A Cahn-Hilliard-Keller-Segel model with generalized logistic source describing tumor growth

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Outline

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Setting

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

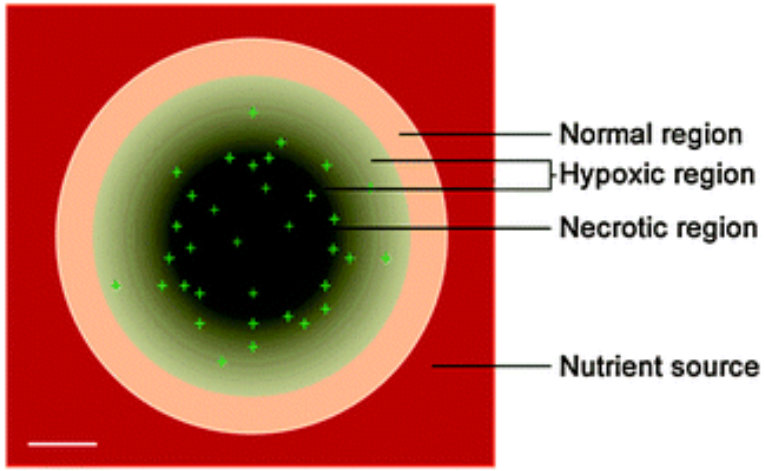


Figure: Zhang et al. Integr. Biol., 2012, 4, 1072–1080. Scale bar 100μm = 0:1mm

A continuum thermodynamically consistent model is introduced with the ansatz:

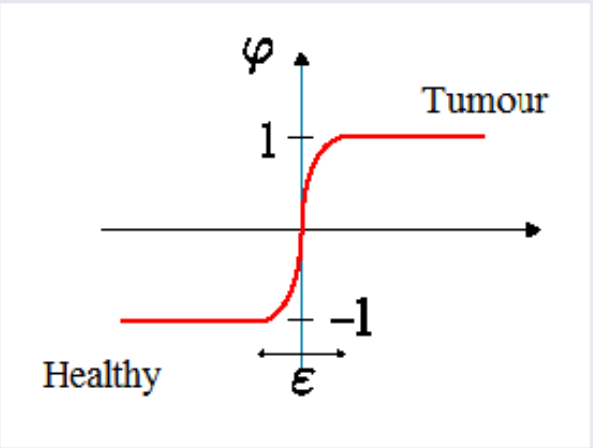
- sharp interfaces are replaced by narrow transition layers arising due to adhesive forces among the cell species: a diffuse interface separates tumor and healthy cell regions
- proliferating tumor cells surrounded by (healthy) host cells, and a nutrient (e.g. glucose)

Diffuse interfaces

Two possible modelling approaches

- Sharp interface / Free boundary models:
  Interface Γ is modelled as idealised moving hypersurface
- Diffuse interface / Phase field models:
  Interface Γ is modelled with thin transition layer

Diffuse interface



Advantages of diffuse interfaces in tumor growth models

- 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)

Regarding modeling of diffuse interface tumor growth we can quote, e.g.,

- Ciarletta, Cristini, Frieboes, Garcke, Hawkins, Hilhorst, Lam, Lowengrub, Oden, Wise, also for their numerical simulations $\rightarrow$ complex changes in tumor morphologies due to the interactions with nutrients or toxic agents and also due to mechanical stresses
- Frieboes, Jin, Chuang, Wise, Lowengrub, Cristini, Garcke, Lam, Nürnberg, Sitka, for the interaction of multiple tumor cell species described by *multiphase mixture models*

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The variables and physical features

- Basic variables
  - $\varphi \in [-1, 1]$: local proportion (*phase field*) of tumor cells,
  - $\sigma \geq 0$: concentration of a chemical substance (*nutrient or drug*) affecting the tumor evolution,
  - μ: chemical potential of the phase separation process.

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- Physical effects and main model features:
  - presence of a mass source: the tumor may grow, or shrink, depending on the effect of nutrient availability;
  - presence, also, of a nutrient source;
  - consumption of the nutrient by means of tumor cells;
  - active transport: the nutrient tends to migrate, somehow "attracted" by tumor cells;
  - presence of non-constant mobility coefficients; singular potential of Flory-Huggins type.

The model equations

$$\varphi_t - \operatorname{div}\left(\mathbb{m}(\varphi,\sigma)\nabla\mu\right) = S(\varphi,\sigma), \tag{CH1}$$

$$\mu = -\Delta\varphi + f(\varphi) - \chi\sigma, \tag{CH2}$$

$$\sigma_t - \operatorname{div}\left(\sigma\mathbb{m}(\varphi,\sigma)\nabla(\ln\sigma + \chi(1-\varphi))\right) = b(\varphi,\sigma). \tag{nutr}$$

- In smooth bounded $\Omega \subset \mathbb{R}^d$, $d \in \{2,3\}$. No-flux b.c. for all variables.

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- Specific forms of the mass and nutrient sources.
- Keller-Segel-like cross diffusion $\rightarrow$ we would like to represent chemotaxis, the active movement, in a biological sense, of the tumor cells towards regions of high nutrient concentration.

Choice of the source terms

Mass source: in the Cahn-Hilliard type equation

$$\varphi_t - \operatorname{div}\left(\mathbb{m}(\varphi,\sigma)\nabla\mu\right) = S(\varphi,\sigma)$$

we take

$$S(\varphi,\sigma) = -m\varphi + h(\varphi,\sigma),$$

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- Similarly to other CH-models with mass source and singular potential, m has to be large compared to the L^∞-norm of h.
- If h is a constant, (CH1) reduces to the Cahn-Hilliard-Oono equation.
- The case $S \equiv 0$ may be treated as well.

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we take a logistic nutrient source of the form

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Motivations for the KS choice (and for the logistic term)

Integrating (nutr) (constant mobility for simplicity) over a reference volume $V \subset \Omega$ one obtains

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_V \sigma = \int_{\partial V} \partial_n \sigma - \chi \int_{\partial V} \sigma \partial_n \varphi + \int_V \beta(\varphi)(\kappa_\infty \sigma^p - \kappa_0 \sigma)$$

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- If the proportion of tumor cells is higher outside V than inside V ($\partial_n \varphi > 0$), then the nutrient flows away from V proportionally to its concentration;
- The Keller-Segel dynamics, moreover, guarantees preservation of the nonnegativity of σ;
- For large values of the concentration ($\kappa_\infty \sigma^p > \kappa_0 \sigma$), there is a volumic source effect leading σ to decrease due to consumption;
- In the reference case β is monotone increasing. Namely, the larger is φ,
  - (for σ large), the faster the nutrient is consumed;
  - (for σ small), the faster the nutrient tends to chemotactically move inwards V.

Coercivity of the energy functional

- The model has a variational derivation in terms of the energy

$$\mathcal{F}(\varphi,\sigma)=\underbrace{\int_\Omega\left(\frac{1}{2}|\nabla\varphi|^2+F(\varphi)\right)}_{=:\mathcal{E}(\varphi)}+\underbrace{\int_\Omega\big(\sigma(\ln\sigma-1)+\chi\sigma(1-\varphi)\big)}_{=:\mathcal{M}(\varphi,\sigma)},$$

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- This feature is lost if the singular potential is regularized, or is simply replaced by a "smooth" potential of controlled growth like $F(\varphi)\sim(\varphi^2-1)^2$.

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Comparison with previous models

- A vast literature has been dedicated to the case when the nutrient equation has a form like (or generalizations of it)

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  - Drawback #1: no minimum principle for σ: interpretation as a concentration is somehow lost
  - Drawback #2: the nutrient consumption, or growth, is independent of the proportion of tumor cells.

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(A4) Mobility coefficients $\mathbb{m}(\varphi,\sigma), \mathbb{n}(\varphi,\sigma)$ assumed smooth, bounded, Lipschitz continuous, strongly positive (i.e., everywhere larger than some $m_0 > 0$), plus some technical assumption (for instance $\partial_\varphi \mathbb{m}$ also uniformly bounded)

Existence of weak solutions

Theorem (Rocca, Schimperna, Signori, arXiv:2202.11007, 2022)

Assume **(A1)-(A4)**. Let $\chi > 0$ and let $d \in \{2, 3\}$. Let the initial data satisfy

$$\varphi_0 \in H^1(\Omega), \qquad F(\varphi_0) \in L^1(\Omega), \qquad (\varphi_0)_\Omega \in (-1, 1),$$
$$\sigma_0 \geq 0 \ \text{ a.e. in } \ \Omega, \qquad \sigma_0 \ln \sigma_0 \in L^1(\Omega).$$

Assume also

$$p \in [3/2, 2] \ \text{ if } d = 2, \quad p \in [8/5, 2] \ \text{ if } d = 3.$$

Then, there exists at least one weak solution in the regularity class

$$\varphi \in H^1(0, T; H^1(\Omega)^*) \cap L^\infty(0, T; H^1(\Omega)) \cap L^p(0, T; W^{2,p}(\Omega)),$$
$$\sigma \in C^0([0, T]; W^*) \cap L^\infty(0, T; L^1(\Omega)),$$
$$-1 \leq \varphi(\cdot, \cdot) \leq 1, \qquad \sigma(\cdot, \cdot) \geq 0,$$
$$\mu \in L^2(0, T; H^1(\Omega)),$$
$$F(\varphi) \in L^\infty(0, T; L^1(\Omega)), \quad f(\varphi)(= F'(\varphi)) \in L^p((0, T) \times \Omega).$$

Additional regularity

Theorem (Rocca, Schimperna, Signori, arXiv:2202.11007, 2022)

Assume, **in addition**,

$$\sigma_0 \in L^2(\Omega), \quad p = 2,$$

$$\text{if } d = 3, \quad \mathbb{m} \equiv 1 \text{ and } \chi < (2\kappa_\infty b_0)^{1/2},$$

Then, the regularity of weak solutions is improved (for $d = 3$) up to

$$\varphi \in H^1(0,T;H^1(\Omega)^*) \cap L^4(0,T;H^2(\Omega)) \cap L^2(0,T;W^{2,6}(\Omega)),$$
$$\sigma \in H^1(0,T;H^1(\Omega)^*) \cap C^0([0,T];L^2(\Omega)) \cap L^2(0,T;H^1(\Omega)),$$

In the true-logistic case and for constant mobilities $\mathbb{m} \equiv \mathbb{n} \equiv 1$ we have additional regularity results (including "separation property" for $d = 2$).

Uniqueness

Theorem (Rocca, Schimperna, Signori, arXiv:2202.11007, 2022)

Assume, **in addition**,

$$\mathbb{m} \equiv \mathbb{n} \equiv 1, \quad p = 2, \quad \beta \equiv 1$$

Given two weak solutions $(\varphi_1, \mu_1, \sigma_1)$ and $(\varphi_2, \mu_2, \sigma_2)$ originating from the same initial data and additionally satisfying $(d = 3)$

$$\varphi_1 \in L^2(0, T; W^{2,6}(\Omega)),$$
$$\sigma_1 \in L^4(0, T; L^2(\Omega)),$$
$$\sigma_2 \in L^4(0, T; L^6(\Omega)).$$

Then $(\varphi_1, \mu_1, \sigma_1) \equiv (\varphi_2, \mu_2, \sigma_2)$ provided that

either h is a constant,

or $F''(\varphi_1), F''(\varphi_2) \in L^2((0, T) \times \Omega)$.

Outline

Perspectives for the Analysis and the Applications

- to study the optimal control and long-time behavior with different proliferating terms or different potentials (cf. Lennard Johns potential)
- to include mechanics (large deformations) in the model (joint project with Abramo Agosti, Pierluigi Colli, and Harald Garcke)
- to investigate different optimal control problems (sliding modes) so that the trajectory reaches a desired state in finite time and stays there till time T
- to give hints to the medical doctor about the therapy using simulations - for glioblastoma multiforme - in collaboration with the "San Matteo" Hospital in Pavia and Abramo Agosti
- ...

Many thanks to all of you for the attention!

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

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\end{aligned}$$

- T_n suitably designed truncation, $\gamma_n = T_n^{-1}$, $s = T_n(\sigma)$.
- f_n is constructed smoothing out the monotone part of f but keeping sufficiently fast growth, in such a way that the quantity

$$F_n(\varphi) + L_n(\sigma) + \chi T_n(\sigma)(1-\varphi), \quad L_n(\sigma) = \int_0^\sigma T_n'(r)\ln r\,\mathrm{d}r,$$

is uniformly (in n) coercive.

Proof of existence: further remarks

- The critical exponent $p^* = p^*(d)$ is derived using interpolation methods. We only have a positive result (existence for $p \geq p^*$). It would also be interesting to prove a negative result (actual blowup for smaller p).

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- An integration by parts is also needed to take the limit of $-\operatorname{div}(\mathbb{m}(\varphi,\sigma)\nabla\sigma)$.

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- The proof of uniqueness is rather standard, and assumptions are not likely optimal.
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- Otherwise the result becomes strongly conditional, at least for logarithmic potentials.