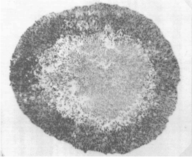
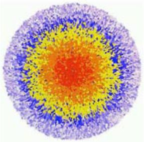
Hele-Shaw models for tumor growth

Benoît Perthame

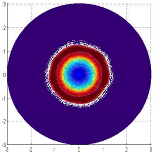


Suzerland et al , Cancer Res.,

Rotschild et al, The lancet,



Byrne-Drasdo JMB,

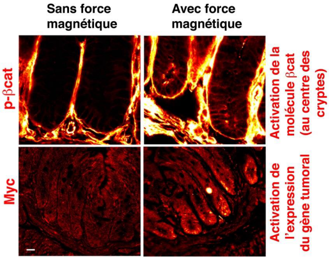


M. Tang, Vauchelet

Introduction

What is a living tissue ? A mechanistic view

- Physicists
  Benamar, Drasdo, Preziosi,
  Joanny-Prost-Jüllicher,
  E. Farge



- Mathematical models
  Byrne-Chaplain-Preziosi,
  Lowengrub et al, Friedman, Maini,
  MONC (Bordeaux) $\rightarrow$ Colin, Benzékry

- Pressure, contact inhibition rather than carrying capacity

Organisation of the talk

1. Two kinds of models :
    - cell density (compressible)
    - Free boundary problem (incompressible)
2. The Hele-Shaw asymptotics
3. Nutrients/drugs
4. Active motion
5. Elastic or viscoelastic tissus

Models of cell number density

Simplest model is mechanical only :

$n(x,t) =$ population density of tumor cells at location x, time t,

$v(x,t) =$ cell velocity at location x and time t,

$p(x,t) =$ pressure in the tissue,

$$\overbrace{\frac{\partial n}{\partial t}}^{\text{Change in number of cells}} = \underbrace{-\mathrm{div}\left(nv\right)}_{\text{movement of cells}} + \textit{divison} - \textit{death}$$

Darcy's law for friction (with ECM) dominated flow

$$v = -\nabla p(x,t),$$

Constitutive law (compressible fluid)

$$p(x,t) \equiv \Pi(n) := n^{\gamma}, \quad \gamma > 1$$

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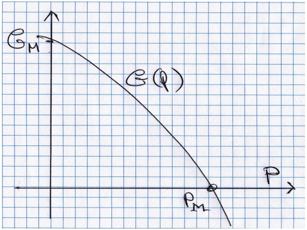
Models of cell number density

$n(x,t)$ = population density of tumor cells
$1 - n(x,t)$ = healthy cells

$$\begin{cases} \frac{\partial}{\partial t} n + \mathrm{div}\big(nv\big) = n\, G\big(p(x,t)\big), \\ v(x,t) = -\nabla p(x,t), \qquad p(x,t) \equiv \Pi(n) := n^{\gamma}, \quad \gamma > 1 \end{cases}$$

Contact inhibition : Byrne-Drasdo, Joanny-Prost-Jülicher...
'homeostatic pressure' p_M



Main property : $\frac{\partial}{\partial t} n(t) \geq -\frac{K}{t} e^{-\gamma r_G t}$

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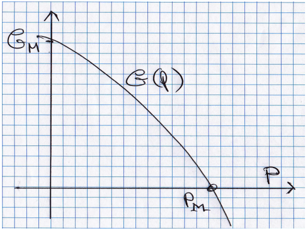

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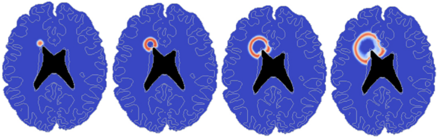
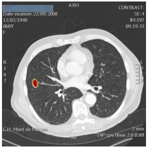
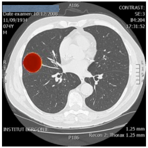
Free boundary/incompressible models

Image based predictions : include

- Active cells
- Nutrients and vasculature
- Quiescent, necrotic, healthy cells





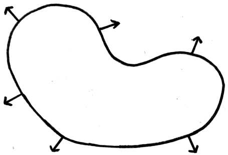


Credit for pictures : INRIA team Monc (Bordeaux)

DO NOT USE THIS FORMALISM

Free boundary/incompressible models

Tumor domain $\Omega(t)$



Evolve $\partial\Omega(t)$ with Darcy's law

$$v(x,t) = -\nabla p(x,t).$$

using the pressure

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

Surface tension is often included

$$p(x,t) = \eta\kappa(x,t), \quad \text{on } \partial\Omega(t) \qquad \kappa = \text{the mean curvature}$$

Hele-Shaw free boundary problem
Boundary is smooth

Free boundary/incompressible models

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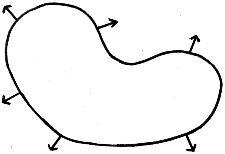

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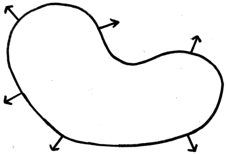

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- Hele-Shaw free boundary problem
- Boundary is smooth

From cell densities to free boundary

How to relate these two approaches
cell density and free boundary ?

$$\begin{cases} \frac{\partial}{\partial t} n_\gamma + \operatorname{div}\big(n_\gamma v_\gamma\big) = n_\gamma G\big(p_\gamma(x,t)\big), & x \in \mathbb{R}^d \\ v_\gamma = -\nabla p_\gamma(x,t), \qquad p_\gamma(x,t) \equiv \Pi(n_\gamma) := n^\gamma, \end{cases}$$

The stiff pressure law the limit, $\gamma \to \infty$
Hele-Shaw free boundary problem

Benilan, Igbida, Gil, Quiros, Vazquez, X. Chen et al, Caffarelli, Friedman, Escher...etc

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Theorem (Hele-Shaw limit) : As $\gamma \to \infty$

$$n_\gamma \to n_\infty \leq 1, \qquad p_\gamma \to p_\infty \leq p_M$$

$$\nabla p_\gamma \rightharpoonup \nabla p_\infty \qquad L^2\text{-}w$$

$$\begin{cases} \frac{\partial}{\partial t} n_\infty - \mathrm{div}\big(n_\infty \nabla p_\infty\big) = n_\infty G\big(p_\infty\big), \\ p_\infty = 0 \quad \text{for} \quad n_\infty(x,t) < 1. \end{cases}$$

Theorem (complementary relation) : We also have

$$p_\infty \big[\, \Delta p_\infty + G(p_\infty)\big] = 0,$$

$$\nabla p_\gamma \to \nabla p_\infty \qquad \text{strongly in } L^2\big((0,T)\times\mathbb{R}^d\big),$$

The geometric form of the Hele-Shaw problem follows when

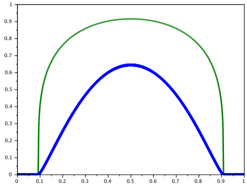
$$n^0(x) = \mathbb{1}_{\{\Omega^0\}}, \qquad \Omega^0 = \{\ p^0 > 0\}.$$

Then

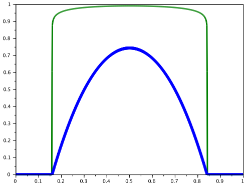
$$n(x,t) = \mathbb{1}_{\{\Omega(t)\}}, \qquad \Omega(t) = \{\ p(t) > 0\},$$

And

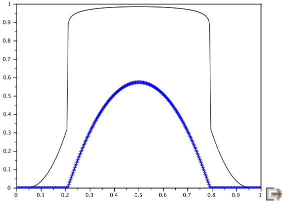
Weak formulation $\iff$ Free boundary problem



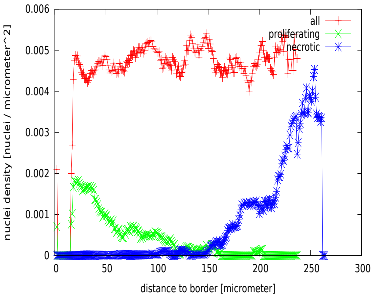
Left : $\gamma = 4$

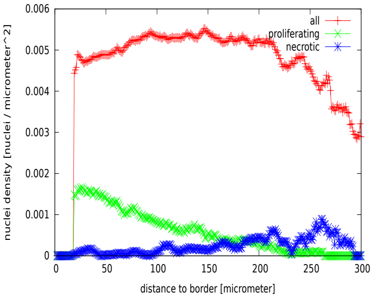


Center : $\gamma = 40$



From cell densities to free boundary



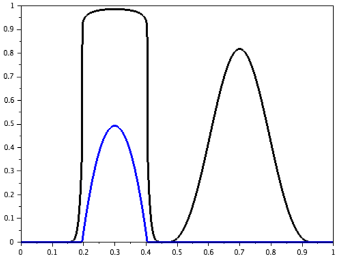


Cell culture data in vitro at two different times. From N. Jagiella PhD thesis, INRIA and UPMC (2012)

The geometric form of the Hele-Shaw problem

theorem After a waiting time, the free boundary is smooth and the weak form is equivalent to the Hele-Shaw problem.

But there are transient singularities.



Organisation of the talk

1. Cell density models (compressible)
2. Free boundary problem (incompressible)
3. The Hele-Shaw asymptotics
4. **Nutrients**
5. **Active motion**
6. **Viscoelastic model**

Model with nutrient

$$
\begin{cases}
\frac{\partial}{\partial t} n + \operatorname{div}\big(nv\big) = nG\big(p(x,t), \underbrace{c(x,t)}_{\text{nutrients}}\big), \\
v = -\nabla p, \qquad p = n^{\gamma}, \\
\frac{\partial}{\partial t} c - \Delta c + \underbrace{R(n)c = c_B}_{\text{nutrients consumption/release}}
\end{cases}
$$

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Theorem (Hele-Shaw limit) As $\gamma \to \infty$, we have

$$\begin{cases} \frac{\partial}{\partial t} n_\infty + \mathrm{div}\big(n_\infty v_\infty\big) = n_\infty G\big(p_\infty, c_\infty\big), \qquad v_\infty = -\nabla p_\infty, \\ p_\infty(1 - n_\infty) = 0, \qquad 0 \le n_\infty \le 1, \end{cases}$$

Open question

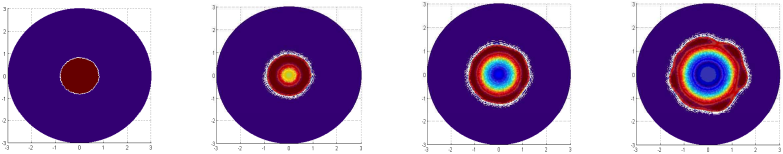
$$p_\infty\big[-\Delta p_\infty - G\big(p_\infty, c_\infty\big)\big] = 0?$$

Model with nutrient

$$\begin{cases} \frac{\partial}{\partial t} n + \mathrm{div}\big(nv\big) = nG\big(p(x,t), \underbrace{c(x,t)}_{\text{nutrients}}\big), \\ v = -\nabla p, \qquad p = n^\gamma, \\ \frac{\partial}{\partial t} c - \Delta c + \underbrace{R(n)c = c_B}_{\text{nutrients consumption/release}} \end{cases}$$

Necrotic core, instabilities

With nutrients tumor cells can die



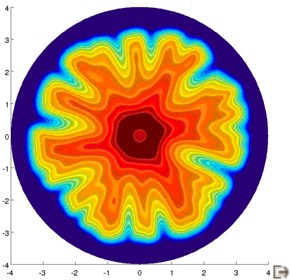
effect of nutrient consumption. Credit for pictures M. Tang, N. Vauchelet

Model of with nutrient

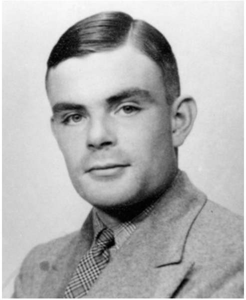
Closely related to instability in thermo-chemical reactions

$$
\begin{cases}
\frac{\partial}{\partial t} u - \alpha \Delta u = \frac{u^2 v}{\alpha}, & \text{temperature} \\
\frac{\partial}{\partial t} v - \Delta v = -\frac{u^2 v}{\alpha}, & \text{reactant}
\end{cases}
$$

Dynamical Turing instability (see M. Kowalczyk, BP, N. Vauchelet : Transversal instability of 1D traveling wave)



Credit for picture N. Vauchelet



Model with active movment

$$\begin{cases} \frac{\partial}{\partial t} n + \operatorname{div}\big(nv\big) - \overbrace{\nu \Delta n}^{\text{active movement}} = nG\big(p(x,t)\big), \\ v = -\nabla p \qquad p = n^\gamma, \qquad \text{Darcy's law}, \end{cases}$$

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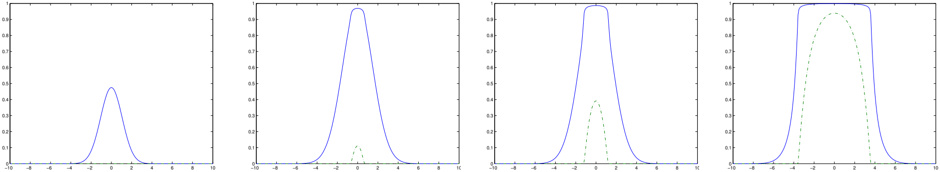
Hele-Shaw limit : We still have

$$p\ \big(\Delta p + G(p)\big) = 0$$



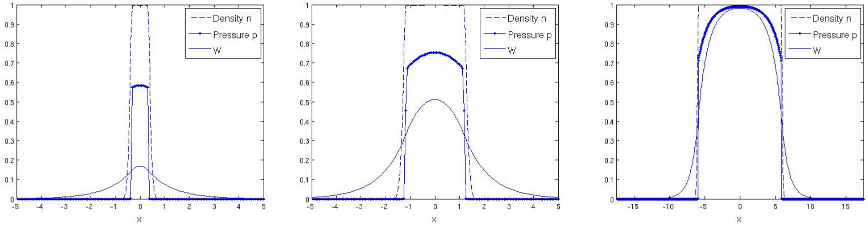
Effect of active movement (cell density is smooth)

More complete models

$$
\begin{cases}
\frac{\partial}{\partial t} n + \mathrm{div}\big(nv\big) = nG\big(p(x,t)\big), \\
-\nu \Delta v + v = -\nabla p, \qquad p = n^\gamma,
\end{cases}
$$

visco-elastic fluid

Why tissues are under-going visco-elastic law ?

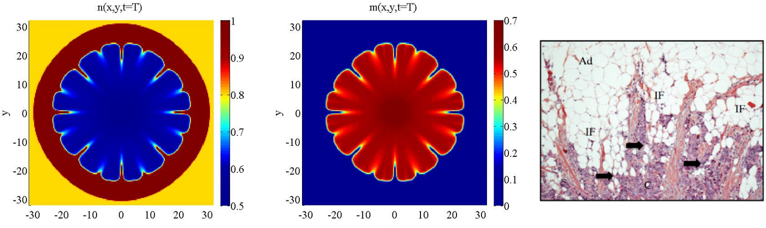


Effect of viscosity (pressure jump)

More complete models

$$\begin{cases} \frac{\partial}{\partial t} n_P + \operatorname{div}\big(\mu_P n_P v\big) = n_P G\big(p(x,t)\big) - \alpha n_P, \\ \frac{\partial}{\partial t} n_Q + \operatorname{div}\big(\mu_Q n_Q v\big) = \alpha n_P - d n_Q, \\ v = -\nabla p, \qquad p = (n_P + n_Q)^\gamma \end{cases}$$

- n_P = proliferative cells
- n_Q = quiescent cells



Credit for picture A. Lorz, T. Lorenzi (Saffman-Taylor instability ? growth is important)

Conclusions

- Sophisticated mathematical models are effectively used in biology and medicine
- They lead to various mathematical questions
  - Asymptotic analysis arises naturally because of the many scales
  - Systems of PDEs (unstability)
- **Challenges**
  - Variability
  - Adaptation

Thanks to my collaborators

F. Quiros, J.-L. Vazquez,

M. Tang, N. Vauchelet,

A. Lorz, T. Lorenzi,

D. Drasdo

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F. Quiros, J.-L. Vazquez, A. Mellet,

M. Tang, N. Vauchelet,

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THANK YOU