Initial/boundary-value problems of tumor growth in mixture theory

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Basic Framework from Mixture Theory

Tumors as multicomponent systems:

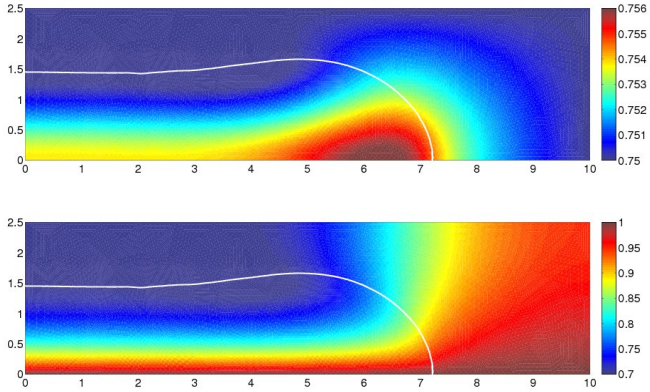
- Extracellular fluid
  Always present but possibly neglected due to small stress
- Healthy cells ($\alpha = H$)
  They form the host environment
- Tumor cells ($\alpha = T$)
  They invade the host tissue
- Extracellular matrix (ECM, $\alpha = M$)
  Fibrous scaffold for cell adhesion, it is produced, degraded, and remodeled by cells
- Nutrient
  Diffusing "massless" molecules (e.g., oxygen)

$\frac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha \mathbf{v}_\alpha) = \Gamma_\alpha$	Mass balance for constituent α
$-\nabla \cdot (\phi_\alpha \mathbb{T}_\alpha) + \phi_\alpha \nabla p = \mathbf{m}_\alpha$	Stress balance for constituent α (no inertia)
$\frac{\partial c}{\partial t} - \nabla \cdot (\mathbb{D} \nabla c) = \sum_\alpha Q_\alpha$	Nutrient diffusion and consumption by constituent α

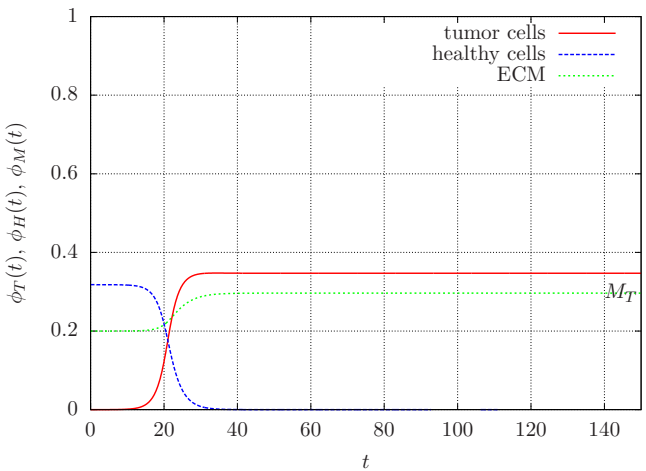
Models of Tumor Invasion and Fibrosis

1) Invasion of healthy tissue

$$\begin{cases} \dfrac{\partial \phi}{\partial t} - \kappa_m \nabla \cdot [\phi \nabla (\phi \Sigma(\phi))] = \Gamma(\phi,\, c) \\ \dfrac{\partial c}{\partial t} - D \Delta c = Q(\phi,\, c) \end{cases}$$



- Segregation of tumor and host cells
- Cell growth affected by nutrient and stress state
- ECM is treated as a rigid scaffold



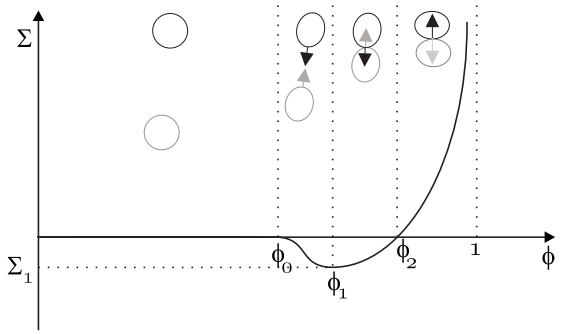
2) Matrix remodeling and fibrosis

$$\begin{cases} \dfrac{d\phi_\alpha}{dt} = [\gamma_\alpha(\phi_M) H_{\epsilon_\alpha}(\psi_\alpha - \psi) - \delta_\alpha]\phi_\alpha \\ \dfrac{d\phi_M}{dt} = \sum_\alpha (\mu_\alpha(\phi_M) H_{\epsilon_M}(\psi_M - \psi) - \nu_\alpha \phi_M)\phi_\alpha \end{cases}$$

- Cell populations are not necessarily segregated
- ECM can be degraded and produced
- Nutrient dynamics are disregarded

Tumor Invasion: Model Details

- Cell stress tensor $\mathbb{T}_H = \mathbb{T}_T = -\Sigma(\phi)\mathbb{I}$



- Cell growth $\Gamma_\alpha(\phi, c) = \underbrace{f^p_\alpha(\phi) g^p_\alpha(c)}_{\text{proliferation}} - \underbrace{f^d_\alpha(\phi) g^d_\alpha(c)}_{\text{death}} - \underbrace{\delta\phi}_{\text{apoptosis}}$
  - Contact inhibition cues, e.g., $f^p_\alpha(\phi) \propto \phi(1-\phi)$
  - Number of cells to be fed, e.g., $f^d_\alpha(\phi) \propto \phi$
  - Nutrient availability, e.g., $g^p_\alpha(c) \propto (c - c_0)^+$, $g^d_\alpha(c) \propto (c - c_0)^-$

- Nutrient absorption $Q_\alpha(\phi, c) = -\underbrace{h_\alpha(\phi)}_{\text{how many cells}} \underbrace{q_\alpha(c)}_{\text{how much nutrient}}$
  - Prototypes: $h_\alpha(\phi) \propto \phi$, $q_\alpha(c) \propto c$

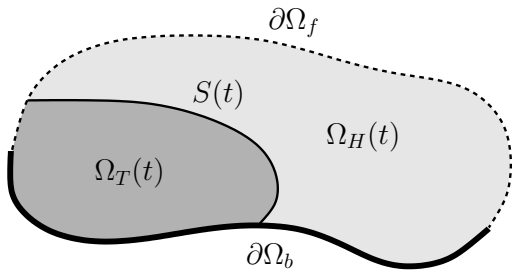
Mathematical Formulation of Initial/Boundary-Value Problems

- Nonlinear diffusion Set $\Phi'(\phi) := \phi(\phi\Sigma(\phi))'$ to get $\nabla \cdot [\phi \nabla(\phi\Sigma(\phi))] = \Delta\Phi(\phi)$
- Weak formulation to properly handle interface and boundary conditions

$$\int_\Omega \left(\frac{\partial \phi}{\partial t} v_1 + \frac{\partial c}{\partial t} v_2\right) dx + \int_\Omega (\kappa_m \nabla\Phi(\phi) \cdot \nabla v_1 + D\nabla c \cdot \nabla v_2)\, dx$$

$$+ \underbrace{\int_{S(t)} \kappa_m [\![\nabla\Phi(\phi)]\!] \cdot \mathbf{n} v_1 \, d\sigma}_{\text{cell flux jump across the interface}} + \underbrace{\int_{\partial\Omega_b} \eta(c - c_b) v_2 \, d\sigma}_{\text{Robin b.c. on the nutrient}}$$

$$= \sum_{\alpha=T,H} \int_{\Omega_\alpha(t)} (\Gamma_\alpha(\phi,\, c) v_1 + Q_\alpha(\phi,\, c) v_2)\, dx$$



- Boundary conditions
  - Robin on $\partial\Omega_b$ (source of nutrient, e.g., blood vessel): $-D\nabla c \cdot \mathbf{n} = \eta(c - c_b)$
  - Neumann on $\partial\Omega_b$ (no flux of cells across the vessel wall): $\kappa_m \nabla\Phi(\phi) \cdot \mathbf{n} = 0$
  - Dirichlet on $\partial\Omega_f$ (physiological conditions): $c = c_b$, $\phi = \phi^\star$
- Interface conditions
  - Continuity of the normal velocity and of the stress: $\kappa_m [\![\nabla\Phi(\phi)]\!] \cdot \mathbf{n} = 0$

A priori estimates

- Take $\Omega \subset \mathbb{R}^d$ bounded
- Choose initial data ϕ_0, $c_0 \in L^2(\Omega)$ s.t. $0 \leq \phi_0 \leq 1$, $0 \leq c_0 \leq c_b$ a.e. in Ω, and look for ϕ, $c \in L^2(0, T; H^1(\Omega))$

Time-dependent problem Any weak solution (ϕ, c) satisfies:

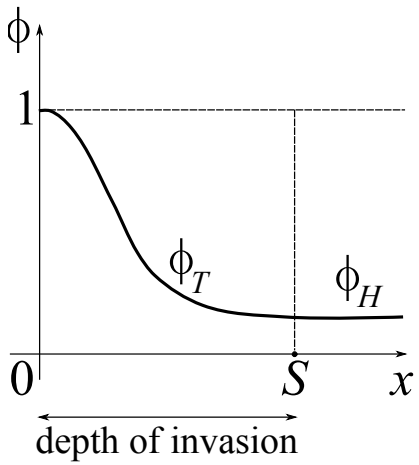
- boundedness $0 \leq \phi(t, x) \leq 1$, $0 \leq c(t, x) \leq c_b$ for a.e. $x \in \Omega$, $t \in (0, T]$
- uniqueness for given initial data
- continuous dependence on the initial data

Stationary problem Any weak solution (ϕ, c) satisfies:

- boundedness $0 \leq \phi \leq 1$, $0 \leq c \leq c_b$ a.e. in Ω
- uniqueness if parameters are sufficiently small

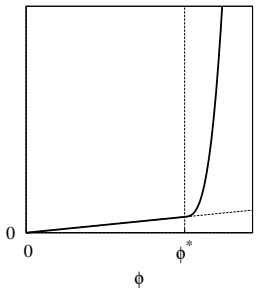
In addition, in the 1D case,

- existence in $H^1(\Omega)$
- estimates on the depth of invasion

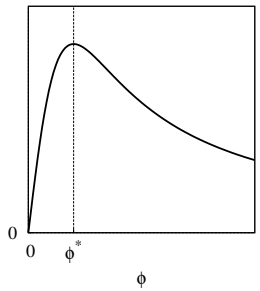


Under which assumptions?

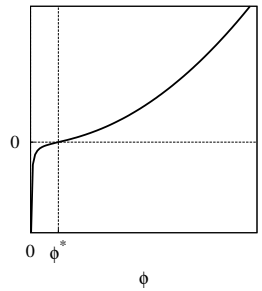
- Nonlinear diffusion
  - Φ **smooth**, $\Phi \in C^1(\mathbb{R})$, and **strictly increasing**, $\Phi' > 0$ in $\mathbb{R} \setminus \{0\}$
  - From the modeling point of view, it is meaningful to reason on Σ



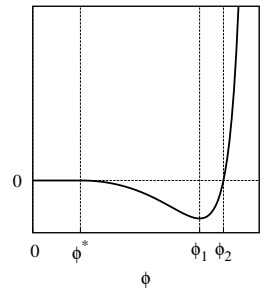
Good
(pressure-like)



Good
(release of stress)



Good
(adhesiveness+repulsion)



Poor
(adhesiveness+repulsion)

- Cell growth Γ_α, nutrient consumption Q_α
  - Proper **sign** also <u>outside</u> the physical ranges of ϕ, c:

	$(-\infty,\ 0)$	$[0,\ 1]$	$(1,\ c_b]$	$(c_b,\ +\infty)$
$f_\alpha^p(\phi)$	$+$	$+$	$-$	
$f_\alpha^d(\phi)$	$-$	$+$	$+$	
$g_\alpha^{p,d}(c)$	$+$	$+$		$+$
$h_\alpha(\phi)$	$+$	$+$	$+$	
$q_\alpha(c)$	$-$	$+$		$+$

  - **Boundedness**, **Lipschitz continuity**, **monotonicity** <u>within</u> the physical ranges of ϕ, c

Conclusions

- Modeling framework to deal with tumor invasion at tissue level
- Interplay between the mechanics of growth and the dynamics of nutrient
- Modeling guidelines to treat phenomenological terms such as
  - intercellular stress
  - cell growth
  - nutrient consumption
- A priori estimates on the solutions of the models, with a view to
  - physical/biological consistency
  - mathematical robustness

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