sitka, and V. Styles, Math. Models Methods Appl. (2016)] and the subsequent analytical results) :

1. the so-called Cahn-Hilliard-Hele-Shaw system ([J. Lowengrub, E. Titi, K. Zhao, European J. Appl. Math. (2013)], [X. Wang, H. Wu, Asymptot. Anal. (2012)], [X. Wang, Z. Zhang, Ann. Inst. H. Poincaré Anal. Nonlinéaire (2013)]) in which the nutrient n, the source of tumor S_T and the fraction S_D of the dead cells are neglected

Comparison with some other models including velocities

- Numerical simulations of diffuse-interface models for tumor growth have been carried out in several papers (cf., e.g., [Cristini, Lowengrub, Cambridge Univ. Press, 2010] and more recently [H. Garcke, K.-F. Lam, E. Sitka, V. Styles, Math. Models Methods Appl. (2016)], [H. Garcke, K.F. Lam, R. Nuernberg, and E. Sitka, preprint (2017)])
- However, a rigorous mathematical analysis of the resulting PDEs is still in its beginning and mostly for one species models with regular potentials (cf. the model introduced in [H. Garcke, K.F. Lam, E. Sitka, and V. Styles, Math. Models Methods Appl. (2016)] and the subsequent analytical results) :

1. the so-called Cahn-Hilliard-Hele-Shaw system ([J. Lowengrub, E. Titi, K. Zhao, European J. Appl. Math. (2013)], [X. Wang, H. Wu, Asymptot. Anal. (2012)], [X. Wang, Z. Zhang, Ann. Inst. H. Poincaré Anal. Nonlinéaire (2013)]) in which the nutrient n, the source of tumor S_T and the fraction S_D of the dead cells are neglected
2. [J. Jang, H. Wu, S. Zheng, J. Differential Equations (2015)] where S_T is not 0 but it's not depending on the other variables but just on time and space

Comparison with some other models including velocities

- Numerical simulations of diffuse-interface models for tumor growth have been carried out in several papers (cf., e.g., [Cristini, Lowengrub, Cambridge Univ. Press, 2010] and more recently [H. Garcke, K.-F. Lam, E. Sitka, V. Styles, Math. Models Methods Appl. (2016)], [H. Garcke, K.F. Lam, R. Nuernberg, and E. Sitka, preprint (2017)])
- However, a rigorous mathematical analysis of the resulting PDEs is still in its beginning and mostly for one species models with regular potentials (cf. the model introduced in [H. Garcke, K.F. Lam, E. Sitka, and V. Styles, Math. Models Methods Appl. (2016)] and the subsequent analytical results) :

1. the so-called Cahn-Hilliard-Hele-Shaw system ([J. Lowengrub, E. Titi, K. Zhao, European J. Appl. Math. (2013)], [X. Wang, H. Wu, Asymptot. Anal. (2012)], [X. Wang, Z. Zhang, Ann. Inst. H. Poincaré Anal. Nonlinéaire (2013)]) in which the nutrient n, the source of tumor S_T and the fraction S_D of the dead cells are neglected
2. [J. Jang, H. Wu, S. Zheng, J. Differential Equations (2015)] where S_T is not 0 but it's not depending on the other variables but just on time and space
3. [M. Dai, E. Feireisl, E. R., G. Schimperna, M. Schonbek, Nonlinearity (2017)] where we consider the same model of FLRS with equal mobilities (this changes a lot the system) and Dirichlet boundary conditions for μ

Outline

Perspectives and Open problems - the case with velocities

1. The sharp interface limit as $\varepsilon \searrow 0$ in the coupled Cahn-Hilliard-Darcy system where

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

Perspectives and Open problems - the case with velocities

1. The sharp interface limit as $\varepsilon \searrow 0$ in the coupled Cahn-Hilliard-Darcy system where

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

In [S. Melchionna, E. Rocca, Interfaces and Free Boundaries, to appear]: Varifold solutions at the limit as $\varepsilon \searrow 0$ in case we just consider the Cahn-Hilliard-Darcy system coupling the Φ equation to the $\boldsymbol{u}$ equation (neglecting the nutrient)

Perspectives and Open problems - the case with velocities

1. The sharp interface limit as $\varepsilon \searrow 0$ in the coupled Cahn-Hilliard-Darcy system where

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

   In [S. Melchionna, E. Rocca, Interfaces and Free Boundaries, to appear]: Varifold solutions at the limit as $\varepsilon \searrow 0$ in case we just consider the Cahn-Hilliard-Darcy system coupling the Φ equation to the $\boldsymbol{u}$ equation (neglecting the nutrient)

2. To add the mechanics in the problem: for example considering the tumor sample as a porous media (ongoing project with P. Krejčí and J. Sprekels)

Perspectives and Open problems - the case with velocities

1. The sharp interface limit as $\varepsilon \searrow 0$ in the coupled Cahn-Hilliard-Darcy system where

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

   In [S. Melchionna, E. Rocca, Interfaces and Free Boundaries, to appear]: Varifold solutions at the limit as $\varepsilon \searrow 0$ in case we just consider the Cahn-Hilliard-Darcy system coupling the Φ equation to the $\boldsymbol{u}$ equation (neglecting the nutrient)

2. To add the mechanics in the problem: for example considering the tumor sample as a porous media (ongoing project with P. Krejčí and J. Sprekels)

3. The case with different densities: we are studying a model introduced by [Lee, Lowengrub and Goodman (2001)] in cooperaton with Andrea Giorgini (a post doc in Pavia) and P. Colli, G. Schimperna, and M. Grasselli. Other models with different assumptions are available (cf. [L. Dedè, H. Garcke, K.-F. Lam, J. Math. Fluid Mech., to appear])

Perspectives and Open problems - the case without velocities

1. The sharp interface limit. In [E.R., R. Scala, J. Nonlinear Sci. (2017)]: Γ-convergence for a gradient type system (neglecting velocities):

$$\begin{cases} \varphi_t - \Delta\mu = 2\sigma + \varphi - \mu \\ \sigma_t - \Delta\sigma = -2\sigma - \varphi + \mu \\ \mu = \frac{1}{\varepsilon}\Psi'(\varphi) - \varepsilon\Delta\varphi \end{cases}$$

Perspectives and Open problems - the case without velocities

1. The sharp interface limit. In [E.R., R. Scala, J. Nonlinear Sci. (2017)]: Γ-convergence for a gradient type system (neglecting velocities):

$$\begin{cases} \varphi_t - \Delta\mu = 2\sigma + \varphi - \mu \\ \sigma_t - \Delta\sigma = -2\sigma - \varphi + \mu \\ \mu = \frac{1}{\varepsilon}\Psi'(\varphi) - \varepsilon\Delta\varphi \end{cases}$$

   - We assumed the regularity of the limit interface, hence there is a death time T^* until the evolution is regular. After the death time the evolution is undetermined!

Perspectives and Open problems - the case without velocities

1. The sharp interface limit. In [E.R., R. Scala, J. Nonlinear Sci. (2017)]: Γ-convergence for a gradient type system (neglecting velocities):

$$\begin{cases} \varphi_t - \Delta\mu = 2\sigma + \varphi - \mu \\ \sigma_t - \Delta\sigma = -2\sigma - \varphi + \mu \\ \mu = \frac{1}{\varepsilon}\Psi'(\varphi) - \varepsilon\Delta\varphi \end{cases}$$

   - We assumed the regularity of the limit interface, hence there is a death time T^* until the evolution is regular. After the death time the evolution is undetermined!
   - We made a technical hypothesis on the convergence of the measures

$$\frac{\varepsilon}{2}|\nabla\varphi^\varepsilon|^2 + \frac{\Psi(\varphi^\varepsilon)}{\varepsilon} \rightharpoonup 2c_\Psi\, d\mathcal{H}^2 \llcorner \Gamma$$

     This is unknown in general, but is proved under higher regularity of the chemical potential μ^ε and conjectured by Tonegawa to hold in the general case

Perspectives and Open problems - the case without velocities

1. The sharp interface limit. In [E.R., R. Scala, J. Nonlinear Sci. (2017)]: Γ-convergence for a gradient type system (neglecting velocities):

$$\begin{cases} \varphi_t - \Delta\mu = 2\sigma + \varphi - \mu \\ \sigma_t - \Delta\sigma = -2\sigma - \varphi + \mu \\ \mu = \frac{1}{\varepsilon}\Psi'(\varphi) - \varepsilon\Delta\varphi \end{cases}$$

   - We assumed the regularity of the limit interface, hence there is a death time T^* until the evolution is regular. After the death time the evolution is undetermined!
   - We made a technical hypothesis on the convergence of the measures

$$\frac{\varepsilon}{2}|\nabla\varphi^\varepsilon|^2 + \frac{\Psi(\varphi^\varepsilon)}{\varepsilon} \rightharpoonup 2c_\Psi\, d\mathcal{H}^2 \llcorner \Gamma$$

     This is unknown in general, but is proved under higher regularity of the chemical potential μ^ε and conjectured by Tonegawa to hold in the general case

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

Many thanks to all of you for the attention!

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

Issues with the well-posedness

The state equations

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

satisfies the energy identity

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

$$= \int_\Omega h(\varphi)\left(\mathcal{P}\sigma - \mathcal{A} - \alpha u\right)\mu.$$

Issues with the well-posedness

The state equations

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

satisfies the energy identity

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

We can estimate the right-hand side as

$$\delta \|\mu\|_{L^2}^2 + \frac{C}{\delta} (\mathcal{P}^2 \|\sigma\|_{L^2}^2 + \dots) \quad \text{for some } \delta > 0,$$

leading to

Issues with the well-posedness

The state equations

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

satisfies the energy identity

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

$$= \int_\Omega h(\varphi)\left(\mathcal{P}\sigma - \mathcal{A} - \alpha u\right)\mu.$$

We can estimate the right-hand side as

$$\delta \|\mu\|_{L^2}^2 + \frac{C}{\delta}(\mathcal{P}^2\|\sigma\|_{L^2}^2 + \dots) \quad \text{for some } \delta > 0,$$

leading to

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

Issues with the well-posedness

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

To apply Poincaré inequality to the $\|\mu\|_{L^2(L^2)}$ on the RHS, we need to estimate the square of the mean of μ using

$$\mu = \Psi'(\varphi) - \Delta \varphi.$$

If $|\Psi'(s)| \leq C(1 + |s|^p)$ for some p, then we have

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

But, to control $\|\varphi\|^{2p}_{L^{2p}(L^{2p})}$ in the absence of any a priori estimate, we need $p = 1$! I.e., Ψ can only be a quadratic potential [Garcke, L.].

Issues with the well-posedness

If σ is bounded in Q, then

$$\left| \int_\Omega h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u)\mu \right| \leq C\|\mu\|_{L^1}$$

and by the Poincaré inequality, we have

$$\|\mu\|_{L^1} \leq C\|\nabla\mu\|_{L^1} + C\left| \frac{1}{|\Omega|} \int_\Omega \mu \right|.$$

Issues with the well-posedness

If σ is bounded in Q, then

$$\left| \int_\Omega h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u)\mu \right| \leq C\|\mu\|_{L^1}$$

and by the Poincaré inequality, we have

$$\|\mu\|_{L^1} \leq C\|\nabla\mu\|_{L^1} + C\left| \frac{1}{|\Omega|} \int_\Omega \mu \right|.$$

Then one obtains

$$\begin{aligned} &\mathcal{E}(t) + \int_0^t \int_\Omega \left(|\nabla\mu|^2 + |\nabla\sigma|^2 \right) \\ &\qquad \leq \mathcal{E}(0) + C \int_0^t \left(\delta\|\nabla\mu\|_{L^1} + \|\Psi'(\varphi)\|_{L^1} + \text{ other terms...} \right). \end{aligned}$$

Issues with the well-posedness

If σ is bounded in Q, then

$$\left| \int_\Omega h(\varphi)(\mathcal{P}\sigma - \mathcal{A} - \alpha u)\mu \right| \leq C\|\mu\|_{L^1}$$

and by the Poincaré inequality, we have

$$\|\mu\|_{L^1} \leq C\|\nabla\mu\|_{L^1} + C\left| \frac{1}{|\Omega|} \int_\Omega \mu \right|.$$

Then one obtains

$$\begin{aligned} &\mathcal{E}(t) + \int_0^t \int_\Omega \left(|\nabla\mu|^2 + |\nabla\sigma|^2 \right) \\ &\qquad \leq \mathcal{E}(0) + C \int_0^t \left(\delta\|\nabla\mu\|_{L^1} + \|\Psi'(\varphi)\|_{L^1} + \text{ other terms...} \right). \end{aligned}$$

With an assumption like

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

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

The Schauder argument

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

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

where σ solves

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

The Schauder argument

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

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

where σ solves

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

Then define the mapping

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

where φ solves

$$\partial_t \varphi = \Delta \mu - h(\varphi)(\mathcal{P} M_1(\phi) - \mathcal{A} - \alpha u), \quad \mu = \Psi'(\varphi) - \Delta \varphi.$$

The Schauder argument

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

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

where σ solves

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

Then define the mapping

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

where φ solves

$$\partial_t \varphi = \Delta \mu - h(\varphi)(\mathcal{P} M_1(\phi) - \mathcal{A} - \alpha u), \quad \mu = \Psi'(\varphi) - \Delta \varphi.$$

The solution to the fixed point problem

$$z = M_2(z)$$

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