Derivation of free boundary problem for tumor growth

Nicolas Vauchelet
vauchelet@math.univ-paris13.fr

collaboration with P. Degond, S. Hecht, B. Perthame, F. Quiròs, M. Tang, E. Zatorska

July 1st-5th, 2019
Derivation of Hele-Shaw problem for tumor growth
1. Derivation of Hele-Shaw model: incompressible limit
   - Setting of the problem
   - Properties of the cell mechanical model
   - Statement of the results
   - Proof of the main result
   - Derivation for the model with active motion

2. Extension to a model with visco-elasticity
   - Presentation of the problem
   - Statement of the results
   - Extension to Navier-Stokes

3. Extension to a model with two populations
   - Presentation of the problem
   - Numerical simulations
Outline

1. Derivation of Hele-Shaw model: incompressible limit
   - Setting of the problem
   - Properties of the cell mechanical model
   - Statement of the results
   - Proof of the main result
   - Derivation for the model with active motion

2. Extension to a model with visco-elasticity
   - Presentation of the problem
   - Statement of the results
   - Extension to Navier-Stokes

3. Extension to a model with two populations
   - Presentation of the problem
   - Numerical simulations

N. Vauchelet  Imperial College
Reminder: continuum model of tumor growth

Unkowns:
\( \rho(t, x) \): density of tumor cells at time \( t \geq 0 \) and position \( x \in \mathbb{R}^d \),
\( p(t, x) \): elastic pressure on cells, given by a law \( p = P(\rho) \),
\( v(t, x) \): velocity field,
\( c(t, x) \): nutrient concentration.

The system governing these quantities reads

\[
\begin{aligned}
\partial_t \rho + \text{div}_x (\rho v) &= \rho G(p, c) + \nu \Delta_x \rho, \\
\text{mechanical pressure} & \quad \text{Growth term} & \quad \text{active motion} \\
\end{aligned}
\]

\[

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

\[
\partial_t c - \Delta_x c + \lambda c \rho = 0,
\text{Nutrient consumption.}
\]
Reminder : the Hele-Shaw free boundary 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 $\Omega(t)$.

With the same notation as for the mechanical model, the Hele-Shaw model reads

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

The velocity of the boundary is given by the Darcy law

$$v = -\nabla_x p.$$ 

As usual, $G$ is the growth function.

One assumes to have constant density in the domain $\Omega$ (*incompressibility*).
Continuum model of tumor growth: summary

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

**Mechanical model**

\[
\begin{align*}
\partial_t \rho + \text{div}_x (\rho \nu) &= \rho G(p), & \text{on } \mathbb{R}^d, \\
\nu &= -\nabla_x p, & p = P(\rho).
\end{align*}
\]

**Free boundary model**

\[
\begin{align*}
-\Delta p &= G(p), & \text{on } \Omega(t), \\
p &= 0, & \text{on } \partial\Omega(t),
\end{align*}
\]

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

\[\nu = -\nabla_x p.\]
**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

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

Therefore we can rewrite equation

$$\partial_t \rho_k + \text{div}(\rho_k \nu) = \rho_k G(p_k).$$

as the porous medium equation

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

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 $\rho$ is plotted in **blue** solid line whereas the pressure $p$ is represented in **green** dashed line.
Incompressible limit: numerical observations

**Figure** – First steps of the initiation of the free boundary. The density $\rho$ is plotted in **blue** solid line whereas the pressure $p$ is represented in **green** dashed line.
Incompressible limit : numerical observations

**Figure** – First steps of the initiation of the free boundary. The density $\rho$ is plotted in blue solid line whereas the pressure $p$ is represented in green dashed line.
Incompressible limit: numerical observations

**Figure** — First steps of the initiation of the free boundary. The density $\rho$ is plotted in blue solid line whereas the pressure $p$ is represented in green dashed line.
Outline

1 Derivation of Hele-Shaw model: incompressible limit
   - Setting of the problem
   - Properties of the cell mechanical model
   - Statement of the results
   - Proof of the main result
   - Derivation for the model with active motion

2 Extension to a model with visco-elasticity
   - Presentation of the problem
   - Statement of the results
   - Extension to Navier-Stokes

3 Extension to a model with two populations
   - Presentation of the problem
   - Numerical simulations
Properties for the Cell mechanical model

We consider the following fluid mechanical model of tumor growth with only pressure dependancy

$$\partial_t \rho + \text{div}(\rho \nu) = \rho G(p), \quad x \in \mathbb{R}^d, t \geq 0,$$

$$\rho(t = 0, x) = \rho^0(x) \geq 0,$$

$$\nu = -\nabla_x p, \quad p = P(\rho) = \rho^k, \quad k > 1.$$
Properties for the Cell mechanical model

We consider the following fluid mechanical model of tumor growth with only pressure dependancy

\[
\frac{\partial}{\partial t} \rho + \text{div}(\rho \mathbf{v}) = \rho G(p), \quad x \in \mathbb{R}^d, t \geq 0, \\
\rho(t = 0, x) = \rho^0(x) \geq 0, \\
\mathbf{v} = -\nabla_x p, \quad p = P(\rho) = \rho^k, \quad k > 1.
\]

Let us mention that with the choice \( P(\rho) = \rho^k \), we have

\[
\rho \mathbf{v} = -\rho \nabla p = -\frac{k}{k + 1} \nabla \rho^{k+1}.
\]

Therefore we can rewrite the first equation as

\[
\frac{\partial}{\partial t} \rho - \frac{k}{k + 1} \Delta(\rho^{k+1}) = \rho G(p).
\]

We recognize the porous medium equation, well-known in fluid mechanics\(^1\), with a growth term.

Digression: porous medium equation

Nonlinear diffusion equation

$$\partial_t u = \Delta u^m = \text{div}((m-1)p(u)\nabla u), \quad m > 1,$$

with a density-dependent diffusivity $p(u) = \frac{m}{m-1}u^{m-1}$, degenerates at $u = 0$. When $m < 1$ this equation belongs to the class of fast diffusion equations.

Many applications: flow of an isentropic gas in a porous medium (Leibenzon, Muskat \(\sim\) 1930), underground water infiltration (Boussinesq 1903), plasma radiation (Zel’dovich-Raizer \(\sim\) 1950), ...
Digression: porous medium equation

This equation also reads

\[ \partial_t u - (m - 1) \nabla p(u) \nabla u - (m - 1) p(u) \Delta u = 0. \]
Digression: porous medium equation

This equation also reads

$$\partial_t u - (m - 1) \nabla p(u) \nabla u - (m - 1) p(u) \Delta u = 0.$$  

Multiplying by $p'(u)$, we get

$$\partial_t p(u) - (m - 1) \nabla p(u) \nabla p(u) - (m - 1) p(u) p'(u) \Delta u = 0.$$
Digression : porous medium equation

This equation also reads

$$\partial_t u - (m - 1) \nabla p(u) \nabla u - (m - 1) p(u) \Delta u = 0.$$  

Multiplying by $p'(u)$, we get

$$\partial_t p(u) - (m - 1) \nabla p(u) \nabla p(u) - (m - 1) p(u) p'(u) \Delta u = 0.$$  

We observe that

$$\Delta p(u) = \text{div}(p'(u) \nabla u) = p''(u) |\nabla u|^2 + p'(u) \Delta u,$$

and also $(m - 1) p(u) p''(u) = (m - 2) p'(u)^2$. 

N. Vauchelet
Imperial College
Digression: porous medium equation

This equation also reads

$$\partial_t u - (m - 1) \nabla p(u) \nabla u - (m - 1) p(u) \Delta u = 0.$$ 

Multiplying by $p'(u)$, we get

$$\partial_t p(u) - (m - 1) \nabla p(u) \nabla p(u) - (m - 1) p(u) p'(u) \Delta u = 0.$$ 

We observe that

$$\Delta p(u) = \text{div}(p'(u) \nabla u) = p''(u)|\nabla u|^2 + p'(u) \Delta u,$$

and also $(m - 1) p(u) p''(u) = (m - 2) p'(u)^2$. Then,

$$\partial_t p(u) - (m - 1)|\nabla p(u)|^2 + (m - 2) p'(u)^2 |\nabla u|^2 - (m - 1) p(u) \Delta p(u) = 0.$$ 

We obtain an equation for the pressure

$$\partial_t p - |\nabla p|^2 - (m - 1) p \Delta p = 0.$$
Basic estimates $\partial_t u - \Delta u^m = 0$.

- Boundedness estimates: For all $p > 1$,
  $$\int_{\mathbb{R}^d} u^p(t, x) \, dx \leq \int_{\mathbb{R}^d} u_0(x) \, dx.$$

- Multiplying the equation by $u^m$ and integrating we get
  $$\int_{\mathbb{R}^d} |u|^{m+1} \, dx + (m + 1) \int_0^T \int_{\mathbb{R}^d} |\nabla u^m|^2 \, dx = \int_{\mathbb{R}^d} |u_0|^{m+1} \, dx.$$

- Multiplying the equation by $\partial_t(u^m)$ and integrating we also get an estimate on the time derivative
  $$\int_{\mathbb{R}^d} |\nabla u^m|^2 \, dx + \frac{8m}{(m + 1)^2} \int_0^T \int_{\mathbb{R}^d} |\partial_t(u^{(m+1)/2})|^2 \, dx = \int_{\mathbb{R}^d} |\nabla u_0^m|^2 \, dx.$$
Properties for the Cell mechanical model

Let us come back to our mechanical model for tumor growth

\[ \partial_t \rho - \text{div}(\rho v) = \rho G(p), \quad v = -\nabla_x p, \quad p = P(\rho) = \rho^k. \]
Properties for the Cell mechanical model

Let us come back to our mechanical model for tumor growth

$$\frac{\partial \rho}{\partial t} - \text{div}(\rho v) = \rho G(p), \quad v = -\nabla_x p, \quad p = P(\rho) = \rho^k.$$ 

An important information is that we can derive an equation for the pressure starting from the equation on the cell density,

$$\frac{\partial \rho}{\partial t} - \text{div}(\rho \nabla p) = \rho G(p).$$
Properties for the Cell mechanical model

Let us come back to our mechanical model for tumor growth

\[
\frac{\partial}{\partial t} \rho - \text{div}(\rho \mathbf{v}) = \rho G(p), \quad \mathbf{v} = -\nabla_x p, \quad p = P(\rho) = \rho^k.
\]

An important information is that we can derive an equation for the pressure starting from the equation on the cell density,

\[
\frac{\partial}{\partial t} \rho - \text{div}(\rho \nabla p) = \rho G(p).
\]

Recalling that \( p = P(\rho) \), we multiply by \( P'(\rho) \),

\[
\frac{\partial}{\partial t} p - \rho P'(\rho) \Delta p - |\nabla p|^2 = \rho P'(\rho) G(p).
\]
Properties for the Cell mechanical model

Let us come back to our mechanical model for tumor growth

\[
\frac{\partial t}{\partial t}\rho - \text{div}(\rho v) = \rho G(p), \quad v = -\nabla_x p, \quad p = P(\rho) = \rho^k.
\]

An important information is that we can derive an equation for the pressure starting from the equation on the cell density,

\[
\frac{\partial t}{\partial t}\rho - \text{div}(\rho \nabla p) = \rho G(p).
\]

Recalling that \( p = P(\rho) \), we multiply by \( P'(\rho) \),

\[
\frac{\partial t}{\partial t}p - \rho P'(\rho)\Delta p - |\nabla p|^2 = \rho P'(\rho)G(p).
\]

For the special case \( P(\rho) = \rho^k \) at hand, we find

**Equation for the pressure**

\[
\frac{\partial t}{\partial t}p - kp\Delta p - |\nabla p|^2 = kpG(p).
\]
### Existence and properties

#### System of equations

We consider the model

\[
\partial_t \rho + \text{div}(\rho v) = \rho G(p), \quad v = -\nabla_x p, \quad p = P(\rho) = \rho^k,
\]

\[
\rho(t = 0, x) = \rho^0(x) \geq 0,
\]

with \( G(0) = G_M, \ G'(\cdot) < 0, \) and \( G(P_M) = 0. \)

#### Theorem

Let \( \rho^0 \in L^1 \cap L^\infty(\mathbb{R}^d) \), the above system admits a unique solution \( \rho \in C(\mathbb{R}^+, L^1(\mathbb{R}^d)) \cap L^\infty(\mathbb{R}^+ \times \mathbb{R}^d) \) and we have

- **Comparison principle**: if \( \rho^0_1 \leq \rho^0_2 \), then the corresponding solutions satisfy \( \rho_1 \leq \rho_2. \)
- \( p^0 \leq P_M \implies p \leq P_M. \)
- \( \partial_t \rho^0 \geq 0 \implies \partial_t \rho \geq 0. \)
- \( \text{supp}(\rho^0) \subset B_R(0) \implies \forall T > 0, \ \forall t \in [0, T], \ \exists R_T(t) > 0, \ \text{supp}(\rho) \subset B_{R_T(t)}. \)
Proof

■ **Comparison principle.**

By noting $Q(\rho) = \frac{k}{k+1} \rho^{k+1}$ and $\Gamma(\rho) = \rho G(P(\rho))$, we rewrite the system as

$$\partial_t \rho - \Delta Q(\rho) = \Gamma(\rho).$$

For two initial data $\rho_1^0$ and $\rho_2^0$, the corresponding solution satisfies

$$\partial_t (\rho_2 - \rho_1) - \Delta (Q(\rho_2) - Q(\rho_1)) = \Gamma(\rho_2) - \Gamma(\rho_1).$$

By convexity of $(\cdot)^+$ (positive part), and the fact that $\text{sign}(\rho_2 - \rho_1) = \text{sign}(Q(\rho_2) - Q(\rho_1))$, we find

$$\partial_t (\rho_2 - \rho_1)^+ - \Delta (Q(\rho_2) - Q(\rho_1))^+ \leq |\Gamma(\rho_2) - \Gamma(\rho_1)|1_{\rho_2 - \rho_1 \geq 0} \leq C_\Gamma (\rho_2 - \rho_1)^+,$$

with $C_\Gamma$ a Lipschitz constant for $\Gamma$.  

N. Vauchelet  Imperial College
Proof

Integrating,

\[ \frac{d}{dt} \int_{\mathbb{R}^d} (\rho_2 - \rho_1)^+ \, dx \leq C_\Gamma \int_{\mathbb{R}^d} (\rho_2 - \rho_1)^+ \, dx. \]

Using a Gronwall lemma, we obtain,

\[ \int_{\mathbb{R}^d} |\rho_2 - \rho_1|^+ \, dx \leq e^{C_\Gamma t} \int_{\mathbb{R}^d} (\rho_0^2 - \rho_0^1)^+ \, dx. \]

Notice that the choice \( \rho_2 = 0 \) implies \( \rho \geq 0 \) when \( \rho^0 \geq 0 \).

Comparison principle

\[ \rho^0_1 \leq \rho^0_2 \implies \rho_1 \leq \rho_2. \]
Proof

- **$L^\infty$ bound.**

Let $\rho_M$ be such that $P(\rho_M) = P_M$, i.e. $\rho_M = P_M^{1/k}$. It is clear that the constant $\rho = \rho_M$ is a solution (since $G(P(\rho_M)) = 0$). Thus, by comparison principle, $p \leq P_M$, also $\rho \leq \rho_M$.

- **Time derivative.**

Differentiating in time the equation,

$$\partial_t (\partial_t \rho) - \text{div}(Q'(\rho) \partial_t \rho) = \Gamma'(\rho) \partial_t \rho.$$

We use again the comparison principle: the constant 0 is a solution. Then if $\partial_t \rho^0 \geq 0$, we have $\partial_t \rho \geq 0$. 
Proof

Control of the support.

We compare the pressure to the function

$$\tilde{p}(t, x) = \left( C - \frac{|x|^2}{4(\tau + t)} \right)^+,$$

which is non-zero only on $B_{R(t)}$, with $R(t) = 2\sqrt{C(\tau + t)}$. We compute

$$\partial_t \tilde{p}(t, x) = \frac{|x|^2}{4(\tau + t)^2} 1_{\{|x| \leq R(t)\}},$$

$$|\nabla \tilde{p}|^2 = \frac{|x|^2}{4(\tau + t)^2} 1_{\{|x| \leq R(t)\}},$$

$$\Delta \tilde{p} = -\frac{d}{2(\tau + t)} \quad \text{for } |x| < R(t).$$

However, $\Delta \tilde{p}$ has positive Dirac mass at $|x| = R(t)$. Since $\tilde{p}$ vanishes whenever $|x| = R(t)$, we have

$$\partial_t \tilde{p} - k\tilde{p}\Delta \tilde{p} - |\nabla \tilde{p}|^2 - k\tilde{p}G_M = k\tilde{p} \left( \frac{d}{2(\tau + t)} - G_M \right) \geq 0, \quad \text{for } t \in [0, \tau].$$
Proof

Therefore, if we take $C$ large enough such that $\tilde{p}(t = 0) \geq p^0$, then $\tilde{p}$ is a super-solution for the equation for $p$ for $t \in [0, \tau]$. Thus, by comparison principle, $p \leq \tilde{p}$ for $t \in [0, \tau]$, with $\tau = \frac{d}{4GM}$.

Since $p$ is uniformly bounded in $L^\infty$, we may iterate the process from the time $\tau$ and construct a supersolution on $[\tau, 2\tau]$. After applying several iterations, we reach the final time $T$.

Then $\text{supp}(\rho) \subset B_{R(t)}$ where $R(t) \leq 2\sqrt{C(T + t)}$. 
Remark: Barenblatt profile

For the porous medium equation,

$$\partial_t u - \Delta u^m = 0,$$

there exist explicit solutions called Barenblatt profiles (Zel'dovich and Kompaneets\(^3\), Barenblatt\(^4\)). There are source solutions, i.e. the initial data is a Dirac mass (a point source).

Barenblatt profiles

For any \( C > 0 \),

$$U(t, x) = t^{-\alpha}(C - k|x|^2t^{-2\beta})^{\frac{1}{m-1}},$$

where \( \alpha = \frac{d}{d(m-1)+2}, \beta = \frac{\alpha}{d}, k = \frac{\alpha(m-1)}{2md}. \)

---


Spatial model with active motion

System of equations with active motion

We consider the model

\[
\partial_t \rho + \text{div}(\rho v) - \varepsilon \Delta \rho = \rho G(p), \quad v = -\nabla_x p, \quad p = P(\rho) = \rho^k,
\]

\[
\rho(t = 0, x) = \rho^0(x) \geq 0,
\]

with \(G(0) = G_M, \ G'(\cdot) < 0, \) and \(G(P_M) = 0.\)

By the same token, we still have the comparison principle. However, we do not keep the property for the support.

**Theorem**

Let \(\rho^0 \in L^1 \cap L^\infty(\mathbb{R}^d),\) the above system admits a unique solution \(\rho \in C(\mathbb{R}^+, L^1(\mathbb{R}^d)) \cap L^\infty(\mathbb{R}^+ \times \mathbb{R}^d)\) and we have

- **Comparison principle**: if \(\rho^0_1 \leq \rho^0_2,\) then \(\rho_1 \leq \rho_2.\)
- \(p^0 \leq P_M \implies p \leq P_M.\)
- \(\partial_t \rho^0 \geq 0 \implies \partial_t \rho \geq 0.\)
Outline

1. Derivation of Hele-Shaw model: incompressible limit
   - Setting of the problem
   - Properties of the cell mechanical model
   - Statement of the results
   - Proof of the main result
   - Derivation for the model with active motion

2. Extension to a model with visco-elasticity
   - Presentation of the problem
   - Statement of the results
   - Extension to Navier-Stokes

3. Extension to a model with two populations
   - Presentation of the problem
   - Numerical simulations
Idea : equation on the pressure

Formally, starting from

\[ \partial_t \rho_k - \text{div}(\rho_k \nabla p_k) = \rho_k G(p_k). \]
Idea : equation on the pressure

Formally, starting from

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

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

$$\partial_t p_k - \rho_k p' \Delta p_k - |\nabla p_k|^2 = \rho_k p'(\rho_k) G(p_k).$$
Derivation of Hele-Shaw model \textsuperscript{:} incompressible limit

Statement of the results

Idea : equation on the pressure

Formally, starting from

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

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

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

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

$$\partial_t p_k - k p_k \Delta p_k - |\nabla p_k|^2 = k p_k G(p_k).$$
Idea : equation on the pressure

Formally, starting from

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

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

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

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

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

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

$$p_\infty (\Delta p_\infty + G(p_\infty)) = 0.$$
Idea: equation on the pressure

This equation is called the complementary relation,

\[ p_{\infty}(\Delta p_{\infty} + G(p_{\infty})) = 0. \]

One deduces that we can distinguish two regions by defining
\[ \Omega(t) = \{ p_{\infty}(t) > 0 \}. \]
On \( \Omega(t) \), we have

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

On \( \mathbb{R}^d \setminus \Omega(t) \), we have

\[
\begin{aligned}
\partial_t \rho_{\infty} - \text{div}(\rho_{\infty} \nabla p_{\infty}) &= \rho_{\infty} G(p_{\infty}), \quad x \in \mathbb{R}^d \setminus \Omega(t), \ t \geq 0, \\
\rho_{\infty} &= 1, \quad x \in \Omega(t).
\end{aligned}
\]
Convergence result

These formal computations can be made rigorous.

**Assumptions**: We consider that

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

We complement the system

\[
\begin{align*}
\partial_t \rho_k - \text{div}(\rho_k \nabla p_k) &= \rho_k G(p_k), \\
p_k &= \rho_k^k,
\end{align*}
\]

with initial conditions \( \rho^{\text{ini}} \geq 0. \)

We assume that the initial data \( \rho^{\text{ini}} \) is uniformly bounded in \( L^1 \cap L^\infty(\mathbb{R}^d), \nabla_x \rho^{\text{ini}} \)

is uniformly bounded in \( L^1(\mathbb{R}^d). \) Moreover, \( \rho^{\text{ini}} \) is such that \( p^{\text{ini}}_k \leq P_M \) and is well

prepared, i.e.

\[
\text{div}(\rho^{\text{ini}} \nabla p^{\text{ini}}_k) + \rho^{\text{ini}} G(\rho^{\text{ini}}) \geq 0.
\]
Convergence result

**Theorem**

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

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

such that $0 \leq \rho_\infty \leq 1$ and $0 \leq p_\infty \leq P_M$ and $p_\infty \in P_\infty(\rho_\infty)$ where $P_\infty$ is the Hele-Shaw monotone graph

\[
P_\infty(\rho) = \begin{cases} 
0, & 0 \leq \rho < 1, \\
\geq 0, & \rho = 1.
\end{cases}
\]

Moreover, $(\rho_\infty, p_\infty)$ satisfies in the weak sense

\[
\partial_t \rho_\infty - \text{div}(\rho_\infty \nabla p_\infty) = \rho_\infty G(p_\infty),
\]

and the complementary relation.

---

5. Perthame, Quirós, Vázquez, ARMA Vol 212, 2014
With non-overlapping constraint

For physical reasons, it may be important to consider that cells do not overlap, i.e. $\rho_k \leq 1$ for any $k$. In order to model this, we may choose

$$p_k = P(\rho_k) = \frac{1}{k} \frac{\rho_k}{1 - \rho_k}.$$

The incompressible limit is obtained by letting $k$ going to $+\infty$. We recover the same results. 6

For instance we may notice that clearly $(1 - \rho_k)p_k = \frac{1}{k}\rho_k \to 0$ as $k \to +\infty$.

---

Interpretation of this result

By definition of the Hele-Shaw graph, we expect

$$\Omega(t) = \{ x ; p_\infty(t,x) > 0 \} = \{ x ; \rho_\infty(t,x) = 1 \}.$$  

Thus $\Omega$ may be regarded as the *tumor region*, whereas the region $0 < \rho_\infty < 1$ correspond to the *precancer cells* (also called the mushy region). The complementary relation indicates that the limit pressure satisfies

$$-\Delta p_\infty(t) = G(p_\infty(t)) \quad \text{in} \quad \Omega(t).$$

From the transport equation for $\rho_\infty$ and the complementary relation, we deduce that

$$\partial_t p_\infty = |\nabla p_\infty|^2, \quad \text{at} \quad \partial \Omega(t),$$

which leads to a geometric motion with normal velocity $V = |\nabla p_\infty|$ at the boundary of $\Omega(t)$.
Outline

1 Derivation of Hele-Shaw model: incompressible limit
   - Setting of the problem
   - Properties of the cell mechanical model
   - Statement of the results
   - Proof of the main result
   - Derivation for the model with active motion

2 Extension to a model with visco-elasticity
   - Presentation of the problem
   - Statement of the results
   - Extension to Navier-Stokes

3 Extension to a model with two populations
   - Presentation of the problem
   - Numerical simulations
Idea of the proof

The proof follows the main idea as for the Stefan problem. The main steps are the following:

- Uniform bound on the sequences $(\rho_k)_k$ and $(p_k)_k$ in $L^1 \cap L^\infty([0, T] \times \mathbb{R}^d)$ and on the derivatives in $L^1([0, T] \times \mathbb{R}^d)$.

- By compactness result (Helly Theorem), we deduce the strong convergence in $L^1_{loc}(\mathbb{R}^+ \times \mathbb{R}^d)$.

- We can pass to the limit in the equations.

- To recover the complementary relation, we need strong convergence of the gradient of $p_k$.

- Uniqueness gives the convergence of the whole sequence.
Estimates

In order to have compactness, we need to establish some \textit{a priori} estimates:

- \textit{uniform bound in} $L^1 \cap L^\infty$ for $\rho_k$ and $p_k$:
  Since 0 is a subsolution, we clearly have $\rho_k \geq 0$, thus $p_k = \rho_k^k \geq 0$.
  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 pressure law $p_k = \rho_k^k$,
  
  $$0 \leq \rho_k \leq P_M^{1/k} \xrightarrow{k \to \infty} 1.$$  

  Integrating equation on $\rho_k$ we deduce the uniform in $k$ $L^1$ bound
  
  $$\int_{\mathbb{R}^d} \rho_k(t) \leq e^{G(0)t} \int_{\mathbb{R}^d} \rho^{\text{ini}}, \quad \int_{\mathbb{R}^d} p_k(t) \leq Ce^{G(0)t} \int_{\mathbb{R}^d} \rho^{\text{ini}}.$$  

  It gives weak compactness. However to get strong compactness we need estimates on the derivatives.
Estimates

- **uniform bound on time derivatives:**
  We consider the equation for the density
  \[
  \partial_t \rho_k - \frac{k}{k+1} \Delta \rho_k^{k+1} = \rho_k G(\rho_k^k) = \tilde{G}_k(\rho_k).
  \]

  Deriving with respect to \( t \), setting \( w_k = \partial_t \rho_k \),
  \[
  \partial_t w_k - k\Delta(\rho_k^k w_k) = w_k \tilde{G}'_k(\rho_k),
  \]
  which may be rewritten
  \[
  \partial_t w_k - k\rho_k^k \Delta w_k - 2k \nabla \rho_k^k \cdot \nabla w_k = w_k \left( \tilde{G}'_k(\rho_k) + \Delta w_k \right).
  \]

  Since 0 is a subsolution for this equation (since by assumption \( w_k(t = 0) \geq 0 \)), we deduce (comparison principle) that \( w_k \geq 0 \), thus \( \partial_t \rho_k \geq 0 \). It yields \( \partial_t p_k \geq 0 \). Bounds follow easily,
  \[
  \| \partial_t \rho_k \|_{L^1(\mathbb{R}^d)} = \frac{d}{dt} \int_{\mathbb{R}^d} \rho_k(t,x) \, dx \leq G(0) \| \rho_k \|_{L^1}.
  \]
  \[
  \| \partial_t p_k \|_{L^1((0,T) \times \mathbb{R}^d)} = \int_0^T \frac{d}{dt} \int_{\mathbb{R}^d} p_k(t,x) \, dx \, dt \leq \| p_k(T) \|_{L^1}.
  \]
Estimates

\textbf{uniform bound on the gradients :}
We consider the equation for the density

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

Deriving with respect to \(x_i\),

\[
\partial_t \partial_{x_i} \rho_k - k \Delta (\rho_k^k \partial_{x_i} \rho_k) = \partial_{x_i} \rho_k G(p_k) + \rho_k \partial_{x_i} p_k G'(p_k).
\]

Multiplying by \(\text{sign} (\partial_{x_i} \rho_k) = \text{sign} (\partial_{x_i} p_k)\),

\[
\partial_t |\partial_{x_i} \rho_k| - k \Delta (\rho_k^k |\partial_{x_i} \rho_k|) \leq |\partial_{x_i} \rho_k| G(p_k) + \rho_k \partial_{x_i} p_k G'(p_k)
\leq |\partial_{x_i} \rho_k| G(0) - (\min_{0,P_M} |G'|) \rho_k |\partial_{x_i} p_k|.
\]

Integrating on \([0, T] \times \mathbb{R}^d\) one deduces

\[
\| \partial_{x_i} \rho_k(t) \|_{L^1(\mathbb{R}^d)} + (\min_{0,P_M} |G'|) \int_0^t \int_{\mathbb{R}^d} \rho_k |\partial_{x_i} p_k| d\tau dx \leq e^{G(0)t} \| \partial_{x_i} \rho_{ini} \|_{L^1(\mathbb{R}^d)}.
\]
Estimates

Thus on one hand we deduce that

$$\left\| \partial_t \rho_k(t) \right\|_{L^1(\mathbb{R}^d)} \leq C.$$ 

On the other hand, by definition $p_k = \rho_k^k$, we have

$$\left\| \partial_x \rho_k \right\|_{L^1} \leq \int \int \{\rho_k \leq 1/2\} k\rho_k^{k-1} |\partial_x \rho_k| \, dt \, dx + \int \int \{\rho_k \geq 1/2\} 2\rho_k |\partial_x p_k| \, dt \, dx.$$ 

Using the previous estimate, we get that

$$\left\| \partial_x p_k \right\|_{L^1([0,T] \times \mathbb{R}^d)} \leq C.$$ 

We conclude that we have a bound of $(\rho_k)_k$ and $(p_k)_k$ in $W^{1,1}([0,T] \times \mathbb{R}^d)$. 
Estimates

Convergence and identification of the limit:
With our estimates, we deduce the strong compactness in $L^1_{loc}(\mathbb{R}^+ \times \mathbb{R}^d)$ of $(\rho_k)_k$ and $(p_k)_k$. By controlling the tail, one may prove that the convergence is actually global. Thus, up to an extraction of subsequences,

$$\rho_k \to \rho_\infty, \quad p_k \to p_\infty \quad \text{in } L^1([0, T] \times \mathbb{R}^d).$$

with $0 \leq \rho_\infty \leq 1$, $0 \leq p_\infty \leq P_M$ and $\rho_\infty$ and $p_\infty$ are in $BV([0, T] \times \mathbb{R}^d)$, for all $T > 0$.

Moreover, passing to the limit in the equality $p_k \rho_k = p_k^{1+1/k}$, yields

$$p_\infty (1 - \rho_\infty) = 0.$$

Due to the strong convergence of $(\rho_k)_k$ and $(p_k)_k$ we can pass into the limit in the porous medium equation satisfied by $\rho_k$ and obtain, in the weak sense

$$\partial_t \rho_\infty - \Delta p_\infty = \rho_\infty G(p_\infty).$$
Estimates : intermediate conclusion

At this stage we have obtained the following points:

- We have obtained the strong convergence of the sequences \((\rho_k)_k\) and \((p_k)_k\) towards \(\rho_\infty\) and \(p_\infty\) that satisfy \(0 \leq \rho_\infty \leq 1, 0 \leq p_\infty \leq P_M\).

- The relation
  \[ p_\infty (1 - \rho_\infty) = 0, \]

  implies that \(p_\infty = 0\) on \(\{0 \leq \rho_\infty < 1\}\). Then \(p_\infty \in P_\infty(\rho_\infty)\), where \(P_\infty\) is the Hele-Shaw monotone graph

\[
P_\infty(\rho) = \begin{cases} 
0, & 0 \leq \rho < 1, \\
\geq 0, & \rho = 1.
\end{cases}
\]
Recalling the equation satisfied by the pressure

\[ \partial_t p_k - kp_k \Delta p_k - |\nabla p_k|^2 = kp_k G(p_k), \]

we have by a simple integration by part

\[ \frac{d}{dt} \int_{\mathbb{R}^d} p_k \, dx + (k - 1) \int_{\mathbb{R}^d} |\nabla p_k|^2 \, dx = k \int_{\mathbb{R}^d} p_k G(p_k) \, dx. \]

It implies a bound of \((\nabla p_k)_k\) in \(L^2((0, T] \times \mathbb{R}^d)\).

Thus the strong convergence of \((\rho_k)_k\) and \((p_k)_k\) combined with the weak convergence of \((\nabla p_k)_k\) allow to pass into the limit of the equation satisfied by \(\rho_k\). We get

\[ \partial_t \rho_\infty - \text{div}(\rho_\infty \nabla p_\infty) = \rho_\infty G(p_\infty). \]

Then we are left to prove the complementary relation.
Complementary relation

\[ p_{\infty}(\Delta p_{\infty} + G(p_{\infty})) = 0. \]

In the weak sense, after an integration by part, we deduce that we want to establish that, for all test function \( \phi \in \mathcal{D}((0, T) \times \mathbb{R}^d) \),

\[
\iint (-\phi |\nabla p_{\infty}|^2 - p_{\infty} \nabla \phi \cdot \nabla p_{\infty} + p_{\infty} \phi G(p_{\infty})) = 0.
\]

We show the following

Lemma

The complementary relation holds if and only if we have the strong convergence of \( \nabla p_k \) in \( L^2((0, T) \times \mathbb{R}^d) \).
Complementary relation

**Proof.** Starting from the equation for the pressure

\[ \partial_t p_k - |\nabla p_k|^2 = k p_k (\Delta p_k + G(p_k)), \]

we deduce by multiplying with a test function \( \phi \in D((0, T) \times \mathbb{R}^d) \),

\[ \int \int \phi p_k (\Delta p_k + G(p_k)) \, dx \, dt = \frac{1}{k} \int \int (\partial_t p_k - |\nabla p_k|^2) \, dx \, dt \xrightarrow{k \to +\infty} 0. \]

Integrating by parts, it implies

\[ \int \int \left( -\phi |\nabla p_k|^2 - p_k \nabla \phi \cdot \nabla p_k + p_k \phi G(p_k) \right) \, dx \, dt \xrightarrow{k \to +\infty} 0. \]

However, from the strong convergence of \((p_k)_k\) and the weak convergence of \((\nabla p_k)_k\), we can pass to the limit in the last two terms. Thus the complementary relation holds if and only if

\[ \int \int \phi |\nabla p_k|^2 \, dt \, dx \xrightarrow{k \to +\infty} \int \int \phi |\nabla p_\infty|^2 \, dt \, dx. \]

It is equivalent to the strong convergence of \((\nabla p_k)_k\) (weak convergence + convergence of the norm).
Complementary relation

Thus we are left to prove that the sequence \((\nabla p_k)_k\) converges strongly in \(L^2\). Integrating the equation

\[
\partial_t \rho_k - \frac{k}{k+1} \Delta (\rho_k^{k+1}) = \rho_k G(p_k),
\]

we obtain

\[
\int |\Delta (\rho_k^{k+1}(t, x))| \, dx \leq C e^{G M t}.
\]

It gives compactness in space. But not in time.

Then we use a time regularization argument à la Steklov to obtain time compactness : for any regularizing kernel \(\omega_\epsilon(t)\), we have that the sequence \(\nabla p_k \ast \omega_\epsilon\) is compact (where the convolution is only in the time variable), then we can work with this sequence and pass to the limit \(\epsilon \to 0\) (not obvious).
Uniqueness for the limit problem

We have proved that we can extract from $(ρ_k, p_k)_k$ a subsequence that converges to a solution $(ρ_∞, p_∞)$ to

$$\partial_t ρ_∞ - \Delta p_∞ = ρ_∞ G(p_∞), \quad p_∞ \in P_∞(ρ_∞),$$

where we recall that $P_∞$ is the Hele-Shaw monotone graph

$$P_∞(ρ) = \begin{cases} 0, & 0 \leq ρ < 1, \\ ≥ 0, & ρ = 1. \end{cases}$$

Uniqueness

There is a unique pair $(ρ_∞, p_∞)$ solution to the above equation such that $ρ_∞, p_∞ \in L^∞((0, T], L^1(\mathbb{R}^d)), \nabla p_∞ \in L^2((0, T] \times \mathbb{R}^d)$ and $\partial_t p_∞, \partial_t ρ_∞$ bounded measures.

We conclude that the whole sequence $(ρ_k, p_k)_k$ is converging.
Proof of uniqueness (Hilbert’s duality method)

For two pairs of solutions \((\rho_1, p_1)\) and \((\rho_2, p_2)\), let \(\Omega\) a bounded domain containing the supports of both solutions. We have for any test functions \(\phi\),

\[
\iint_{\Omega_T} \left( (\rho_1 - \rho_2) \partial_t \phi + (p_1 - p_2) \Delta \phi + (\rho_1 G(p_1) - \rho_2 G(p_2)) \phi \right) \, dx \, dt = 0.
\]

It may be rewritten

\[
\iint_{\Omega_T} \left( (\rho_1 - \rho_2 + p_1 - p_2) \left( A_1 \partial_t \phi + A_2 \Delta \phi + A_1 G(p_1) \phi - A_3 A_2 \phi \right) \right) \, dx \, dt = 0,
\]

where (recall that \(p_i \in P_\infty(\rho_i)\)) for a constant \(C > 0\),

\[
0 \leq A_1 = \frac{\rho_1 - \rho_2}{\rho_1 - \rho_2 + p_1 - p_2} \leq 1,
\]

\[
0 \leq A_2 = \frac{p_1 - p_2}{\rho_1 - \rho_2 + p_1 - p_2} \leq 1,
\]

\[
0 \leq A_3 = -\rho_2 \frac{G(p_1) - G(p_2)}{p_1 - p_2} \leq C,
\]

where we set \(A = 0\) when \(\rho_1 = \rho_2\) (whatever the value of \(p_1 - p_2\)) and \(B = 0\) when \(p_1 = p_2\) (whatever the value of \(\rho_1 - \rho_2\)).
Proof of uniqueness (Hilbert’s duality method)

The Hilbert’s duality method consists in solving the dual problem

\[
\begin{cases}
A_1 \partial_t \phi + A_2 \Delta \phi + A_1 G(p_1) \phi - A_3 A_2 \phi = A_1 \psi, & \text{on } \Omega_T, \\
\phi = 0, & \text{in } \partial \Omega \times (0, T), \\
\phi(\cdot, T) = 0, & \text{in } \Omega,
\end{cases}
\]

for any smooth function \( \psi \). Then if such a function \( \phi \) exists for any smooth \( \psi \), we may take this function \( \phi \) in the above weak formulation and get

\[
\int\int_{\Omega_T} (\rho_1 - \rho_2) \psi \, dt \, dx = 0.
\]

We deduce straightforwardly that \( \rho_1 = \rho_2 \). Coming back to the initial formulation, we obtain the equality for the pressures.

The existence of a solution \( \phi \) for any smooth function \( \psi \) is obtained by a regularization argument.
Outline

1. **Derivation of Hele-Shaw model: incompressible limit**
   - Setting of the problem
   - Properties of the cell mechanical model
   - Statement of the results
   - Proof of the main result
   - Derivation for the model with active motion

2. **Extension to a model with visco-elasticity**
   - Presentation of the problem
   - Statement of the results
   - Extension to Navier-Stokes

3. **Extension to a model with two populations**
   - Presentation of the problem
   - Numerical simulations
Model with active motion

We extend this result when active motion of cells is not neglected. The mechanical system reads

\[ \partial_t \rho_k - \text{div}(\rho_k \nabla p_k) - \nu \Delta \rho_k = \rho_k G(p_k), \]

\[ p_k = \rho_k^k, \]

\[ \rho(t = 0) = \rho^{ini} \geq 0, \]

with diffusion coefficient \( \nu > 0 \).

Since cells are allowed to move randomly, we expect to have a faster spread and smoother front. This is observed in the following numerical simulations.
Model with active motion

**Figure** – Comparison of the density $\rho$ and the pressure $p$ between the model with active motion $\nu = 0.5$ (Left) and the model without active motion $\nu = 0$ (Right). The density $\rho$ is plotted in blue solid line whereas the pressure $p$ is represented in green dashed line. The initial data is the same in both model and the numerical results are plotted at the same time.
Formal derivation with active motion

With active motion, we start from

$$\partial_t \rho_k - \text{div}(\rho_k \nabla p_k) - \nu \Delta \rho_k = \rho_k G(p_k).$$
Formal derivation with active motion

With active motion, we start from

\[ \partial_t \rho_k - \text{div} (\rho_k \nabla p_k) - \nu \Delta \rho_k = \rho_k G(p_k). \]

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

\[ \partial_t p_k - \rho_k p'(\rho_k) \Delta p_k - |\nabla p_k|^2 - \nu \Delta p_k = \rho_k p'(\rho_k) G(p_k) - \nu p''(\rho_k) |\nabla \rho_k|^2. \]
Formal derivation with active motion

With active motion, we start from

\[ \partial_t \rho_k - \text{div}(\rho_k \nabla p_k) - \nu \Delta \rho_k = \rho_k G(p_k). \]

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

\[ \partial_t p_k - \rho_k p'(\rho_k) \Delta p_k - |\nabla p_k|^2 - \nu \Delta p_k = \rho_k p'(\rho_k) G(p_k) - \nu p''(\rho_k) |\nabla \rho_k|^2. \]

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

\[ \partial_t p_k - k p_k \Delta p_k - |\nabla p_k|^2 - \nu \Delta p_k = k p_k G(p_k) - \nu (k - 1) \frac{\nabla p_k \cdot \nabla \rho_k}{\rho_k}. \]
Formal derivation with active motion

With active motion, we start from

\[ \partial_t \rho_k - \text{div}(\rho_k \nabla p_k) - \nu \Delta \rho_k = \rho_k G(p_k). \]

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

\[ \partial_t p_k - \rho_k p'(\rho_k) \Delta p_k - |\nabla p_k|^2 - \nu \Delta p_k = \rho_k p'(\rho_k) G(p_k) - \nu p''(\rho_k) |\nabla \rho_k|^2. \]

For the special case \( p_k = \rho^k_k \) at hand, we find

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

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

\[ -p_\infty \Delta p_\infty = p_\infty G(p_\infty) - \nu \frac{\nabla p_\infty \cdot \nabla \rho_\infty}{\rho_\infty}. \]
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. Indeed, although 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 $\nu = -\nabla p_\infty$, but with a faster one.
Convergence result

These formal computations can be made rigorous. We take the same set of assumptions as before.

**Assumptions**: We consider that

\[ G' < 0 \]  
and that for some \( P_M > 0, \ G(P_M) = 0. \]

We complement the system

\[
\begin{align*}
\partial_t \rho_k - \text{div}(\rho_k \nabla p_k) - \nu \Delta \rho_k &= \rho_k G(p_k), \\
p_k &= \rho_k^k,
\end{align*}
\]

with initial conditions \( \rho^{ini} \geq 0. \)

We assume that the initial data \( \rho^{ini} \) is uniformly bounded in \( L^1 \cap L^\infty(\mathbb{R}^d) \), \( \nabla_x \rho^{ini} \) is uniformly bounded in \( L^1(\mathbb{R}^d) \). Moreover, \( \rho^{ini} \) is such that \( p^{ini}_k \leq P_M \) and is well prepared, i.e.

\[
\text{div}(\rho^{ini} \nabla p^{ini}_k) + \nu \Delta \rho^{ini} + \rho^{ini} G(\rho^{ini}) \geq 0.
\]
Convergence result

Theorem

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

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

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

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

$$\partial_t \rho_\infty - \text{div}(\rho_\infty \nabla p_\infty) - \nu \Delta \rho_\infty = \rho_\infty G(p_\infty),$$

and the complementary relation

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

7. Perthame, Quirós, Tang, Vauchelet, IFB vol 16, 2014
Interpretation

As in the case without active motion, we expect

\[ \Omega(t) = \{ x; p_\infty(t, x) > 0 \} = \{ x; \rho_\infty(t, x) = 1 \}. \]

Thus \( \Omega \) may be regarded as the tumor region, whereas the region \( 0 < \rho_\infty < 1 \) correspond to the precancer cells (also called the mushy region). The complementary relation indicates that the limit pressure satisfy

\[ -\Delta p_\infty(t) = G(p_\infty(t)) \quad \text{in} \ \Omega(t). \]

However, since the transport equation for \( \rho_\infty \) is changed, the geometric motion of the boundary does not satisfy the same rule. That is why we numerically observe a faster front speed of the boundary.
Estimates

The proof of this result follows the same approach in the case without active motion, with some technicalities. We recall the main ideas.

In order to have compactness, we first establish a priori estimates:

- As previously we obtain an uniform bound in $L^1 \cap L^\infty$ for $\rho_k$ and $p_k$ (using the maximum principle, since $G(p) < 0$ for $p > P_M$).
- Bound on the time derivative: assuming the $\partial_t \rho_{\text{ini}} \geq 0$ (i.e. the well-prepared assumption on initial data, $-\text{div}(\rho_{\text{ini}} \nabla p_{\text{ini}}) - \nu \Delta \rho_{\text{ini}} \leq \rho_{\text{ini}} G(p_{\text{ini}})$), then by maximum principle

$$\partial_t \rho_k \geq 0, \quad \text{and} \quad \partial_t p_k \geq 0.$$

Integrating then the equation for $\rho_k$ and $p_k$ we deduce

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

- bound on the space derivative: multiplying by $\rho_k$ the equation

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

we get after an integration

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

where we use the fact that $\partial_t \rho_k \geq 0$. Integrating the equation on $p_k$,

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

Thus there exists a (uniform in $k$) constant $C \geq 0$ such that

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

where we use also an integration of the equation on $p_k$ for the bound on $\nabla p_k$. 
Sketch of the proof

Idea of the proof:

- From the uniform bound, we deduce that \((\rho_k, p_k) \rightarrow (\rho_\infty, p_\infty)\) strongly in \(L^q\), \(1 \leq q < \infty\), and \((\nabla \rho_k, \nabla p_k) \rightharpoonup (\nabla \rho_\infty, \nabla p_\infty)\). Then we may pass to the limit in the transport equation for \(\rho_k\).

- We have \(\rho_k p_k = \rho_k^{k+1} = (p_k)^{1+1/k} \rightarrow p_\infty\), strongly. This implies \(p_\infty (1 - \rho_\infty) = 0\).

We deduce clearly that there is a region where \(\rho_\infty = 1\) and \(p_\infty = 0\), and a region where \(p_\infty = 0\) and \(\rho_\infty < 1\). In other words, \(p_\infty \in P_\infty(\rho_\infty)\).

- For the passage to the limit in the complementary relation, we need the strong convergence of \(\nabla p_k\), which is obtained from a regularizing argument (à la Steklov).

- The uniqueness for the limiting problem is obtained thanks to a Hilbert’s duality method.
Lecture 4

Some extensions
1 Derivation of Hele-Shaw model: incompressible limit
   - Setting of the problem
   - Properties of the cell mechanical model
   - Statement of the results
   - Proof of the main result
   - Derivation for the model with active motion

2 Extension to a model with visco-elasticity
   - Presentation of the problem
   - Statement of the results
   - Extension to Navier-Stokes

3 Extension to a model with two populations
   - Presentation of the problem
   - Numerical simulations
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’s law is used instead of Darcy’s law:

\[
\partial_t \rho_k - \text{div}(\rho_k \nabla W_k) = \rho_k G(p_k),
\]

\[-\nu \Delta W_k + W_k = p_k := \rho_k^k,
\]

where \( \nu > 0 \) is the bulk viscosity.

Such visco-elastic models for tumor growth have been also proposed in the literature:

Model with visco-elasticity

\[ \frac{\partial_t \rho_k}{\rho_k} - \text{div}(\rho_k \nabla W_k) = \rho_k G(p_k), \]
\[ -\nu \Delta W_k + W_k = p_k := \rho_k. \]

The first equation is a transport equation with velocity \( \nabla W_k \).
The second equation is an elliptic equation, with a right hand side that depends nonlinearly on \( \rho_k \).
Then this system falls into the class of transport equation coupled to elliptic equation.
Existence of weak solutions for such systems is known\(^8\). In particular, blow-up may occur for solutions of such system in the aggregative case. However in the case under investigation, we are in the repulsive framework and solutions stay bounded.

---

Formal computations

We are interested in the \textit{incompressible limit} $k \to +\infty$.

\[ \partial_t \rho_k - \text{div}(\rho_k \nabla W_k) = \rho_k G(p_k). \]

Multiplying 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

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

Then letting $k \to +\infty$ we recover the \textit{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 when $G$ is non-increasing).
Defining as above $\Omega(t) = \{p_\infty(t) > 0\}$, we deduce, with $H = (I - \nu G)^{-1}$:

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

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Density and pressure for the model with visco-elasticity. We observe a jump of the pressure at the free boundary.}
\end{figure}
Outline

1. Derivation of Hele-Shaw model: incompressible limit
   - Setting of the problem
   - Properties of the cell mechanical model
   - Statement of the results
   - Proof of the main result
   - Derivation for the model with active motion

2. Extension to a model with visco-elasticity
   - Presentation of the problem
   - Statement of the results
   - Extension to Navier-Stokes

3. Extension to a model with two populations
   - Presentation of the problem
   - Numerical simulations
Convergence result

These formal computations can be made rigorous. We take the same kind of assumptions as before.

**Assumptions :** We consider that

$$G' \leq \alpha < 0$$

and that for some $P_M > 0$, $G(P_M) = 0$.

We complement the system on $\mathbb{R}^d$

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

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

with initial conditions $\rho^{ini} \geq 0$.

We assume that the initial data $\rho^{ini}_k$ is uniformly bounded in $L^1 \cap L^\infty(\mathbb{R}^d)$.

Moreover, $\rho^{ini}_k$ is such that $p^{ini}_k (\rho^{ini}_k)^k \leq P_M$ and is well-prepared, i.e. for some open set $\Omega^0$, $\rho^{ini}_k = 0$ in $\mathbb{R}^d \setminus \Omega^0$ and $(\rho^{ini}_k)^k \xrightarrow{k \to \infty} p_\infty = H(W_0)$ a.e. in $\Omega^0$. 

Convergence result

Theorem

Under the above assumptions, we have up to a subsequence,

- $(\rho_k, p_k)$ converges strongly in $L^1_{loc}((0, T) \times \mathbb{R}^d)^2$, for all $T > 0$, as $k \to +\infty$ towards $(\rho_\infty, p_\infty)$ belonging to $L^1 \cap L^\infty((0, T) \times \mathbb{R}^d)^2$;

- $W_k \to W_\infty$ strongly in $L^1((0, T); W^{1,q}_{loc}(\mathbb{R}^d))$, for all $q \geq 1$.

Moreover,

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

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

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

The latter equation replaces the usual \textit{complementary relation}.

As usual, since $G(p) < 0$ for $p > P_M$, we expect to have a uniform bound on the pressure and thus on the density.

We expect to have discontinuity of the pressure at the boundary of the tumor region. Indeed at this boundary, the pressure jumps from $H(W_\infty)$ to 0. Thus, we do not have regularity of the gradients.

As already mentioned, the system under investigation can be seen as a transport equation whose velocity is obtained by solving an elliptic equation. Then, we follow the strategy developed in [B. Perthame, A.L. Dalibard, Trans. Am. Math. Soc. 361, 2009] based on kinetic reformulation.
Comments

Plot of the density $\rho$ (dashed line), pressure $p$ (line with dot), $W$ (continuous line). Comparison between the model with viscosity $\nu = 1$ (Left) at final time $T = 25\, s$ and without viscosity $\nu = 0$ (Right) at final time $T = 12.5\, s$.

Left. We notice a jump for the density from 0 to 1 at the front and a jump of the pressure.

Right. In this case, we have $p = W$ and there is no jump on the pressure. Moreover the front move faster in the case with viscosity. This observation is compatible with the interpretation that viscosity acts as a friction.
Proof for the model with visco-elasticity

Idea of the proof

As usual, since \( G(P_M) = 0 \) and \( G \) nonincreasing, we deduce from a maximum principle that \( 0 \leq p_k \leq P_M \). Then as above, we obtain that \((\rho_k)_k\) and \((p_k)_k\) are uniformly bounded in \( L^1 \cap L^\infty((0, T) \times \mathbb{R}^d) \). We deduce the weak convergence, up to a subsequence, \( \rho_k \rightharpoonup \rho_\infty \) and \( p_k \rightharpoonup p_\infty \).

Since \( W_k \) is solution of an elliptic problem, we have: \( W_k = K \ast p_k \). Then we also have weak convergence, up to an extraction, of \((W_k)_k\) towards a function \( W_\infty \). The weak convergence allows to pass to the limit in the equation for \( W \), we deduce that \( W_\infty \) satisfies, in the weak sense,

\[
-\nu \Delta W_\infty + W_\infty = p_\infty.
\]

However, we have no uniform estimates on the derivatives of \( \rho_k \) or \( p_k \) and no uniform estimates on the time. Thus we cannot recover strong compactness on \((\rho_k)_k\) and \((p_k)_k\). And strong convergence is needed to pass to the limit in the equations.
Proof for the model with visco-elasticity

A key estimate is that there exists a nonnegative number $C$ such that

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

- **Strong convergence for** $(W_k)_k$. The above estimate allows to obtain an estimate on the time derivative. Indeed, we have, on the one hand,

$$\partial_t p_k - \nabla p_k \cdot \nabla W_k = kp_k (G(p_k) + \Delta W_k) = kp_k (p_k - W_k - \nu G(p_k)).$$

On the other hand

$$W_k = K \star p_k, \quad K(x) = \frac{1}{4\pi} \int_0^\infty \frac{1}{4\pi \nu} e^{-\left(\frac{|x|^2}{4\nu} + \frac{s}{4\pi}\right)} \, ds \, \frac{ds}{s^{d/2}}.$$ 

Thus taking the convolution of the above equation, we deduce

$$\partial_t W_k = K \star (\nabla p_k \cdot \nabla W_k) + kK \star (p_k (p_k - W_k - \nu G(p_k))).$$

We can prove that it implies a bound on the time derivative. Thus $(W_k)_k$ is strongly compact. We may do the same for $(\nabla W_k)_k$.

$$W_k \to W_\infty \text{ strongly in } L^1((0, T); W^{1,q}_{loc}(\mathbb{R}^d)), \text{ for all } q \geq 1.$$
Proof for the model with visco-elasticity

We are left to prove the strong convergence of the density and the pressure.

The previous key estimate with the notation $H = (I - \nu G)^{-1}$ reads

$$k \int_0^T \int_{\mathbb{R}^d} p_k |W_k - H^{-1}(p_k)| \, dx \, dt \leq C.$$

This latter estimate implies that for any positive numbers $\beta_1, \beta_2$, we have

**Lemma**

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

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

To recover strong convergence, we use an approach based on kinetic reformulation.
Outline

1. Derivation of Hele-Shaw model: incompressible limit
   - Setting of the problem
   - Properties of the cell mechanical model
   - Statement of the results
   - Proof of the main result
   - Derivation for the model with active motion

2. Extension to a model with visco-elasticity
   - Presentation of the problem
   - Statement of the results
   - Extension to Navier-Stokes

3. Extension to a model with two populations
   - Presentation of the problem
   - Numerical simulations
A Navier-Stokes system with growth term

We consider the following Navier-Stokes system with growth term,

$$
\begin{align*}
\partial_t \rho + \text{div}(\rho \mathbf{u}) &= \rho G(p), \\
\rho \left( \partial_t \mathbf{u} + \mathbf{u} \cdot \nabla \mathbf{u} \right) - \mu \Delta \mathbf{u} - \xi \nabla \text{div} \mathbf{u} + \nabla p &= 0.
\end{align*}
$$

We use the notations:

- $\rho$ is the density,
- $\mathbf{u}$ is the velocity field,
- $p$ is the pressure, given by the pressure law $p = \rho^k$.
- $\mu > 0$, $\mu + \xi > 0$ are the viscosity coefficients.

The incompressible limit is obtained by letting $k \to +\infty$.

**Remark**: Neglecting the acceleration term and assuming that the viscous resisting force is proportional to the velocity, then the momentum equation in Navier-Stokes system reduces to the Darcy law: $\nu \mathbf{u} + \nabla p = 0$. 

N. Vauchelet

Imperial College
**Incompressible limit**

Formally, if we assume that all quantities are converging, then the limiting system reads

\[
\begin{align*}
\partial_t \rho_\infty + \text{div}(\rho_\infty \mathbf{u}_\infty) &= \rho_\infty G(p_\infty), \\
\rho_\infty \left( \partial_t \mathbf{u}_\infty + \mathbf{u}_\infty \cdot \nabla \mathbf{u}_\infty \right) - \mu \Delta \mathbf{u}_\infty - \xi \nabla \text{div} \mathbf{u}_\infty + \nabla p_\infty &= 0, \\
0 \leq \rho_\infty \leq 1, \quad p_\infty (1 - \rho_\infty) &= 0.
\end{align*}
\]

Indeed, from the expression \( p_k = \rho_k^k \), we deduce \( \rho_k = p_k^{\frac{1}{k}} \). Then:

- We have \( p_k = \rho_k p_k^{\frac{k-1}{k}} \). Thus, at the limit \( p_\infty = p_\infty \rho_\infty \), which is the last relation.
- \( 0 \leq \rho_k = p_k^{\frac{1}{k}} \leq P_M^{\frac{1}{k}} \to 1 \) as \( k \) goes to \( +\infty \).
Incompressible limit

Introduce the set $\Omega = \{ p_\infty > 0 \} \subset \mathbb{R}^d$, we have two cases:

- On $\mathbb{R}^d \setminus \Omega$, we have $p_\infty = 0$, then

$$
\partial_t \rho_\infty + \text{div}(\rho_\infty \mathbf{u}_\infty) = \rho_\infty G(p_\infty),
$$

$$
\rho_\infty (\partial_t \mathbf{u}_\infty + \mathbf{u}_\infty \cdot \nabla \mathbf{u}_\infty) - \mu \Delta \mathbf{u}_\infty - \zeta \nabla \text{div} \mathbf{u}_\infty + \nabla p_\infty = 0,
$$

which is the compressible pressureless Navier-Stokes system with the source term.

- On $\Omega$, we have $\rho_\infty = 1$. Then,

$$
\text{div} \mathbf{u}_\infty = G(p_\infty),
$$

$$
\partial_t \mathbf{u}_\infty + \mathbf{u}_\infty \cdot \nabla \mathbf{u}_\infty - \mu \Delta \mathbf{u}_\infty - \zeta \nabla \text{div} \mathbf{u}_\infty + \nabla p_\infty = 0,
$$

which might be seen as the incompressible Navier-Stokes system.
Main result \(^\text{11}\)

**Theorem**

Let \( T > 0 \). Let us assume that \( G \) is linear. Up to extraction of a subsequence, the solution to the Navier-Stokes system with growth \( \{(\rho_k, u_k, p_k)\}_k \) converges to a solution \( (\rho_\infty, u_\infty, p_\infty) \) to the above limiting system with

\[
\rho_k \rightarrow \rho_\infty \quad \text{strongly in } L^q((0, T) \times \mathbb{R}^d), \quad \text{for any } q \geq 1,
\]
\[
u_k \rightharpoonup u_\infty \quad \text{weakly in } L^2(0, T; H^1_{loc}(\mathbb{R}^d)),
\]
\[
\rho^k \rightarrow p_\infty \quad \text{weakly in } L^2((0, T) \times \mathbb{R}^d).
\]

**Ideas of the proof**

- Energy estimates to get bounds.
- Compactness method in the same spirit as in Bresch and Jabin\(^\text{10}\) to get strong convergence for the density. However, we only have weak convergence for the pressure, this is the reason why we restrict to linear growth term.

---

Outline

1 Derivation of Hele-Shaw model: incompressible limit
   - Setting of the problem
   - Properties of the cell mechanical model
   - Statement of the results
   - Proof of the main result
   - Derivation for the model with active motion

2 Extension to a model with visco-elasticity
   - Presentation of the problem
   - Statement of the results
   - Extension to Navier-Stokes

3 Extension to a model with two populations
   - Presentation of the problem
   - Numerical simulations
A two cell populations model

We consider two cell populations of densities $n_1$ and $n_2$. Restricting to the one dimensional domain $(-L, L)$, the system of equations reads

$$\partial_t n_1 \varepsilon - \partial_x (n_1 \varepsilon \partial_x p \varepsilon) = n_1 \varepsilon G_1 (p \varepsilon),$$

$$\partial_t n_2 \varepsilon - \partial_x (n_2 \varepsilon \partial_x p \varepsilon) = n_2 \varepsilon G_2 (p \varepsilon),$$

$$p \varepsilon = P (n \varepsilon) = \varepsilon \frac{n \varepsilon}{1 - n \varepsilon},$$

$$n \varepsilon = n_1 \varepsilon + n_2 \varepsilon,$$
Segregation property \(^{12}\)

Let \( \epsilon > 0 \) be fixed. Assume initial data satisfy

\[
\exists \zeta^0 \in \mathbb{R} \text{ such that } n_{1\epsilon}^{\text{ini}} = n_{\epsilon}^{\text{ini}} 1_{x \leq \zeta^0} \text{ and } n_{2\epsilon}^{\text{ini}} = n_{\epsilon}^{\text{ini}} 1_{x \geq \zeta^0},
\]

and

\[
n_{1\epsilon}^{\text{ini}}, n_{2\epsilon}^{\text{ini}} \geq 0 \text{ and } 0 < A_0 \leq n_{1\epsilon}^{\text{ini}} + n_{2\epsilon}^{\text{ini}} \leq B_0 < 1.
\]

Then there exists \( \zeta_{\epsilon} \in C([0, \infty)) \cap C^1((0, \infty)) \) such that

\[
n_{1\epsilon}(t, x) = n_{\epsilon}(t, x) 1_{x \leq \zeta_{\epsilon}(t)} \quad \text{and} \quad n_{2\epsilon}(t, x) = n_{\epsilon}(t, x) 1_{x \geq \zeta_{\epsilon}(t)},
\]

and

\[
\begin{cases}
\partial_t n_{\epsilon} - \partial_x (n_{\epsilon} \partial_x p_{\epsilon}) = n_{\epsilon} G_1(p_{\epsilon}) & \text{on } \{(t, x), x \leq \zeta_{\epsilon}(t)\}, \\
\partial_t n_{\epsilon} - \partial_x (n_{\epsilon} \partial_x p_{\epsilon}) = n_{\epsilon} G_2(p_{\epsilon}) & \text{on } \{(t, x), x \geq \zeta_{\epsilon}(t)\}, \\
n_{\epsilon}(t, \zeta_{\epsilon}(t)^-) = n_{\epsilon}(t, \zeta_{\epsilon}(t)^+), \\
\zeta'_{\epsilon}(t) = -\partial_x p_{\epsilon}(t, \zeta_{\epsilon}(t)^-) = -\partial_x p_{\epsilon}(t, \zeta_{\epsilon}(t)^+),
\end{cases}
\]

The incompressible limit is obtained by letting $\epsilon \to 0$.

Formal computations:

- We firstly remark that by adding equations for $n_1$ and $n_2$, we get,

$$\partial_t n_\epsilon - \partial_x (n_\epsilon \partial_x p_\epsilon) = n_1 \epsilon G_1(p_\epsilon) + n_2 \epsilon G_2(p_\epsilon)$$

Multiplying by $P'(n_\epsilon)$ we find an equation for the pressure,

$$\partial_t p_\epsilon - \left(\frac{p_\epsilon^2}{\epsilon} + p_\epsilon\right) \partial_{xx} p_\epsilon - |\partial_x p_\epsilon|^2 = \frac{1}{\epsilon} (p_\epsilon + \epsilon)^2 (n_1 \epsilon G_1(p_\epsilon) + n_2 \epsilon G_2(p_\epsilon)).$$

Formally, passing at the limit $\epsilon \to 0$, we expect the relation,

$$-p_0^2 \partial_{xx} p_0 = p_0^2 (n_{10} G_1(p_0) + n_{20} G_2(p_0)).$$

- As usual, we also have $(1 - n_0) p_0 = 0$. 

N. Vauchelet
Imperial College
Incompressible limit

We consider the domain $\Omega_0(t) = \{x \in (-L, L), p_0(x, t) > 0\}$.

- On $\Omega_0$, $n_0 = 1$. From the segregation property, we have $n_1\epsilon n_2\epsilon = 0$ when the two densities are initially segregated. Passing to the limit $\epsilon \to 0$ into this relation implies $n_{10} n_{20} = 0$. Then we may split $\Omega_0(t)$ into two disjoint sets $\Omega_1(t) = \{x \in (-L, L), n_{10}(x, t) = 1\}$ and $\Omega_2(t) = \{x \in (-L, L), n_{20}(x, t) = 1\}$. Moreover, from the equation on the pressure

$$-p_0^2 \partial_{xx} p_0 = \begin{cases} p_0^2 G_1(p_0) & \text{on } \Omega_1(t), \\ p_0^2 G_2(p_0) & \text{on } \Omega_2(t). \end{cases}$$

Then we obtain a free boundary problem of Hele-Shaw type: On $\Omega_1(t)$, we have $n_{10} = 1$ and $-\partial_{xx} p_0 = G_1(p_0)$, on $\Omega_2(t)$, we have $n_{20} = 1$ and $-\partial_{xx} p_0 = G_2(p_0)$. 
**Main result**

**Theorem**

Up to extraction, \( n_{1\epsilon}, n_{2\epsilon}, p_{\epsilon} \) converge strongly in \( L^1 \) as \( \epsilon \to 0 \) towards the respective limit \( n_{10}, n_{20} \in L^\infty([0, T]; L^1(-L, L)) \cap BV(Q_T) \), and \( p_0 \in BV(Q_T) \cap L^2([0, T]; H^1(-L, L)) \), which satisfy:

\[
0 \leq n_{10}(t, x) \leq 1, \quad 0 \leq n_{20}(t, x) \leq 1, \quad 0 \leq p_0 \leq P_M,
\]

\[
\partial_t n_{10} - \partial_x (n_{10} \partial_x p_0) = n_{10} G_1(p_0),
\]

\[
\partial_t n_{20} - \partial_x (n_{20} \partial_x p_0) = n_{20} G_2(p_0),
\]

complemented with Neumann boundary conditions \( \partial_x p_0(\pm L) = 0 \). Moreover, we have

\[
(1 - n_0) p_0 = 0.
\]

and the complementary relation

\[
p_0^2( - \partial_{xx} p_0 + n_{10} G_1(p_0) + n_{20} G_2(p_0)) = 0,
\]


14. Degond, Hecht, V., Preprint 2019
1. Derivation of Hele-Shaw model: incompressible limit
   - Setting of the problem
   - Properties of the cell mechanical model
   - Statement of the results
   - Proof of the main result
   - Derivation for the model with active motion

2. Extension to a model with visco-elasticity
   - Presentation of the problem
   - Statement of the results
   - Extension to Navier-Stokes

3. Extension to a model with two populations
   - Presentation of the problem
   - Numerical simulations
Numerical simulations

Consider the growth functions $G_1(p) = 10(1 - p)$ and $G_2(p) = 10\left(1 - \frac{p}{2}\right)$.

**Figure** – Dynamics of $n_1$, $n_2$, and $p$ for different value of $\epsilon$: $\epsilon = 1$ (top), $\epsilon = 0.01$ (bottom).
Notice that with this choice of growth function, we have $P_M^1 = 1$ and $P_M^2 = 2$. From the relation $n_\epsilon = \frac{p_\epsilon}{\epsilon + p_\epsilon}$, we deduce that

$$0 \leq n_{1,\epsilon} \leq \frac{P_M^1}{\epsilon + P_M^1} \quad \epsilon \to 0 \quad \to 1,$$

$$0 \leq n_{2,\epsilon} \leq \frac{P_M^2}{\epsilon + P_M^2} \quad \epsilon \to 0 \quad \to 1.$$
Numerical simulations

Notice that with this choice of growth function, we have $P_1^M = 1$ and $P_2^M = 2$. From the relation $n_\epsilon = \frac{p_\epsilon}{\epsilon + p_\epsilon}$, we deduce that

$$0 \leq n_{1,\epsilon} \leq \frac{P_1^M}{\epsilon + P_1^M} \to 1, \quad 0 \leq n_{2,\epsilon} \leq \frac{P_2^M}{\epsilon + P_2^M} \to 1.$$

In the next example, we consider the influence of the growth function and then plot the solutions, with the same initial data, for the two following set of growth function:

$$G_1(p) = 10(1 - p), \quad G_2(p) = 10(1 - \frac{p}{2});$$

and

$$G_1(p) = 10(4 - p), \quad G_2(p) = 10(1 - \frac{p}{2}).$$
Numerical simulations

Figure – Dynamics of $n_1$, $n_2$, and $p$ for different growth function: $G_1(p) = 10(1 - p)$ and $G_2(p) = 10(1 - \frac{p}{2})$ (top); $G_1(p) = 10(4 - p)$ and $G_2(p) = 10(1 - \frac{p}{2})$ (bottom).
Conclusion
Conclusion

As a conclusion, we have presented a link between mechanical model for tumor growth and free boundary model of Hele-Shaw type. The link is obtained by performing a so-called *incompressible limit*. Three different models for one population density have been considered: a standard model, a model with active motion, a model with visco-elasticity. Even in the simplest case, techniques are not simple and we have to restrict our set of assumption in particular on the initial data and on the dependency of the growth term on the pressure (not the nutrient). However, let us mention that

- more general initial data may be considered using further regularity, see also [I. Kim, N. Pozar, Preprint 2015; A. Mellet, B. Perthame, F. Quiros, Preprint 2015];
- nutrient dependency may be considered but the complementary relation is not proved.
Conclusion

There are still many open questions related to these works:

- Consider model with different kind of cells (proliferative, quiescent, dead, ...).
- Recover the surface tension at the boundary for the limiting free boundary model.
- Instabilities?

Thank you for your attention
Proof for the model with visco-elasticity

**Idea :** Kinetic reformulation

- We define
  \[ \chi_k(t, x, \xi) = 1_{\{0 < \xi < p_k(t, x)\}}. \]
  It converges in \( L^\infty - w^* \) as \( k \to +\infty \) towards a function \( \chi \). From the above Lemma, we have
  \[ \chi(t, x, \xi) = f(t, x)1_{\{0 < \xi < H(W_\infty(t, x))\}}, \]
  where \( f \) is a measurable function \( 0 \leq f \leq 1 \).
- Let \( S \) be any smooth function \([0, \infty) \to \mathbb{R}\), we have
  \[ S(p_k) - S(0) = \int_0^\infty S'(\xi)\chi_k(t, x, \xi) \, d\xi \to \int_0^\infty S'(\xi)\chi(t, x, \xi) \, d\xi. \]
  Replacing with the above expression of \( \chi \), we get
  \[ S(p_k) \to S(0)(1 - f) + S(H(W_\infty))f. \]
  It means that \( p_k \) oscillates between the values 0 and \( H(W_\infty(x, t)) \) with the weights \( 1 - f(x, t) \) and \( f(x, t) \). Notice that for \( S(p) = p \), we find
  \[ p_\infty = f \cdot H(W_\infty). \]
Proof for the model with visco-elasticity

Then the following steps are

1. Find the equation satisfied by \( f \).
   We may prove that there exists a positive measure \( \mu \) such that
   \[
   \partial_t f - \nabla f \cdot \nabla W_\infty = \mu \geq 0.
   \]

2. Deduce that \( f = 1_{\{p_\infty > 0\}} \).
   To do so we compare \( f \) with the solution \( g \) to
   \[
   \partial_t g - \nabla g \cdot \nabla W_\infty = 0, \quad g(t = 0) = f(t = 0).
   \]
   By comparison, we have \( g \leq f \) and \( 0 \leq f \leq 1 \). Then \( f = 1 \) on the set \( \{g(t, x) = 1\} \). And by assumption, \( f(t = 0) = 1_\Omega^0 \).

3. Prove that it implies the local strong convergence of \( (p_k)_k \) towards \( H(W_\infty)1_{\{p_\infty > 0\}} \) in \( L^1((0, T) \times \mathbb{R}^d) \).

4. Recover the strong convergence of \( (\rho_k)_k \). This is due to the fact that \( \rho_k \) satisfies a transport equation whose velocity and right hand side converges strongly\(^{15} \).

---

Proof for the model with visco-elasticity

Finally, we present the idea to obtain the equation satisfied by $f$. Starting from the equation on the pressure

$$\partial_t p_k - \nabla p_k \cdot \nabla W_k = \frac{k}{\nu} p_k Q_k, \quad Q_k = W_k - p_k + \nu G(p_k),$$

we obtain an equation on $S(p_k)$ by multiplying it by $S'(p_k)$,

$$\partial_t S(p_k) - \nabla S(p_k) \cdot \nabla W_k = kp_k Q_k S'(p_k).$$

Denoting by $\delta$ the Dirac mass, we can rewrite the later equation as

$$\partial_t \int_0^\infty S'(\xi) \chi_k d\xi - \nabla \int_0^\infty S'(\xi) \chi_k d\xi \cdot \nabla W_k = \int_0^\infty S'(\xi) \mu_k(x, \xi, t) d\xi,$$

$$\mu_k(x, \xi, t) := \frac{k}{\nu} p_k Q_k \delta\{\xi=p_k\} = \frac{k}{\nu} p_k [W_k - p_k + \nu G(p_k)] \delta\{\xi=p_k\}.$$

Eliminating the test function $S'(\cdot)$, this is equivalent to write

$$\partial_t \chi_k - \nabla \chi_k \cdot \nabla W_k = \mu_k.$$

The equation on $f$ is obtained by passing to the limit $k \to +\infty$. However, we do not have enough regularity to do so, we need to reformulate the equation in the divergence form!