Institut Camille Jordan - Université Claude Bernard - Lyon 1

On the incompressible limit for porous medium models of tumor growth

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Based on joint works with T. Dębiec, B. Perthame, M. Schmidtchen

Diffusion in Warsaw - MIMUW, Warsaw

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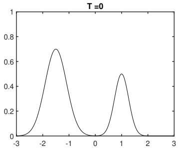
Introduction

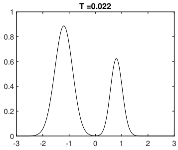
Motivations: macroscopic models of tumor growth

Compressible models

$$\partial_t n = \nabla \cdot (n \nabla p) - \nabla \cdot (n \nabla V) + nG$$

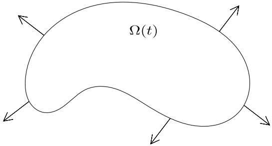
$$n = n(x,t), \quad x \in \mathbb{R}^d, \; t > 0$$





Free boundary problems

$$\begin{cases} -\Delta p = G(p), \text{ in } \Omega(t) = \{p > 0\} \\ v_\nu = -\nabla p \cdot \nu, \text{ on } \partial\Omega(t) \end{cases}$$



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$$\partial_t n = \nabla \cdot (n \nabla p) - \nabla \cdot (n \nabla V) + nG$$

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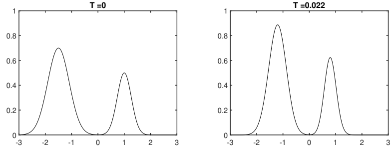

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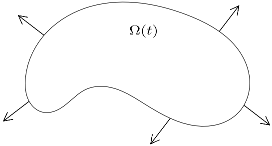

How can we link *compressible* and *geometrical* models?

Outline of the talk

- Mechanical model with drift
- Incompressible limit: formal idea
- State of the art: the Aronson-Bénilan estimate
- Strategy: compactness of the pressure gradient
- Rate of convergence

Mechanical models of tumor growth

$$\partial_t n - \nabla \cdot (n \nabla p) + \nabla \cdot (n \nabla V) = nG(p)$$

- The dynamics of the cell population density $n(x,t)$ is governed by mechanical pressure, drifts towards chemo-attractants or nutrients, and division/necrosis
- $\vec{v} = -\nabla p \; + \; \nabla V$, Darcy's law + drift
- $G = G(p)$, pressure-dependent growth rate, $G'(p) < 0$

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- **Compressible law of state:**

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- **Incompressible limit** $\gamma \to \infty$: bridging the gap between *density-based models* and *free boundary problems* of Hele-Shaw type

Incompressible limit

Passing to the **limit** $\gamma \to \infty$

Graph relation:

$$p_\infty(1 - n_\infty) = 0$$

$\Omega(t) := \{x;\ p_\infty(x,t) > 0\}$ *Tumor region*

$\{x;\ 0 < n_\infty(x,t) < 1\}$ *Precancer cells*

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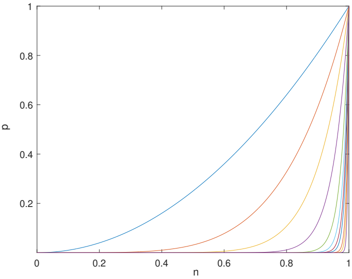

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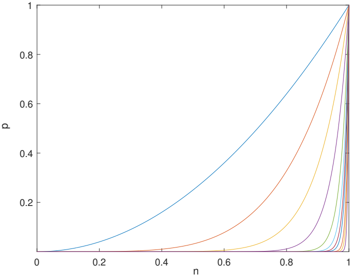

$$\overbrace{\gamma n^{\gamma - 1}}^{p'} \cdot \partial_t n = \partial_t p = \gamma p(\Delta p - \Delta V + G(p)) + |\nabla p|^2 - \nabla p \cdot \nabla V$$

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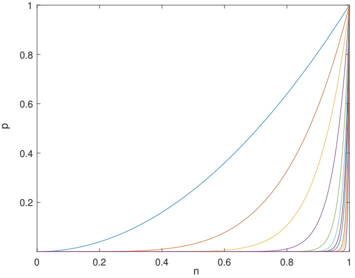
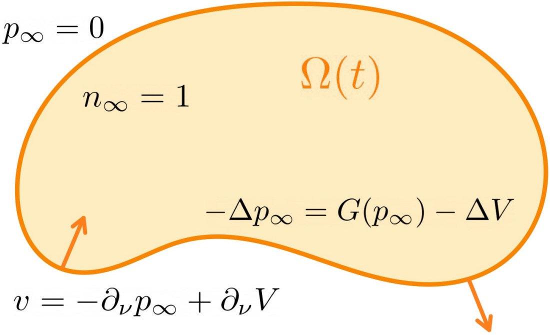


$$\partial_t p = \gamma p(\Delta p - \Delta V + G(p)) + |\nabla p|^2 - \nabla p \cdot \nabla V$$

Complementarity relation:

$$p_\infty(\Delta p_\infty - \Delta V + G(p_\infty)) = 0$$

Free boundary problem



Limit model: Hele-Shaw free boundary problem

State of the art

Some historical remarks

- **Porous Medium Equation (PME):** $\partial_t n = \Delta n^\gamma$, $\gamma \to \infty$:
  Caffarelli, Friedman ’87; Bénilan, Boccardo, Herrero ’89; Aronson, Gil, Vázquez ’98; Gil, Quirós ’01 ...

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- **Model with proliferation:** $\partial_t n = \nabla \cdot (n \nabla p) + nG(p)$, $p \sim n^\gamma$
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- **Visco-elastic models (Brinkman’s law):** Drasdo, Perthame, Tang, Vauchelet ’14; Dębiec, Perthame, Schmidtchen, Vauchelet ’20 ...

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- **Multi-species models**: Carrillo, Fagioli, Santambrogio, Schmidtchen '18, Gwiazda, Perthame, Świerczewska-Gwiazda '18, Bubba, Perthame, Pouchol, Schmidtchen '20; Dębiec, Perthame, Schmidtchen, Vauchelet '20; Price, Xu '20; Liu, Xu '21...

Some historical remarks: the PME

$$\partial_t n = \nabla \cdot (n \nabla p), \quad p = n^\gamma, \qquad n(x,0) = n_0(x) \in L^\infty(\mathbb{R}^d) \cap L^1(\mathbb{R}^d)$$

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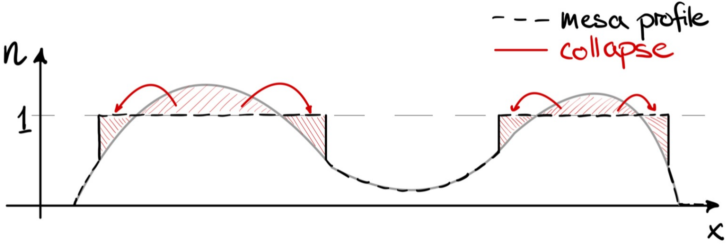
$$\partial_t n = \nabla \cdot ((\gamma+1)n^\gamma \nabla n), \qquad n(x,0) = n_0(x) \in L^\infty(\mathbb{R}^d) \cap L^1(\mathbb{R}^d)$$

$$(\gamma+1)n^\gamma \to \begin{cases} 0, & \text{if } n < 1 \\ \infty, & \text{if } n \geq 1 \end{cases} \qquad n_\gamma(x,t) \to n_\infty(x) = \begin{cases} n_0(x) & \text{in } \{n_\infty < 1\} \\ 1 & \text{otherwise} \end{cases}$$



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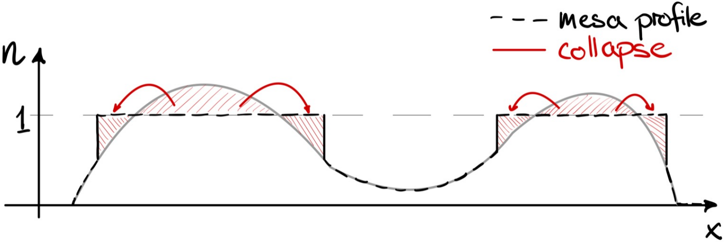

Fundamental estimate of the PME, Aronson, Bénilan '79: $\Delta p \geq -\frac{C}{\gamma t}$

PME: the Aronson-Bénilan estimate

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We set $w := \Delta p$. Then

$$\partial_t w = 2\gamma \nabla p \cdot \nabla w + \gamma w^2 + \gamma p \Delta w + 2\nabla p \cdot \nabla w + 2\sum_{i,j}\left(\partial^2_{i,j} p\right)^2$$

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$$\partial_t w \geq 2(\gamma + 1) \nabla p \cdot \nabla w + \gamma p \Delta w + \gamma w^2$$

Comparison principle $\Rightarrow$ $\Delta p \geq -\frac{1}{\gamma t}$ (AB estimate)

Purely mechanical model: solutions behavior

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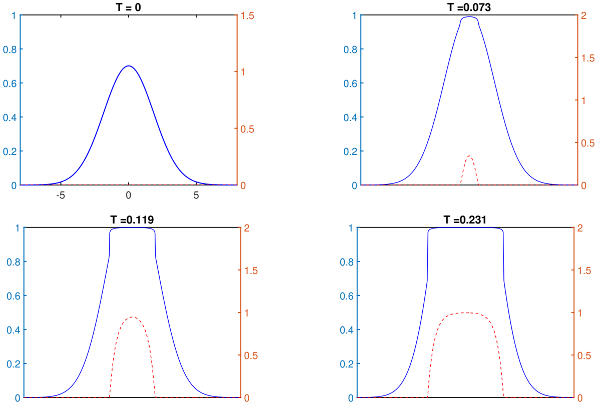

Density (blue line), pressure (red dashed line), $\gamma = 90$

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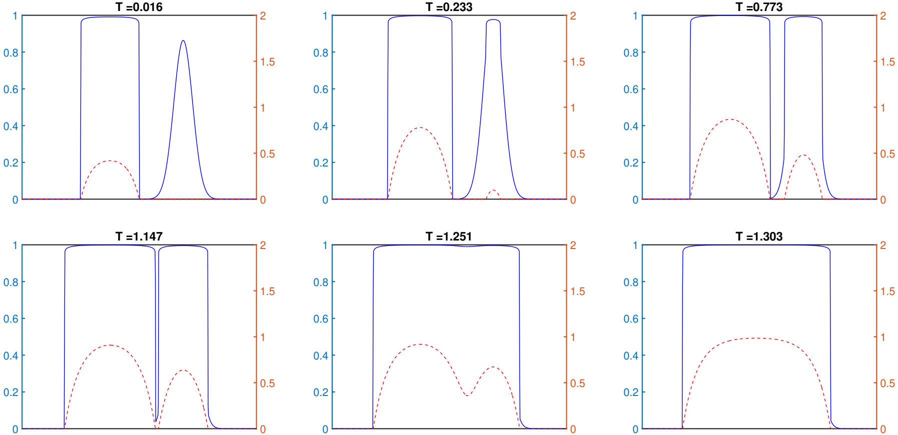

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Aronson-Bénilan estimate (*à la* Perthame, Quirós, Vázquez)

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Aronson-Bénilan estimate $\Longrightarrow$ Complementarity relation

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Aronson-Bénilan estimate $\Longrightarrow p_\infty(\Delta p_\infty + G(p_\infty)) = 0$

Incompressible limit of a tumor growth model with drift

Stiff limit of a model with drift

Theorem: limit $\gamma \to \infty$

$$p_\gamma \to p_\infty, \quad n_\gamma \to n_\infty \leq 1 \text{ in } L^1_{x,t}, \quad \nabla p_\gamma \rightharpoonup \nabla p_\infty \text{ weakly in } L^2_{x,t},$$

$$\partial_t n_\infty = \nabla \cdot (n_\infty \nabla p_\infty) - \nabla \cdot (n_\infty \nabla V) + n_\infty G(p_\infty)$$

$$p_\infty (1 - n_\infty) = 0$$

N.D., M. Schmidtchen, On the incompressible limit of a tumor growth model incorporating convective effects, CPAM, to appear, 2022

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Theorem: complementarity relation

$$p_\infty (\Delta p_\infty - \Delta V + G(p_\infty)) = 0 \quad \text{in} \quad \mathcal{D}'(\mathbb{R}^d \times (0, \infty))$$

Complementarity relation $\Longleftrightarrow$ L^2-strong compactness of ∇p_γ

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Assumptions

Initial data

- $n_{0,\gamma} \geq 0$, $n_{0,\gamma} \in BV(\mathbb{R}^d) \cap L^\infty(\mathbb{R}^d)$,
- $\|\Delta n_{0,\gamma}^{\gamma+1}\|_{L^1(\mathbb{R}^d)} < C$,
- $n_{0,\gamma}$ compactly supported

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Proliferation rate $G(p)$

- $G \in C^1, \quad G'(p) \leq -\alpha < 0$
- $\exists\ p_M > 0$ such that $G(p_M) = 0$

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Drift $V(x,t)$

- $D^2 V \in L^\infty_{loc}(\mathbb{R}^d \times (0,\infty))$
- $\Delta(\partial_{x_i} V) \in L^{12/5}_{loc}(\mathbb{R}^d \times (0,\infty)), \;\; i = 1, ..., d$
- some mild control on $\partial_t \nabla V, \partial_t \Delta V$

A priori estimates

The following hold uniformly with respect to γ

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- $\nabla p_\gamma \in L^2(\mathbb{R}^d \times (0, T))$
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Thus

$$n_\gamma \to n_\infty \leq 1, \qquad p_\gamma \to p_\infty, \quad \text{in } L^1(\mathbb{R}^d \times (0,T))$$

$$\nabla p_\gamma \rightharpoonup \nabla p_\infty \quad \text{weakly in } L^2(\mathbb{R}^d \times (0,T))$$

Strong compactness of the gradient: strategy

Goal: $\nabla p_\gamma \to \nabla p_\infty$ **strongly** in $L^2_{x,t} \iff p_\infty(\Delta p_\infty - \Delta V + G(p_\infty)) = 0$

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- **L^4-bound** of ∇p_γ

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- L^3-version of the **Aronson-Bénilan estimate**

$$(\Delta p_\gamma + G(p_\gamma))_- \in L^3(\mathbb{R}^d \times (0,T))$$

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- L^3-version of the **Aronson-Bénilan estimate**

$$(\Delta p_\gamma + G(p_\gamma))_- \in L^3(\mathbb{R}^d \times (0,T))$$

$$\Rightarrow \Delta p_\gamma \in L^1(\mathbb{R}^d \times (0,T))$$

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Strong compactness of the gradient: strategy

Goal: $\nabla p_\gamma \to \nabla p_\infty$ **strongly** in $L^2_{x,t}$ $\iff$ $p_\infty(\Delta p_\infty - \Delta V + G(p_\infty)) = 0$

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Kim, Zhang '20: $\Delta p_\gamma + G \geq -C/\gamma t - C$, but requires $V \in C^{4,1}_{x,t}$

Sketch of the proof: L^4-estimate (no drift)

- $\partial_t p = \gamma p(\Delta p + G) + |\nabla p|^2$

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- $p \in L^\infty_{x,t} \;\Rightarrow\; pD^2 p \in L^2_{x,t} \;\Rightarrow\; p \in W^{1,4}_{x,t}$

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Also: Gwiazda, Perthame, Świerczewska-Gwiazda '19, Bevilacqua, Perthame, Schmidtchen '21

A short break on multi-species models

$$\begin{cases} \partial_t n_1 - \nabla \cdot (n_1 \nabla p) = n_1 G_{1,1}(p) + n_2 G_{2,1}(p) \\ \partial_t n_2 - \nabla \cdot (n_2 \nabla p) = n_1 G_{1,2}(p) + n_2 G_{2,2}(p) \\ p = n^\gamma,\ n := n_1 + n_2 \end{cases}$$

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- *BV*-bounds on n_i do **not** propagate
- To prove **existence** and **incompressible limit**: ∇p strongly compact!

Some remarks

AB estimate:

- multi-species:

  -[*Gwiadza et al. '19*] $(\Delta p + G)_- \in L^2$ (if $G_1(0) = G_2(0)$): gives **existence**

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- [D.,Perthame '21]: $\nabla p_\gamma \in L^4$ is sharp: counter-example is the **focusing solution**

Rate of convergence

Incompressible limit: rate of convergence

$$\partial_t n_\gamma = \Delta n_\gamma^\gamma - \nabla \cdot (n_\gamma \nabla V) + n_\gamma g(x,t)$$

N.D., T. Dębiec, B. Perthame, Convergence rate for the incompressible limit of nonlinear diffusion-advection equations, Annales IHP (C), 2022.

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Previous result for $\boldsymbol{g = 0}$: Alexandre, Kim, Yao '14

$$\sup_{t\in[0,T]} W_2(n_\gamma(t), n_\infty(t)) \le \frac{C}{\gamma^{1/24}},$$

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Assumption on the drift:

$$D^2 V \geq \left(\lambda + \frac{1}{2}\Delta V\right) I_d, \quad \lambda \in \mathbb{R}$$

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- $\partial_t n = \nabla \cdot (n \nabla p) + \nabla \cdot (n \nabla V) + ng(x,t), \qquad p = \frac{\gamma}{\gamma-1} n^{\gamma-1}$

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- $\varphi_\gamma := \mathcal{K} \star n_\gamma, \quad -\Delta \varphi_\gamma = n_\gamma$

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For simplicity, let us assume $n_\gamma, n_{\gamma'} \leq 1$

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$s^\gamma(1-s) \leq s/\gamma$

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$\gamma < \gamma', \quad \gamma' \to \infty$

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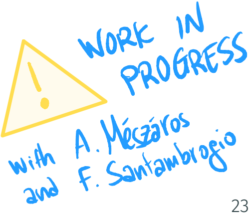

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with A. Mészáros
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Thank you!