On some diffuse interface models of multispecies tumor growth

E. Rocca

Università degli Studi di Pavia

Eleventh Workshop on Mathematical Modelling of Environmental and Life Sciences Problems

Constanta, October 12–16, 2016

Supported by the FP7-IDEAS-ERC-StG Grant "EntroPhase" #256872

Plan of the Lecture

- Diffuse interface models in **Biology: tumor growth models**

Plan of the Lecture

- Diffuse interface models in **Biology: tumor growth models**
  Sharp interfaces $\Longrightarrow$ narrow transition layers - differential adhesive forces among cell-species

Plan of the Lecture

- Diffuse interface models in **Biology: tumor growth models**
  Sharp interfaces $\Longrightarrow$ narrow transition layers - differential adhesive forces among cell-species
  The main *advantages of the diffuse interface* formulation are:

Plan of the Lecture

- Diffuse interface models in **Biology: tumor growth models**
  Sharp interfaces $\Longrightarrow$ narrow transition layers - differential adhesive forces among cell-species
  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

Plan of the Lecture

- Diffuse interface models in **Biology: tumor growth models**
  Sharp interfaces $\Longrightarrow$ narrow transition layers - differential adhesive forces among cell-species
  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

Part 1. **Multispecies model**: Existence of solutions: **[DFRSS]** M. Dai, E. Feireisl, E.R., G. Schimperna, M. Schonbek, preprint arXiv:1507.07683 (2015) $\Longrightarrow$ **Existence of weak solutions** for the PDE system corresponding to the recent model by [**CWSL**: Y. Chen, S.M. Wise, V.B Shenoy, J.S. Lowengrub, Int. J. Numer. Methods Biomed. Eng., 2014] coupled with suitable initial and boundary conditions

Plan of the Lecture

- Diffuse interface models in **Biology: tumor growth models**
  Sharp interfaces $\Longrightarrow$ narrow transition layers - differential adhesive forces among cell-species
  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

Part 1. **Multispecies model**: Existence of solutions: **[DFRSS]** M. Dai, E. Feireisl, E.R., G. Schimperna, M. Schonbek, preprint arXiv:1507.07683 (2015) $\Longrightarrow$ **Existence of weak solutions** for the PDE system corresponding to the recent model by [**CWSL**: Y. Chen, S.M. Wise, V.B Shenoy, J.S. Lowengrub, Int. J. Numer. Methods Biomed. Eng., 2014] coupled with suitable initial and boundary conditions

Part 2. **One Species model**: Optimal control: **[GLR]** H. Garcke, K.-F. Lam, E.R., manuscript (2016) $\Longrightarrow$ **First order necessary optimality conditions** for both the cytotoxic concentration and the treatment time

Plan of the Lecture

- Diffuse interface models in **Biology: tumor growth models**
  Sharp interfaces $\Longrightarrow$ narrow transition layers - differential adhesive forces among cell-species
  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

Part 1. **Multispecies model**: Existence of solutions: **[DFRSS]** M. Dai, E. Feireisl, E.R., G. Schimperna, M. Schonbek, preprint arXiv:1507.07683 (2015) $\Longrightarrow$ **Existence of weak solutions** for the PDE system corresponding to the recent model by [**CWSL**: Y. Chen, S.M. Wise, V.B Shenoy, J.S. Lowengrub, Int. J. Numer. Methods Biomed. Eng., 2014] coupled with suitable initial and boundary conditions

Part 2. **One Species model**: Optimal control: **[GLR]** H. Garcke, K.-F. Lam, E.R., manuscript (2016) $\Longrightarrow$ **First order necessary optimality conditions** for both the cytotoxic concentration and the treatment time

- Ongoing projects and open problems

Part 1 - Multispecies Model

DFRSS: The model

Typical structure of tumors grown in vitro:

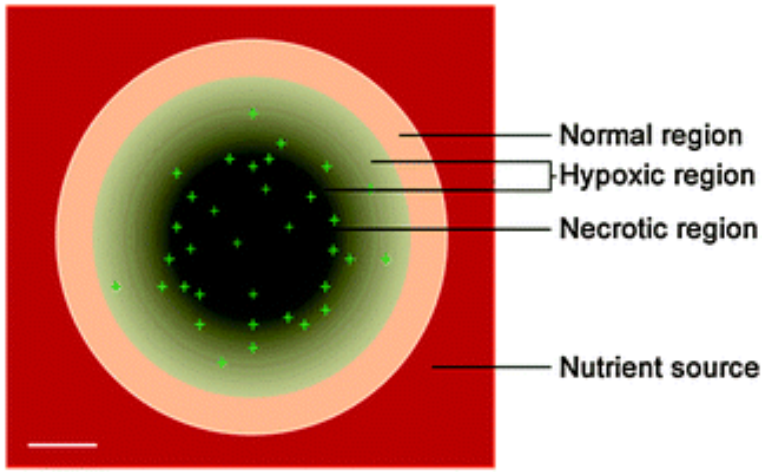

Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100μm = 0:1mm

DFRSS: The model

Typical structure of tumors grown in vitro:

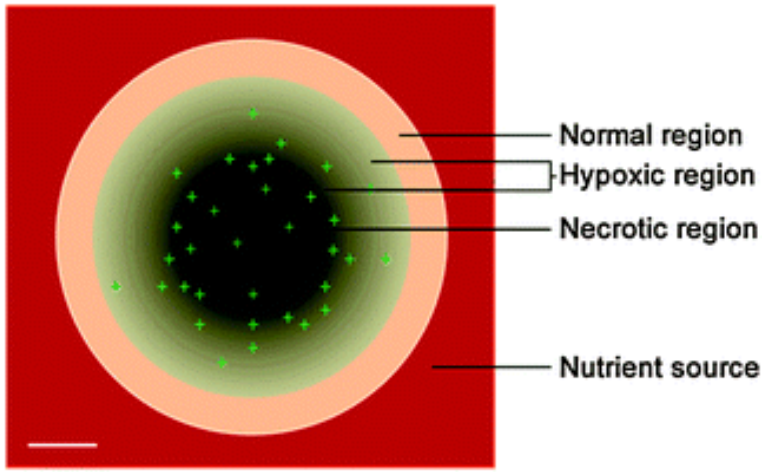

Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100μm = 0:1mm

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)

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
  - $\phi_3 = \phi_H$: healthy cell fraction

  The variables above are naturally constrained by the relation $\sum_{i=1}^{3} \phi_i = \phi_H + \Phi = 1$

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
  - $\phi_3 = \phi_H$: healthy cell fraction

  The variables above are naturally constrained by the relation $\sum_{i=1}^{3} \phi_i = \phi_H + \Phi = 1$
- $\Phi = \phi_D + P$: **the volume fraction of the tumor cells** split into the sum of the dead tumor cells and of the proliferating cells

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
  - $\phi_3 = \phi_H$: healthy cell fraction

  The variables above are naturally constrained by the relation $\sum_{i=1}^{3} \phi_i = \phi_H + \Phi = 1$
- $\Phi = \phi_D + P$: **the volume fraction of the tumor cells** split into the sum of the dead tumor cells and of the proliferating cells
- n: **the nutrient concentration**

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
  - $\phi_3 = \phi_H$: healthy cell fraction

  The variables above are naturally constrained by the relation $\sum_{i=1}^{3} \phi_i = \phi_H + \Phi = 1$
- $\Phi = \phi_D + P$: **the volume fraction of the tumor cells** split into the sum of the dead tumor cells and of the proliferating cells
- n: **the nutrient concentration**
- $\mathbf{u} := \mathbf{u}_i, i = 1, 2, 3$: **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: Mass conservation and choice of the energy

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

DFRSS: Mass conservation and choice of the energy

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
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

DFRSS: Mass conservation and choice of the energy

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
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
The fluxes $\mathbf{J}_\Phi$ and $\mathbf{J}_H$ that account for mechanical interactions among the species are 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

DFRSS: The convective Cahn-Hilliard equation for the tumor cells fraction

For the source of mass in the host tissue, accounting for gains due to proliferation of cells and loss due to cell death, we have the following relations:

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

DFRSS: The convective Cahn-Hilliard equation for the tumor cells fraction

For the source of mass in the host tissue, accounting for gains due to proliferation of cells and loss due to cell death, we have the following relations:

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

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

$$\partial_t \Phi + \mathrm{div}_x(\mathbf{u}\Phi) = -\mathrm{div}_x \mathbf{J}_\Phi + \Phi(S_2 + S_1)$$
$$\partial_t \phi_H + \mathrm{div}_x(\mathbf{u}\phi_H) = -\mathrm{div}_x \mathbf{J}_H + \Phi S_3$$

DFRSS: The convective Cahn-Hilliard equation for the tumor cells fraction

For the source of mass in the host tissue, accounting for gains due to proliferation of cells and loss due to cell death, we have the following relations:

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

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

$$\partial_t \Phi + \mathrm{div}_x(\mathbf{u}\Phi) = -\mathrm{div}_x \mathbf{J}_\Phi + \Phi(S_2 + S_1)$$
$$\partial_t \phi_H + \mathrm{div}_x(\mathbf{u}\phi_H) = -\mathrm{div}_x \mathbf{J}_H + \Phi S_3$$

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

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

DFRSS: The convective Cahn-Hilliard equation for the tumor cells fraction

For the source of mass in the host tissue, accounting for gains due to proliferation of cells and loss due to cell death, we have the following relations:

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

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

$$\partial_t \Phi + \mathrm{div}_x(\mathbf{u}\Phi) = -\mathrm{div}_x \mathbf{J}_\Phi + \Phi(S_2 + S_1)$$
$$\partial_t \phi_H + \mathrm{div}_x(\mathbf{u}\phi_H) = -\mathrm{div}_x \mathbf{J}_H + \Phi S_3$$

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

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

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

DFRSS: The transport equation for the proliferating cells fraction

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

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

DFRSS: The transport equation for the proliferating cells fraction

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

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

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

DFRSS: The Darcy law for the velocity field

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

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

where, for simplicity, the motility has been taken constant and equal to 1

DFRSS: The Darcy law for the velocity field

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

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

where, for simplicity, the motility has been taken constant and equal to 1

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 $\mathbf{J}_H = -\mathbf{J}_\Phi$, we end up with the following constraint for the velocity field:

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

DFRSS: The quasistatic reaction diffusion equation for the nutrient

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

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

DFRSS: The quasistatic reaction diffusion equation for the nutrient

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

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

where the nutrient capillarity term T_c is

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

DFRSS: The quasistatic reaction diffusion equation for the nutrient

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

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

where the nutrient capillarity term T_c is

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

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 $\nu_1(1 - Q(\Phi)) + \nu_2 Q(\Phi) \geq 0$

DFRSS: The boundary conditions

- 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 $\partial\Omega$):

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

DFRSS: The boundary conditions

- 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 $\partial\Omega$):

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

- On the other hand, under the homogeneous Neumann boundary conditions suggested in **[CWSL]** for P, we could not show that the system had weak solutions.

DFRSS: The boundary conditions

- 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 $\partial\Omega$):

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

- On the other hand, under the homogeneous Neumann boundary conditions suggested in **[CWSL]** for P, we could not show that the system had weak solutions. For this reason, we chose the boundary conditions:

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

DFRSS: The boundary conditions

- 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 $\partial\Omega$):

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

- On the other hand, under the homogeneous Neumann boundary conditions suggested in **[CWSL]** for P, we could not show that the system had weak solutions. For this reason, we chose the boundary conditions:

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

- They are natural in connection with the transport equation for P

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

DFRSS: The boundary conditions

- 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 $\partial\Omega$):

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

- On the other hand, under the homogeneous Neumann boundary conditions suggested in **[CWSL]** for P, we could not show that the system had weak solutions. For this reason, we chose the boundary conditions:

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

- They are natural in connection with the transport equation for P

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

- 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

DFRSS: The boundary conditions

- 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 $\partial\Omega$):

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

- On the other hand, under the homogeneous Neumann boundary conditions suggested in **[CWSL]** for P, we could not show that the system had weak solutions. For this reason, we chose the boundary conditions:

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

- They are natural in connection with the transport equation for P

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

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

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 $\lambda_M = \nu_U = 1$, $\lambda_A = \lambda_1$, $\lambda_N = \lambda_2$, $\lambda_L = \lambda_3$.

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 $\lambda_M = \nu_U = 1$, $\lambda_A = \lambda_1$, $\lambda_N = \lambda_2$, $\lambda_L = \lambda_3$.
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

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* $[0, T]$

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

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

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

$$P \geq 0$$

DFRSS: The maximum principle

- The transport equation for the density function P is

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

  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

$$P \geq 0$$

- 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

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

for $P = 1$, 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

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

it follows that

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

DFRSS: Main estimates on Φ

Testing by μ the Cahn-Hilliard equation

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

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

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

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

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

where, by means of Gagliardo-Nirenberg interpolation inequality,

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

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

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

DFRSS: Main estimates on **u**

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 **(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

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

DFRSS: Main estimates on **u**

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 **(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

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

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

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. [Garcke, Lam, J. Appl. Math and arXiv:1604.00287, 2016])

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. [Garcke, Lam, J. Appl. Math and arXiv:1604.00287, 2016])

- To the best of our knowledge, the first related mathematical papers study simplified models:

  - 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

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. [Garcke, Lam, J. Appl. Math and arXiv:1604.00287, 2016])

- To the best of our knowledge, the first related mathematical papers study simplified models:
  - 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

Perspectives and Open problems

- 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:

Perspectives and Open problems

- 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:
  - 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
  - the choice of the right boundary conditions for $\boldsymbol{u}$ and μ_i: apparently $M_i \nabla \mu_i \cdot \nu + \phi_i \boldsymbol{u} \cdot \nu = 0$ on $\partial\Omega$ works!

Perspectives and Open problems

- 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:
  - 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
  - the choice of the right boundary conditions for $\boldsymbol{u}$ and μ_i: apparently $M_i \nabla \mu_i \cdot \nu + \phi_i \boldsymbol{u} \cdot \nu = 0$ on $\partial\Omega$ works!
- To study the **sharp interface limit** as $\varepsilon \searrow 0$ in the coupled Cahn-Hilliard-Darcy system where

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

  - Very partial result in **[DFRSS]** assuming strict convexity of $\mathcal{F}$ and $S_T = S_D = 0$

Perspectives and Open problems

- 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:
  - 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
  - the choice of the right boundary conditions for $\boldsymbol{u}$ and μ_i: apparently $M_i \nabla \mu_i \cdot \nu + \phi_i \boldsymbol{u} \cdot \nu = 0$ on $\partial\Omega$ works!
- To study the **sharp interface limit** as $\varepsilon \searrow 0$ in the coupled Cahn-Hilliard-Darcy system where

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

  - Very partial result in **[DFRSS]** assuming strict convexity of $\mathcal{F}$ and $S_T = S_D = 0$
  - An ongoing project with S. Melchionna: **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)

Part 2 - One Species Model: Optimal Control

One Species Diffuse Interface Model

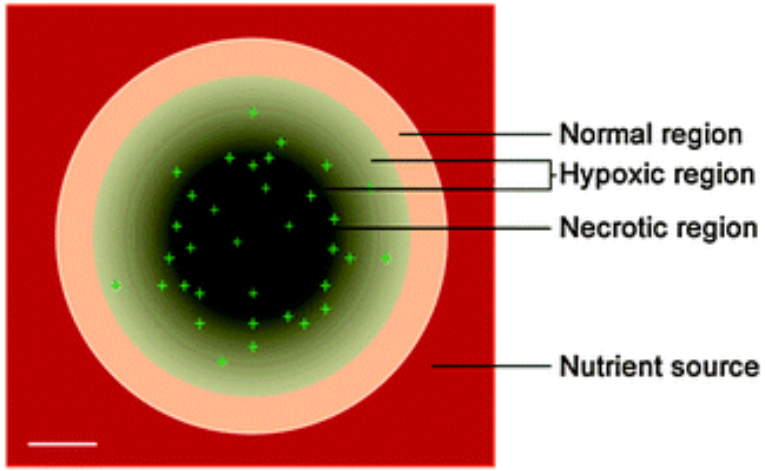

Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100μm = 0:1mm

One Species Diffuse Interface Model

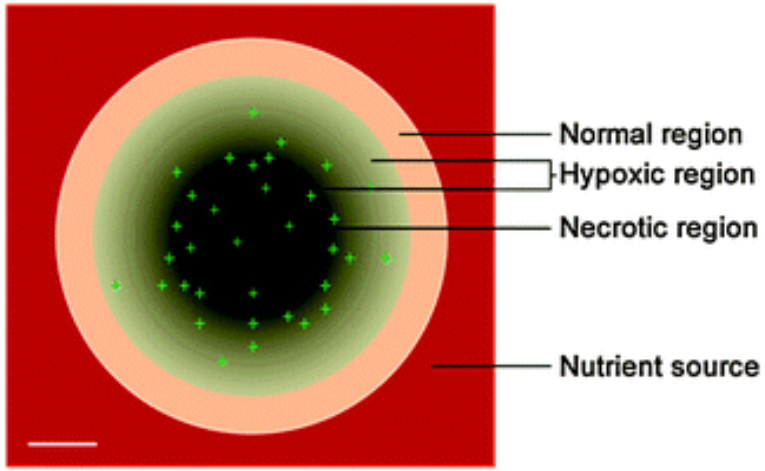

Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100μm = 0:1mm

In **[GLR] H. Garcke, K.-F. Lam, E.R., Optimal control of treatment time in a diffuse interface model of tumor growth, manuscript (2016)** we study the case where there are only proliferating tumor cells surrounded by (healthy) host cells, and a nutrient (e.g. glucose) is present and we neglect velocities

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.
- Surgery.

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.
- 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. The length of a full course of treatment is typically 6 months (i.e., 6 cycles).

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.
- 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. The length of a full course of treatment is typically 6 months (i.e., 6 cycles).

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).

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.
- 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. The length of a full course of treatment is typically 6 months (i.e., 6 cycles).

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.

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.
- 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. The length of a full course of treatment is typically 6 months (i.e., 6 cycles).

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.

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

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

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

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

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

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

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

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

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

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

The source term $\mathcal{M}$ accounts for biological mechanisms related to proliferation and death. Introduce a nutrient for the tumor cells

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

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

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

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

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

The source term $\mathcal{M}$ accounts for biological mechanisms related to proliferation and death. Introduce a nutrient for the tumor cells

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

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

We consider

- Linear kinetics (as in Part 1) [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.
- A regular double-well potential Ψ
- Reaction-diffusion equation for the nutrient (here σ, while it was n in Part 1)

GLR: Objective functional

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

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

GLR: Objective functional

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

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

- 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.

GLR: Objective functional

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

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

- 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.

GLR: Objective functional

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

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

- 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.

However, we will not study this functional, but a relaxed version! Let $r > 0$ be fixed and let $T \in (0, \infty)$ denote a maximal time, we define

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

GLR: Relaxed objective functional

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

GLR: Fréchet differentiability with respect to time

Lemma

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

$$\mathrm{D}_\tau \left(\int_0^\tau \int_\Omega |f|^2 \right) = \int_\Omega |f(\tau)|^2 \,.$$

GLR: Fréchet differentiability with respect to time

Lemma

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

$$\mathrm{D}_\tau \left(\int_0^\tau \int_\Omega |f|^2 \right) = \int_\Omega |f(\tau)|^2 .$$

Then, for

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

we have

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

GLR: Fréchet differentiability with respect to time

Lemma

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

$$\mathrm{D}_\tau \left(\int_0^\tau \int_\Omega |f|^2 \right) = \int_\Omega |f(\tau)|^2 .$$

Then, for

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

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.

GLR: 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

GLR: 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

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

Open related problem

To deal with the original functional:

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

Open related problem

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

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

Open related problem

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 and to apply the lemma, we need

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

Open related problem

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 and to apply the lemma, 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 some fixed $K > 0$, and impose $\varphi_0 \in H^5$, $\sigma_0 \in H^3$, then it is possible to obtain

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

Open related problem

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 and to apply the lemma, 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 some fixed $K > 0$, and impose $\varphi_0 \in H^5$, $\sigma_0 \in H^3$, then it is possible to obtain

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

However, to require the a-priori boundedness of $\partial_t u$ is not meaningful (difficult to verify in applications).

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 $\mathcal{S}$:

- Linear phenomenological laws for chemical reactions [Hawkins–Daarud, Prudhomme, van der Zee, Oden], [Frigeri, Grasselli, E.R.], [Colli, Gilardi, E.R., Sprekels: optimal control without time dependence and with the control in the nutrient equation]:

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

- 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, preprint arXiv:1606.04663 (2016)]**:

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

Many thanks to all of you for the attention!

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