Mathematical study of a cell model for tumor growth : travelling front and incompressible limit

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Introduction

Tumor is an abnormal growth of tissue resulting from uncontrolled, progressive multiplication of cells : cells proliferate or refrain from dying (apoptosis).

Cancer is the first cause of death in France : $\sim 30\%$ of deaths.

The problem is really complex :

- Different scaling : from molecule size to entire organ
- Angiogenesis
- Metastasis
- Therapy

Continuum model of tumor growth

Recent models of cancer growth consider tumor cells as elastic materials to describe the cells multiplication within a tissue.

We can distinguish two classes of model :

- Individual-based model (IBM) : description of small-scale phenomena
- Continuum model : macroscopic description

IBM : Take into account the mechanical properties of the cells. Very accurate but numerically very expensive.
Continuum model : Less accurate but well adapted for large-scale behaviour and less expensive in a numerical purpose.

In this talk, we will mainly focus on the description from a mathematical point of view of the growth of tumor by using macroscopic model of tumor growth.

Plan

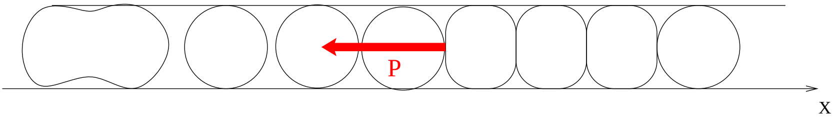
1. Macroscopic model of tumor growth
2. Derivation of Hele-Shaw model : incompressible limit
3. Invasion of tumor : travelling waves

Outline

1. Macroscopic model of tumor growth
2. Derivation of Hele-Shaw model : incompressible limit
3. Invasion of tumor : travelling waves

Cells model

Recent models of cancer growth consider tumor cells as elastic materials to describe the cells multiplication within a tissue.
The invasion ability of tumor cells is mainly driven by cell division which depends on local density and nutrient concentration and on pressure forces.



- In a favorable environment, cells growth by mitosis.
- Under mechanical stresses P, cells are compressed and can deform. If P is too large, there is no cells division.
- Influence of the nutrient c.

Continuum model of tumor growth

Unknowns :
$\rho(t,x)$: density of tumor cells at time t and position x,
$p(t,x)$: elastic pressure given by a law $p = P(\rho)$,
$v(t,x)$: velocity field,
$c(t,x)$: nutrient concentration.

The system governing these quantities reads

$$\partial_t \rho + \underbrace{\text{div}_x(\rho v)}_{\text{mechanical pressure}} = \underbrace{\rho G(p,c)}_{\text{Growth term}} + \underbrace{\epsilon \Delta_x \rho}_{\text{active motion}},$$

$$v = -C_S \nabla_x p, \qquad \text{Darcy law},$$

$$\partial_t c - \Delta_x c + \lambda c \rho = 0, \qquad \text{Nutrient consumption}.$$

Continuum model of tumor growth

- ϵ is a diffusion coefficient, $C_S > 0$, $\lambda > 0$.
- The growth function is given by $G(p,c)$ and satisfies $\partial G/\partial p \leq 0$, $\partial G/\partial c \geq 0$. In this talk, we will consider G only depending on p or c.
  - If $G = G(p)$, we assume that there exists P_M such that $G(P_M) = 0$. In the physicist litterature (see [Prost et al]), P_M is usually called the homeostatic pressure.
  - If $G = G(c)$, the lack of nutrients leading to cells necrosis is modeled by : $\exists\, \overline{c}$, such that $G(c) < 0$ for $c < \overline{c}$. Then we observe a proliferative rim and a necrotic core.

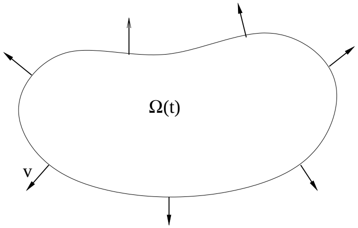
References : Bellomo & Preziosi ['00], Byrne & Drasdo [J Math Bio '09], Byrne & Chaplain [Math Biosc '96], Preziosi & Tosin [J Math Bio '09].

Free boundary model : Hele-Shaw model

Another class of macroscopic model for tumor growth is geometric model as Hele-Shaw, which describes the tumor by the dynamics of its domain $\Omega(t)$.

The model reads

$$\begin{aligned} -\Delta p = G(p), &\quad \text{on } \Omega(t), \\ p = 0, &\quad \text{on } \partial\Omega(t). \end{aligned}$$



The velocity of the boundary is given by the Darcy law

$$v = -\nabla_x p.$$

References : Lowengrub et al. [Nonlinearity '10], Roose, Chapman & Maini [SIAM '07], Friedman [DCDS B '04], Friedman & Hu [TAMS '08], Greenspan ['72].

Outline

1. Macroscopic model of tumor growth
2. Derivation of Hele-Shaw model : incompressible limit
3. Invasion of tumor : travelling waves

Continuum model of tumor growth : summary

To simplify, we neglect the influence of the nutrient and we can only deal with $G = G(p)$. We are interested in the link between the two following models :

Mechanical model

$$\partial_t \rho + \text{ div }_x(\rho v) = \rho G(p) + \epsilon \Delta_x \rho, \qquad \text{on } \mathbb{R}^d$$

$$v = -\nabla_x p, \qquad p = P(\rho).$$

Free boundary model

$$\begin{aligned} -\Delta p &= G(p), && \text{on } \Omega(t), \\ p &= 0, && \text{on } \partial\Omega(t), \end{aligned}$$

where the velocity of the boundary of the domain is given by the Darcy law

$$v = -\nabla_x p.$$

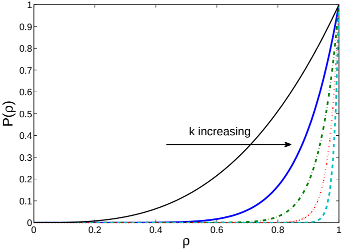
Incompressible limit

Objective : derive free boundary model of Hele-Shaw type from a mechanical model of tumor growth.

Idea : We consider an incompressible limit for the pressure.

Let us define the pressure law : $P(\rho) = \rho^k$ and letting $k \to +\infty$. Then formally at the limit we obtain that :

- $P(\rho_\infty) = 0$ if $\rho_\infty < 1$,
- $P(\rho_\infty) \in [0, +\infty)$ if $\rho_\infty = 1$.



We can distinguish two regions : a region where $\rho_\infty < 1$ and $p_\infty = 0$, and a region where $\rho_\infty = 1$ and $p_\infty > 0$.

Incompressible limit : porous medium equation

Taking $p_k = \rho_k^k$ we have that

$$\rho_k v = -\rho_k \nabla p_k = -\frac{k}{k+1} \nabla \rho_k^{k+1}.$$

Therefore we can rewrite equation

$$\partial_t \rho_k + \mathrm{div}(\rho_k v) = \rho_k G(p_k) + \epsilon \Delta \rho_k.$$

as the porous medium equation

$$\partial_t \rho_k - \frac{k}{k+1} \Delta(\rho_k^{k+1}) = \rho_k G(p_k) + \epsilon \Delta \rho_k.$$

We are interested in the limit $k \to +\infty$ of this model.

Incompressible limit : numerical observations

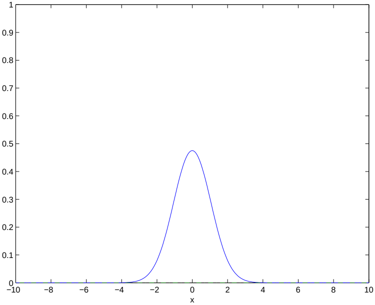
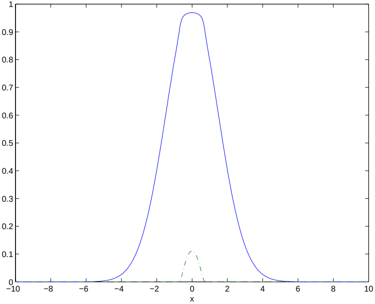


FIGURE: First steps of the initiation of the free boundary. The density ρ is plotted in blue solid line whereas the pressure p is represented in green dashed line.

Incompressible limit : numerical observations



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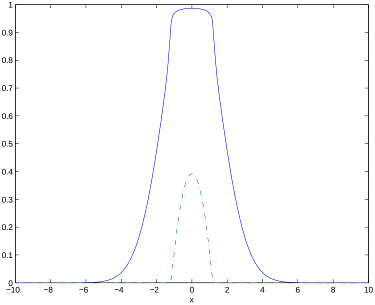

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Incompressible limit : numerical observations

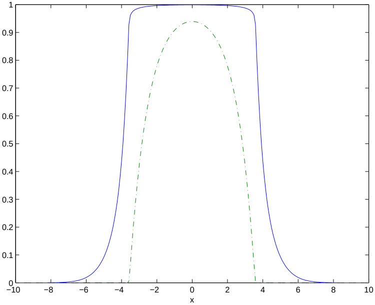

FIGURE: First steps of the initiation of the free boundary. The density ρ is plotted in blue solid line whereas the pressure p is represented in green dashed line.

Formal derivation with no active motion

Formally, starting from

$$\partial_t \rho_k - \mathrm{div}\big(\rho_k \nabla p_k\big) = \rho_k G\big(p_k\big).$$

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Multiplying by $p'(\rho_k)$, we get

$$\partial_t p_k - \rho_k p'(\rho_k)\Delta p_k + |\nabla p_k|^2 = \rho_k p'(\rho_k) G\big(p_k\big).$$

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For the special case $p_k = \rho_k^k$ at hand, we find

$$\partial_t p_k - k p_k \Delta p_k + |\nabla p_k|^2 = k p_k G(p_k).$$

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$$\partial_t p_k - k p_k \Delta p_k + |\nabla p_k|^2 = k p_k G(p_k).$$

Letting formally $k \to \infty$ we find, in the sense of distribution

$$p_\infty(\Delta p_\infty + G(p_\infty)) = 0.$$

Formal derivation with no active motion

Thus we can distinguish two regions by defining $\Omega(t) = \{p_\infty(t) > 0\}$:

$$\begin{cases} -\Delta p_\infty &= G(p_\infty) \quad \text{in } \Omega(t) = \{p_\infty(t) > 0\}, \\ p_\infty &= 0 \qquad\quad\ \ \text{on } \partial\Omega(t), \end{cases}$$

$$\begin{cases} \partial_t \rho_\infty - \operatorname{div}\big(\rho_\infty \nabla p_\infty\big) = \rho_\infty G\big(p_\infty\big), \qquad x \in \mathbb{R}^d \setminus \Omega(t),\ t \geq 0, \\ \rho_\infty = 1, \qquad x \in \Omega(t). \end{cases}$$

Moreover, we notice that if $\rho_\infty = \mathbf{1}_{\Omega(t)}$, then the front velocity from the latter equation is given by $v = -\nabla_x p_\infty$, that is the Darcy law.

Formal derivation with active motion

With active motion, we start from

$$\partial_t \rho_k - \mathrm{div}\big(\rho_k \nabla p_k\big) - \epsilon \Delta \rho_k = \rho_k G\big(p_k\big).$$

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Multiplying by $p'(\rho_k)$, we get

$$\partial_t p_k - \rho_k p'(\rho_k) \Delta p_k - |\nabla p_k|^2 - \epsilon \Delta p_k = \rho_k p'(\rho_k) G\big(p_k\big) - \epsilon p''(\rho_k) |\nabla \rho_k|^2.$$

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For the special case $p_k = \rho_k^k$ at hand, we find

$$\partial_t p_k - k p_k \Delta p_k - |\nabla p_k|^2 - \epsilon \Delta p_k = k p_k G(p_k) - \epsilon (k-1) \frac{\nabla p_k \cdot \nabla \rho_k}{\rho_k}.$$

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Letting formally $k \to \infty$ we find, in the sense of distribution

$$-p_\infty \Delta p_\infty = p_\infty G(p_\infty) - \epsilon \frac{\nabla p_\infty \cdot \nabla \rho_\infty}{\rho_\infty}.$$

Formal derivation with active motion

However, defining as above $\Omega(t) = \{p_\infty(t) > 0\}$, we expect

- $\nabla p_\infty = 0$ on $\mathbb{R}^d \setminus \Omega(t)$,
- $\rho_\infty = 1$, therefore $\nabla \rho_\infty = 0$, on $\Omega(t)$.

Thus, we expect $\nabla p_\infty \cdot \nabla \rho_\infty = 0$. Then we get the similar relation :

$$p_\infty \left(\Delta p_\infty + G(p_\infty) \right) = 0.$$

Let us remark that this similar complementary relation does not mean that active motion has no effect in the limit. Though the pressure equation is the same one as for the case $\nu = 0$, the free boundary $\partial\Omega(t)$ is not expected to move with the usual Hele-Shaw rule $v = -\nabla p_\infty$, but with a faster one.

Convergence result

These formal computations can be made rigorous.
We consider that

$$G' < 0 \text{ and that for some } P_M > 0, \quad G(P_M) = 0.$$

We complement the system

$$\partial_t \rho_k - \operatorname{div}(\rho_k \nabla p_k) - \epsilon \Delta \rho_k = \rho_k G(p_k),$$

$$p_k = \rho_k^k,$$

with initial conditions ρ_k^{ini} and p_k^{ini}.
We assume that the initial data are uniformly bounded in $L^1 \cap L^\infty(\mathbb{R}^d)$ with $p_k^{ini} \leq P_M$.

Convergence result

Theorem [Perthame, Quirós, Vázquez ARMA '14] [Perthame, Quirós, Tang, V. IFB '14]

Let $T > 0$. Under previous assumptions, $(\rho_k)_k$, $(p_k)_k$ converge strongly, up to subsequences, in $L^q((0,T) \times \mathbb{R}^d)$, $1 \leq q < \infty$, to limits

$$\rho_\infty \in C\big([0,\infty); L^1(\mathbb{R}^d)\big) \cap L^\infty((0,T); H^1(\mathbb{R}^d)),$$
$$p_\infty \in L^\infty((0,T); H^1(\mathbb{R}^d)),$$

such that $0 \leq \rho_\infty \leq 1$ and $0 \leq p_\infty \leq P_M$. Moreover, (ρ_∞, p_∞) satisfies in the weak sense

$$\partial_t \rho_\infty - \operatorname{div}\big(\rho_\infty \nabla p_\infty\big) - \epsilon \Delta \rho_\infty = \rho_\infty G\big(p_\infty\big),$$

and the *complementary relation*

$$p_\infty \left(\Delta p_\infty + G\big(p_\infty\big)\right) = 0.$$

Estimates

In order to have compactness, we need to establish some *a priori* estimates :

- uniform bound in $L^1 \cap L^\infty$ for ρ_k and p_k : by a maximum principle, since $G(p) < 0$ for $p > P_M$, we get

$$0 \leq p_k \leq P_M.$$

We deduce from the law $p_k = \rho_k^k$,

$$0 \leq \rho_k \leq P_M^{1/k} \underset{k\to\infty}{\longrightarrow} 1,$$

and the uniform in k L^1 bound

$$\int_{\mathbb{R}^d} \rho_k(t) \leq e^{G(0)t} \int_{\mathbb{R}^d} \rho^{\text{ini}}, \qquad \int_{\mathbb{R}^d} p_k(t) \leq Ce^{G(0)t} \int_{\mathbb{R}^d} \rho^{\text{ini}}.$$

Estimates

- bound on the space derivative : multiplying by ρ_k the equation

$$\partial_t \rho_k - \mathrm{div}(\rho_k \nabla p_k) - \epsilon \Delta \rho_k = \rho_k G(p_k),$$

we get after an integration

$$\int_{\mathbb{R}^d} \left(\epsilon |\nabla \rho_k|^2 + k \rho_k^{k-1} |\nabla \rho_k|^2 \right) \leq G(0) \int_{\mathbb{R}^d} \rho_k^2,$$

where we use the fact that $\partial_t \rho_k \geq 0$. Thus there exists a (uniform in k) constant $C \geq 0$ such that

$$\int_{\mathbb{R}^d} \left(\epsilon |\nabla \rho_k|^2 + k \rho_k^{k-1} |\nabla \rho_k|^2 + |\nabla p_k|^2 \right)(t) \leq C \quad \text{for all } t \in (0, T),$$

where we use also an integration of the equation on p_k for the bound on ∇p_k.

Estimates

- bound on the time derivative : assuming the $\partial_t \rho^{ini} \geq 0$ (i.e. $-\mathrm{div}\big(\rho_k^{\mathrm{ini}} \nabla p_k^{\mathrm{ini}}\big) - \nu \Delta \rho_k^{\mathrm{ini}} \leq \rho_k^{\mathrm{ini}} G\big(p_k^{\mathrm{ini}}\big)$), then by maximum principle

$$\partial_t \rho_k, \quad \partial_t p_k \geq 0.$$

Integrating then the equation for ρ_k and p_k we deduce

$$\partial_t \rho_k \text{ is bounded in } L^\infty((0,T);L^1(\mathbb{R}^d)),$$

$$\partial_t p_k \text{ is bounded in } L^1((0,T) \times \mathbb{R}^d).$$

Sketch of the proof

Idea of the proof :

- From the uniform bound, we deduce that $(\rho_k, p_k) \to (\rho_\infty, p_\infty)$ strongly in L^q, $1 \leq q < \infty$, and $(\nabla \rho_k, \nabla p_k) \underset{L^2-w}{\rightharpoonup} (\nabla \rho_\infty, \nabla p_\infty)$.
- We have $\rho_k p_k = \rho_k^{k+1} = (p_k)^{1+1/k} \to p_\infty$, strongly. This implies $p_\infty(1-\rho_\infty) = 0$.
  We deduce clearly that there is a region where $\rho_\infty = 1$ and a region where $p_\infty = 0$.
- For the passage to the limit in the complementary relation, we need the strong convergence of ∇p_k, which is obtained from a regularizing argument (à la Steklov).

Model with visco-elasticity

We can extend this result to a model with viscosity, which is a way to represent friction between cells themselves, considering the tissue as a Newtonian fluid. Then Brinkman law is used instead of Darcy's law :

$$\partial_t \rho_k - \mathrm{div}(\rho_k \nabla W_k) = \rho_k G\big(p_k\big),$$

$$-\nu \Delta W_k + W_k = p_k := \rho_k^k.$$

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As above, we consider the *incompressible limit* $k \to +\infty$. Multiplying equation by $p'(\rho_k)$ and using the chain rule, we deduce

$$\partial_t p_k - \rho_k p'(\rho_k) \Delta W_k - \nabla p_k \cdot \nabla W_k = \rho_k p'(\rho_k) G(p_k).$$

From our choice $p(\rho) = \rho^k$, we deduce

$$\partial_t p_k - k p_k \Delta W_k - \nabla p_k \cdot \nabla W_k = k p_k G(p_k).$$

Model with visco-elasticity

Then letting $k \to +\infty$ we recover the *complementary relation*

$$p_\infty(\Delta W_\infty + G(p_\infty)) = 0.$$

But since we have $-\nu \Delta W_\infty + W_\infty = p_\infty$, we deduce

$$p_\infty(W_\infty - H^{-1}(p_\infty)) = 0,$$

where $H := (I - \nu G)^{-1}$ (invertible since G is non-increasing).

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where $H := (I - \nu G)^{-1}$ (invertible since G is non-increasing).

Defining as above $\Omega(t) = \{p_\infty(t) > 0\}$, we deduce :

- on $\Omega(t)$, we have

$$\rho_\infty = 1, \quad p_\infty = H(W_\infty), \quad -\nu \Delta W_\infty + W_\infty - H(W_\infty) = 0;$$

- on $\mathbb{R}^d \setminus \Omega(t)$, we have $p_\infty = 0$ and

$$\partial_t \rho_\infty - \operatorname{div}(\rho_\infty \nabla W_\infty) = \rho_\infty G(0), \quad -\nu \Delta W_\infty + W_\infty = 0.$$

Model with visco-elasticity

Theorem [Perthame, V., '15]

Under the same assumptions as above and assuming moreover that $\rho_k(t=0)$ is 'well prepared', i.e. for some open set Ω^0, $\rho_k(t=0)=0$ in $\mathbb{R}^d \setminus \Omega^0$ and $p(\rho_k(t=0)) \underset{k\to\infty}{\longrightarrow} p_\infty^0 = H(W_\infty^0)$ a.e. in Ω^0.

Then, up to a subsequence,

- (ρ_k, p_k) converges strongly in $L^1_{loc}\big((0,T)\times\mathbb{R}^d\big)^2$, for all $T>0$, as $k\to+\infty$ towards (ρ_∞, p_∞) belonging to $L^1\cap L^\infty\big((0,T)\times\mathbb{R}^d\big)^2$;
- $W_k \to W_\infty$ strongly in $L^1\big((0,T);W^{1,q}_{loc}(\mathbb{R}^d)\big)$, for all $q\geq 1$.

Moreover,

$$\partial_t\rho_\infty - \mathrm{div}(\rho_\infty \nabla W_\infty) = \rho_\infty G(p_\infty), \quad -\nu\Delta W_\infty + W_\infty = p_\infty,$$

$$p_\infty = H(W_\infty)\mathbf{1}_{\{p_\infty>0\}}, \qquad p_\infty(1-\rho_\infty)=0,$$

$$p_\infty\big(p_\infty - W_\infty - \nu G(p_\infty)\big) = 0, \quad \text{a.e.}$$

Model with visco-elasticity

We deduce that at the limit, there is a region where $p_\infty = 0$ and a region where $p_\infty = (Id - \nu G)^{-1}(W_\infty)$. It implies a jump of the pressure at the free boundary.

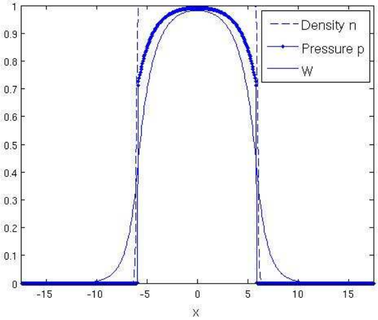

FIGURE: Density and pressure for the model with visco-elasticity. We observe a jump of the pressure at the free boundary.

Model with visco-elasticity

Idea of the proof :

- Since $G(P_M) = 0$ and G nonincreasing, we deduce from a maximum principle $0 \leq p_k \leq P_M$ and ρ_k, p_k are uniformly bounded in $L^1 \cap L^\infty$. We deduce the weak convergence $\rho_k \rightharpoonup \rho_\infty$ and $p_k \rightharpoonup p_\infty$.
- Since W_k is solution of an elliptic problem, we have : $W_k = K * p_k$. We deduce strong compactness for the sequence (W_k).
- We have the estimate

$$k \int_0^T \int_{\mathbb{R}^d} p_k |p_k - W_k - \nu G(p_k)| dx dt \leq C$$

It implies that for any positive numbers β_1, β_2, we have

$$\text{meas}\{\beta_1 \leq p_k(t,x) \leq H(W_\infty(t,x)) - \beta_2\} \underset{k\to+\infty}{\to} 0,$$
$$\text{meas}\{p_k(t,x) \geq H(W_\infty(t,x)) + \beta_2\} \underset{k\to+\infty}{\to} 0.$$

Outline

1 Macroscopic model of tumor growth

2 Derivation of Hele-Shaw model : incompressible limit

3 Invasion of tumor : travelling waves

Simplified Hele-Shaw model

We consider in this part that the growth term is nutrient dependent. The simplified model we are considered

$$\begin{cases} \partial_t \rho - \mathrm{div}(\rho \nabla p) = \rho G(c), & \text{in } \Omega_0(t), \qquad \Omega_0(t) = \{p(t,x) = 0\}, \\ \rho(x,t) = 1 & \text{in } \Omega(t), \qquad \Omega(t) = \{p(t,x) > 0\}, \\ -\Delta c + \psi(\rho) c = 0, & \lim_{x \to +\infty} c(x) = c_B, \\ -\Delta p = G(c), & \text{in } \Omega(t), \\ p = 0, & \text{on } \partial\Omega(t). \end{cases}$$

The growth term G is assumed to satisfy the conditions

$$G'(\cdot) > 0, \qquad G(\overline{c}) = 0 \quad \text{for some } \overline{c} > 0.$$

This models the cells necrosis due to the lack of nutrient in the center of the tumor.

Continuum model of tumor growth : 1D travelling waves

Numerical simulations in one dimension shows travelling waves :

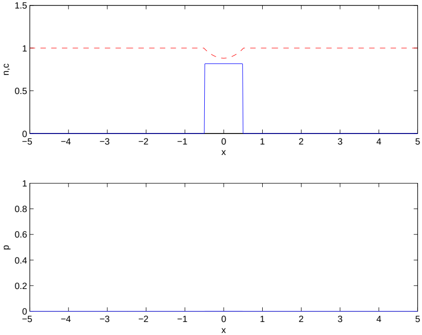

FIGURE: Time dynamics of the density distribution (top solide line), nutrient concentration (top dashed line) and pressure (bottom).

Continuum model of tumor growth : 1D travelling waves

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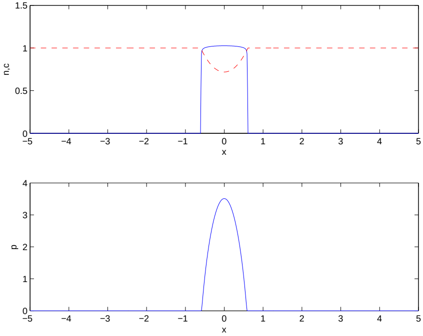

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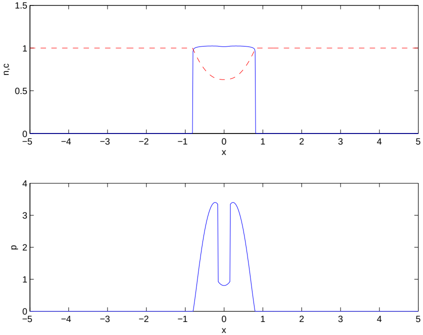

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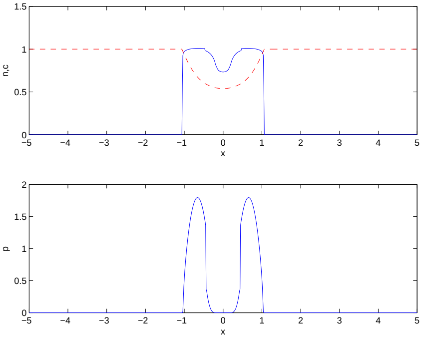

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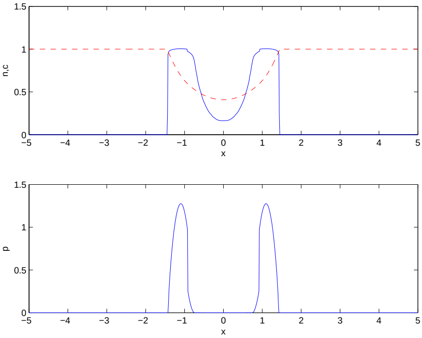

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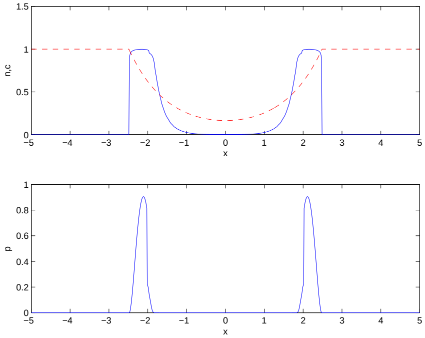

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1D Travelling waves

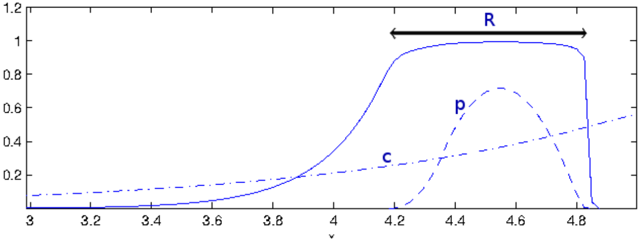


FIGURE: Zoom of the density profile (solid line), pressure (dashed line) and nutrient concentration (dashed dotted lines). We denote by R the length of the region where $p \neq 0$.

We consider 3 regions :

- Necrotic core,
- Proliferative rim,
- Healthy tissue.

1D Travelling waves

From a mathematical point of view, studying the invasion process at a constant speed is equivalent to prove existence of *travelling waves*.

Travelling waves are solutions which can be written under the form

$$\rho(t,x) = \rho(x - \sigma t), \quad c(t,x) = c(x - \sigma t), \quad p(t,x) = p(x - \sigma t),$$

where $\sigma > 0$ is a constant representing the travelling wave velocity.

We look for a solution such that

- c is increasing, $\lim_{x \to +\infty} c = c_B$,
- $p = 0$ on $(-\infty, 0) \cup (R, +\infty)$,
- $\rho = 1$ on $(0, R)$, $\rho = 0$ on $(R, +\infty)$.

Travelling waves

This leads to the following, time independent, system :

$$\begin{cases} -\sigma\rho' = \rho G(c), \qquad \text{in } (-\infty, 0) \\ \rho = 1, \quad \text{in } [0, R], \qquad \rho = 0, \quad \text{in } (R, +\infty), \\ -c'' + \psi(\rho)c = 0, \qquad \lim_{x\to+\infty} c(x) = c_B, \\ -p'' = G(c), \qquad \text{in } [0, R], \\ p(0) = 0, \qquad p(R) = 0. \end{cases}$$

Moreover, the jump relation implies

$$\sigma = -p'(R^-), \qquad p'(0) = 0, \qquad \rho(0) = 1.$$

The unknows of the system are : ρ, c, p, σ and R.

Existence of travelling waves

We make the following assumptions :

$$G' \geq 0$$

$$\exists\, \overline{c} > 0 \text{ such that } G(c) = -g_- < 0 \text{ for } c < \overline{c}, \text{ and } G(c) > 0 \text{ for } c > \overline{c},$$

$$\forall\, z \in (0,1), \;\; 0 < \psi(z) \leq \psi(1), \quad \psi(0) = 0.$$

Theorem : existence of travelling waves

Let us assume that $c_B > \overline{c} > 0$ and that G and ψ are C^1 functions as above.
Then, there exist $\sigma > 0$ and $R > 0$ such that the system admits a solution with c increasing, ρ increasing on $(-\infty, 0]$ and $\lim_{x \to -\infty} \rho(x) = 0$.

Existence of travelling waves

Idea of the proof :

- For a given value $\sigma > 0$, we build a solution $(\rho_\sigma, c_\sigma, p_\sigma)$. To do so, we need to fix the parameter R_σ. Therefore, we split the line into the necrotic, the proliferative and the healthy regions

$$\mathbb{R} = (-\infty, 0) \cup [0, R_\sigma] \cup (R_\sigma, +\infty),$$

  and we build the solution successively on each interval. In particular on $[0, R_\sigma]$, we have to solve :

$$-p''_\sigma = G(c_\sigma), \qquad p_\sigma(0) = 0, \quad p'_\sigma(0) = 0, \quad p_\sigma(R_\sigma) = 0.$$

  It gives a nonlinear relation for R_σ which admits a solution.
- Then, the value of σ is determined by the fixed point problem

$$\sigma = -p'_\sigma(R_\sigma).$$

Continuum model of tumor growth : instabilities

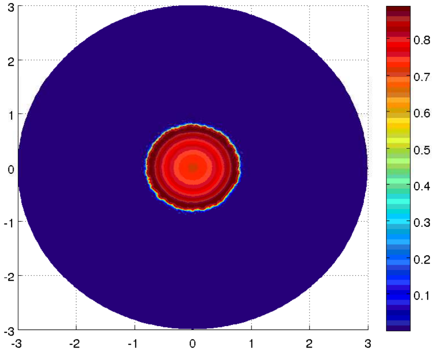
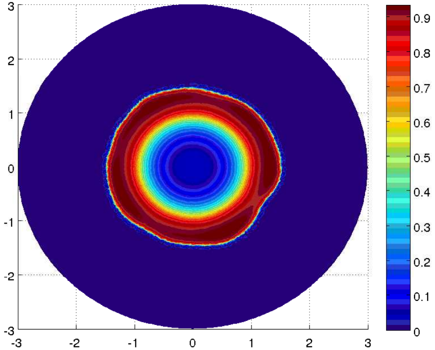


FIGURE: Dynamics of the density of tumor cells.

Continuum model of tumor growth : instabilities



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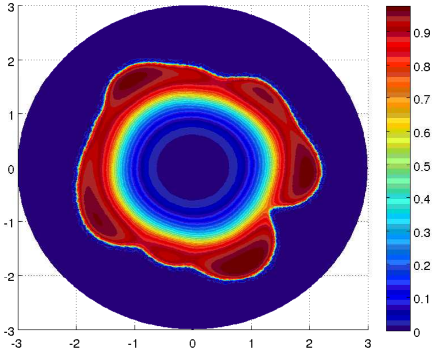

FIGURE: Dynamics of the density of tumor cells.

Conclusion and perspectives

- Study of instabilities which are numerically observed on the model with nutrients.
- Derivation of incompressible limit towards geometric model in a more general setting (nutrient dependent growth term, model with proliferative and quiescent populations, . . .)
- How to derive model with surface tension in this framework ?