A PDE approach to studying evolutionary and spatial dynamics in cancer cell populations

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LJLL, 30th June 2017

University of St Andrews

StAMBio

Synopsis

- Object of study : a theoretical framework based on PDE models to studying the dynamics of cancer cell populations

- Aim : use such mathematical models to address questions concerning the mechanisms which drive the dynamics of cancer

- Method : integrate numerical simulation with qualitative analysis to achieve biological conclusions with broad structural stability

- Ultimate goal : complement empirical research by

$$\begin{cases} \text{offering alternative means of interpreting experimental data} \\ \\ \text{enabling extrapolation beyond empirical observation} \end{cases}$$

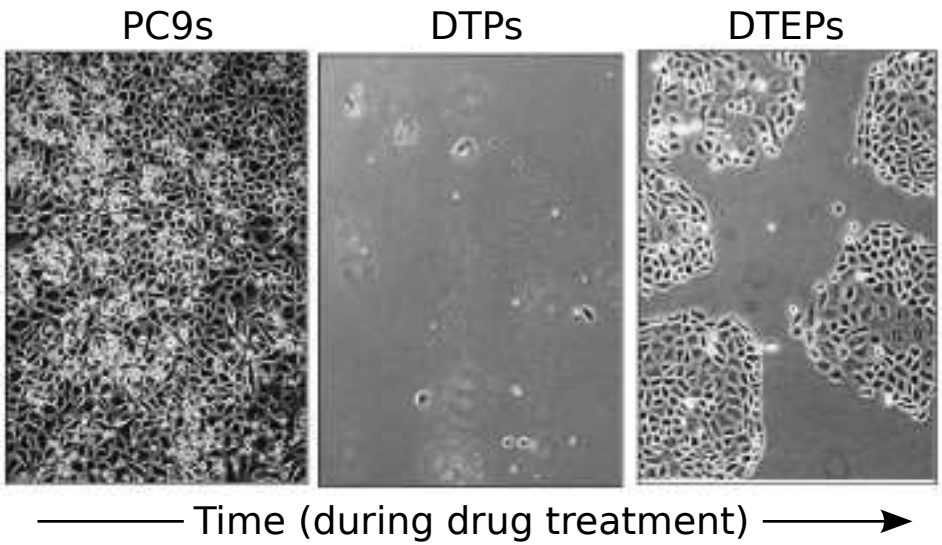
Plan of the talk

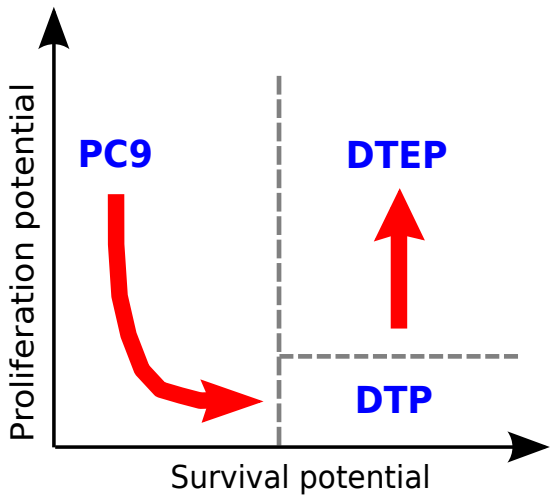
PDE models to study :

1. the emergence of cytotoxic-drug resistance in cancer cell populations
2. the development of phenotypic heterogeneity in solid tumours
3. the formation of infiltrating patterns of cancer-cell invasion

PDE model to study the emergence of cytotoxic-drug resistance in cancer cell populations

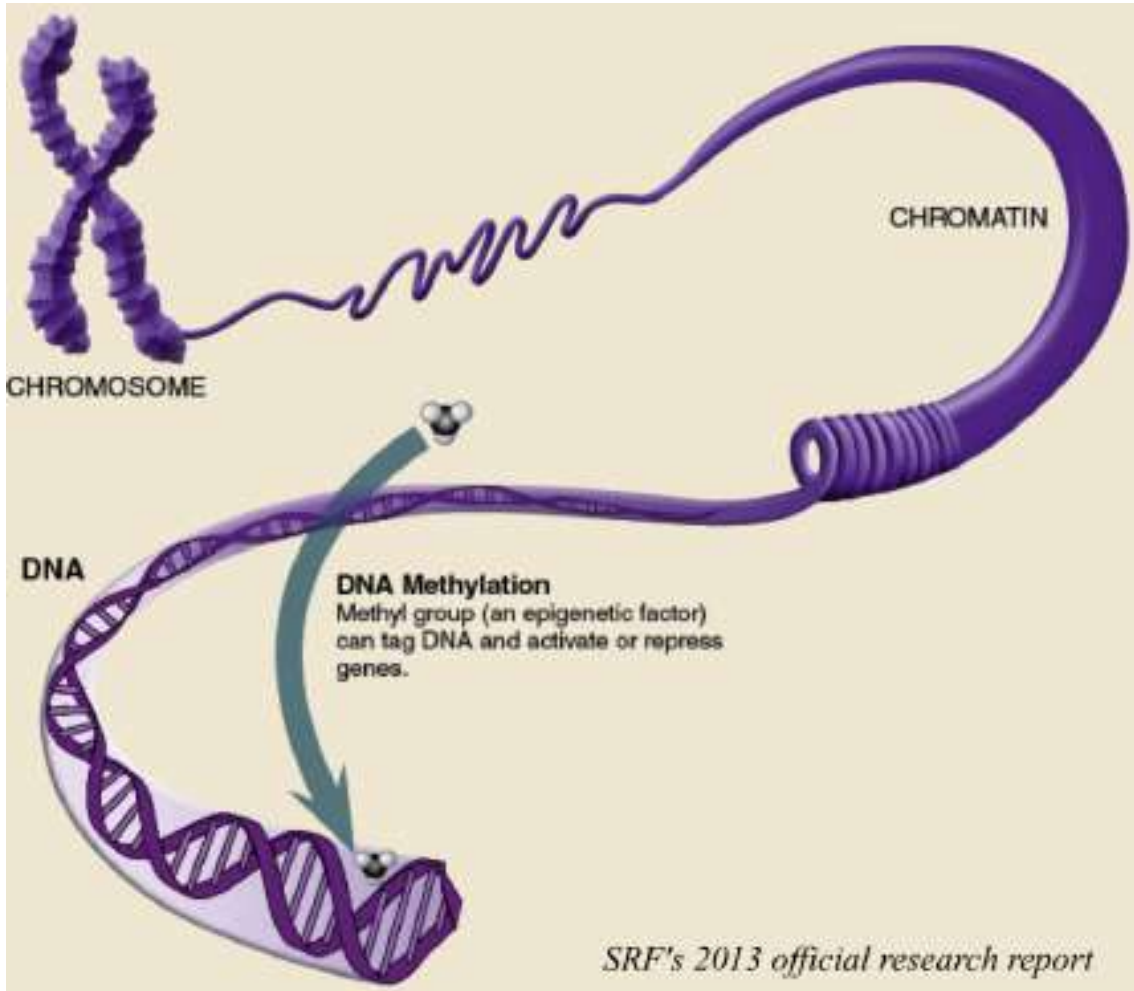
In vitro experiments reveal a reversible drug-tolerant phenotype





Sharma et al. Cell 141:69–80, 2010.

Mutations VS epimutations



Can these results be explained as the outcome of an evolutionary process driven by epimutations and natural selection?

Integrated Systems and Technologies: *Mathematical Oncology*

Cancer Research

Emergence of Drug Tolerance in Cancer Cell Populations: An Evolutionary Outcome of Selection, Nongenetic Instability, and Stress-Induced Adaptation

Rebecca H. Chisholm[1,2,3*], Tommaso Lorenzi[1,2,3,4*], Alexander Lorz[1,2,3], Annette K. Larsen[5,6], Luís Neves de Almeida[1,2,3], Alexandre Escargueil[5,6], and Jean Clairambault[1,2,3]

PDE model

- System under study : well-mixed *in vitro* population of cancer cells

- State of cancer cells :

$$\mathbf{y} = (y_1, y_2) \in \Omega \equiv [0,1] \times [0,1]$$

  expression of a gene which controls drug resistance : $y_1 \in [0,1]$
  expression of a gene which controls cell proliferation : $y_2 \in [0,1]$

- Population density : $n(t, \mathbf{y})$

- Population size : $\rho(t) = \int_\Omega n(t, \mathbf{y})\, d\mathbf{y}$

- Constant concentration of a cytotoxic drug : c

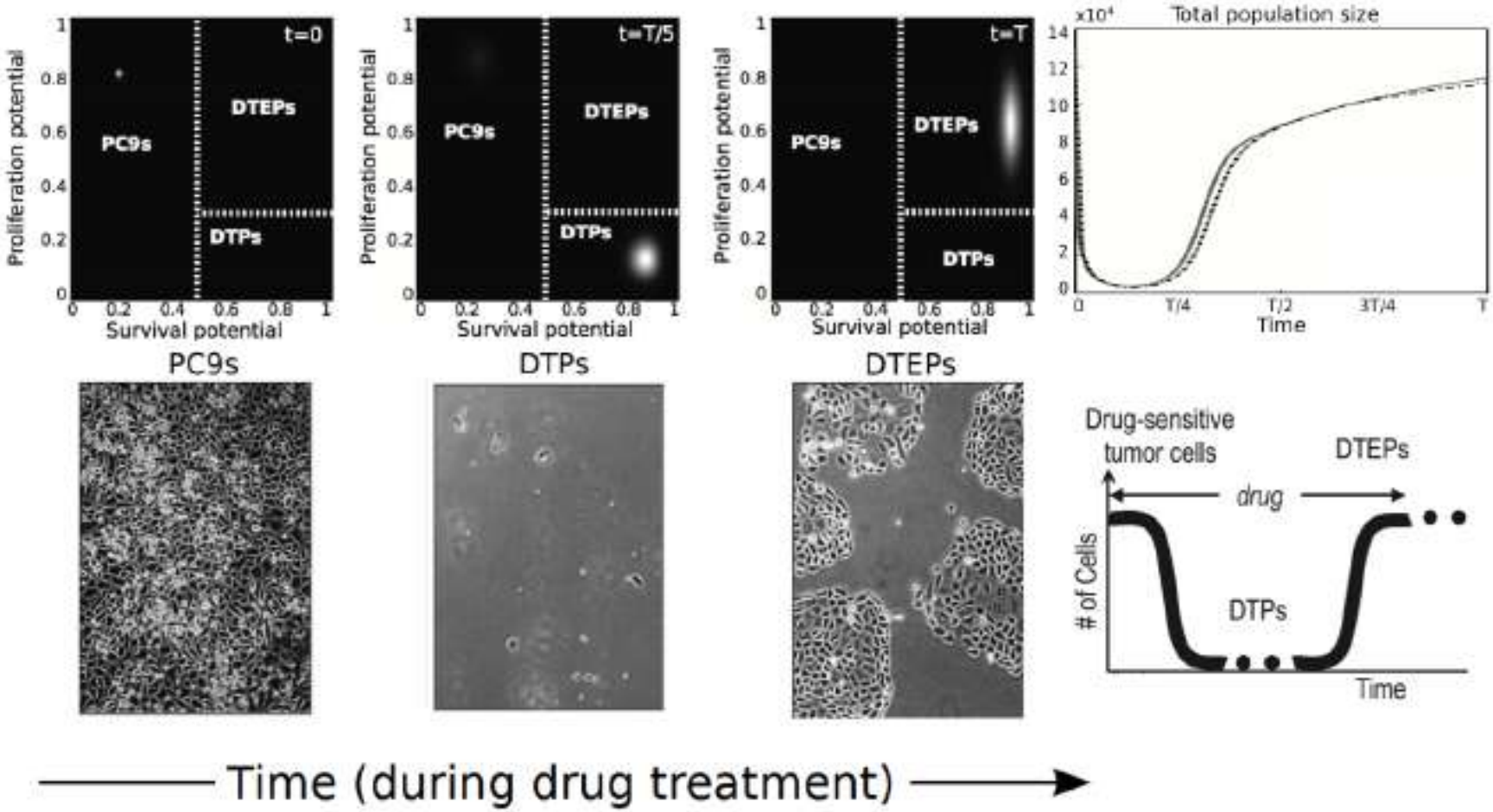
PDE model

$$\frac{\partial n}{\partial t}(t,\mathbf{y}) \quad + \underbrace{\alpha\,\nabla\cdot(v_c(\mathbf{y})\,n(t,\mathbf{y}))}_{\substack{\text{stress-induced}\\ \text{epimutations}}} = \underbrace{R_c(\mathbf{y},\rho(t))\,n(t,\mathbf{y})}_{\text{proliferation/death}} \quad + \underbrace{\beta\,\Delta n(t,\mathbf{y})}_{\substack{\text{random}\\ \text{epimutations}}}$$

$$R_c(\mathbf{y},\rho(t)) \quad = \quad \overbrace{p(\mathbf{y},\rho(t))}^{\substack{\text{proliferation and}\\ \text{competition for resources}}} \quad - \quad \overbrace{c\,k(\mathbf{y})}^{\substack{\text{cytotoxic}\\ \text{action}}}$$

$$v_c(\mathbf{y}) = c\,a(\mathbf{y})$$

Numerical solutions of the PDE model



Asymptotic analysis

- We consider the case in which

$$\mathbf{y} \in \mathbb{R}^N \quad \text{with} \quad N \geq 1$$

- Epimutations are less frequent than proliferation/death:

$$\frac{\partial n}{\partial t}(t,\mathbf{y}) + \varepsilon \nabla \cdot (v_c(\mathbf{y})\, n(t,\mathbf{y})) = R_c(\mathbf{y}, \rho(t))\, n(t,\mathbf{y}) + \varepsilon \Delta n(t,\mathbf{y})$$

- Random epimutations occur on a timescale slower than that of stress-induced epimutations:

$$\frac{\partial n}{\partial t}(t,\mathbf{y}) + \varepsilon \nabla \cdot (v_c(\mathbf{y})\, n(t,\mathbf{y})) = R_c(\mathbf{y}, \rho(t))\, n(t,\mathbf{y}) + \varepsilon^2 \Delta n(t,\mathbf{y})$$

- Time rescaling to observe the effects of epimutations:

$$\varepsilon \frac{\partial n_\varepsilon}{\partial t}(t,\mathbf{y}) + \varepsilon \nabla \cdot (v_c(\mathbf{y})\, n_\varepsilon(t,\mathbf{y})) = R_c(\mathbf{y}, \rho_\varepsilon(t))\, n_\varepsilon(t,\mathbf{y}) + \varepsilon^2 \Delta n_\varepsilon(t,\mathbf{y})$$

Asymptotic analysis

COMMUN. MATH. SCI.
Vol. 14, No. 4, pp. 1181–1188

FAST COMMUNICATION

EFFECTS OF AN ADVECTION TERM IN NONLOCAL LOTKA–VOLTERRA EQUATIONS*

REBECCA H. CHISHOLM†, TOMMASO LORENZI‡, AND ALEXANDER LORZ§

Method of proof : WKB method developed by Perthame & Barles (2008) and Lorz, Mirrahimi & Perthame (2011)

Asymptotic analysis

Theorem (Chisholm-L.-Lorz)

With technical assumptions on the functions v_c and R_c, there exists a subsequence of ρ_ε, denoted again as ρ_ε, such that

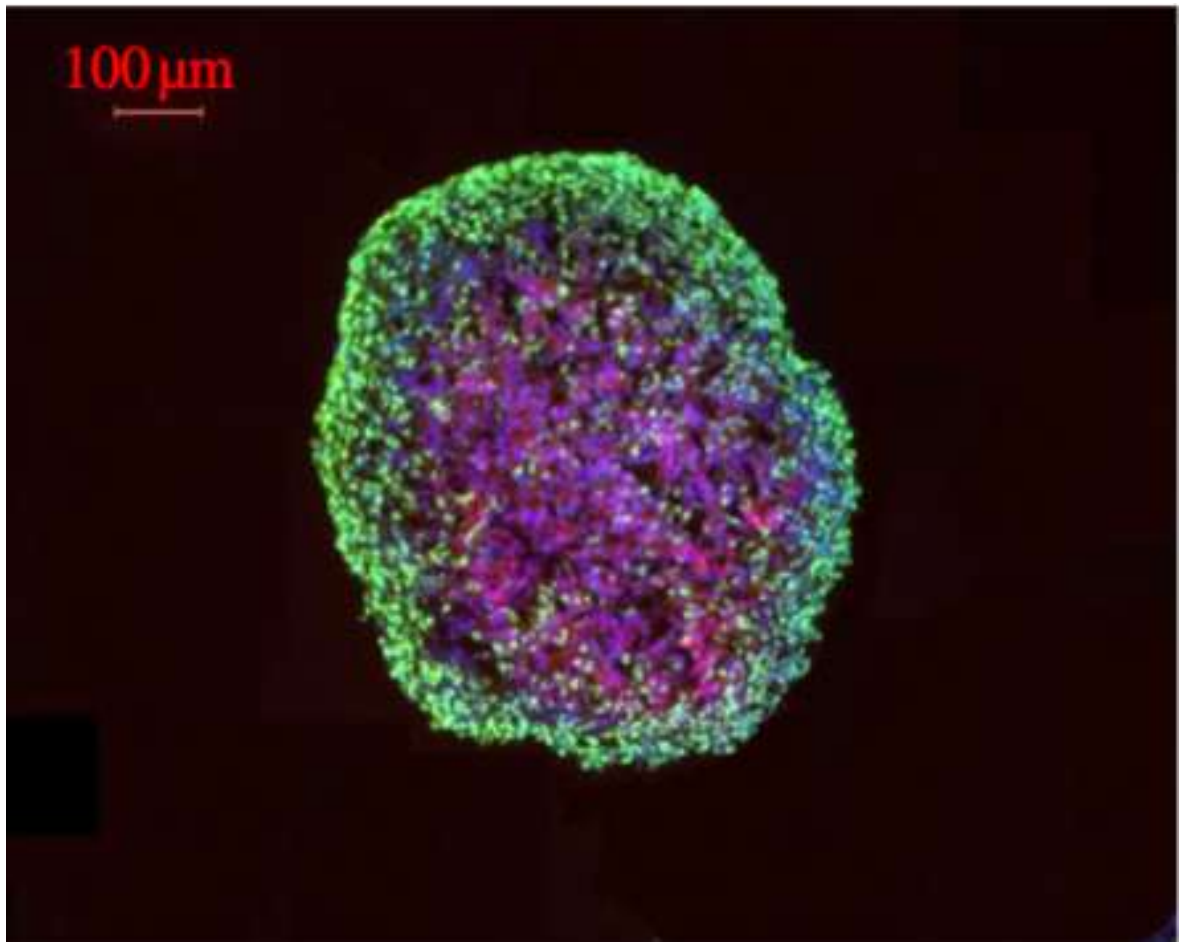
$$\rho_\varepsilon(t) \to \rho(t) \quad \text{as} \quad \varepsilon \to 0. \tag{1}$$

Moreover, weakly in measures,

$$n_\varepsilon(t, \mathbf{y}) \rightharpoonup \rho(t)\delta(\mathbf{y} - \overline{\mathbf{y}}(t)) \quad \text{as} \quad \varepsilon \to 0. \tag{2}$$

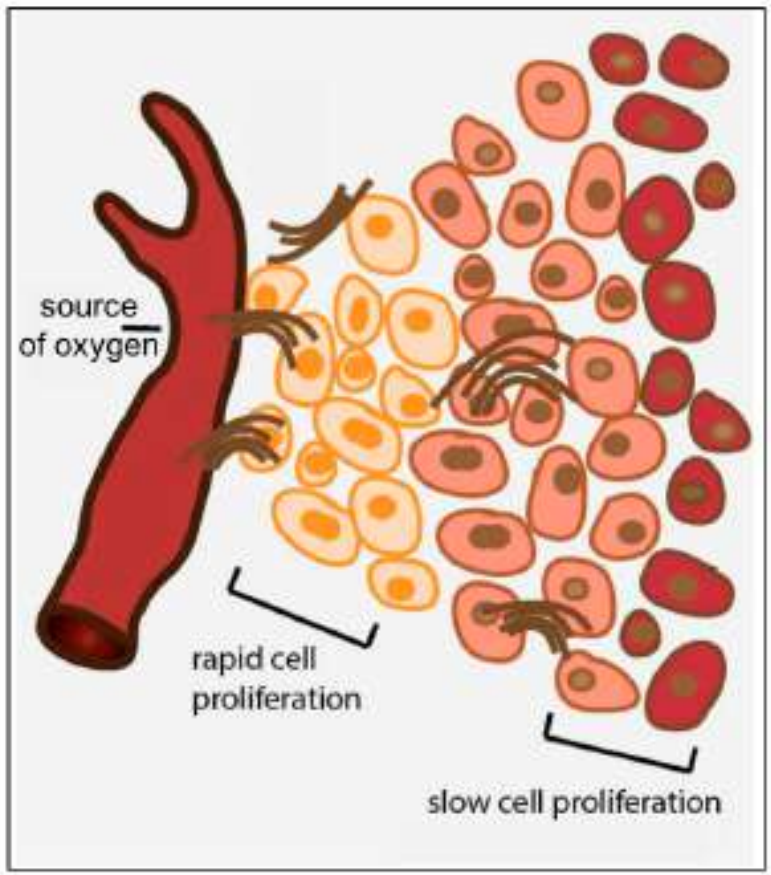
PDE model to study the development of phenotypic heterogeneity in solid tumours

Role of oxygen distribution in the development of intratumour phenotypic heterogeneity



Grimes *et al.* J R Soc Interface 11: 20131124, 2014

Role of oxygen distribution in the development of intratumour phenotypic heterogeneity



Zhang *et al.* Int J Mol Sci 16:27313–27326, 2015

Role of oxygen distribution in the development of intratumour phenotypic heterogeneity

Alfarouk *et al.* Evol Appl 6:46–53, 2013

Can spatial variations in the distribution of oxygen lead to the creation of distinct local niches and thus provide ecological opportunities for diversification?

Bull Math Biol
DOI 10.1007/s11538-014-0046-4

Society for Mathematical Biology

ORIGINAL ARTICLE

Modeling the Effects of Space Structure and Combination Therapies on Phenotypic Heterogeneity and Drug Resistance in Solid Tumors

Alexander Lorz · Tommaso Lorenzi · Jean Clairambault · Alexandre Escargueil · Benoît Perthame

The role of spatial variations of abiotic factors in mediating intratumor phenotypic heterogeneity

Authors: Tommaso Lorenzi[1†], Chandrasekhar Venkataraman[1†], Alexander Lorz[2,3] and Mark A.J. Chaplain[1].

PDE model

- System under study : solid tumour $\approx$ spatial domain $\Omega \subset \mathbb{R}^3$
- State of cancer cells :
  1. position in the tumour : $\mathbf{x} \in \Omega$
  2. normalised expression level of a hypoxia responsive gene : $y \in [0,1]$

$y \to 0$: **higher** proliferation rates $\qquad$ $y \to 1$: **lower** proliferation rates

PDE model

- Population density at position $\mathbf{x}$: $n(t,\mathbf{x},y)$
- Density of cancer cells at position $\mathbf{x}$: $\rho(t,\mathbf{x}) = \int_0^1 n(t,\mathbf{x},y)\,\mathrm{d}y$
- Mean phenotype at position $\mathbf{x}$: $\mu(t,\mathbf{x}) = \frac{1}{\rho(t,\mathbf{x})}\int_0^1 y\,n(t,\mathbf{x},y)\,\mathrm{d}y$
- Concentration of oxygen at position $\mathbf{x}$: $s(t,\mathbf{x})$

PDE model

$$\frac{\partial}{\partial t} n(t,\mathbf{x},y) = \underbrace{R(y,\rho(t,\mathbf{x}),s(t,\mathbf{x}))}_{\text{proliferation/death}} n(t,\mathbf{x},y)$$

$$R(y,\rho(t,\mathbf{x}),s(t,\mathbf{x})) = \overbrace{p(y,s(t,\mathbf{x}))}^{\text{proliferation}} - \overbrace{d\rho(t,\mathbf{x})}^{\substack{\text{competition}\\ \text{for space}}}$$

$$p(y,s(t,\mathbf{x})) = \underbrace{f(y)}_{\substack{\text{proliferation in}\\ \text{hypoxic conditions}}} + \underbrace{r(y,s(t,\mathbf{x}))}_{\substack{\text{proliferation in}\\ \text{oxygenated environments}}}$$

$$f(y) = \zeta\left[1-(1-y)^2\right] \quad \text{and} \quad r(y,s(t,\mathbf{x})) = \gamma_s \frac{s(t,\mathbf{x})}{\alpha_s + s(t,\mathbf{x})}\left(1-y^2\right)$$

PDE model

$$\underbrace{\beta_s \, \Delta s(t,\mathbf{x})}_{\text{diffusion}} \quad = \quad \underbrace{\eta_s \int_0^1 r\big(y, s(t,\mathbf{x})\big) n(t,\mathbf{x},y) \, \mathrm{d}y}_{\text{consumption}} \quad + \quad \underbrace{\lambda_s \, s(t,\mathbf{x})}_{\text{natural decay}}$$

Dirichlet boundary conditions on $\partial\Omega$

Formal analysis

Proposition

Let $\overline{s}(\mathbf{x})$ be the long-term limit of $s(t,\mathbf{x})$. Under biologically consistent assumptions,

$$\rho(t,\mathbf{x}) \xrightarrow[t\to\infty]{} \overline{\rho}(\mathbf{x}) = \frac{1}{d}\left[A_{\overline{s}}(\mathbf{x}) + \frac{\zeta^2}{\zeta + A_{\overline{s}}(\mathbf{x})}\right] \tag{3}$$

and

$$\mu(t,\mathbf{x}) \xrightarrow[t\to\infty]{} \overline{\mu}(\mathbf{x}) = \frac{\zeta}{\zeta + A_{\overline{s}}(\mathbf{x})}, \tag{4}$$

where

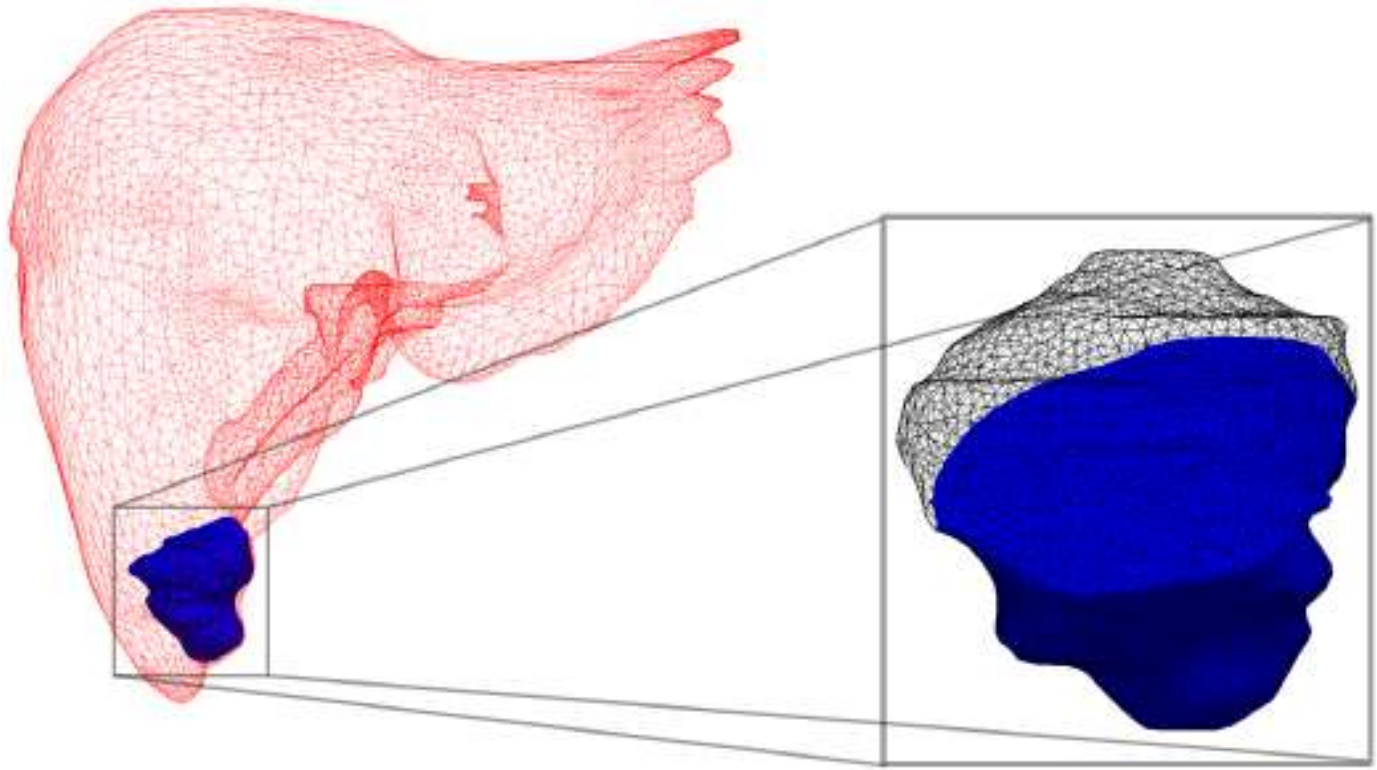
$$A_{\overline{s}}(\mathbf{x}) = \gamma_s \frac{\overline{s}(\mathbf{x})}{\alpha_s + \overline{s}(\mathbf{x})}.$$

Remark : A rigorous asymptotic analysis for a similar problem has been developed by Mirrahimi & Perthame (2015) and Jabin & Schram (2016)

Numerical solutions of the PDE model

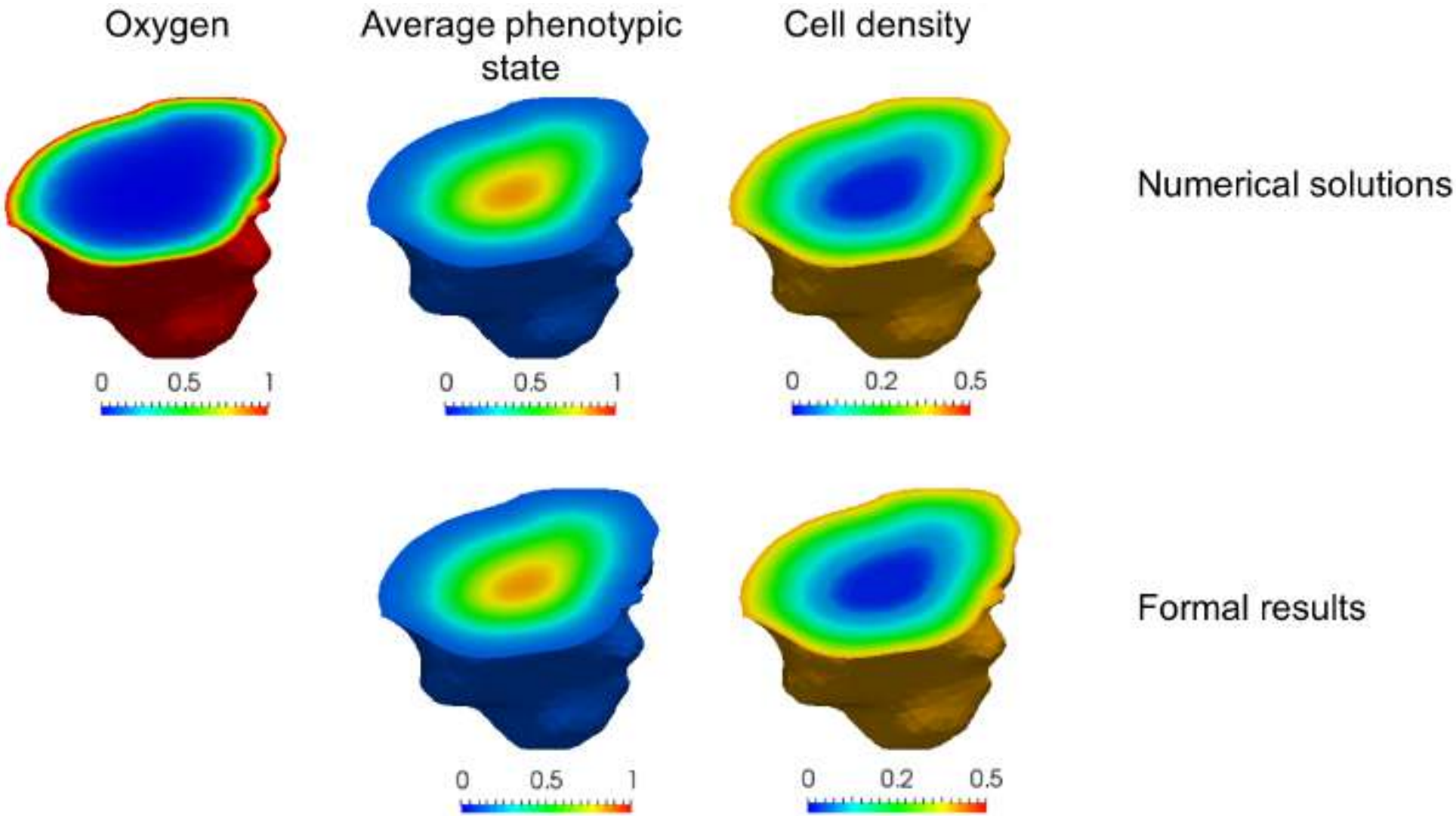
Parameter	Biological meaning	Value	Reference
α_c	Michaelis-Menten constant of cytotoxic drug	$2 \times 10^{-6}\ g\,cm^{-3}$	[21, 36]
α_s	Michaelis-Menten constant of oxygen	$1.5 \times 10^{-7}\ g\,cm^{-3}$	[37]
β_c	Diffusion coefficient of cytotoxic drug	$5 \times 10^{-6}\ cm^2\,s^{-1}$	[21, 38]
β_s	Diffusion coefficient of oxygen	$2 \times 10^{-5}\ cm^2\,s^{-1}$	[39]
γ_c	Maximum cell death rate induced by cytotoxic drug	$1.8 \times 10^{-4}\ s^{-1}$	[21, 36]
γ_s	Maximum cell proliferation rate in oxygenated environments	$1 \times 10^{-5}\ s^{-1}$	[23, 37]
ζ	Maximum cell proliferation rate under hypoxic conditions	$1 \times 10^{-6}\ s^{-1}$	[29]
d	Rate of cell death due to competition for space	$2 \times 10^{-14}\ cm^3\,s^{-1}\,cell^{-1}$	[40]
η_c	Scaling factor for cell consumption of cytotoxic drug	$4 \times 10^{-12}\ g\,cell^{-1}$	[21, 36]
η_s	Scaling factor for cell consumption of oxygen	$2 \times 10^{-12}\ g\,cell^{-1}$	[37]
λ_c	Decay rate of cytotoxic drug	$0.1\ s^{-1}$	[41]
λ_s	Decay rate of oxygen	$0.3\ s^{-1}$	[22]
ρ_0	Reference value for the local cell density	$10^9\ cells\,cm^{-3}$	[40]
s_0	Reference value for the local concentration of oxygen	$6.3996 \times 10^{-7}\ g\,cm^{-3}$	[42]
c_0	Reference value for the local concentration of cytotoxic drug	$10^{-5}\ g\,cm^{-3}$	[21]

Numerical solutions of the PDE model



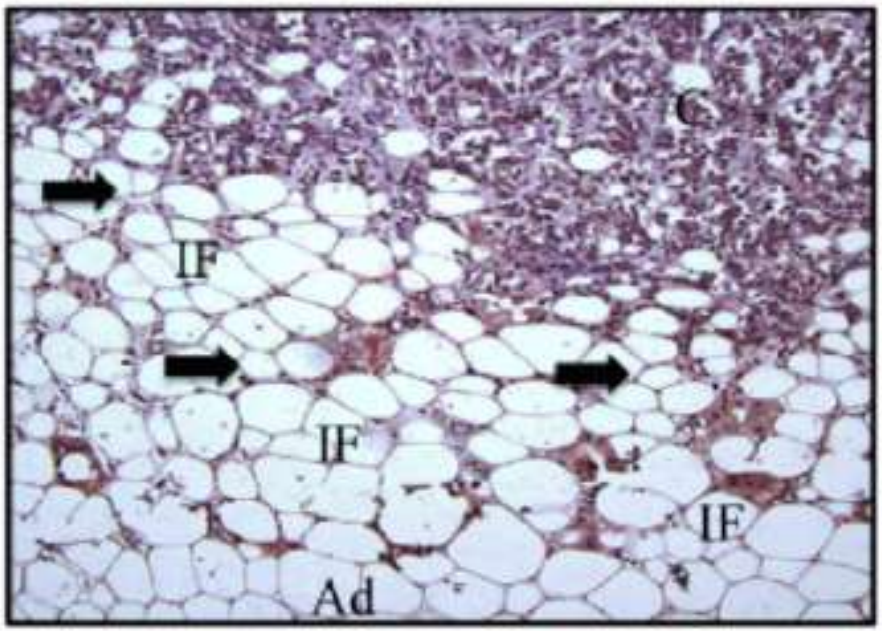
Data obtained from the 3D-IRCADb-01 database

Numerical solutions of the PDE model

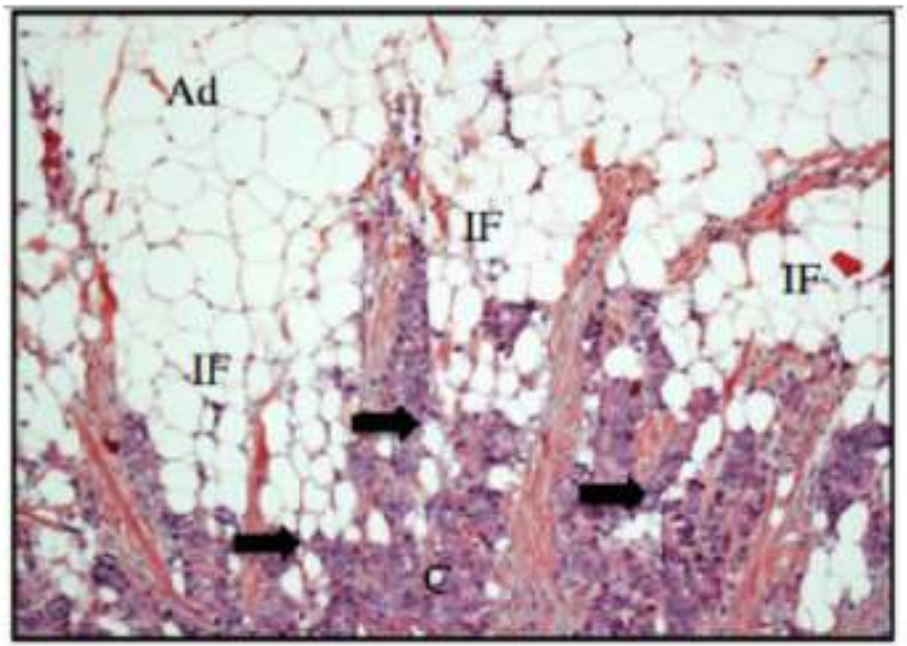


PDE model to study the formation of infiltrating patterns of cancer-cell invasion

Infiltrating patterns of cancer-cell invasion

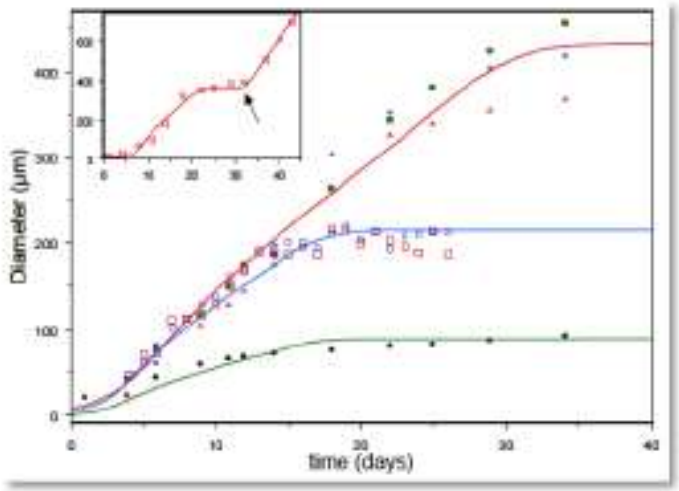


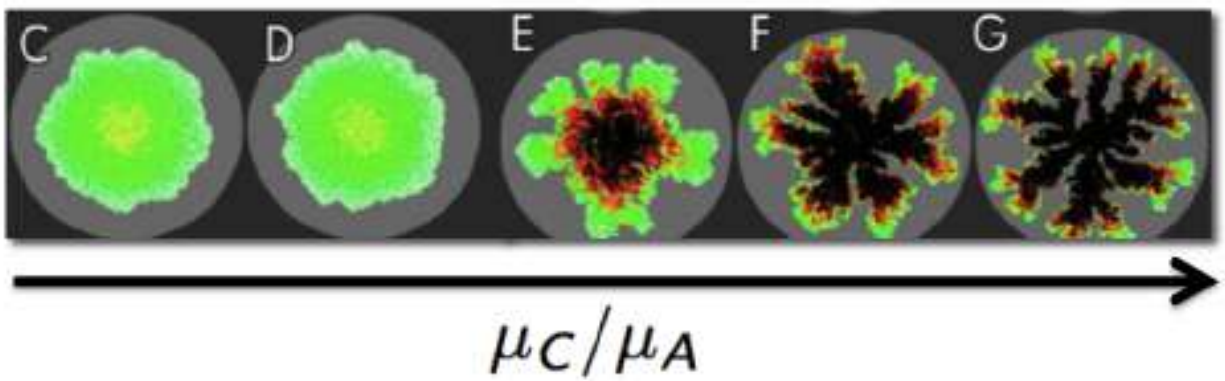
Unpublished data from the group of M. Sabbah



Wang, Y.-Y., *et al.*, Cancer letters, 2012

Computational results from an individual-based model





Can a minimal fluid mechanical PDE model reproduce such patterns?

Kinetic and Related Models
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ON INTERFACES BETWEEN CELL POPULATIONS WITH DIFFERENT MOBILITIES

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PDE model

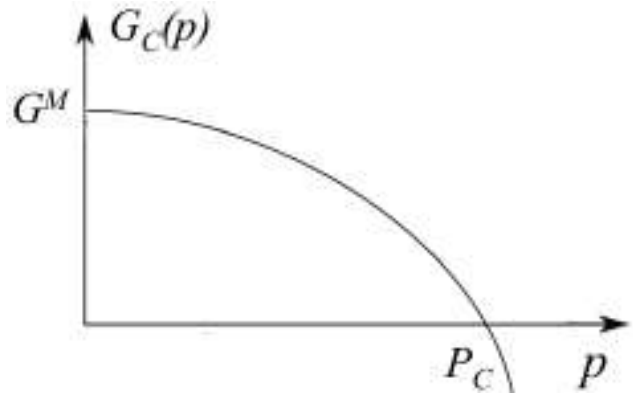
- System under study : dividing cells embedded in a system of non-dividing cells
- Cell state : spatial position $\mathbf{x} = (x_1, x_2) \in \Omega \subseteq \mathbb{R}^2$
- Local density of dividing cells : $\rho_C(t, \mathbf{x}) \geq 0$
- Local density of non-dividing cells : $\rho_A(t, \mathbf{x}) \geq 0$
- Local pressure : $p(t, \mathbf{x}) = K_\gamma \left(\rho_A + \rho_C\right)^\gamma$ with $\gamma \geq 1$

PDE model

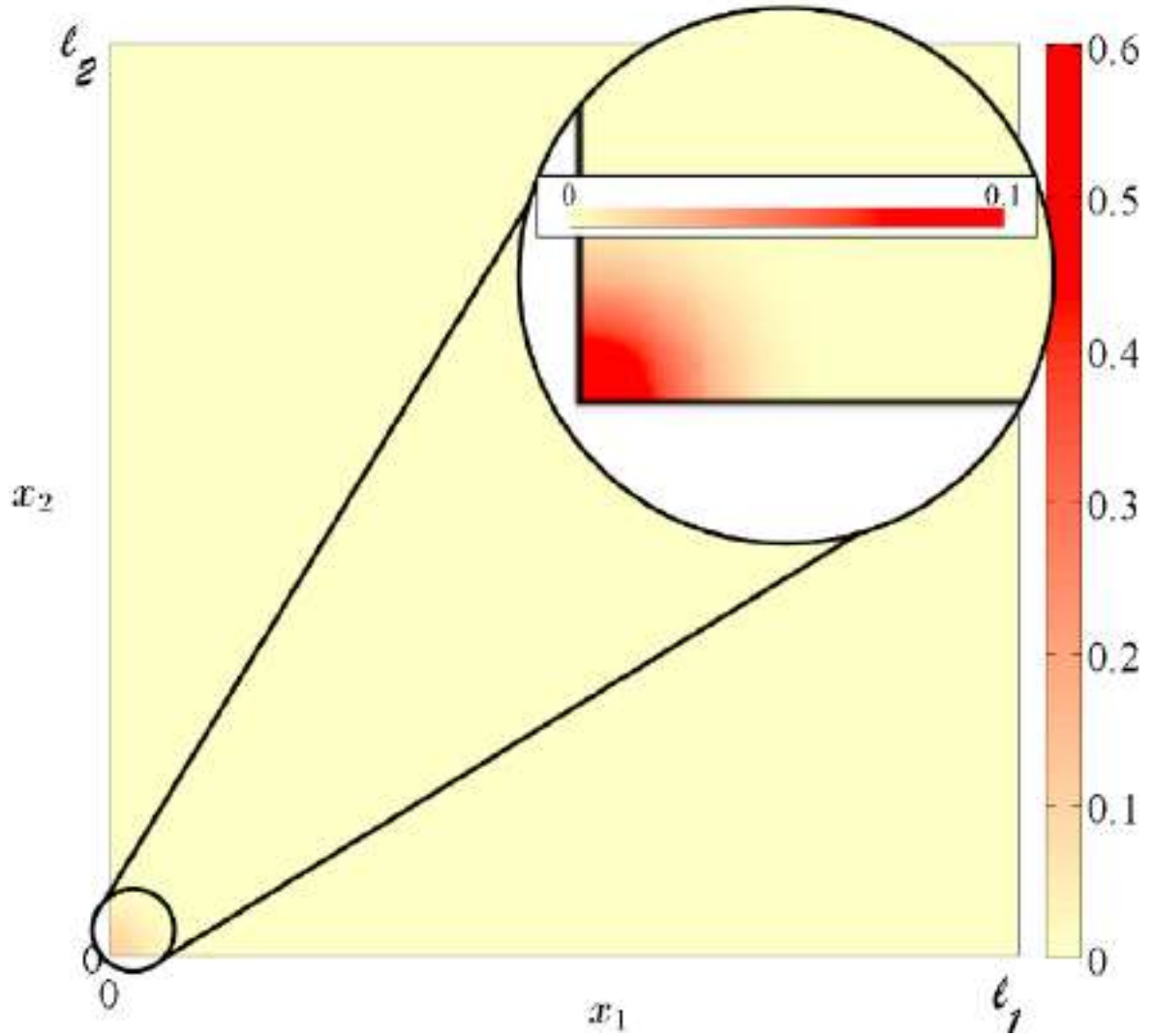
$$\begin{cases} \dfrac{\partial \rho_A}{\partial t}(t,\mathbf{x}) - \underbrace{\mu_A \nabla \cdot \left(\rho_A(t,\mathbf{x}) \nabla p(t,\mathbf{x})\right)}_{\text{mechanical motion}} = 0, \\ \dfrac{\partial \rho_C}{\partial t}(t,\mathbf{x}) - \underbrace{\mu_C \nabla \cdot \left(\rho_C(t,\mathbf{x}) \nabla p(t,\mathbf{x})\right)}_{\text{mechanical motion}} = \underbrace{G_C(p)\, \rho_C(t,\mathbf{x})}_{\text{proliferation}} \end{cases} \tag{5}$$

The growth rate G_C is such that

$$G_C'(\cdot) \leq 0, \qquad G_C(P_C) = 0$$

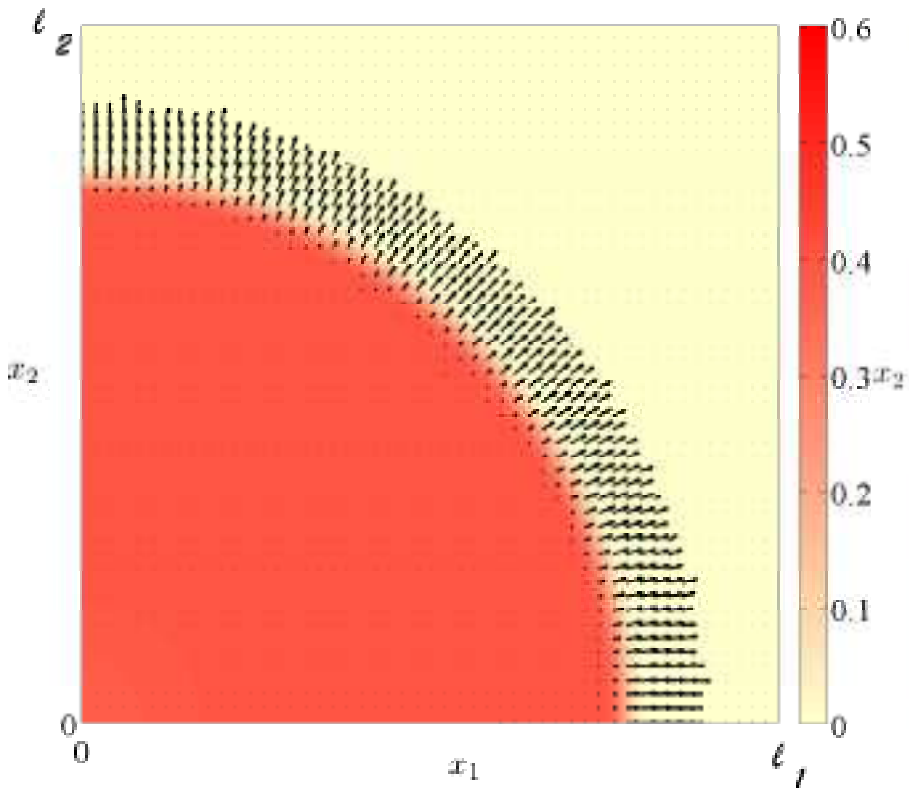


Numerical solutions of the PDE model

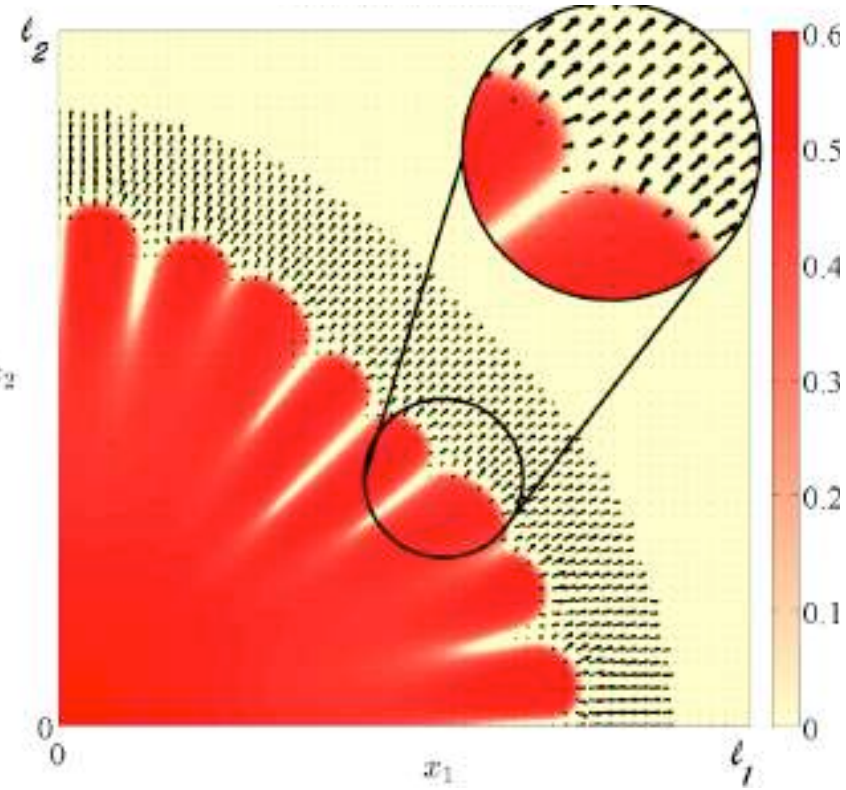


Numerical solutions of the PDE model

$\mu_C \leq \mu_A$



$\mu_C > \mu_A$



Travelling-wave solutions

We search for 1D travelling-wave solutions that satisfy

$$\begin{cases} -\sigma\,\rho_A' - \mu_A\left(\rho_A\,p'\right)' = 0, \\ \\ -\sigma\,\rho_C' - \mu_C\left(\rho_C\,p'\right)' = G_C(p)\,\rho_C \end{cases} \tag{6}$$

with the additional conditions

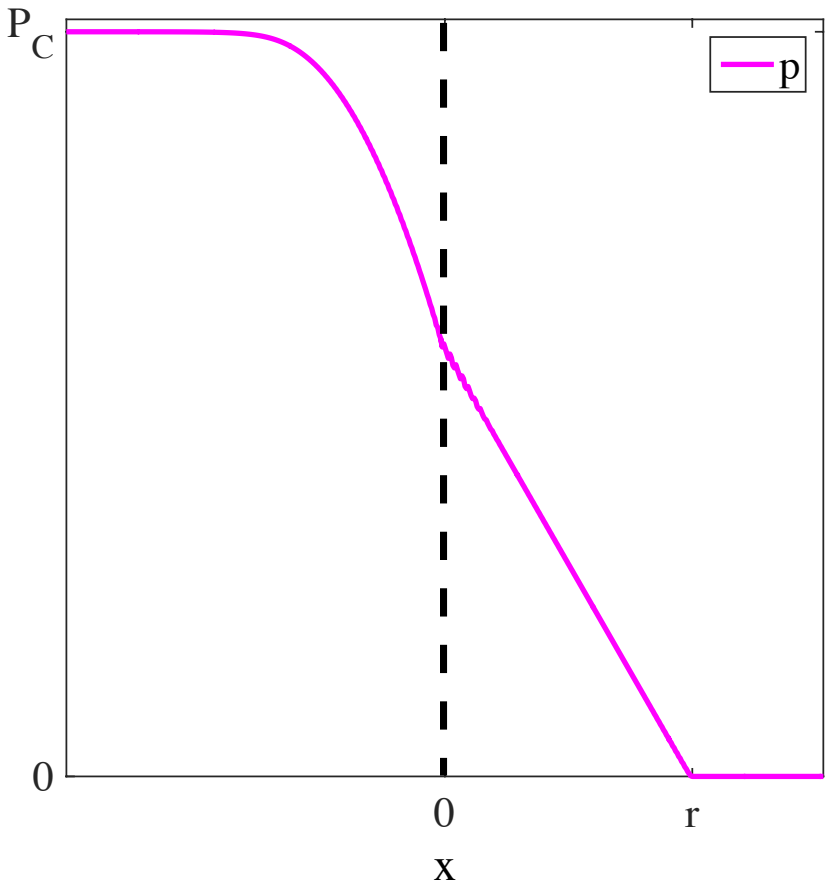
$$\rho_C > 0 \quad \text{on} \quad (-\infty, 0], \tag{7}$$

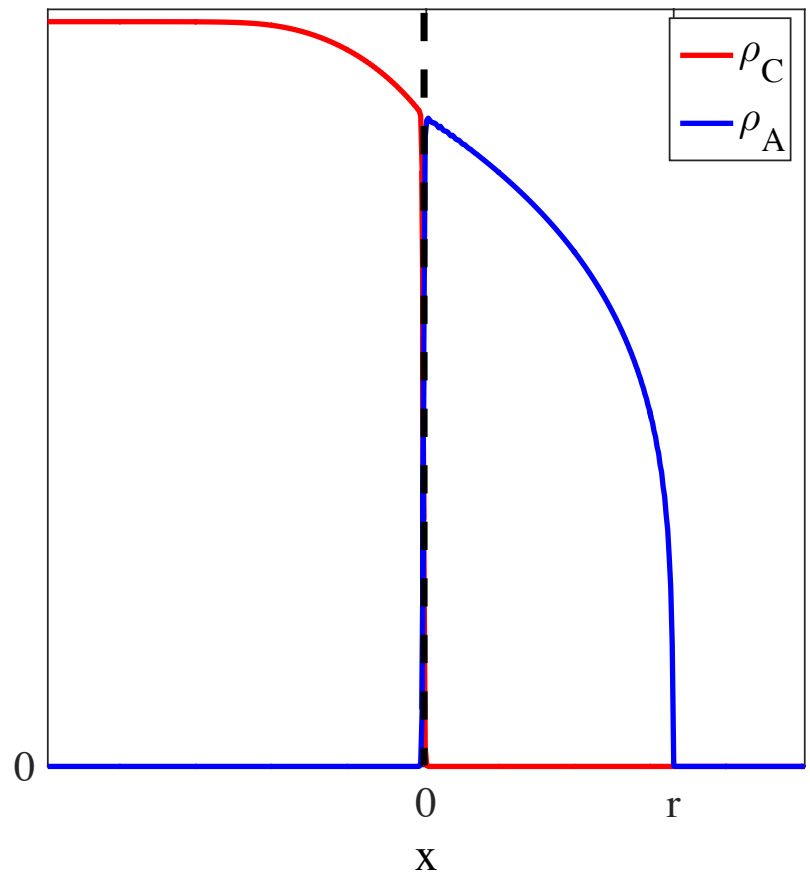
$$\rho_A > 0 \quad \text{on} \quad [0, r] \tag{8}$$

and

$$p(x) \xrightarrow[x\to-\infty]{} P_C \tag{9}$$

Numerical solutions of the PDE model in 1D for $\mu_A > \mu_C$





Travelling-wave solutions

Theorem (L.-Lorz-Perthame)

There exist $\sigma > 0$ and $r > 0$ such that the solution of (6) exists, satisfies conditions (7)-(9), with ρ_C non-increasing and ρ_A that satisfies

$$\int_0^r \rho_A(x)\,dx = M_A > 0.$$

The pressure p has a kink at $x = 0$ with

$$\operatorname{sgn}([p']) = \operatorname{sgn}(\mu_C - \mu_A)$$

and

$$\mu_C\, p'(0^-) = \mu_A\, p'(0^+).$$

Remark : Such travelling-wave solutions are unstable if $\mu_C > \mu_A$.

A PDE approach to studying evolutionary and spatial dynamics in cancer cell populations

Tommaso Lorenzi

LJLL, 30th June 2017