Diffuse interface models in Biology

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Plan of the Lecture

Part 1. One Species model: Optimal control: **[GLR]** H. Garcke, K.-F. Lam, E.R., preprint arXiv:1608.00488 (2016) $\Longrightarrow$ **First order necessary optimality conditions** for both the cytotoxic concentration and the treatment time

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- **From Diffuse to Sharp interfaces**: **[MR]** S. Melchionna, E. Rocca, preprint arXiv:1610.04478 and **[RS]** E. Rocca, R. Scala, J. Nonlinear Sci, to appear

Part 1 - One Species Model: Optimal Control

One Species Diffuse Interface Model

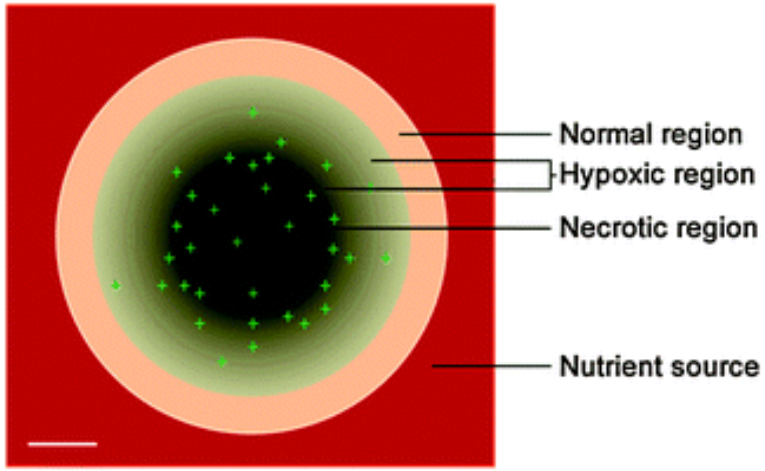

Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100μm = 0:1mm

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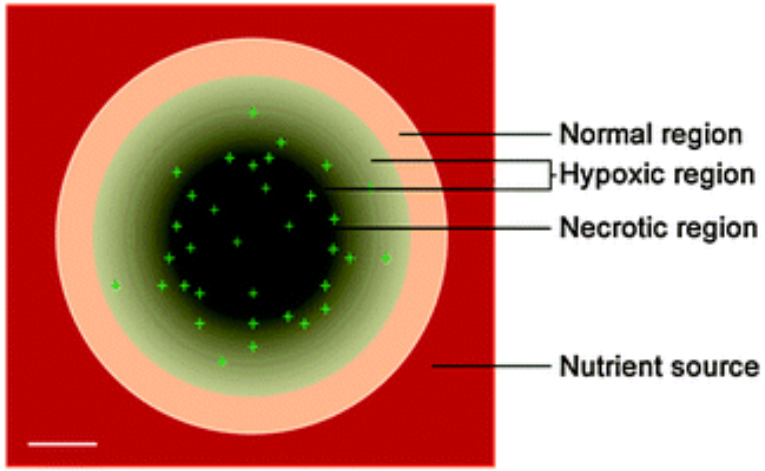

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A continuum thermodynamically consistent model is introduced with the ansatz:

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

GLR: Optimization over the treatment time

Common treatment for tumors are

- Cytotoxic drugs - target and damage rapidly dividing cells.
- Cytostatic drugs - blocks proliferation.
- Radiation therapy.
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Worst case scenario: Cytotoxins may have cancer-causing effects, and tumor cells can mutate to become resistant to the drug.

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

The state equations: Cahn-Hilliard + nutrient models with sources

The simplest phase field model is a Cahn–Hilliard system with source terms

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

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

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- Linear kinetics [Chen, Wise, Shenoy, Lowengrub], [Garcke, L.]

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

  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,
  - $h(\varphi)\alpha u$ - 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 $u = 1$ represnts full dosage, $u = 0$ represents no dosage.
- A regular double-well potential Ψ, e.g., $\Psi(s) = 1/4(1 - s^2)^2$

GLR: Objective functional

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

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

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- the variable τ denotes the unknown treatment time **to be optimised**,
- φ_Q is a desired evolution of the tumor over the treatment,
- φ_Ω is a desired final state of the tumor (stable equilibrium of the system),
- the term $\frac{1+\varphi(\tau)}{2}$ measures the size of the tumor at the end of the treatment,
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Expectation: An optimal control will be a pair (u_*, τ_*) and we will obtain two optimality conditions.

Some Comments

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;

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- 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;
- We consider $T \in (0, \infty)$ as a fixed maximal time in which the patient is allowed to undergo a treatment obtained from this optimal control problem.

GLR: Relaxed objective functional

However, we will not study the functional

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

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

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The optimal control problem is

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

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

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

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

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with Neumann boundary conditions and zero initial conditions

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Theorem

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

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

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

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

GLR: Fréchet differentiability with respect to time

Lemma

For $f \in H^1(0,T;L^2) \subset C^0([0,T];L^2)$,

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we have

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

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

Note that the control u does not appear explicitly.

GLR: First order optimality conditions

Introducing the adjoint system

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\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, \\
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Theorem

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

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

and

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

Open related problem

1. To deal with the **original functional**:

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

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

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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 it is possible to obtain $\varphi \in H^2(0, T; L^2) \cap W^{1,\infty}(0, T; H^1)$.

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2. To prove the **convergence to stationary solutions** by means of suitable Simon-Lojasiewicz techniques: 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.

Comparison with some other models

In the phase field model we introduced

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

where $\mathcal{M}$ accounts for biological mechanisms related to proliferation and death and $\mathcal{S}$ models interaction with the tumor cells, we could choose different form of $\mathcal{M}$ and $\mathcal{S}$:

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- Simplified law for chemical reaction leading to a Gradient-Flow structure **[RS: E.R., R. Scala, A rigorous sharp interface limit of a diffuse interface model related to tumor growth, J. Nonlinear Sci, to appear]**:

$$\mathcal{M} = \mathcal{S} = 2\sigma + \varphi - \mu$$

Part 2 - Ongoing projects and open problems

DFRSS: A multispecies model with velocities

Typical structure of tumors grown in vitro:

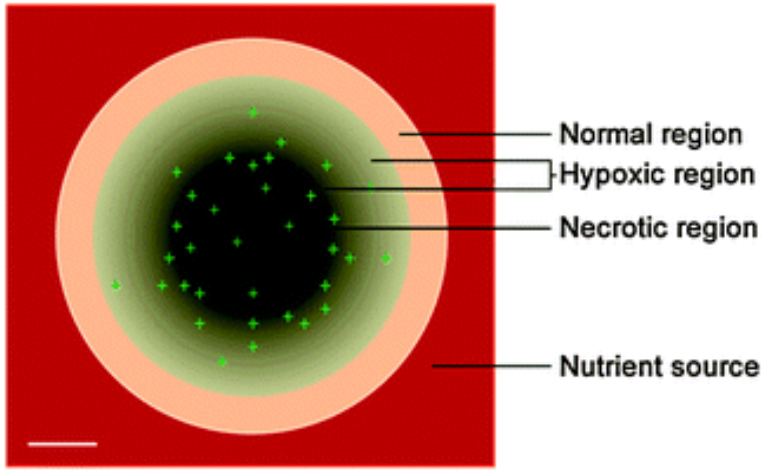

Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100μm = 0:1mm

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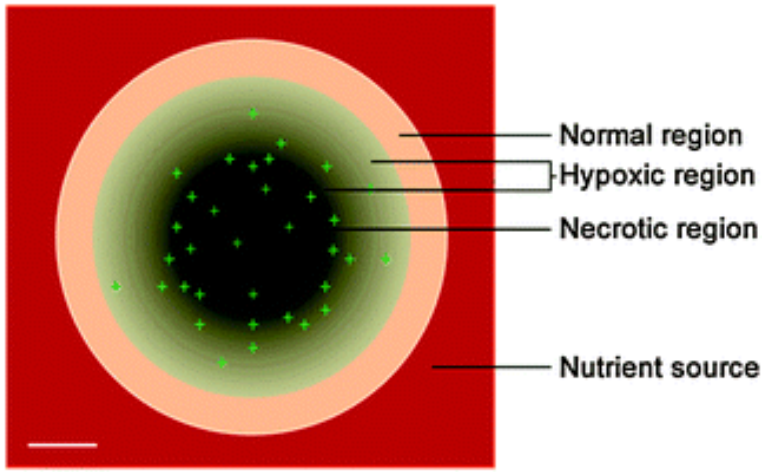

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A continuum thermodynamically consistent model is introduced with the ansatz:

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

DFRSS: The state variables

- $\phi_i, i = 1, 2, 3$: the volume fractions of the cells:
  - $\phi_1 = P$: **proliferating tumor cell fraction**
  - $\phi_2 = \phi_D$: dead tumor cell fraction
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  The variables above are naturally constrained by the relation $\sum_{i=1}^{3} \phi_i = \phi_H + \Phi = 1$

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- n: **the nutrient concentration** (it was σ before)
- $\mathbf{u} := \mathbf{u}_i, i = 1, 2, 3$: **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
- Π: the cell-to-cell **pressure**

DFRSS: The PDEs

In summary, let $\Omega \subset \mathbb{R}^3$ be a bounded domain and $T > 0$ the final time of the process. For simplicity, choose $\lambda_M = \nu_U = 1$, $\lambda_A = \lambda_1$, $\lambda_N = \lambda_2$, $\lambda_L = \lambda_3$.

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Then, in $\Omega \times (0, T)$, we have the following system of equations:

$$\textbf{(Cahn - Hilliard)} \qquad \partial_t \Phi + \mathrm{div}_x(\mathbf{u}\Phi) - \mathrm{div}_x(\nabla_x \mu) = \Phi S_T, \ \mu = -\Delta \Phi + \mathcal{F}'(\Phi)$$

$$\textbf{(Darcy)} \qquad \mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi, \quad \mathrm{div}_x \mathbf{u} = S_T$$

$$\textbf{(Transport)} \qquad \partial_t P + \mathrm{div}_x(\mathbf{u}P) = \Phi(S_T - S_D)$$

$$\textbf{(Reac - Diff)} \qquad -\Delta n + nP = T_c(n, \Phi)$$

where

$$\textbf{(Source - Tumor)} \qquad S_T(n, P, \Phi) = nP - \lambda_3(\Phi - P)$$

$$\textbf{(Source - Dead)} \qquad S_D(n, P, \Phi) = (\lambda_1 + \lambda_2 H(n_N - n))\, P - \lambda_3(\Phi - P)$$

$$\textbf{(Nutrient - Capill)} \qquad T_c(n, \Phi) = [\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)]\,(n_c - n)$$

coupled with the boundary conditions on $\partial\Omega \times (0, T)$: $\mu = \Pi = 0$, $n = 1$, $\nabla_x \Phi \cdot \nu = 0$, $P\mathbf{u} \cdot \nu \geq 0$ and with the initial conditions $\Phi(0) = \Phi_0$, $P(0) = P_0$ in Ω

DFRSS: Assumptions on the potential $\mathcal{F}$

We suppose that the potential $\mathcal{F}$ supports the natural bounds

$$0 \leq \Phi(t,x) \leq 1$$

To this end, we take $\mathcal{F} = \mathcal{C} + \mathcal{B}$, where $\mathcal{B} \in C^2(\mathbb{R})$ and

$$\mathcal{C} : \mathbb{R} \mapsto [0,\infty] \text{ convex, lower-semi continuous, } \mathcal{C}(\Phi) = \infty \text{ for } \Phi < 0 \text{ or } \Phi > 1$$

Moreover, we ask that

$$\mathcal{C} \in C^1(0,1), \quad \lim_{\Phi \to 0^+} \mathcal{C}'(\Phi) = \lim_{\Phi \to 1^-} \mathcal{C}'(\Phi) = \infty$$

A typical example of such $\mathcal{C}$ is the *logarithmic potential*

$$\mathcal{C}(\Phi) = \begin{cases} \Phi \log(\Phi) + (1-\Phi)\log(1-\Phi) \text{ for } \Phi \in [0,1], \\ \\ \infty \text{ otherwise} \end{cases}$$

DFRSS: Assumptions on the other data

Regarding the functions the constants in the definitions of S_T and S_D, we assume $Q, H \in C^1(\mathbb{R})$ and

$$\lambda_i \geq 0 \text{ for } i = 1, 2, 3, \quad H \geq 0$$

$$[\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)] \geq 0, \quad 0 < n_c < 1$$

Finally, we suppose Ω be a bounded domain with smooth boundary in $\mathbb{R}^3$ and impose the following conditions on the initial data:

$$\Phi_0 \in H^1(\Omega), \quad 0 \leq \Phi_0 \leq 1, \quad \mathcal{C}(\Phi_0) \in L^1(\Omega)$$

$$P_0 \in L^2(\Omega), \quad 0 \leq P_0 \leq 1 \quad \text{a.e. in } \Omega$$

DFRSS: Weak formulation

$(\Phi, \mathbf{u}, P, n)$ is a weak solution to the problem in $(0, T) \times \Omega$ if

(i) these functions belong to the regularity class:

$$\Phi \in C^0([0, T]; H^1(\Omega)) \cap L^2(0, T; W^{2,6}(\Omega))$$

$$\mathcal{C}(\Phi) \in L^\infty(0, T; L^1(\Omega)), \quad \text{hence, in particular, } 0 \le \Phi \le 1 \text{ a.a. in } (0, T) \times \Omega$$

$$\mathbf{u} \in L^2((0, T) \times \Omega; \mathbb{R}^3), \ \operatorname{div} \mathbf{u} \in L^\infty((0, T) \times \Omega)$$

$$\Pi \in L^2(0, T; W_0^{1,2}(\Omega)), \quad \mu \in L^2(0, T; W_0^{1,2}(\Omega))$$

$$P \in L^\infty((0, T) \times \Omega), \ 0 \le P \le 1 \ \text{ a.a. in } (0, T) \times \Omega$$

$$n \in L^2(0, T; W^{2,2}(\Omega)), \ 0 \le n \le 1 \ \text{ a.a. in } (0, T) \times \Omega$$

(ii) the following integral relations hold:

$$\int_0^T \int_\Omega [\Phi \partial_t \varphi + \Phi \mathbf{u} \cdot \nabla_x \varphi + \mu \Delta \varphi + \Phi S_T \varphi] \ \mathrm{d}x \ \mathrm{d}t = - \int_\Omega \Phi_0 \varphi(0, \cdot) \ \mathrm{d}x$$

for any $\varphi \in C_c^\infty([0, T) \times \Omega)$, where

$$\mu = -\Delta \Phi + \mathcal{F}'(\Phi), \ \mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi$$

$$\operatorname{div}_x \mathbf{u} = S_T \text{ a.a. in } (0, T) \times \Omega; \quad \nabla_x \Phi \cdot \nu|_{\partial\Omega} = 0$$

$$\int_0^T \int_\Omega [P \partial_t \varphi + P \mathbf{u} \cdot \nabla_x \varphi + \Phi (S_T - S_D) \varphi] \ \mathrm{d}x \ \mathrm{d}t \ge - \int_\Omega P_0 \varphi(0, \cdot) \ \mathrm{d}x$$

for any $\varphi \in C_c^\infty([0, T) \times \overline{\Omega})$, $\varphi|_{\partial\Omega} \ge 0$

$$-\Delta n + nP = T_c(n, \Phi) \text{ a.a. in } (0, T) \times \Omega; \ n|_{\partial\Omega} = 1$$

DFRSS: Existence of weak solutions

The main result of **[M. Dai, E. Feireisl, E.R., G. Schimperna, M. Schonbek, Analysis of a diffuse interface model of multispecies tumor growth, Nonlinearity, to appear (2017)]**

Theorem

Let $T > 0$ be given. Under the previous assumptions the variational formulation of our initial-boundary value problem admits **at least one solution** *on the time interval* $[0, T]$

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 [Garcke, Lam, Sitka, Styles, arXiv:1508.00437, 2015]).
- However, a **rigorous mathematical analysis** of the resulting PDEs is still in its beginning and only for **one species models with regular potentials** (cf. [H. Garcke, K.F. Lam, E. Sitka, and V. Styles, Math. Models Methods Appl. (2016)]) and only very recently on **multiphase models** (cf. [H. Garcke, K.F. Lam, R. Nuernberg, and E. Sitka, arXiv:1701.06656, 2017])

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  - 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 or

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  - [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

Perspectives and Open problems - models with velocities

- An ongoing project with S. Frigeri, K.-F. Lam, G. Schimperna: To study the **multispecies model** introduced in **[CWSL]** including **different mobilities** and non-Dirichlet b.c.s on the chemical potential $\Longrightarrow$ the main problems are:

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  - we have two different Cahn-Hilliard equations with different mobilities M_i: $\partial_t \varphi_i = M_i \Delta \mu_i - \mathrm{div}(\varphi_i \boldsymbol{u}) + S_i$ and if we do not choose the Dirichlet b.c.s on μ then we need to estimate the means of μ_i (containing a multiwell logarithmic type potential)
  - we need the mean values of φ_i (the proliferating and dead cells phases) in the two Cahn-Hilliard equations to be away from the potential bareers $\Longrightarrow$ ad hoc estimate based on ODEs technique
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Perspectives and Open problems - models with velocities

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  - In **[MR]** S. Melchionna, E. Rocca, preprint arXiv:1610.04478: **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 - models without velocities

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  - It is possible regularize the gradient flow by means of suitable s-power of the Laplacian replacing Δ both in the φ and the σ equations. Unfortunately in that case it is nontrivial (and out of reach) to prove the analogous of the interface property $[\frac{\partial\mu}{\partial n}] = -2V$ unless $s = 2$

Many thanks to all of you for the attention!

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