Diffuse interface models for multiphase tumor growth

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jointly with Sergio Frigeri (Brescia)-Kei Fong Lam (Hong-Kong)-Giulio Schimperna (Pavia)
originated by a previous cooperation with Mimi Dai (Colorado), Eduard Feireisl (Prague), Maria Schonbek (California), Giulio Schimperna (Pavia)

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Outline

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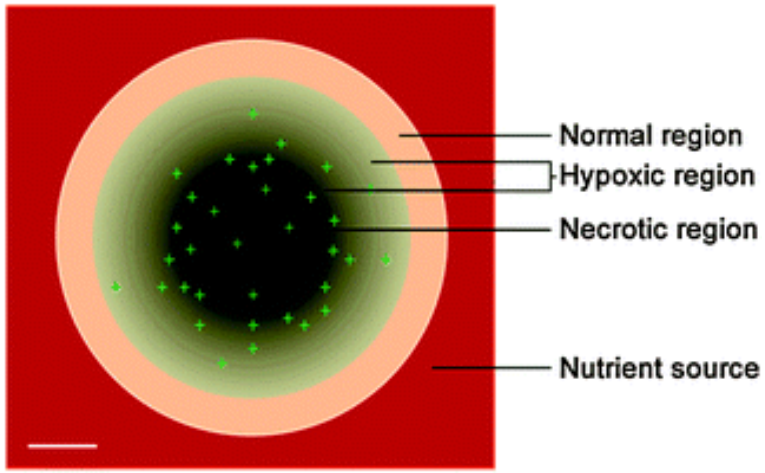
Setting

Typical structure of tumors grown in vitro:



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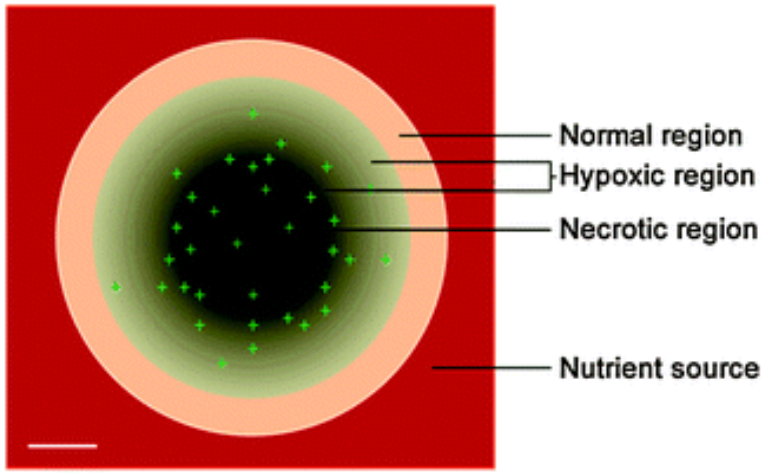

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A continuum thermodynamically consistent model is introduced with the ansatz:

- sharp interfaces are replaced by narrow transition layers - diffuse interfaces - arising due to adhesive forces among the cell species
- 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

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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)

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- $\varphi_p, \varphi_d, \varphi_h \in [0,1]$: 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 $\Delta := \{\boldsymbol{y} \in \mathbb{R}^2 : \ 0 \leq y_1, y_2, \ y_1 + y_2 \leq 1\} \subset \mathbb{R}^2$

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- n: the nutrient concentration
- $\boldsymbol{u} := \boldsymbol{u}_i$, $i = 1,2,3$: 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
- Π: 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, for matched densities of the components, reads as

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

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

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

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

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

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

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

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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:

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

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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

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- 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 in S_i 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 crucial

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:

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

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

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

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

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

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

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

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

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: $(S_p, S_d) = \Sigma + \underline{\underline{M}}(\varphi_p, \varphi_d)^T$

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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

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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,
- $(\frac{1}{|\Omega|}\int_\Omega \varphi_{p,0}(x)\,dx, \frac{1}{|\Omega|}\int_\Omega \varphi_{d,0}(x)\,dx) \in \operatorname{int}\Delta_0$ 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 $n_c \in (0, 1)$.

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- 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

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

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&\boldsymbol{u} \in L^2(Q) \text{ with } \operatorname{div} \boldsymbol{u} \in L^2(Q), \quad \Pi \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

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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

Testing by 1 the mass balances

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

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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:

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

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

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

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

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

Outline

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- we considered equal mobilities in the mass balances
- and homogeneous Dirichlet boundary conditions on the chemical potential
- the resulting PDE system is completely different

DFRSS: The state variables

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- $\phi_i, i = p, d, h$: the volume fractions of the cells:
  - $\phi_p = P$: proliferating tumor cell fraction
  - ϕ_d: dead tumor cell fraction
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- n: the nutrient concentration
- $\boldsymbol{u} := \boldsymbol{u}_i, i = 1, 2, 3$: 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
- Π: the cell-to-cell pressure

DFRSS: Mass conservation and choice of the energy

The volume fractions obey the mass conservation (advection-reaction-diffusion) equations, where we have taken matched densities of the components:

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Assuming:

- the total energy adhesion takes into account only of diffuse interfaces between tumor and healthy phases:

$$E = \int_\Omega \left(\mathcal{F}(\Phi) + \frac{1}{2}|\nabla_x \Phi|^2 \right) \, \mathrm{d}x$$

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we recover the convective Cahn-Hilliard equation for Φ in the form

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- The main difference here is that for P we have a transport equation and so we couple a Cahn-Hilliard type equation for Φ with a transport equation for P and the nutrient and velocity evolution
- Moreover the singular potential here is a function of only one variable Φ while in FLRS it depends on both the proliferating and dead cells phases

DFRSS: The boundary conditions

The other main difference with respect to FLRS is the choice of boundary conditions:

- In DFRSS we chose the b.c.s of [CWSL: Y. Chen, S.M. Wise, V.B Shenoy, J.S. Lowengrub, Int. J. Numer. Methods Biomed. Eng. (2014)] for μ, Π, n, and Φ (ν is the outer normal unit vector to $\partial\Omega$):

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- As $P \geq 0$, the boundary condition $P\boldsymbol{u} \cdot \nu \geq 0$ means $P = 0$ whenever $\boldsymbol{u} \cdot \nu < 0$ i.e. on the part of the inflow part of the boundary

DFRSS: The PDEs

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

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

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

$$\text{(Transport)} \qquad \partial_t P + \mathrm{div}_x(\boldsymbol{u}P) = \Phi(S_T - S_d)$$

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

where

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

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

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

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

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 (2017)] reads as follows

Theorem

Let $T > 0$ be given. Under suitable assumptions on the nonlinear function F and on the initial data the weak formulation of our initial-boundary value problem admits at least one solution *on the time interval* $[0, T]$

Outline

Comparison with 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)])

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  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

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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

Outline

Perspectives and Open problems

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

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

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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)

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

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2. To add the mechanics in Lagrangean coordinates 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 Hele-Shaw-Cahn-Hilliard 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])

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BUT A SPECIAL THANKS GOES TO ...

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- In the years after 2007 Eduard came several times in Milan, Berlin and Pavia. A lot of cooperations started with him, Giulio Schimperna, and also Arghir Zarnescu, Mimi Dai, and Maria Schonbek on two-phase immiscible fluids, liquid cristals, and finally on tumor growth

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- We also had the occasion to attend his lessons for a PhD course he gave in Milan this year and into two Schools:
  - in Cetraro in 2015 (which we also organized together) and in Milan in 2013


  - attracting numerous students from many different countries

But I think that what one can immediately appreciate in the cooperation with Eduard is the energy - somethimes entropy ... 😉 - that he emanates at the blackboard!

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HAPPY BIRTHDAY EDUARD!

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

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

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

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

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

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

(i) these functions belong to the regularity class:

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

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

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

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

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

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

(ii) the following integral relations hold:

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

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

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

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

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

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: Idea of the proof

- Approximation: regularize the equations
- Perform uniform a priori estimates
- Use compactness arguments in order to pass to the limit

DFRSS: The maximum principle

- The transport equation for the density function P is

$$\partial_t P + \boldsymbol{u} \cdot \nabla_x P = -PS_T + \Phi(S_T - S_d) = P\left[-S_T + \Phi\left(n - (\lambda_1 + \lambda_2 H(n_N - n))\right)\right]$$

Thus, provided

$$P(0,\cdot) = P_0 \geq 0, \text{ and } P(t,x) \geq 0 \text{ for } x \in \partial\Omega, \ \boldsymbol{u} \cdot \nu > 0$$

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- In order to obtain positivity of n we need

$$(-\Delta n =) - nP + T_c(n,\varphi) = -nP + \left[\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi)\right](n_c - n)$$

to be positive (non-negative) whenever $n < 0$. Then we assume

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

This assumption also implies that $n \leq 1$, so we may conclude that

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

DFRSS: The upper bound for P

Hence, using $\Phi, n \in [0,1]$, and evaluating the expression on the right-hand side of

$$\partial_t P + \boldsymbol{u} \cdot \nabla_x P = -PS_T + \Phi(S_T - S_d) = P\left[-S_T + \Phi\left(n - (\lambda_1 + \lambda_2 H(n_N - n))\right)\right]$$

for $P = 1$, due to $-\Phi\left(\lambda_1 + \lambda_2 H(n_N - n)\right) \leq 0$, yields

$$P\left[\lambda_3(\Phi - P) - nP + \Phi\left(n - (\lambda_1 + \lambda_2 H(n_N - n))\right)\right] \leq \lambda_3(\Phi - 1) + n(\Phi - 1)$$

Consequently, provided

$$0 \leq P(0,\cdot) = P_0 \leq 1, \text{ and } 0 \leq P(t,x) \leq 1 \text{ for } x \in \partial\Omega,\ \boldsymbol{u} \cdot \nu > 0$$

it follows that

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

DFRSS: Main estimates on Φ

Testing by μ the Cahn-Hilliard equation

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

and by $\boldsymbol{u}$ the $(\text{Darcy} - \text{law})$: $\quad \boldsymbol{u} = -\nabla_x \Pi + \mu \nabla_x \Phi$, gives

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_\Omega \left[\frac{1}{2} |\nabla_x \Phi|^2 + \mathcal{F}(\Phi) \right] \mathrm{d}x + \int_\Omega \left[|\nabla_x \mu|^2 + |\boldsymbol{u}|^2 \right] \mathrm{d}x = \int_\Omega \Pi S_T \, \mathrm{d}x \leq \|S_T\|_{L^\infty(\Omega)} \|\Pi\|_{L^1(\Omega)}$$

Seeing that Π solves the Dirichlet problem

$$-\Delta \Pi = S_T - \operatorname{div}_x(\mu \nabla_x \Phi), \ \ \Pi|_{\partial\Omega} = 0$$

we deduce that

$$\|\Pi(t,\cdot)\|_{H^1(\Omega)} \leq \|S_T(t,\cdot)\|_{L^2(\Omega)} + \|\mu \nabla_x \Phi\|_{L^2(\Omega;\mathbb{R}^3)}$$

where, by means of Gagliardo-Nirenberg interpolation inequality,

$$\|\mu \nabla_x \Phi\|_{L^2(\Omega;\mathbb{R}^3)} \leq c \|\mu(t,\cdot)\|_{L^4(\Omega)} \left(\|\Phi(t,\cdot)\|^{1/2}_{L^\infty(\Omega)} \left(\|\mu\|^{1/2}_{L^2(\Omega)} + \|\nabla \Phi\|^{1/2}_{L^2(\Omega)} \right) + c \right)$$

Applying a standard Grönwall's lemma and by comparison arguments, we deduce

$$\sup_{t \in (0,T)} \|\Phi\|_{H^1(\Omega)} + \int_0^T \left[\|\nabla_x \mu\|^2_{L^2(\Omega;\mathbb{R}^3)} + |\boldsymbol{u}|^2 + \|\Phi\|^2_{W^{2,6}(\Omega)} \right] \mathrm{d}t \leq c$$

DFRSS: Main estimates on u

Note that we already know

$$\mathrm{div}_x \boldsymbol{u} = S_T \text{ bounded in } L^\infty((0,T)\times\Omega) \quad \text{and } \boldsymbol{u} \text{ bounded in } L^2((0,T)\times\Omega;\mathbb{R}^3)$$

Next, we compute from the (Darcy − law) : $\boldsymbol{u} = -\nabla_x \Pi + \mu \nabla_x \Phi$ the

$$\mathrm{curl}_x \boldsymbol{u} = \nabla_x \mu \wedge \nabla_x \Phi \in L^2(0,T;L^1(\Omega)) \cap L^1(0,T;L^2(\Omega))$$

Hence, in view of the fact that $\mathrm{div}_x(\varphi \boldsymbol{u})$ and $\mathrm{curl}(\varphi \boldsymbol{u})$ for any test function $\varphi \in C^\infty(\mathbb{R}^3)$ are bounded in $L^1(0,T;L^2(\mathbb{R}^3))$, we then obtain that $\varphi \boldsymbol{u}$ is bounded in $L^1(0,T;H^1(\mathbb{R}^3))$ and so $\boldsymbol{u}$ satisfies

$$\int_0^T \|\boldsymbol{u}\|_{H^1_{loc}(\Omega;\mathbb{R}^3)} \, \mathrm{d}t \leq c$$

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These estimates are sufficient in order to pass to the limit in the regularized system and to obtain our weak solutions