11ième Biennale Française de Mathématiques Appliquées et Industrielles:

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A mixture-like model for tumor-immune system interactions

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Minisymposia F.Hubert, M.Mezache

Cutaneous squamous cell carcinomas

- 70,000 new cases of cutaneous carcinoma appear each year in France.
  https://www.santemagazine.fr/
- Treatments for cutaneous carcinoma?
  - **First curative treatment:** *In bloc surgical resection with safe margins* $(6 - 10mm)$ *sentinel node dissection for no high risk tumor*,
  - **Lymph node dissection for Np**,
  - **Adjuvant radiotherapy for bad prognosis tumor**,
  - **Adjuvant chemotherapy**,
  - **New biotherapies**: *Anti EGFR, Immunotherapy Anti-PD1.*

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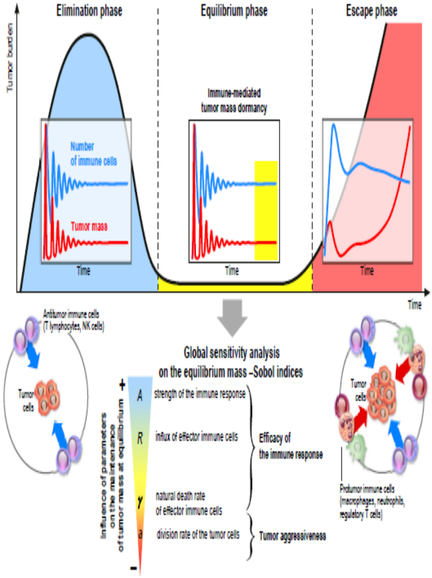

- **Elimination** : tumor cells are simply destroyed by the immune response,
- **Equilibrium** : the immune system maintains and controls the tumor in a viable state,
- **Escape** : with the unlimited growth of the tumor.

K. Atsou, F. Anjuère, V. M. Braud, T. Goudon. J. Theor. Biol, 2020.

K. Atsou, F. Anjuère, V. M. Braud, T. Goudon. Plos One, 2021.

T. Goudon and al. Front Oncol, 2022.

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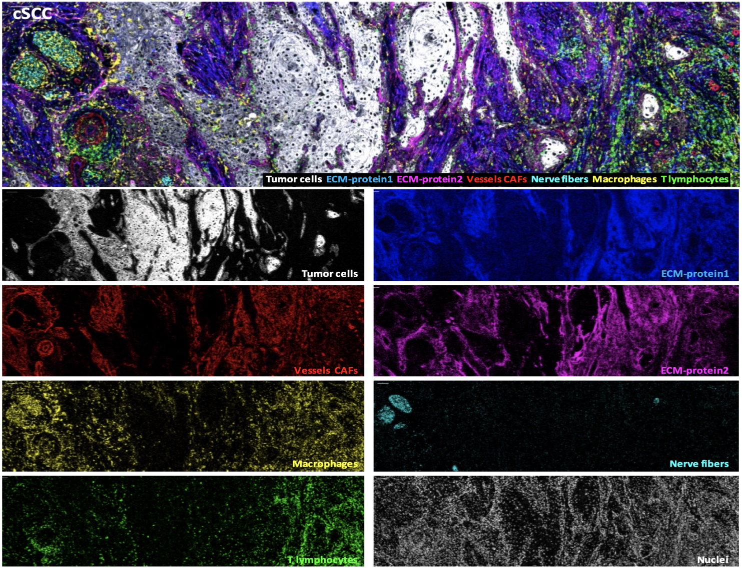
Imaging mass cytometry reveals TME of cutaneous squamous cell carcinoma



Elali and al. Frontiers in Immunology, 2021

A patient with cutaneous squamous carcinoma: Case of 1D simulation of tumor-immune system interactions

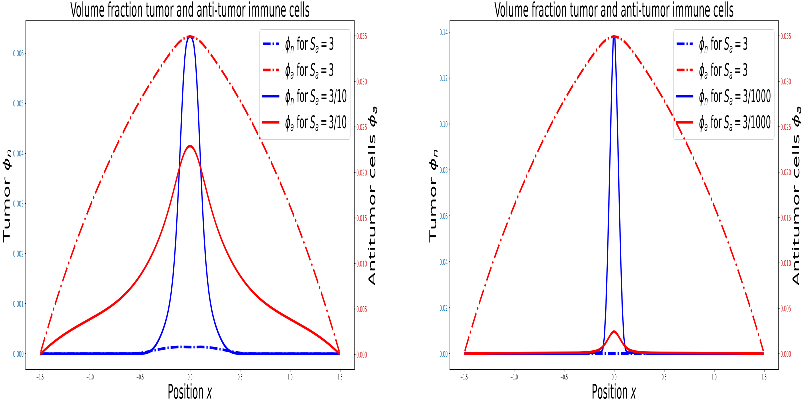


Figure: ϕ_n : volume fraction of tumor cells, ϕ_a : volume fraction of antitumor immune cells.

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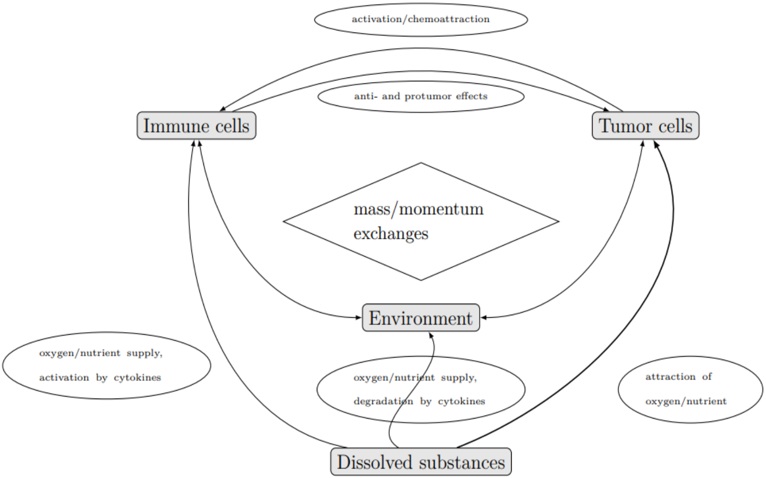
Model description

Competition for space and resources: schematic view of the main mechanisms

- *"constituents"*: **tumor**, (anti- and protumor) **immune cells** and **environment** (other cells and tissues, extracellular matrix and interstitial fluid...).
- *"substances"*: **nutrient, oxygen, cytokines and chemokines**.



- *"constituents"*: volume fractions ϕ_j of phases $j \in \{1, ..., J\}$

$$\partial_t(\rho_j \phi_j) + \nabla_x \cdot \mathscr{J}_j = \Gamma_j,$$

with

ρ_j the typical mass density of the phase j,
Γ_j the mass exchange term,
$\mathscr{J}_j$ the mass fluxes.

- *"substances"*: concentration α_k $k \in \{1, ..., K\}$ obey convection-diffusion equations, with gain and loss reaction terms.

References:
D.Ambrosi and L.Preziosi. Math.Mod.Meth.Appl.Sci, 2002.
B.Polizzi, O.Bernard and M.Ribot. J.Theor.Biol, 2017.

S.Labarthe, B.Polizzi, T.Phan, T.Goudon, M.Ribot and B.Laroche. J.Theor.Biol, 2019.

Mass exchange terms and substances equations

The mass exchange term Γ_j can naturally be split into **gain** and **loss** terms:

$$\boxed{\Gamma_j = Q_j - \rho_j \phi_j L_j}$$

Oxygen and nutrient

The concentration O satisfies the Poisson equation

$$\underbrace{\nabla_x \cdot \left(O \chi_O \nabla_x \phi_n \right)}_{\text{convection}} - \underbrace{\nabla_x \cdot \left(D_O \nabla_x O \right)}_{\text{diffusion}} = \mathcal{R},$$

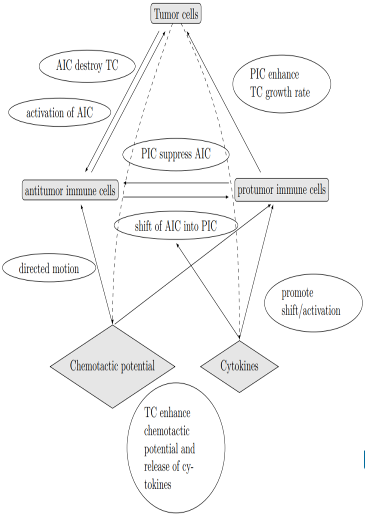
with $\mathcal{R}$ source/consumption term

Cytokines and CAF

The evolution of cytokine concentration is driven by a mere ODE

$$\frac{\mathrm{d}}{\mathrm{d}t} I = \psi - \frac{I}{\tau},$$

with $\tau > 0$ a relaxation time and ψ a threshold function.



Volumic constraints and Stokes-like system

A crucial feature of the model

Constraint on volume fractions

$$\sum_{j=1}^{J} \phi_j = 1$$

summing all mass balance equations

⇓

constraint on the mean volume velocity

$$\nabla_x \cdot \left(\sum_{j=1}^{J} \frac{\mathscr{J}_j}{\rho_j} \right) = \nabla_x \cdot \left(\sum_{j=1}^{J} \phi_j V_j \right) = \sum_{j=1}^{J} \frac{\Gamma_j}{\rho_j}$$

⇓

boundary conditions, must be compatible with this equation

$$\int_{\partial\Omega} \sum_{j=1}^{J} \frac{\mathscr{J}_j}{\rho_j} \cdot \nu_x \, \mathrm{d}\sigma_x = \int_{\Omega} \sum_{j=1}^{J} \frac{\Gamma_j}{\rho_j} \, \mathrm{d}x$$

with ν_x outward unit normal at $x \in \partial\Omega$.

Degraded version of **momentum equations**

⇓

all velocities expressed by means of V_m, Π

$$\begin{aligned} V_n &= V_m - \frac{1}{\phi_m \lambda_{nm}} (\nabla_x \Pi + \nabla_x \mathscr{P}) \\ V_a &= V_m - \frac{1}{\phi_m \lambda_{am}} \left(\nabla_x \Pi - \chi_a \nabla_x \Phi + \frac{D_a}{\phi_a} \nabla_x \phi_a \right), \\ V_p &= V_m - \frac{1}{\phi_m \lambda_{pm}} \left(\nabla_x \Pi - \chi_p \nabla_x \Phi + \frac{D_p}{\phi_p} \nabla_x \phi_p \right). \end{aligned}$$

⇓

that satisfy a Stokes-like system

⇓

$$\begin{pmatrix} -\frac{\mu_m}{\rho_m} \Delta_x & \nabla_x \\ \nabla_x \cdot & -\nabla_x \cdot (\alpha \nabla_x) \end{pmatrix} \begin{pmatrix} V_m \\ \Pi \end{pmatrix} = RHS$$

where V_m **is velocity field of environment**, Π **Lagrange multiplier** of the constraint and α positively valued.

Evolution of an immune-free small tumor volume fraction

Tumor growth model: Competition for space of tumor cells

$$
\begin{cases}
\partial_t(\rho_n\phi_n) - \partial_x\Bigg(\underbrace{\frac{\rho_n\phi_n\mathscr{P}'(\phi_n)}{\lambda_{nm}(1-\phi_n)}\partial_x\phi_n}_{\mathscr{J}_n=\rho_n\phi_n V_n}\Bigg) = \frac{\rho_n\phi_n}{\tau_n}\Upsilon(\mathscr{P}), \\
\phi_n\big|_{x=0,L} = 0,
\end{cases}
$$

where $\Upsilon(\mathscr{P}) = 1 - \frac{\mathscr{P}}{p*}$, and

$$
\mathscr{P}(\phi_n) = \frac{\nu}{\nu-1}\left(\frac{\phi_n}{\phi_*}\right)^{\nu-1}.
$$

$\mathscr{P}(\phi_n)$ describe the homeostatic pressure.

References:

B.Perthame, F.Quirós and J.Vázquez. Arch.Rat.Mech.Anal, 2014.

N.David and B.Perthame. J.Math.Pures Appl, 2021.

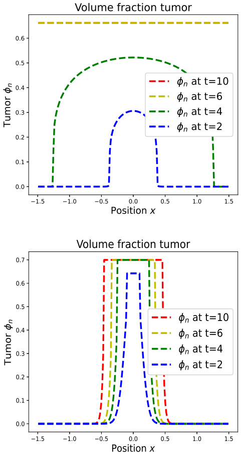


Figure: Evolution of tumor volume fraction ϕ_n, with $\nu = 5$ (top) and $\nu = 50$ (bottom).

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Role of the stress exerted on the tumor(parameter ν)

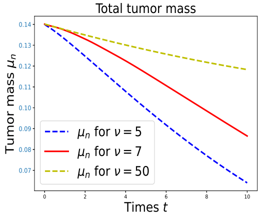
$$\partial_t(\rho_n\phi_n) + \partial_x\left(\rho_n\phi_n\left(V_m - \frac{\partial_x \Pi}{\lambda_{nm}(1-\phi_n)}\right)\right) - \partial_x\left(\frac{\rho_n\phi_n \mathscr{P}'(\phi_n)}{\lambda_{nm}(1-\phi_n)}\partial_x\phi_n\right) = \frac{\rho_n\phi_n}{\tau_n}\Upsilon(\mathscr{P}, O),$$

$$\phi_n\big|_{x=0,L} = 0, \quad \phi_n(0,x) = 0.1 \times \exp^{-40x^2}$$
$$V_m \cdot \nu_x\big|_{x=0,L} = \int_0^L \left(\frac{\Gamma_a}{\rho_a} + \frac{\Gamma_p}{\rho_p} + \frac{\Gamma_n}{\rho_n} + \frac{\Gamma_m}{\rho_m}\right) \mathrm{d}x,$$
$$O\big|_{x=0,L} = O_{bd}.$$

$$\Upsilon(\mathscr{P}, O) = k_{+O}[O-O^*]_+ - \left(k_{-O}[O-O_*]_- + \frac{\mathscr{P}}{p_*}\right)$$

O_* is **necrotic threshold** and O^* is **proliferation threshold**.

- when $O \in [O_*, O^*]$ (quiescent phase), Υ vanishes
- when $O \in [0, O_*[$, $\Upsilon < 0$ necrotic cell death
- when $O^* < O$, $\Upsilon > 0$ proliferation tumor cells



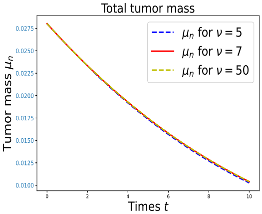


Figure: $O^* = .8$, $O_* = .6$, $\chi_O = .5$ and S_O **inhomogeneous source far** from the tumor; on top initial data multiply by 5, on bottom initial data.

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Ability of the tumor in attracting oxygen/nutrients supplies and degradation of environment by cytokines(parameter f_*)

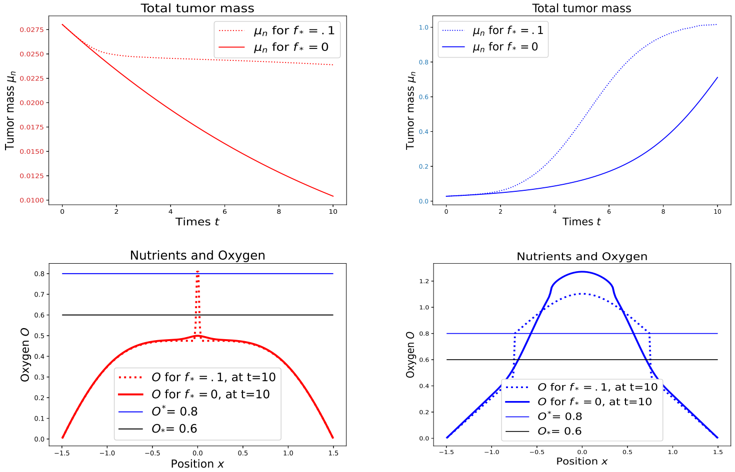

Figure: Source S_O vary: **inhomogeneous source far** from the tumor(left), **inhomogeneous source close** to the tumor(right). $\chi_O = .5$, with a stress on tumor $\nu = 50$.

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Ability of the tumor in attracting oxygen/nutrients supplies and degradation of environment by cytokines(parameter f_*)

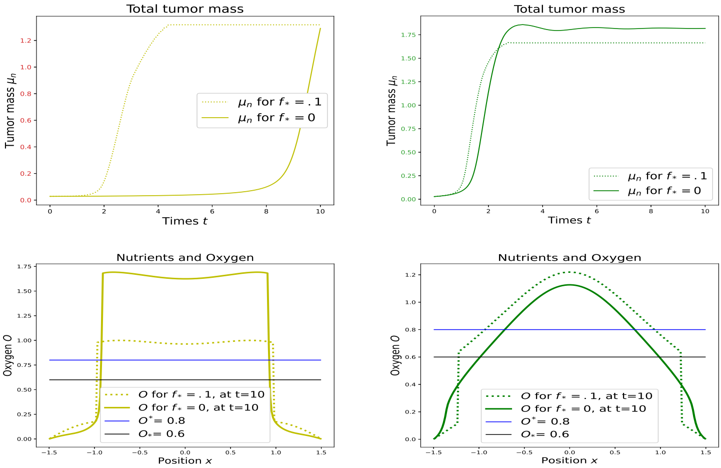

Figure: Source S_O vary: **inhomogeneous source far** from the tumor(left), **inhomogeneous source close** to the tumor(right). $\chi_O = 3.4$, with a stress on tumor $\nu = 50$.

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Antitumor immune response in a complex environment: Equilibrium phases

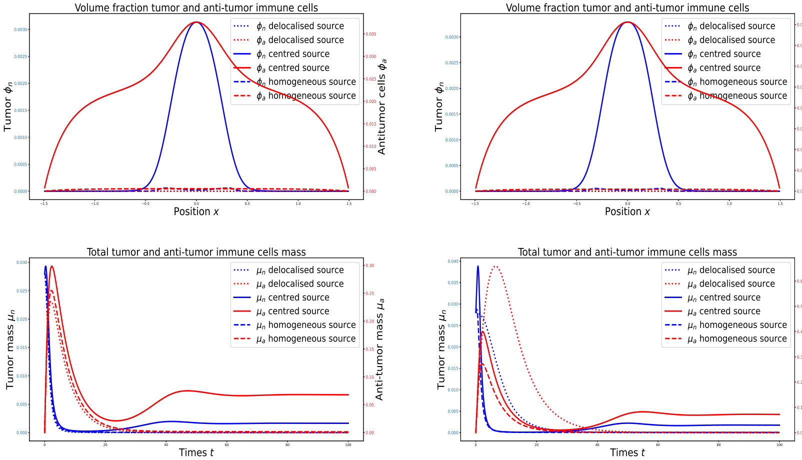

Figure: Source S_O vary, $f_* = 0$ **(no degradation)**. chemotactic coefficient χ_O vary : **on left** $\chi_O = .5$, **on right** $\chi_O = 3.4$; with $\nu = 50$, $A_a = 5, r_m = r_a = r_n/10$.

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Simulation of the full model: from Equilibrium to Escape

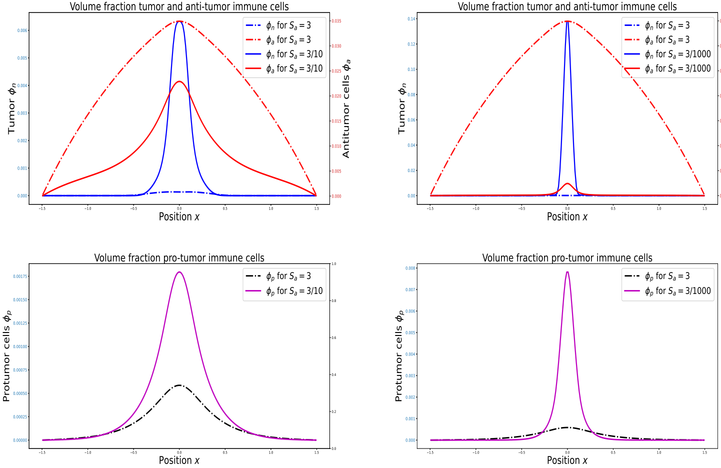

Figure: **On left** $Sa = 3/10$ and **on right** $Sa = 3/1000$; $O^* = .8, O_* = .6, S_p = 3,$ $\chi_O = 1, f_* = 1,$ and S_O **inhomogeneous source far** from the tumor. $\nu = 50,$ $A_a = 5, r_m = r_a = r_p = r_n/10.$

Thank You For

Your Kind Attention!