The long and winding road toward mathematical rigor: an example from tumor growth modeling

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Plan

- modeling tumor growth
- an example of mathematical model
- the equations and the assumptions
- a sequence of simplifications which leads to . . .
- an apparently simple model
- the mathematical rigor comes into play
- the long and winding road explained
- final (obvious) considerations

Morphological evolution of tumors

- understanding the morphological stability of tumors can be important for controlling its spread to surrounding tissues
- it is the result of many factors: cell-cell and cell-matrix adhesion, mechanical stress, cell motility, heterogeneity of cell proliferation, ...
- a possible approach is to treat volume fractions of cell species as inertia-less fluids
- the volume fractions are governed by (nonlinear) advection-reaction-diffusion equations whose (adhesion) fluxes are gradients of suitable Cahn-Hilliard type potentials
- such equations are coupled with reaction-diffusion equations for the nutrients (e.g. oxygen)

The mathematical model

Ref. Wise, Lowengrub, Frieboes & Cristini '08

- continuum theory of mixtures
- diffuse interface approach (i.e. sharp interfaces between different cell species are replaced by narrow transition layers that arise due to differential adhesive forces among the cell species themselves)
- two-tumor species (dead and viable tumor cells)
- single vital nutrient (e.g. oxygen)

State variables

- φ_W: water phase
- φ_V: viable tumor cell phase
- φ_D: dead tumor cell phase
- φ_H: host tissue cell phase

The equations

$$\partial_t \varphi_V + \operatorname{div}(\mathbf{u}_V \varphi_V) = -\operatorname{div} \mathbf{J_V} + S_V$$

$$\partial_t \varphi_D + \operatorname{div}(\mathbf{u}_D \varphi_D) = -\operatorname{div} \mathbf{J_D} + S_D$$

$$\partial_t \varphi_H + \operatorname{div}(\mathbf{u}_H \varphi_H) = -\operatorname{div} \mathbf{J_H} + S_H$$

$$\partial_t \varphi_W + \operatorname{div}(\mathbf{u}_W \varphi_W) = -\operatorname{div}(\mathbf{J_V} + \mathbf{J_D} + \mathbf{J_H}) + S_W$$

$$\text{in } Q_T := \Omega \times (0, T),\ \Omega \subset \mathbb{R}^d,\ d = 2, 3$$

- constant densities
- $\mathbf{J_V}$, $\mathbf{J_D}$, $\mathbf{J_H}$: adhesion fluxes
- S_V, S_D, S_H, S_W: mass exchange/source/sink terms

Total adhesion energy

$$\mathcal{E}(\varphi_{\mathbf{T}}) = \int_{\Omega} \left(\frac{\varepsilon^2}{2} |\nabla \varphi_{\mathbf{T}}|^2 + F(\varphi_{\mathbf{T}}) \right) dx$$

- $\varepsilon > 0$: related to the thickness of the diffuse interface
- $\varphi_{\mathbf{T}} = \varphi_V + \varphi_D$
- F is a double-well potential (with minima at 0 and $1 - \varphi_W$)

Adhesion fluxes

$$\mathbf{J}_V = -m_V(\varphi_V)\nabla\frac{\delta\mathcal{E}}{\delta\varphi_V}$$

$$\mathbf{J}_D = -m_D(\varphi_D)\nabla\frac{\delta\mathcal{E}}{\delta\varphi_E}$$

$$\mathbf{J}_H = -(\mathbf{J}_V + \mathbf{J}_D)$$

- m_V, m_D: mobilities (they may degenerate at 0)
- observe that

$$\frac{\delta\mathcal{E}}{\delta\varphi_V} = \frac{\delta\mathcal{E}}{\delta\varphi_E} = \frac{\delta\mathcal{E}}{\delta\varphi_\mathbf{T}}$$

and

$$\mu = \frac{\delta\mathcal{E}}{\delta\varphi_\mathbf{T}} = -\varepsilon^2\Delta\varphi_\mathbf{T} + F'(\varphi_\mathbf{T})$$

Velocities

- the cells are tightly packed and march together
- define the velocity of the solid component through the Darcy's law

$$\mathbf{u}_S = -\nabla\pi - \mu\nabla\varphi_{\mathbf{T}}$$

- and take

$$\mathbf{u}_V = \mathbf{u}_D = \mathbf{u}_H = \mathbf{u}_S$$

- motility: constant and equal to unity

Mass exchange terms

$$S_V = \frac{\lambda_M}{n_\infty}\varphi_V n - \lambda_A \varphi_V - \lambda_N \mathcal{H}(\bar{n}_N - n)\varphi_V$$

$$S_D = \lambda_A \varphi_V + \lambda_N \mathcal{H}(\bar{n}_N - n)\varphi_V - \lambda_L \varphi_D$$

$$S_H = 0$$

$$S_W = -(S_V + S_D + S_H)$$

- n_N: cell viability limit
- λ_M, λ_A, λ_N, λ_L: rates of volume gain or loss due to cellular mitosis, apoptosis, necrosis, lysing
- n_∞: far-field nutrient level
- $\mathcal{H}$: Heaviside function

Further constraints

$$\operatorname{div} \mathbf{u}_S = \frac{1}{\varphi_S}(S_V + S_D + S_H)$$

$$\operatorname{div} \mathbf{u}_W = -\frac{1}{\varphi_W}(S_V + S_D + S_H)$$

- $u_S = u_T + u_H$
- $\varphi_S = \varphi_{\mathbf{T}} + \varphi_H$
- $\varphi_W = 1 - \varphi_S$

Nutrient diffusion

$$\partial_t n + \operatorname{div}(\mathbf{u}_W n) = \operatorname{div}(D(\varphi_\mathbf{T})\nabla n) + G_C - \nu \frac{\varphi_V}{\varphi_S} n$$

in Q_T

- $D(\varphi_\mathbf{T})$: diffusion coefficient (it differs in the tumor and in the host)
- G_C: additional source due to the presence of capillary network in the tumor and host tissues
- ν: nutrient uptake rate by the viable tumor cells

Simplifying the model further

The system can be (adimensionalized) and further reduced to the variables $\varphi_{\mathbf{T}}$, φ_D

$$\partial_t \varphi_{\mathbf{T}} + \operatorname{div}(\mathbf{u}_S \varphi_{\mathbf{T}}) = \operatorname{div}((m_V + m_D)\nabla\mu) + S_{\mathbf{T}}$$

$$\partial_t \varphi_D + \operatorname{div}(\mathbf{u}_S \varphi_D) = \operatorname{div}(m_D \nabla\mu) + S_D$$

$$\mathbf{u}_S = -\nabla\pi + \mu\nabla\varphi_{\mathbf{T}}, \qquad \operatorname{div}\mathbf{u}_S = S_{\mathbf{T}}$$

$$\mu = -\varepsilon^2\Delta\varphi_{\mathbf{T}} + F'(\varphi_{\mathbf{T}})$$

$$\text{in } Q_T$$

- constant mobilities
- the nutrient n is supposed to be given

One more step: the Cahn-Hilliard-Hele-Shaw system

$$\partial_t \varphi + \mathbf{u} \cdot \nabla \varphi = \Delta \mu$$

$$\mathbf{u} = -\nabla \pi + \mu \nabla \varphi, \qquad \operatorname{div} \mathbf{u} = 0$$

$$\mu = -\varepsilon^2 \Delta \varphi + F'(\varphi)$$

$$\text{in } Q_T$$

- $\varphi = \varphi_{\mathbf{T}}$
- $\mathbf{u} = \mathbf{u}_S$
- $m_V + m_D = 1$
- no mass exchange

General remarks on the CHHS system

- it also models the behavior of a fluid mixture in a Hele-Shaw cell (Lee, Lowengrub & Goodman '02)
- it is a subsystem of several tumor growth diffuse interface models (see, e.g., Chen, Wise, Shenoy & Lowengrub '14)
- the mathematical understanding of this system is a preliminary (but essential) step
- its theoretical analysis is particularly challenging
- very few (and recent) papers are available

Results on the CHHS system: regular potential I

regular potential

$$F(r) = \frac{r^2(1-r)^2}{4} \qquad r \in \mathbb{R}$$

Ω a box or a rectangle

- periodic bdry conditions: $\exists$ and uniqueness of a global strong solution in $2D$, $\exists$ of a local strong solution and blow-up criteria in $3D$ [Wang & Zhang '13]
- periodic bdry conditions: longtime behavior of global solutions and stability of local energy minimizers [Wang & Wu '12]
- no-flux bdry conditions: $\exists$, uniqueness and regularity of strong solutions in $2D$ (global) and $3D$ (local), local exponential stability of constant states outside the spinodal region ($F'' \leq 0$) [Lowengrub, Titi & Zhao '13]

Results on the CHHS system: regular potential II

Ω general domain

presence of a (time dependent) mass source S

- $\exists$ of global weak solutions and local strong solutions, convergence of any global weak solution to a single equilibrium and global longtime behavior (pullback attractor) in $2D$ [Jiang, Wu & Zheng '13]

more general Darcy's law (accounting for different densities)

$$\eta(\varphi)\mathbf{u} = -\nabla\pi + \mathbf{G}(\varphi) + \mu\nabla\varphi$$

- $\exists$ of a global weak solution [Dedè, Garcke & Lam '17]

Results on the CHHS system: regular potential III

numerical analysis

- finite difference [Wise ’10]
- fully discrete FEM approximation which converges to a weak solution [Feng & Wise ’12]
- isogeometric analysis [Dedè, Garcke & Lam ’17]

Inclusion of chemotaxis

Ref. Garcke, Lam, Sitka & Styles '16

$$\partial_t \varphi + \operatorname{div}(\mathbf{u}\varphi) = \operatorname{div}(m_1(\varphi)\nabla\mu) + \Gamma_\varphi$$

$$\mu = -A\Delta\varphi + BF'(\varphi) - \chi n$$

$$\partial_t n + \operatorname{div}(\mathbf{u} \cdot n) = \operatorname{div}(m_2(\varphi)(D\nabla n - \chi\nabla\varphi)) - S_n$$

$$\mathbf{u} = -\nabla\pi + (\mu + \chi\sigma)\nabla\varphi, \qquad \operatorname{div}\mathbf{u} = \Gamma_{\mathbf{u}}$$

$$\text{in } Q_T$$

- non-degenerate mobilities m_1, m_2
- $\chi \geq 0$, $\Gamma_{\mathbf{u}}$ given
- $\exists$ of a global weak solution (Garcke & Lam '16)

Beyond the regular potential

A physically more relevant choice for F is the following

$$F(r) = r\log r + (1-r)\log(1-r) - \alpha r(1-r), \quad r \in (0,1), \alpha > 1$$

so that φ can take values in the admissible range only

- $\exists$ of a global generalized solution to a more refined model which accounts for the nutrient n (stationary case), mass exchange and proliferating cells [Dai, Feireisl, Rocca, Schimperna & Schonbek '17]
- $\exists$ of a global weak solution which satisfies the energy identity, global attractor, uniqueness and regularity of the weak solution in $2D$, strict separation property in $2D$, $\exists$ of a global strong solution in $3D$ close to a local minimizer, convergence to a single equilibrium (weak sol. in $2D$, strong sol. in $3D$) [Giorgini, G. & Wu '17]

Nonconstant mobility and nonlocal interactions

$$\partial_t \varphi + \operatorname{div}(\mathbf{u}\varphi) = \operatorname{div}(m(\varphi)\nabla\mu)$$

- Which mobility? For instance

$$m(r) = m_0 r(1-r), \qquad r \in (0,1),\ m_0 > 0$$

in this case going beyond the mere $\exists$ of a weak solution seems out of reach with the former adhesion energy

- on the other hand a more general nonlocal adhesion energy should be considered (see Wise et al. '08)

$$\mathcal{E}(\varphi) = -\frac{1}{2}\int_{\Omega\times\Omega} J(x-y)\varphi(x)\varphi(y)dxdy + \int_\Omega S(\varphi)dx$$

where $J : \mathbb{R}^d \to \mathbb{R}$ is s.t. $J(x) = J(-x)$ and entropy $\mathcal{S}(r) = r\log r + (1-r)\log(1-r)$

Going nonlocal: pros and cons

$$\partial_t \varphi + \mathbf{u} \cdot \nabla \varphi = \text{ div } (m(\varphi) \nabla \mu)$$

$$\mu = - \int_\Omega J(x-y)\varphi(y)dy + \mathcal{S}'(\varphi)$$

$$\mathbf{u} = -\nabla \pi + \mu \nabla \varphi, \qquad \text{div } \mathbf{u} = 0$$

$$\text{in } Q_T$$

- the equation for φ becomes a second order equation
- many theoretical results are available when **u** given
- in the case of constant mobility the theoretical picture is more complete (for instance, the weak solution is unique even in $3D$) [Della Porta, Giorgini & G. in preparation]
- numerical simulations might be more cumbersome

Mobility and singular potential: a different choice

- "cell-cell interactions should be attractive at a moderate cell volume fraction . . . , because of cell adhesion, and repulsive at a high volume fraction" [Chatelain, Balois, Ciarletta & Ben Amar '11]
- this leads to choose a single-well potential F

$$F(s) = -(1-s^*)\log(1-s) - s^3 - (1-s^*)\frac{s^2}{2} - (1-s^*)s + k$$

where $s \in [0,1)$, $s^* \in (0,1)$ and $k > 0$

- with mobility

$$m(s) = s(1-s)^2$$

- $\mathbf{u} = \mathbf{0}$ [Agosti, Antonietti, Ciarletta, G. & Verani '17]: $\exists$ of different notions of weak solution, full discretization and continuous FEM approximation (cf. also Agosti, in preparation)

Future (possible or impossible) issues

- local and nonlocal CHHS systems with single-well potential [cf. Chatelain et al. '11]
- inclusion of mass exchange/source/sink terms
- inclusion of nutrients
- inclusion of chemotaxis
- unmatched densities
- multi-component models (a very recent paper by Frigeri, Lam, Schimperna & Rocca is now available)
- formulation of suitable control problems

Final truisms

- modeling complex phenomena (e.g. in Biology) is a nontrivial task ;-)
- one of the major difficulties is to choose what to disregard
- nonetheless mathematical models can still be very complicated for numerical simulations
- and certainly out of reach for producing rigorous results (e.g. theorems and proofs)
- therefore there might be further (even harder and more dangerous) simplifying steps . . .
- in order to formulate a mathematical model which can be treated theoretically
- however, even theoretical issues can be affected by too many simplifications (cf. logarithmic potential and nonlocal energy adhesion)

Nested titles

the title of this talk contains the title of a famous (old) song . . .

which one?