Weierstrass Institute for
Applied Analysis and Stochastics

Existence of weak solutions and asymptotics for some diffuse interface models of tumor growth

Elisabetta Rocca

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[Part 1] [**DFRSS**: M. Dai, E. Feireisl, E.R., G. Schimperna, M. Schonbek, WIAS preprint 2150 (2015)]: a model of multispecies tumor growth proposed by [**CWSL**: Y. Chen, S.M. Wise, V.B Shenoy, J.S. Lowengrub, Int. J. Numer. Methods Biomed. Eng., 2014] including the evolution of the velocity:

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- **DFRSS** Existence of weak solutions for the PDE system coupled with suitable initial and boundary conditions
- **DFRSS** Partial results on the singular limit for that model as the diffuse interface coefficient tends to zero

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[Part 2] [**FGR**: S. Frigeri, M. Grasselli, E.R., European J. Appl. Math. (2015)], [**CGRS1**: P. Colli, G. Gilardi, E.R., J. Sprekels, Nonlinear Anal. Real World Appl., (2015)], [**CGRS2**: P. Colli, G. Gilardi, E.R., J. Sprekels, WIAS preprint 2093 (2015), to appear in DCDS-S]: a simpler model proposed by [**HZO**: A. Hawkins-Daarud, K.G. van der Zee, J.T. Oden, Int. J. Numer. Methods Biomed. Eng., 2012] where the velocities are set to zero:

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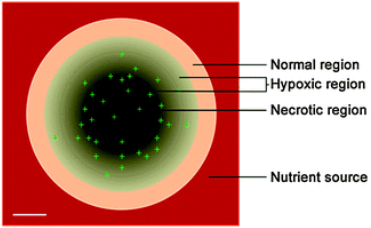
FGR Existence of weak solution, regularity results, existence of the global attractor

CGRS1-2 Viscous approximation of the model, asymptotics, and error estimates

CGRS3 Future work: optimal control problems, rigorously from diffuse to sharp interfaces, ...

Part 1: The CWSL model - multispecies including velocities

Typical structure of tumours grown in vitro:



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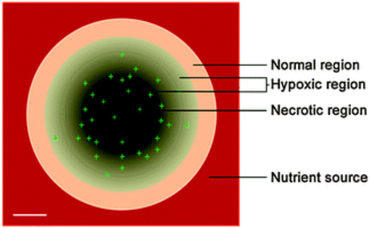

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A continuum thermodynamically consistent model is introduced with the ansatz:

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

- $\phi_i, i = 1, 2, 3$: the volume fractions of the cells:
  - $\phi_1 = P$: **proliferating tumor cell fraction**
  - $\phi_2 = \phi_D$: dead tumor cell fraction
  - $\phi_3 = \phi_H$: host cell fraction

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Moreover, we denote by

- $\mathbf{J}_i$: the fluxes that account for mechanical interactions among the species
- $S_i, i = 1, 2, 3$: the terms accounting for inter-component mass exchange as well as gains due to proliferation of cells and loss due to cell death

The volume fractions obey the mass conservation (advection-reaction-diffusion) equations:

$$\partial_t \phi_i + \mathrm{div}_x(\mathbf{u}\phi_i) = -\mathrm{div}_x \mathbf{J}_i + \Phi S_i$$

We have assumed that the densities of the components are matched

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The total energy adhesion has the form

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

where $\mathcal{F}$ is a logarithmic type mixing potential

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We define the fluxes $\mathbf{J}_\Phi$ and $\mathbf{J}_H$ as follows:

$$\mathbf{J}_\Phi = \mathbf{J}_1 + \mathbf{J}_2 := -\nabla_x \left(\frac{\delta E}{\delta \Phi} \right) = -\nabla_x \left(\mathcal{F}'(\Phi) - \Delta \Phi \right) := -\nabla_x \mu$$

$$\mathbf{J}_H = \mathbf{J}_3 := -\nabla_x \left(\frac{\delta E}{\delta \phi_H} \right) = \nabla_x \left(\frac{\delta E}{\delta \Phi} \right)$$

where we have used in the last equality the fact that $\phi_H = 1 - \Phi$ and where μ is the chemical potential of the system

For the source of mass in the host tissue we have the following relations:

- $S_T = S_D + S_P := S_2 + S_1$
- $\Phi S_H := \Phi S_3 := \phi_H S_T = (1 - \Phi) S_T$

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Assuming the mobility of the system to be constant, then the tumor volume fraction Φ and the host tissue volume fraction ϕ_H obey the following mass conservation equations

$$\partial_t \Phi + \mathrm{div}_x(\mathbf{u}\Phi) = -\mathrm{div}_x \mathbf{J}_\Phi + \Phi(S_2 + S_1)$$

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Using now the fact that $S_T = S_1 + S_2$ and recalling that $\phi_H + \Phi = 1$, $\mathbf{J}_\Phi = -\nabla_x \mu$, we can forget of the equation for ϕ_H and we recover the equation for Φ in the form

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

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Suppose the net source of tumor cells S_T to be given by

$$S_T = S_T(n, P, \Phi) = \lambda_M n P - \lambda_L (\Phi - P)$$

where $\lambda_M \geq 0$ is the mitotic rate and $\lambda_L \geq 0$ is the lysing rate of dead cells

The volume fraction of dead tumor cells ϕ_D would satisfy an equation similar to the one of Φ. However, we prefer to couple the equation for Φ with the one for $P = \Phi - \phi_D$ which then reads

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

where the source of dead cells is taken as

$$S_D = S_D(n, P, \Phi) = (\lambda_A + \lambda_N H(n_N - n))\, P - \lambda_L(\Phi - P)$$

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Here

- $\lambda_A P$ describes the death of cells due to apoptosis with rate $\lambda_A \geq 0$ and the term $\lambda_N H(n_N - n)P$ models the death of cells due to necrosis with rate $\lambda_N \geq 0$
- for mathematical reasons, we choose H to be a regular and nonnegative function of n
- the term n_N represents the necrotic limit, at which the tumor tissue dies due to lack of nutrients

The tumor velocity field $\mathbf{u}$ (given by the mass-averaged velocity of all the components) is assumed to fulfill Darcy's law:

$$\boxed{\mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi}$$

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Summing up the mass balance equations

$$\partial_t \Phi + \mathrm{div}_x(\mathbf{u}\Phi) = -\mathrm{div}_x \mathbf{J}_\Phi + \Phi S_T$$
$$\partial_t \phi_H + \mathrm{div}_x(\mathbf{u}\phi_H) = -\mathrm{div}_x \mathbf{J}_H + (1-\Phi) S_T$$

and using $\Phi + \phi_H = 1$ and $J_H = -J_\Phi$, we end up with the following constraint for the velocity field:

$$\boxed{\mathrm{div}_x \mathbf{u} = S_T = \lambda_M n P - \lambda_L(\Phi - P)}$$

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

$$\boxed{-\Delta n + \nu_U n P = T_c(n, \Phi)}$$

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

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Here

- ν_U represents the nutrient uptake rate by the viable tumor cells
- ν_1, ν_2 denote the nutrient transfer rates for preexisting vascularization in the tumor and host domains
- n_c is the nutrient level of capillaries
- the function $Q(\Phi)$ is regular and satisfies $\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi) \geq 0$

- We chose the boundary conditions proposed in [**CWSL**: Y. Chen, S.M. Wise, V.B Shenoy, J.S. Lowengrub, Int. J. Numer. Methods Biomed. Eng., 2014] for Φ, μ, Π and n (with ν denoting the outer normal unit vector to $\partial\Omega$):

$$\mu = \Pi = 0, \quad n = 1, \quad \nabla_x \Phi \cdot \nu = 0$$

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$$P\mathbf{u} \cdot \nu \geq 0$$

which are natural in connection with the transport equation for P

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In particular, the proliferation function at the boundary has to be nonnegative on the set where the velocity $\mathbf{u}$ satisfies $\mathbf{u} \cdot \nu > 0$. By maximum principle, then $P \geq 0$ in Ω, which is an information we need for proving well-posedness of the system

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:

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

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

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

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

where

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

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

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

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

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

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

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

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

R1. Note that, as $P \geq 0$, the boundary condition $P\mathbf{u} \cdot \nu \geq 0$ should be interpreted as $P = 0$ **whenever** $\mathbf{u} \cdot \nu < 0$, meaning on the part of the inflow part of the boundary.

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R2. Condition

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

has mainly a technical character and is assumed just for the purpose of constructing a not too complicated approximation scheme. At the price of some additional technical work it could be avoided. One may, for instance, consider the case where $\mathcal{C}(\Phi) = I_{[0,1]}(\Phi)$ (the *indicator function* of $[0,1]$), which does not satisfy this condition

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:

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

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

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

(i) these functions belong to the regularity class:

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

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

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

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

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

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

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

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

Now, we are able to state the main result of **[M. Dai, E. Feireisl, E.R., G. Schimperna, M. Schonbek, Analysis of a diffuse interface model of multispecies tumor growth, preprint arXiv:1507.07683 (2015)]**

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 $[0, T]$*

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

- The transport equation for the density function P is

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

Thus, provided

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

we can deduce by maximum principle arguments that

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- In order to obtain positivity of n we need

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

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

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

Since $0 \leq \Phi \leq 1$ and $0 \leq n \leq 1$, we have

$$-\Phi\left(\lambda_1 + \lambda_2 H(n_N - n)\right) \leq 0$$

Hence evaluating the expression on the right-hand side of

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

for $P = 1$ yields

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

Consequently, provided

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

it follows that

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

Testing by μ the Cahn-Hilliard equation

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

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

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

Seeing that Π solves the Dirichlet problem

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

we deduce that

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

where, by means of Gagliardo-Nirenberg interpolation inequality,

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

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

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

Note that we already know

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

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

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

Hence, in view of the fact that $\mathrm{div}_x(\varphi\mathbf{u})$ and $\mathbf{curl}(\varphi\mathbf{u})$ 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 $\varphi\mathbf{u}$ is bounded in $L^1(0,T;H^1(\mathbb{R}^3))$ and so $\mathbf{u}$ satisfies

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

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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

We consider the simplified problem obtained by taking $S_T = S_D = 0$

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Hence we consider the system for Φ and $\mathbf{u}$, decoupled from the rest, of the form

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

$$\mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi, \quad \operatorname{div}_x \mathbf{u} = 0$$

with the boundary conditions

$$\mathbf{u} \cdot \nu|_{\partial\Omega} = 0,\ \nabla_x \Phi \cdot \nu|_{\partial\Omega} = 0,\ \mu|_{\partial\Omega} = 0$$

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Main goal: pass to the limit as $\varepsilon \to 0$

We derive the energy balance

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \left[\frac{\varepsilon^2}{2}|\nabla_x\Phi|^2 + \mathcal{F}(\Phi)\right]\ \mathrm{d}x + \int_\Omega |\nabla_x\mu|^2 + |\mathbf{u}|^2\ \mathrm{d}x = 0$$

Next, we have

$$\int_\Omega \left[\varepsilon^2|\Delta\Phi|^2 + \mathcal{F}''(\Phi)|\nabla_x\Phi|^2\right]\ \mathrm{d}x = \int_\Omega \nabla_x\mu\cdot\nabla_x\Phi\ \mathrm{d}x$$

Then, assuming strict convexity of $\mathcal{F}$, namely

$$\mathcal{F}'' \geq \lambda > 0$$

the following estimates can be deduced

$$\int_0^T \|\varepsilon\Delta\Phi\|^2_{L^2(\Omega)}\ \mathrm{d}t \leq c, \qquad \int_0^T \|\nabla_x\Phi\|^2_{L^2(\Omega;\mathbb{R}^3)}\ \mathrm{d}t \leq c$$

Hence, we may assume there is a subsequence such that

$$\mathbf{u}_\varepsilon \to \mathbf{u} \quad \text{weakly in } L^2((0,T)\times\Omega;\mathbb{R}^3)$$

Obviously, we have $\mathrm{div}_x\mathbf{u} = 0$, $\mathbf{u}\cdot\nu|_{\partial\Omega} = 0$ We can now write

$$\mathbf{u}_\varepsilon = -\nabla_x\left(\Pi_\varepsilon - \mathcal{F}(\Phi_\varepsilon)\right) - \varepsilon^2\Delta\Phi_\varepsilon\nabla_x\Phi_\varepsilon$$

whence, seeing that

$$\varepsilon^2\Delta\Phi_\varepsilon\nabla_x\Phi_\varepsilon \to 0 \text{ in } L^1((0,T)\times\Omega)$$

we conclude that $\mathbf{curl}_x\mathbf{u} = 0$, which, combined with $\mathrm{div}_x\mathbf{u} = 0$, $\mathbf{u}\cdot\nu|_{\partial\Omega} = 0$, yields

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$$\mathbf{u} = 0$$

Therefore, taking $\varepsilon \to 0$, our system converges to

$$\partial_t\Phi - \Delta\mu = 0, \qquad \mu = \mathcal{F}'(\Phi)$$

and satisfies the energy law

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega \mathcal{F}(\Phi)\ \mathrm{d}x + \int_\Omega |\nabla_x\mu|^2\ \mathrm{d}x = 0$$

Theorem

Let the assumptions listed before hold, let $\mathcal{F}$ satisfy the strict convexity assumption, and let $(\Phi_\varepsilon, \mu_\varepsilon, \mathbf{u}_\varepsilon)$ denote a family of weak solutions to the system

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

$$\mathbf{u} = -\nabla_x \Pi + \mu \nabla_x \Phi, \quad \mathrm{div}_x \mathbf{u} = 0$$

with the b.c. $\mathbf{u} \cdot \nu|_{\partial\Omega} = 0$, $\nabla_x \Phi \cdot \nu|_{\partial\Omega} = 0$, $\mu|_{\partial\Omega} = 0$ *and the Cauchy conditions. Then, as* $\varepsilon \to 0$, *the functions* $(\Phi_\varepsilon, \mu_\varepsilon, \mathbf{u}_\varepsilon)$ *suitably tend to a triple* $(\Phi, \mu, 0)$ *satisfying*

$$\partial_t \Phi - \Delta \mu = 0, \qquad \mu = \mathcal{F}'(\Phi)$$

together with the energy law

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_\Omega \mathcal{F}(\Phi) \ \mathrm{d}x + \int_\Omega |\nabla_x \mu|^2 \ \mathrm{d}x = 0$$

and the initial and boundary conditions

- **Numerical simulations** of diffuse-interface models for tumor growth have been carried out in several papers (cf., e.g., [V. Cristini, J. Lowengrub, Cambridge Univ. Press, 2010] and more recently [H. Garcke, K.F. Lam, E. Sitka, V. Styles, arXiv:1508.00437, 2015]). However, a rigorous mathematical analysis of the resulting PDEs is still in its beginning

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- To the best of our knowledge, the first related papers are concerned with a simplified model, 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 [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

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- Moreover, very recent contributions **FGR** and **CGRS1, CGRS2** are devoted to the analysis of a newly proposed simpler model in [A. Hawkins-Daarud, K.G. van der Zee, J.T. Oden, Int. J. Numer. Methods Biomed. Eng., 2012] and [D. Hilhorst, J. Kampmann, T.N. Nguyen, K.G. van der Zee, M3AS, 2015]. In this model, velocities are set to zero and the state variables are reduced to the tumor cell fraction and the nutrient-rich extracellular water fraction

Part 2: the HZO model - two-phase with 0 velocity

Consider a simplified version of a model proposed by [A. Hawkins-Daarud, K.G. van der Zee & J.T. Oden, 2011].

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Then, the new variables are:

- φ: the **tumor cell fraction** obeyng a Cahn-Hilliard equation with reaction
- n: the **nutrient fraction** (e.g. the oxygen) obeyng a reaction-diffusion equation coupled to the Cahn-Hilliard one

$$\varphi_t = \Delta\mu + p(\varphi)(n - \mu), \quad \mu = -\Delta\varphi + F'(\varphi)$$
$$n_t = \Delta n - p(\varphi)(n - \mu)$$

in $\Omega \times (0, \infty)$, where $\Omega \subset \mathbb{R}^3$ is a bounded smooth domain.

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in $\Omega \times (0, \infty)$, where $\Omega \subset \mathbb{R}^3$ is a bounded smooth domain. The coupling is given by reaction terms containing a **proliferation function** p (e.g. $p(s) = p_0(1 - s^2)\chi_{[-1,1]}(s)$ for $s \in \mathbb{R}$, $p_0 > 0$). Here, F is a **double-well potential** associated with the Ginzburg-Landau free-energy functional. The system is endowed with no-flux boundary conditions and initial conditions

Assume $\varphi_0 \in H^1(\Omega)$, $n_0 \in L^2(\Omega)$ and

- $F \in C^2(\mathbb{R})$ s.t. $F(s) = F_0(s) + \lambda(s)$, $\lambda \in C^2(\mathbb{R})$ satisfies $|\lambda''(s)| \leq \alpha$, for some $\alpha \geq 0$, and for $c_1,\ c_2,\ c_3 > 0,\ c_4 \in \mathbb{R}$:

$$c_1(1 + |s|^{\rho-2}) \leq F_0''(s) \leq c_2(1 + |s|^{\rho-2}),\ \rho \in [\mathbf{2}, \mathbf{6}),\ F(s) \geq c_3|s| - c_4$$

- $p \in C^{0,1}_{loc}(\mathbb{R})$ s.t. $0 \leq p(s) \leq c_5(1 + |s|^q), \qquad c_5 > 0, \quad \mathbf{q} \in [\mathbf{1}, \mathbf{9})$

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Theorem

Then, $\forall T > 0\ \exists$ *a weak solution* $\varphi \in L^\infty(0, T; H^1(\Omega)) \cap L^2(0, T; H^3(\Omega))$, $\mu \in L^2(0, T; H^1(\Omega))$, $n \in L^\infty(0, T; L^2(\Omega)) \cap L^2(0, T; H^1(\Omega))$ *satisfying the Energy Inequality (equality if* $q \le 4$*):*

$$\frac{d}{dt}\mathcal{E}(\varphi, n) + \|\nabla\mu\|^2 + \|\nabla n\|^2 + \int_\Omega p(\varphi)(\mu - n)^2 = 0$$

where $\mathcal{E}(\varphi, n) := \frac{1}{2}\|\nabla\varphi\|^2 + \frac{1}{2}\|n\|^2 + \int_\Omega F(\varphi)$

Under the additional assumption

- $p \in C^{0,1}_{loc}(\mathbb{R})$ s.t. $p \geq 0$ and $|p'(s)| \leq c_6(1 + |s|^{q-1}), \quad c_6 > 0, \quad \mathbf{1 \leq q \leq 4}$

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Then, the weak solution is unique and a continuous dependence estimate holds in $H^1(\Omega)' \times H^1(\Omega)'$

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Theorem

Let $\varphi_0 \in H^3(\Omega)$ *and* $n_0 \in H^1(\Omega)$. *Then,* $\forall T > 0 \; \exists$ *a strong solution s.t.* $\varphi \in L^\infty(0,T;H^3(\Omega))$, $\mu \in L^\infty(0,T;H^1(\Omega))$, $n \in L^\infty(0,T;H^1(\Omega))$. *Moreover, the dynamical system* $(\mathcal{W}_M, \{S_M(t)\})$ *generated in the phase-space* $\mathcal{W}_M$ *of bdd. energy* $\mathcal{E} \leq M$ *possesses the global attractor*

The PDE system of [FGR] can also be approximated by the relaxed system

$$\alpha\mu_t + \varphi_t = \Delta\mu + p(\varphi)(n-\mu), \quad \mu = \beta\varphi_t - \Delta\varphi + F'(\varphi)$$
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CGRS1 asymptotics for $(\alpha, \beta) \to (0,0)$ in case of regular (at most exponentially growing) potential & error estimate with $\alpha^{1/2} + \beta^{1/2}$ in case of $F''(r) = O(r^4)$ as $|r| \to \infty$

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- $\alpha \to 0$ and $\beta > 0$ fixed in case of regular (at most exponentially growing) potential. Uniqueness for the limit problem is open in general. We know it is true in case $F''(r) = O(r^2)$ as $|r| \to \infty$ and $p \in \mathbb{R}^+$ & an error estimate of the order $\alpha^{1/2}$

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- $\beta\to 0$ and $\alpha>0$ fixed in case of general F (sum of a convex and a regular part) but with α small & an error estimate of the order $\beta^{1/2}$. The coefficient α has to be small with respect to the Lipschitz constant $L=\mathrm{Lip}(\pi)$ of the smooth and non convex part π of the potential F.

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coupled with homogeneous Neumann BCs and ICs.

Here F is a double well potential and p a nonnegative smooth function of φ. We get:

CGRS1 asymptotics for $(\alpha,\beta)\to(0,0)$ in case of regular (at most exponentially growing) potential & error estimate with $\alpha^{1/2}+\beta^{1/2}$ in case of $F''(r)=O(r^4)$ as $|r|\to\infty$

CGRS2 asymptotics & uniqueness & error estimates for

- $\alpha\to 0$ and $\beta>0$ fixed in case of regular (at most exponentially growing) potential. Uniqueness for the limit problem is open in general. We know it is true in case $F''(r)=O(r^2)$ as $|r|\to\infty$ and $p\in\mathbb{R}^+$ & an error estimate of the order $\alpha^{1/2}$
- $\beta\to 0$ and $\alpha>0$ fixed in case of general F (sum of a convex and a regular part) but with α small & an error estimate of the order $\beta^{1/2}$. The coefficient α has to be small with respect to the Lipschitz constant $L=\mathrm{Lip}(\pi)$ of the smooth and non convex part π of the potential F. We have troubles in the limit problem for $L\alpha=1$!

From the Energy Estimate:

$$\frac{d}{dt}\left[\alpha^{1/2}\|\mu\|^2 + \|\nabla\varphi\|^2 + \|n\|^2 + 2\int_\Omega F(\varphi)\right]$$
$$+ 2\beta^{1/2}\|\varphi_t\|^2 + 2\|\nabla\mu\|^2 + 2\|\nabla n\|^2 + 2\int_\Omega p(\varphi)(\mu - n)^2 = 0$$

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$$\mu = \beta\varphi_t - \Delta\varphi + F'(\varphi)$$

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F' to be controlled by F

which is already estimated in $L^\infty(0,T;L^1(\Omega))$. This corresponds basically to assume that the convex part of F has domain $\mathbb{R}$ and it grows at most exponentially

On the [DFRSS] system:

- It would be interesting to investigate whether similar estimates could be derived for the singular flux

$$\mathbf{u} = -\nabla_x \Pi + \frac{1}{\varepsilon} \mu \nabla_x \Phi$$

However, the above argument does **not** seem to be easily **adaptable** to cover such a situation. For instance, we cannot prove uniform integrability of the product

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On the [FGR] system:

- The **optimal control** problem: almost completed the distributed control case together with P. Colli, G. Gilardi, J. Sprekels
- The rigorous **sharp interface** limit as $\varepsilon \to 0$ in

$$\varphi_t = \Delta\mu + p(\varphi)(n-\mu), \quad \mu = -\varepsilon\Delta\varphi + \frac{1}{\varepsilon}F'(\varphi), \quad n_t = \Delta n - p(\varphi)(n-\mu)$$

This is a very difficult issue. We have some partial results with R. Scala on a related gradient flow system...