On a sliding mode control for a tumor growth problem

Elisabetta Rocca

Università degli Studi di Pavia

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with Pierluigi Colli (Pavia), Gianni Gilardi (Pavia), Gabriela Marinoschi (Bucharest)

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Outline

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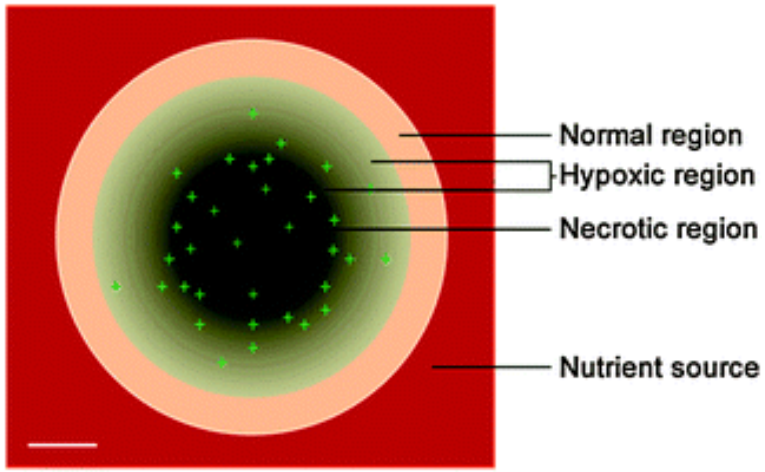
Setting

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



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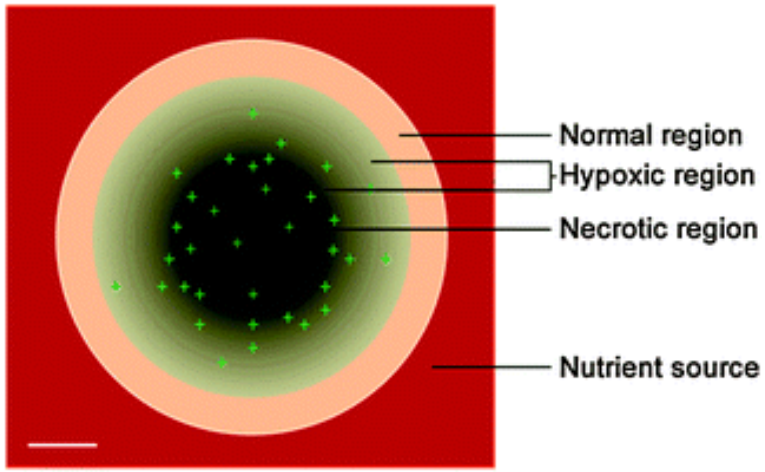

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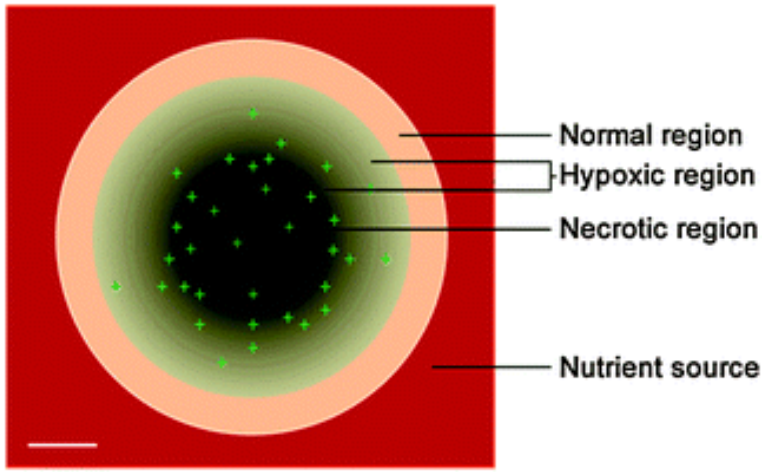

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- proliferating tumor cells surrounded by (healthy) host cells, and a nutrient (e.g. glucose).

We investigate the two-phase case: growth of a tumor in presence of a nutrient and surrounded by host tissues.

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- Ciarletta, Cristini, Frieboes, Garcke, Hawkins-Daarud, Hilhorst, Lam, Lowengrub, Oden, van der Zee, 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

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- Frieboes, Jin, Chuang, Wise, Lowengrub, Cristini, Garcke, Lam, Nürnberg, Sitka, for the interaction of multiple tumor cell species described by *multiphase mixture models*

Outline

The free energy

- $u =$ tumor cell volume fraction $u \in [0, 1]$
- $n =$ nutrient-rich extracellular water volume fraction $n \in [0, 1]$
- $f(u) = \Gamma u^2(1-u)^2$: a double well
- $\chi(u, n) = -\chi_0 un$: chemotaxis driving the tumor cells toward the oxygen supply

$$E = \int_\Omega \left(f(u) + \frac{\epsilon^2}{2} |\nabla u|^2 + \chi(u, n) + \frac{1}{2\delta} n^2 \right) dx. \tag{4}$$

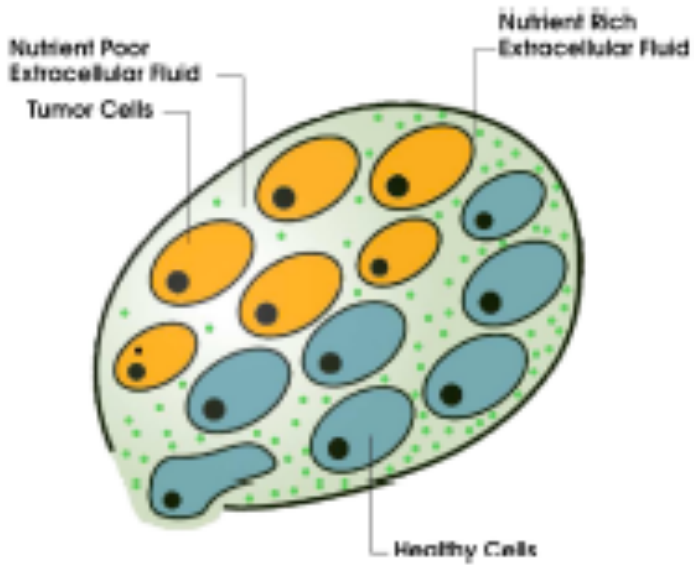

Figure 1. Four-species model: illustration of the four-species mixture. The tumor and healthy cell populations are assumed to have a thin diffuse interface, whereas the nutrient-rich and nutrient-poor extracellular water are segregated by a wide smooth interface.

The plot of the summand $f(u) + \chi(u, n)$

The lowest energy state is when $u = 1$ and $n = 1$, when there is a full interaction between the tumor species and the nutrient-rich extracellular water.

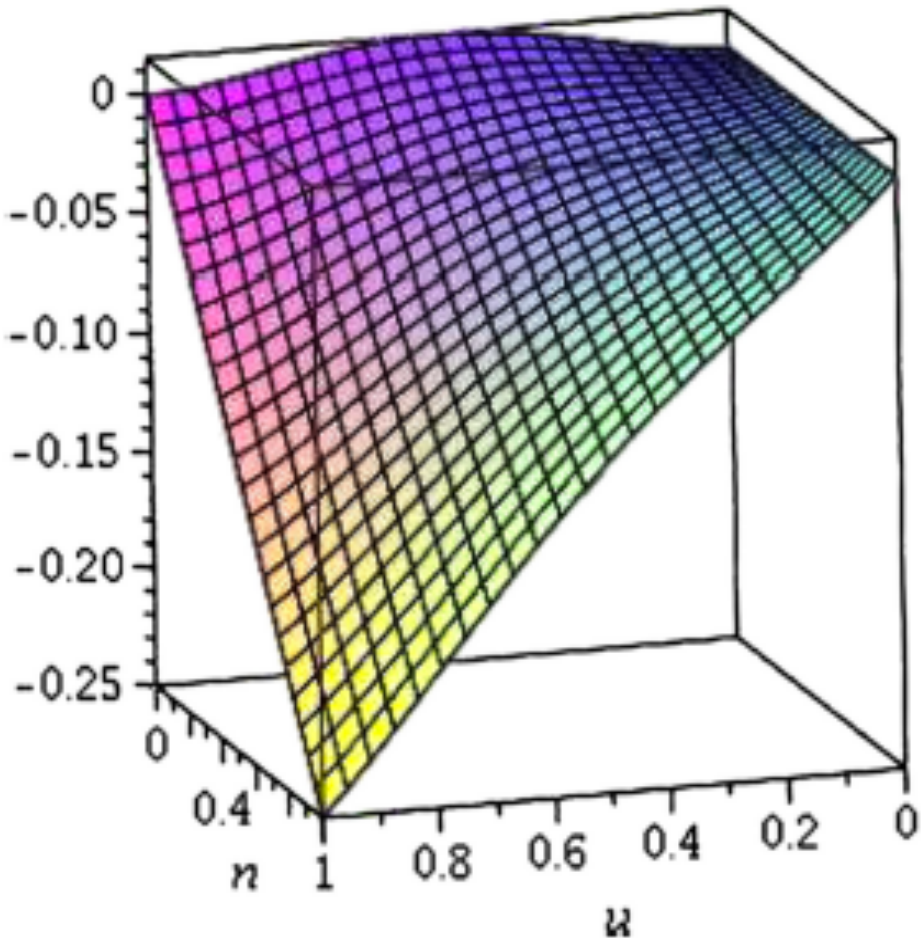

Figure 2. Graph of homogeneous free energy: $f(u) + \chi(u, n)$. ($\Gamma = \chi_0 = 0.25$).

The mass balance equations

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$$u_t = \nabla \cdot (M_u \nabla \mu_u) + \gamma_u, \quad \mu_u = \partial_u E = f'(u) + \partial_u \chi(u, n) - \epsilon \Delta u$$

$$n_t = \nabla \cdot (M_n \nabla \mu_n) + \gamma_n, \quad \mu_n = \partial_n E = \partial_n \chi(u, n) + \frac{1}{\delta} n$$

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We use the linear phenomenological laws (cf. [Lowengrub et al.] and [Garcke et al.])

$$\gamma_u = (\gamma_1 n - \gamma_2) p(u), \quad \gamma_n = -\gamma_3 n p(u) + \gamma_4 (n_s - n)$$

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where

- Here $p(s)$ is an interpolation function such that $p(0) = 0$ and $p(1) = 1$, for example, and
  - $p(u)\gamma_1 n$ - proliferation of tumor cells proportional to nutrient concentration
  - $p(u)\gamma_2$ - apoptosis of tumor cells
  - $p(u)\gamma_3 n$ - consumption of nutrient by the tumor cells
- The constant n_s denotes the nutrient concentration in a pre-existing vasculature, and $\gamma_4(n_s - n)$ models the supply of nutrient from the blood vessels if $n_s > n$ and the transport of nutrient away from the domain Ω if $n_s < n$.

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Other choices are possible: e.g., in [HZO: A. Hawkins-Daarud, K.-G. van der Zee and J.-T. Oden (2011)] they choose:

$$\gamma_u = P(u)(\mu_n - \mu_u), \quad \gamma_n = -\gamma_u, \quad \text{where}$$

$$P(u) = \begin{cases} \delta P_0 u & \text{if } u \geq 0 \\ 0 & \text{elsewhere} \end{cases}$$

being δ a small positive constant and $P_0 \geq 0$. Then they get

$$\gamma_u = P_0 u n + \delta P_0 u(\partial_n \chi(u, n) - \mu_u)$$

and so the dominant term is $P_0 u n$.

Simulations by HZO: the tumor starts growing increasingly more ellipsoidal at first and eventually begins forming buds growing toward the higher levels of nutrient

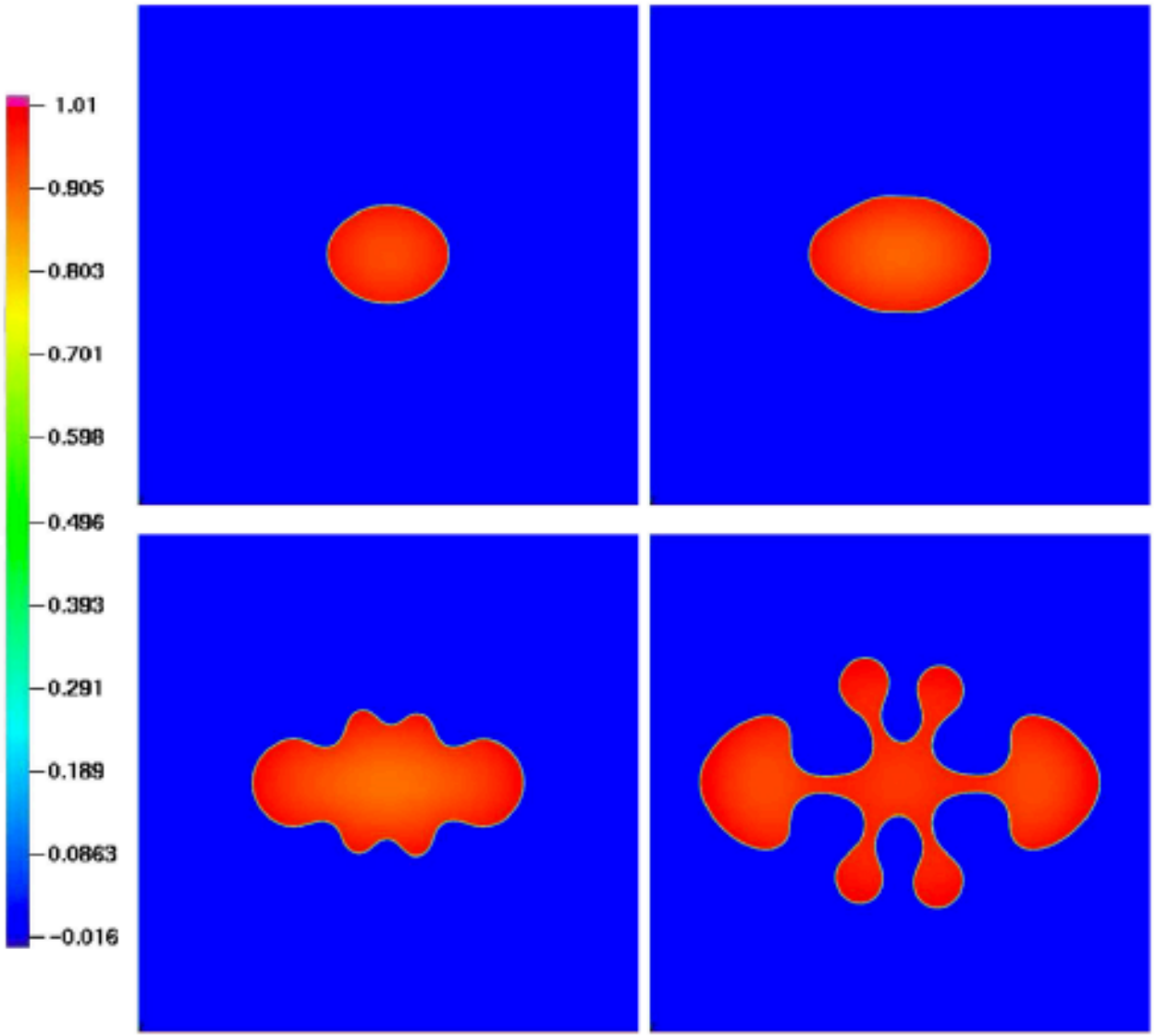


Figure 7. Example simulation: snapshots are shown at $t = 20, 40, 60$, and 80 of a simulation with $\Gamma = 0.045$, $\epsilon = 0.005$, $\chi_0 = 0.05$, $\delta = 0.01$, $P_0 = 0.1$, $\hat{M} = 200$, and $\hat{D} = 1$.

Simulations by HZO: the influence of χ_0 and δ

- When the ratio χ_0/Γ is small, the tumor remains circular $u \sim 0, 1$
- When $\chi_0 \sim \Gamma$ the tumor goes into an ellipse
- When χ_0/Γ and χ_0/ϵ are big, u no longer takes on values close to 0 and 1: it begins moving quickly toward the regions with higher nutrients
- Only when χ_0 is large the value of δ makes a difference in simulations

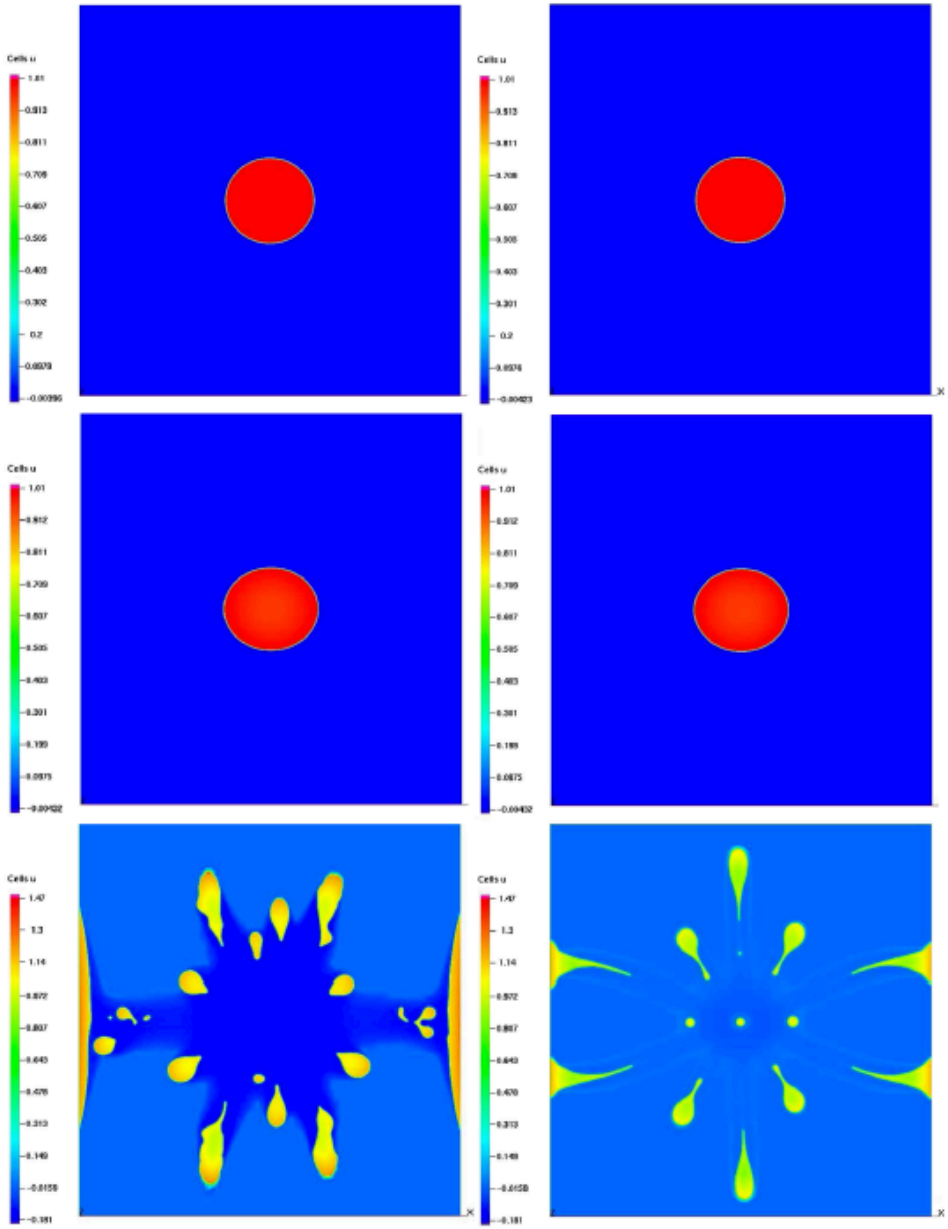
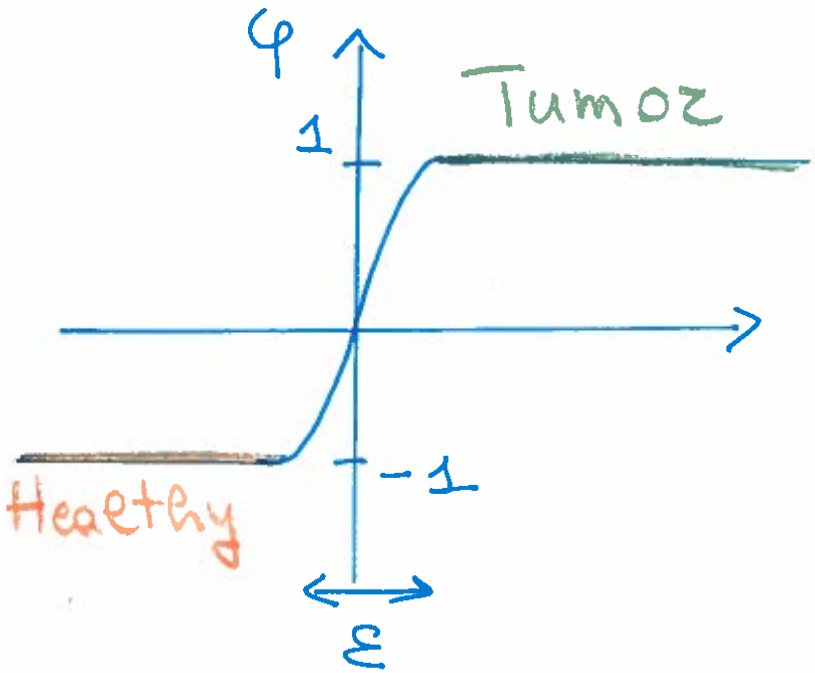


Figure 10. Effects of parameter χ_0: illustrated here are the effects of different values of χ_0 when $\Gamma = 0.045$ and $\epsilon = 0.005$ are held constant. In the first row, $\chi_0 = 0.005$; in the second row, $\chi_0 = 0.05$; and in the third row, $\chi_0 = 0.5$. In the first column, $\delta = 0.1$; and in the second column, $\delta = 0.01$.

Outline

Our notation for the tumor phase parameter $(u =)\phi \in [-1, 1]$



The sharp interface S replaced by a (thickness ε) thin transition layer

$\varphi \equiv -1$ in the Healthy tissue phase

$\varphi \equiv 1$ in the Tumor phase

Theoretical analysis: two-phase models

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- Analytical results related to well-posedness, asymptotic limits, but also optimal control and long-time behavior of solution, have been established in a number of papers of a number of authors which include: Agosti, Ciarletta, Colli, Frigeri, Garcke, Gilardi, Grasselli, Hilhorst, Lam, Marinoschi, Melchionna, E.R., Scala, Sprekels, Wu, etc...

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  - for tumor growth models based on the coupling of Cahn–Hilliard (for the tumor density) and reaction–diffusion (for the nutrient) equations, and
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In this talk we concentrate on a recent result on sliding mode control.

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- The second step is to design a SMC law that forces the system trajectories to stay onto the sliding surface. To this end, we have added the term $\rho\,\mathrm{sign}(\phi - \phi^*)$ in the Cahn–Hilliard evolution for ϕ in order to force ϕ to stay equal to a given desired value ϕ^* in a finite time.

The state system:

viscous Cahn–Hilliard + nutrient model with source terms

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$$\phi_t - \Delta\mu = (\gamma_1\sigma - \gamma_2)p(\phi) \quad \text{in } Q := \Omega \times (0, T)$$
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$$\sigma_t - \Delta\sigma = -\gamma_3\sigma p(\phi) + \gamma_4(\sigma_s - \sigma) + g \quad \text{in } Q$$

- Ω domain in which the evolution takes place, T final time;
- variable ϕ denotes the difference in volume fraction, where $\phi = 1$ represents the tumor phase and $\phi = -1$ represents the healthy tissue phase
- variable μ represents the chemical potential
- variable σ stands for the concentration of the nutrient (e.g., oxigen or glucose)
- coefficients: τ positive viscosity paramenter,γ_i, $i = 1, \ldots, 4$, positive constants standing for proliferation rate, apoptosis (death of cells) rate, nutrient consumption rate, nutrient supply rate, respectively.

Sliding mode control

- classic instrument for regulation of continuous or discrete systems in finite-dimensional settings
- one of the basic approaches to the design of robust controllers for nonlinear complex dynamics that work under uncertainty
- on the other hand, tumor growth dynamics is a main example of complex systems
- in the case of an incipient tumor, i.e., before the development of quiescent cells
- inclusion of the SMC law $\rho\,\mathrm{sign}(\phi - \phi^*)$, with ρ positive parameter that will be chosen large enough
- this term forces the system trajectories onto the sliding surface $\phi = \phi^*$ in finite time

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Sliding mode problem: look for

$\mathcal{M} := \{y \in \mathbb{R}^n : \ g(y) = 0\}$ a manifold in $\mathbb{R}^n$

$y \mapsto u(y)$ a feedback control law

such that the trajectory $t \mapsto y(t)$ starts from an arbitrary initial datum y_0 and reaches the manifold $\mathcal{M}$ in a finite time.

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Advantage: althogh the dynamics is modified, the complexity is reduced since $\mathcal{M}$ is lower-dimentional

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- State-of-the-art monographs

  Young, Özgüner (eds.), Springer-Verlag, 1999
  Edwards, Fossas Colet, Fridman (eds.), Springer, 2006
  Bartolini, Fridman, Pisano, Usai (eds.), Springer, 2008
  Fridman, Moreno, Iriarte (eds.), Springer, 2011

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- On phase field systems of Caginalp type:

  Barbu, Colli, Gilardi, Marinoschi, E. R., SIAM J. Control Optim., 2017
  Colturato, Appl. Math., 2016, and App. Math. Optim., 2017

Still on the system of equations

$$\phi_t - \Delta\mu = (\gamma_1\sigma - \gamma_2)p(\phi) \quad \text{in } Q := \Omega \times (0, T)$$
$$\mu = \tau\phi_t - \Delta\phi + F'(\phi) + \rho\ \text{sign}(\phi - \phi^*) \quad \text{in } Q$$
$$\sigma_t - \Delta\sigma = -\gamma_3\sigma p(\phi) + \gamma_4(\sigma_s - \sigma) + g \quad \text{in } Q$$

data: the constant σ_s denotes the nutrient concentration in a pre-existing vasculature, the function g is a source term which may represent the supply of a nutrient or a drug in a chemotherapy;

the term $\gamma_1 p(\phi)\sigma$ models the proliferation of tumor cells which is proportional to the concentration of the nutrient

the term $-\gamma_2 p(\phi)$ models the apoptosis of tumor cells

the term $-\gamma_3 p(\phi)\sigma$ models the consumption of the nutrient only by the tumor cells

the term $\gamma_4(\sigma_s - \sigma)$ models the supply of nutrient from the blood vessels if $\sigma_s > \sigma$ and the transport of nutrient away from the domain Ω if $\sigma_s < \sigma$

About the potentials

$$\phi_t - \Delta\mu = (\gamma_1\sigma - \gamma_2)p(\phi) \quad \text{in } Q := \Omega \times (0,T)$$
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p is a smooth nonnegative and bounded proliferation function;
F' stands for the derivative of a double-well potential F
$\rightarrow$ typical examples of potentials are

$$F_{reg}(r) = \frac{1}{4}(r^2-1)^2, \quad r \in \mathbb{R}$$
$$F_{log}(r) = (1+r)\ln(1+r) + (1-r)\ln(1-r) - c_0\, r^2, \quad r \in (-1,1)$$
$$F_{obs}(r) = I(r) + c_1(1-r^2), \quad r \in \mathbb{R}$$

where $c_0 > 1$ in order to produce a double-well, c_1 arbitrary positive number and the function I is the indicator function of $[-1,1]$, i.e., it takes the values 0 or $+\infty$ according to whether or not r belongs to $[-1,1]$.

Initial and boundary conditions

System complemented by the initial conditions $\phi(0) = \phi_0$ and $\sigma(0) = \sigma_0$ and suitable boundary conditions: usual homogeneous Neumann conditions for ϕ and σ, that is,

$$\partial_n \phi = 0 \quad \text{and} \quad \partial_n \sigma = 0 \quad \text{on } \Sigma := \Gamma \times (0, T)$$

where Γ is the boundary of Ω and ∂_n is the (say, outward) normal derivative.
Dirichlet boundary condition for the chemical potential, i.e.,

$$\mu = \mu_\Gamma \quad \text{on } \Sigma$$

where μ_Γ is a given smooth function. This choice is twofold:

- from one side it looks reasonable from the modelling point of view since, in case $\mu_\Gamma = 0$, it allows for the free flow of cells across the outer boundary;
- on the other hand, this Dirichlet condition is important for the analysis.

SMC approach

- is well known for its robustness against variations of dynamics, disturbances, time-delays and nonlinearities
- the design procedure of a SMC system is a two-stage process: first step is to choose a set of sliding manifolds such that the original system restricted to the intersection of them has a desired behavior
- the tumor phase parameter should stay constant in time (within finite time) $\longrightarrow$ the phase variable ϕ as close as possible to the constant value $\phi = -1$, corresponding to the case when no tumorous phase is present anymore, or to a configuration ϕ^* which is suitable for surgery
- the second step is to design a SMC law that pushes the system trajectories to stay onto the sliding surface ... then, we have added the term $\rho\,\mathrm{sign}(\phi - \phi^*)$ in the Cahn–Hilliard evolution for ϕ in order to force ϕ to stay equal to ϕ^* in a finite time

Assumptions and structure

Let $F = \widehat{B} + \widehat{\pi}$

$$\gamma_i \in [0, +\infty) \quad \text{for } i = 1, 2, 3, \quad \gamma_4,\ \tau \in (0, +\infty) \quad \text{and} \quad \sigma_s \in \mathbb{R}$$

$$\widehat{B} : \mathbb{R} \to [0, +\infty] \quad \text{is convex, proper and l.s.c.} \quad \text{with} \quad \widehat{B}(0) = 0$$

$$\widehat{\pi} : \mathbb{R} \to \mathbb{R} \quad \text{is a } C^1 \text{ function} \quad \text{and} \quad \widehat{\pi}' \quad \text{is Lipschitz continuous}$$

$$p : \mathbb{R} \to [0, +\infty) \quad \text{is a bounded and Lipschitz continuous function}$$

$$\beta := \partial \widehat{B}, \quad \pi := \widehat{\pi}', \quad L_\pi = \text{the Lipschitz constant of } \pi$$

Denote by $D(\beta)$ and $D(\widehat{B})$ the effective domains of β and $\widehat{B}$, respectively.

$$H := L^2(\Omega), \quad V := H^1(\Omega), \quad V_0 := H^1_0(\Omega)$$

$$W := \left\{ v \in H^2(\Omega) : \partial_{\mathrm{n}} v = 0 \right\} \quad \text{and} \quad W_0 := H^2(\Omega) \cap H^1_0(\Omega)$$

Let C_{sh} be a constant realizing the inequalities

$$\|v\|_\infty \le C_{sh} \, |\Omega|^{1/6} \, \|\Delta v\|_H \quad \text{for every } v \in W_0$$

$$\|v\|_\infty \le C_{sh} \left(|\Omega|^{-1/2} \, \|v\|_H + |\Omega|^{1/6} \, \|\Delta v\|_H \right) \quad \text{for every } v \in W$$

State system with the state-feedback control law

Operator sign : $\mathbb{R} \to 2^{\mathbb{R}}$ defined by

$$\operatorname{sign} r := \frac{r}{|r|} \quad \text{if } r \neq 0 \quad \text{and} \quad \operatorname{sign} 0 := [-1, 1]$$

sign is the subdifferential of the real function $r \mapsto |r|$

Dirichlet boundary condition $\mu = \mu_\Gamma$ reduced to the homogeneous one by introducing the harmonic extension $\mu_\mathcal{H}$ of μ_Γ defined as: for a.a. $t \in (0, T)$, $\mu_\mathcal{H}(t)$ is the unique solution to the problem

$$\mu_\mathcal{H}(t) \in H^1(\Omega), \quad -\Delta \mu_\mathcal{H}(t) = 0 \quad \text{in } \mathcal{D}'(Q), \quad \mu_\mathcal{H}(t)|_\Gamma = \mu_\Gamma(t)\,.$$

Take $\mu - \mu_\mathcal{H}$ as new unknown and still term μ the above difference.

Thus, we are given the functions g, μ_Γ, ϕ^* and the initial data ϕ_0, σ_0 with

$$g \in L^\infty(Q), \quad \mu_\Gamma \in H^1(0, T; L^2(\Gamma)) \cap L^\infty(0, T; H^{3/2}(\Gamma))$$

$$\phi^* \in W \quad \text{and} \quad \inf D(\beta) < \inf \phi^* \leq \sup \phi^* < \sup D(\beta)$$

$$\phi_0 \in W, \quad \beta^\circ(\phi_0) \in H \quad \text{and} \quad \sigma_0 \in V \cap L^\infty(\Omega)$$

where β° denotes the minimal section of β.

Solution to the state system

a quintuplet $(\phi, \mu, \sigma, \xi, \zeta)$ satisfying the regularity requirements

$$\phi \in W^{1,\infty}(0,T;H) \cap H^1(0,T;V) \cap L^\infty(0,T;W)$$
$$\mu \in L^\infty(0,T;W_0)$$
$$\sigma \in H^1(0,T;H) \cap L^\infty(0,T;V) \cap L^2(0,T;W)$$
$$\xi \in L^\infty(0,T;H), \qquad \zeta \in L^\infty(0,T;H)$$

and solving

$$\mathrm{d}t\phi - \Delta\mu = (\gamma_1\sigma - \gamma_2)\, p(\phi) \quad \text{a.e. in } Q$$
$$\mu = \tau\, \mathrm{d}t\phi - \Delta\phi + \xi + \pi(\phi) + \rho\,\zeta - \mu_{\mathcal{H}} \quad \text{a.e. in } Q$$
$$\mathrm{d}t\sigma - \Delta\sigma = -\gamma_3\sigma\, p(\phi) + \gamma_4(\sigma_s - \sigma) + g \quad \text{a.e. in } Q$$
$$\xi \in \beta(\phi) \quad \text{and} \quad \zeta \in \mathrm{sign}(\phi - \phi^*) \quad \text{a.e. in } Q$$
$$\phi(0) = \phi_0 \quad \text{and} \quad \sigma(0) = \sigma_0$$

where ρ is a positive parameter.

Well-posedness

Theorem (Estimates)

For every $\rho > 0$, there exists at least one quintuplet $(\phi, \mu, \sigma, \xi, \zeta)$ solving our problem and satisfying the estimates

$$\|\mu\|_\infty \leq C_{sh} \frac{2|\Omega|^{2/3}}{\tau} \rho + \widehat{C}$$

$$|\sigma| \leq \sigma^* := \max\{\left\|\sigma_s + \gamma_4^{-1} g\right\|_\infty, \|\sigma_0\|_\infty\} \quad \text{a.e. in } Q$$

where C_{sh} is the same as in the Sobolev inequality and the constant $\widehat{C}$ depends only on Ω, T and the quantities involved in assumptions. In particular, $\widehat{C}$ does not depend on ρ. Moreover, the components ϕ and σ of the solution are uniquely determined.

The above result is quite general. In particular, the potentials F_{log} and F_{obs} are certainly allowed.

Sliding mode

- For the problem of sliding mode, we prove a result that only involves the component ϕ of the solution.
- However, we can ensure the existence of a sliding mode at least for ρ large enough only under the following condition

$$C_{sys} := C_{sh} \frac{2|\Omega|^{2/3}}{\tau} < 1$$

where C_{sh} is the constant that appears in the Sobolev inequality.

- Such a condition means that $|\Omega|$ has to be sufficiently small once the shape of Ω is fixed.

The result

Theorem

Assume the smallness condition on Omega is satisfied and

$$\Delta\phi^* \in L^\infty(\Omega).$$

Then, there exists $\rho^* > 0$, *depending only on* Ω, T, *the structure and the data of the problem, such that, for every* $\rho > \rho^*$, *the following is true: if* $(\phi, \mu, \sigma, \xi, \zeta)$ *is a solution to our problem with* μ *satisfying the estimate stated in the previous Theorem, there exists a time* $T^* \in [0, T)$ *such that*

$$\phi(t) = \phi^* \quad \text{a.e. in } \Omega \quad \text{for every } t \in [T^*, T].$$

In particular, there exists a solution for which the sliding mode condition holds true.

Values of ρ^* and T^*

Remark

In the proof we can show that possible values of ρ^* and T^* that fit the above statement are

$$\rho^* = \frac{1}{1 - C_{sys}} \left(\widehat{C} + M + M_\pi^* + \frac{\tau}{T} M_0 \right) \quad \text{and} \quad T^* = \frac{\tau}{\rho - A(\rho)} M_0$$

where M, M_0, M_π^* and $A(\rho)$ are given by

$$M := \|\mu_\Gamma\|_\infty + \|\Delta \phi^*\|_\infty + \|\xi^*\|_\infty \,, \quad M_0 := \|\phi_0 - \phi^*\|_\infty$$
$$M_\pi^* := \sup\{|\pi(\phi^*(x) + r)| : \; x \in \Omega, \; |r| \leq M_0\}$$
$$A(\rho) := C_{sys}\, \rho + \widehat{C} + M + M_\pi^* \quad \text{for } \rho > 0$$

with $\xi^* := \beta^\circ(\phi^*)$. In these formulas, $\widehat{C}$ is the same as in the estimate for μ.
The above definitions ensure that $A(\rho) < \rho$ for $\rho > \rho^*$ and that $T^* \in [0, T)$.

In conclusion ...

- the field is open to related research issues like extensions of the model, other diffuse interface models (vast literature growing and growing), optimal control problems, different SMC laws (e.g., in the equation for σ), numerics, ...

Outline

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P4. Include a stochastic term in phase-field models for tumor growth representing for example uncertainty of a therapy or random oscillations of the tumor phase (with C. Orrieri and L. Scarpa).


Aula Volta of the
Università degli Studi di Pavia
May 8-10, 2019
International Workshop on
Recent advances in Phase-Field modeling: from Engineering to Biology
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Ferdinando Auricchio (Pavia)
Elena Beretta (Polimi)
Luise Blank (Regensburg)
Elena Bonetti (Milano)
Helene Byrne (Oxford)*
Cecilia Cavaterra (Milano)
Pasquale Ciarletta (Polimi)
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Kris Van der Zee (Nottingham)
Vilanova Guillermo (Barcellona)
Organized by:
Elisabetta Rocca and Alessandro Reali
Registration by e-mail:
elisabetta.rocca@unipv.it
web page:
https://sites.google.com/view/phase2019
fondazione cariplo
Regione Lombardia
UNIVERSITÀ DI PAVIA

Many thanks to all of you for the attention!

My contact: elisabetta.rocca@unipv.it