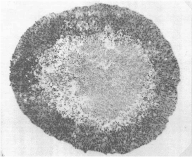
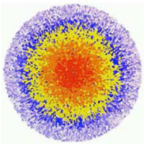
Mathematical models of living tissues and free boundary problem

Benoît Perthame

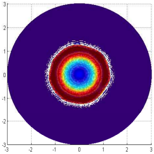


Suzerland et al , Cancer Res.,

Rotschild et al, The lancet,



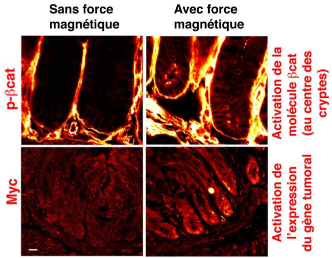
Byrne-Drasdo JMB,



M. Tang, Vauchelet

Introduction

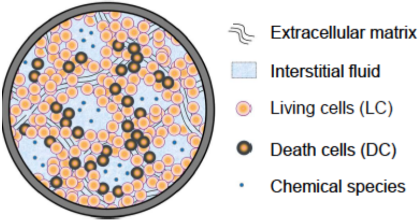
What is a living tissue ? A mechanistic view



- Physicis/Mechanics
  Benamar, Drasdo, Preziosi,
  Joanny-Prost-Jüllicher,
  Goriely, Ciarletta, E. Farge

- Mathematical models
  Byrne-Chaplain, Main, Garcke
  Lowengrub et al, Friedman,
  Hubert, O. Saut et al

- Pressure, contact inhibition
and carrying capacity



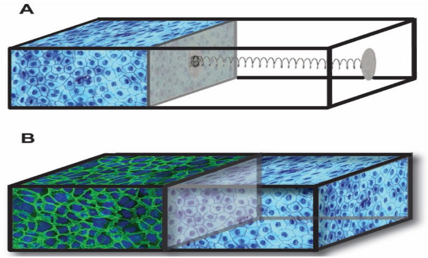
Introduction

- 20-30 years ago, a tumor was considered as an invasion of Fisher/KPP type

$$\frac{\partial}{\partial t} n - \Delta n = rn\,(1 - \frac{n}{K})$$

This is no longer the case

- **Pressure and contact inhibition :** Byrne-Drasdo, Joanny-Prost-Jülicher... 'Homeostatic pressure' p_M



Credit. M. Basan, SU and Institut Curie

Compressible multispecies model

A class of models are compressible

- Number density of various types of cells $n_1, n_2, \dots$
- Fluid mechanics view : pressure p
- Darcy's rule, velocity $v = -\nabla p$

Papers by Chaplain, Byrne, Sherratt, Friedman,...

$$\begin{cases} \frac{\partial}{\partial t} n_1 + \mathrm{div}\big(n_1 v\big) = n_1 F_1\big(p(x,t)\big) + n_2 G_1(p(x,t)) \\ \\ \frac{\partial}{\partial t} n_2 + \mathrm{div}\big(n_2 v\big) = n_1 F_2\big(p(x,t)\big) + n_2 G_2(p(x,t)) \\ \\ v = -\nabla p, \qquad p = \Pi(n) = (n_1 + n_2)^{\gamma} \end{cases}$$

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

Incompressible multispecies model

But another class by Maini, Lowengrub, Colin-Grenier-Saut..

$$\begin{cases} \frac{\partial}{\partial t} n_1 + \mathrm{div}\big(n_1 v\big) = n_1 F_1\big(p(x,t)\big) + n_2 G_1(p(x,t)) \\ \\ \frac{\partial}{\partial t} n_2 + \mathrm{div}\big(n_2 v\big) = n_1 F_2\big(p(x,t)\big) + n_2 G_2(p(x,t)) \\ \\ v = -\nabla p, \end{cases}$$

And add incompressibility

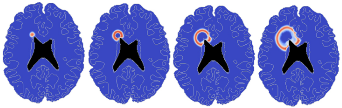
$$n := n_1 + n_2 = 1$$

$$\mathrm{div}\, v = -\Delta p = n_1 F\big(p(x,t)\big) + n_2 G(p(x,t)),$$

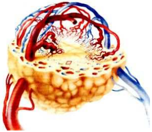
$$F = F_1 + F_2, \qquad\qquad G = G_1 + G_2.$$

Incompressible multispecies model

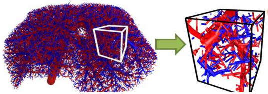
Image based predictions : Swanson, Ayache, Colin-Saut..., Cristini-Wang etc



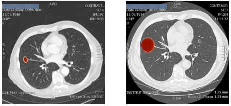
- Liquid/solid tumors
- Active cells



- Immune system, metastasis, resistance to treatment
- Nutrients/drug
- Angiogenesis (new vasculature brings nutrients)



- Healthy, quiescent, necrotic cells
- From molecules to entire organ



- Extra-cellular matrix
- Models of mixture, multiphase flows

L. Preziosi et al, Titi-Lowengrub-Zhao

Credit for pictures : INRIA team MC2 (Bordeaux)

Organisation of the talk

What is the connection ?

Incompressible limit

1. **Single equation**
2. **Nutrients, chemotaxis**
3. **Multispecies**

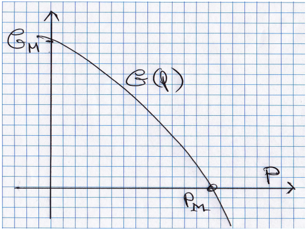
Single equation, compressible

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

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

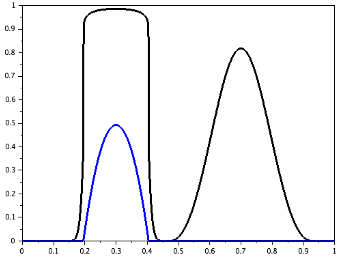
$G'(p) < 0$

$G(p_M) = 0$

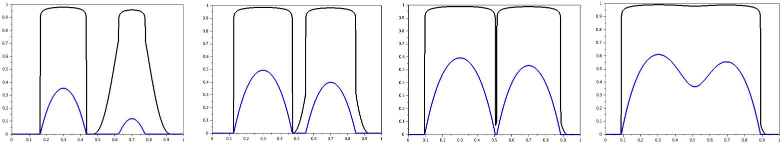


$$\frac{\partial}{\partial t} n(t) \geq -\frac{K}{t} e^{-\gamma r_G t}$$ (Aronson-Bénilan estimate)

Single equation, compressible



Black : cell density ; Blue : pressure

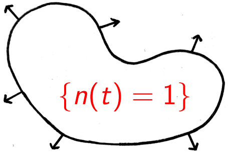


Traveling wave : see Dalibard, Lopez, Perrin

Free boundary/incompressible models

Geometric version

Tumor domain $\Omega(t)$



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

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

with the pressure

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

Also $p = a\kappa$, See A. Friedman, S. Cui, Escher

Free boundary/incompressible models

Two approaches : cell density and free boundary. Which relation ?

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

The stiff pressure law the limit, $\gamma \to \infty$

Hele-Shaw

Bénilan, Igbida, Gil, Quiros, Vazquez, X. Chen *et al*, Caffarelli, Friedman, Escher, Cui,...

Obstacle problem : Kim, Mellet

Viscosity solutions : I. Kim et al.

Optimal transportation : Dambrine, Maury, Santambrogio (congestion)

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

$$n_\gamma \to n_\infty \le 1, \quad p_\gamma \to p_\infty \le p_M$$

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

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

Free boundary/incompressible models

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Theorem The weak solution is unique.

Method à la Oleinik, by 'entropy' see N. Igbida

Free boundary/incompressible models

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Theorem The weak solution is unique.

Theorem (complementarity relation) : We also have

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

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

All the difficulty is when $p_\infty = 0$!

Proof :

$$\frac{\partial}{\partial t}p_\gamma - |\nabla p_\gamma|^2 = \gamma\; p_\gamma\left[\Delta p_\gamma + G\left(p_\gamma(x,t)\right)\right]$$

(i) Uniform L^∞, BV estimates for n_γ, p_γ

(ii) L^2_x estimates for ∇p_γ

(iii) $|\nabla p_\gamma|^2 \to |\nabla p_\infty|^2$, $\nabla p_\gamma \to \nabla p_\infty$ strongly in L^2

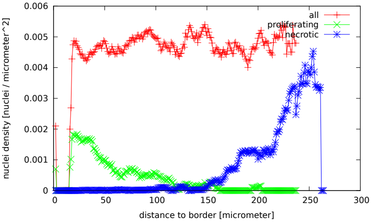
is equivalent to establishing the relation

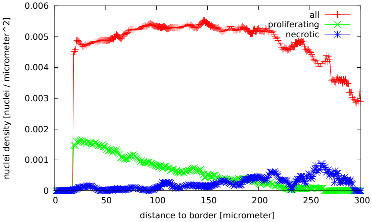
$$p_\infty\left(\Delta p_\infty + G(p_\infty)\right) = 0.$$

Follows from Aronson-Bénilan estimate

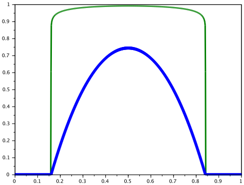
$$\Delta p + G(p) \geq -\frac{C}{t}e^{-\gamma r_G t}$$

Free boundary/incompressible models





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



When $n^0 = \mathbb{1}_{\{\Omega^0\}}$ then $n(t) = \mathbb{1}_{\{\Omega(t)\}}$

Organisation of the talk

1. Single equation
2. Nutrients, chemotaxis
3. Multispecies

Model with nutrient

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

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

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

Theorem (N. David, BP)

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

Proof. Two new ideas :

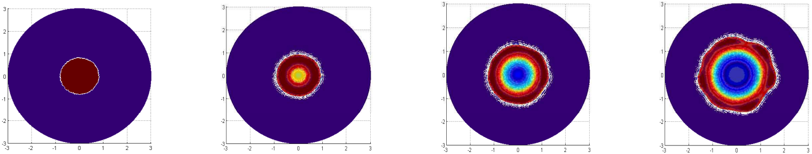
- L^2 Aronson-Bénilan estimate,
- $\nabla p \in L^4_{t,x}$ uniform in γ (see also Alazard-Bresch)

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



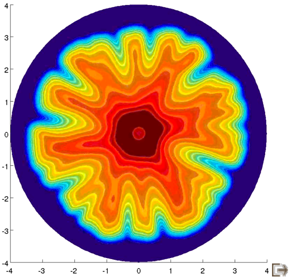
effect of nutrient consumption. Credit for pictures M. Tang, N. Vauchelet

Model with nutrient

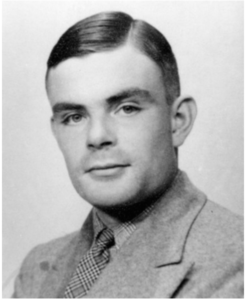
Closely related to instability in thermo-chemical reactions

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

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



Credit for picture N. Vauchelet



Chemotaxis

$$\begin{cases} \frac{\partial}{\partial t} n - \mathrm{div}\big(n \nabla p\big) + \mathrm{div}\big(n \nabla S\big) = 0, \qquad p = n^{\gamma}, \\ -\Delta S = n, \end{cases}$$

Theorem (Hai-Liang Li, Qingyou He, BP)

p_γ and ∇p_γ converge strongly

and

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

and the complementarity condition holds

$$p_\infty [\Delta p_\infty + n_\infty] = 0.$$

Organisation of the talk

1. Single equation
2. Nutrients, chemotaxis
3. Multispecies

Multispecies model

$$\begin{cases} \frac{\partial}{\partial t} n_1 + \operatorname{div}\big(n_1 v\big) = n_1 F_1\big(p(x,t)\big) + n_2 G_1(p(x,t)) \\ \frac{\partial}{\partial t} n_2 + \operatorname{div}\big(n_2 v\big) = n_1 F_2\big(p(x,t)\big) + n_2 G_2(p(x,t)) \\ v = -\nabla p, \qquad p = (n_1 + n_2)^\gamma \end{cases}$$

- Seems easy : $n = n_1 + n_2$ satisfies

$$\frac{\partial}{\partial t} n - \operatorname{div}\big(n \nabla n^\gamma\big) = n_1 F(p) + n_2 G(p)$$

Difficulties

- No BV bounds on $n_1, \ n_2, \ p$ (except 1D)

$$\frac{\partial}{\partial t} p = |\nabla p|^2 + \gamma p \Delta p + \gamma p R(n_1, n_2, p)$$

- For the nonlinear term, we need compactness for either n_i or $v = -\nabla p \in L^2$

Multispecies model

$$\begin{cases} \frac{\partial}{\partial t} n_1 + \mathrm{div}\big(n_1 v\big) = n_1 F_1\big(p(x,t)\big) + n_2 G_1(p(x,t)) \\ \frac{\partial}{\partial t} n_2 + \mathrm{div}\big(n_2 v\big) = n_1 F_2\big(p(x,t)\big) + n_2 G_2(p(x,t)) \\ v = -\nabla p, \qquad p = (n_1 + n_2)^\gamma \end{cases}$$

Existence

- Smooth and $n_1 + n_2 > 0$ (Bertsch, Hilhorst, Mimura et al, 2012)
- dim 1, BV est. for $\frac{n_1}{n}$, (Carrillo, Santambrogio et al, 2018) :

$$\frac{\partial}{\partial t} \frac{n_1}{n_1 + n_2} + v \frac{\partial}{\partial x} \frac{n_1}{n_1 + n_2} = R(n_1, n_2)$$

- Any dim. (Gwiazda, BP, Swierczewska-Gwiazda, 2019) using Aronson-Bénilan estimate in L^2 when $F(0) = G(0)$

Multispecies model

$$\begin{cases} \frac{\partial}{\partial t} n_1 + \mathrm{div}\big(n_1 v\big) = n_1 F_1\big(p(x,t)\big) + n_2 G_1\big(p(x,t)\big), \\ \frac{\partial}{\partial t} n_2 + \mathrm{div}\big(n_2 v\big) = n_1 F_2\big(p(x,t)\big) + n_2 G_2\big(p(x,t)\big), \\ v = -\nabla p, \qquad p = (n_1 + n_2)^\gamma \end{cases}$$

New approaches appeared recently

- Matts Jacobs : A Lagrangian approach + Aronson-Benilan in L^2
  - Existence
  - Limit $\gamma \to \infty$ when initial data is an indicator function
- Price, Xiansheng Xu ; Jian-Guo Liu For simplified RHS
  - Existence (compactness of ∇p_γ)
  - Limit $\gamma \to \infty$

    $n_{i,\gamma}$ converge weakly, ∇p_γ converges strongly
- This method is extended by Noemi David to general RHS (compensated compactness)

Compactness of ∇p_γ

Idea of Price, Xu, Liu, David's method

$$\frac{\partial}{\partial t} n_\gamma - \mathrm{div}\big(n_\gamma \nabla p_\gamma\big) = n_\gamma G\big(p_\gamma(x,t)\big), \qquad p = n^\gamma$$

$$\frac{\partial}{\partial t} n_\gamma - \frac{\gamma}{\gamma+1} \Delta n_\gamma^{\gamma+1} = n_\gamma G\big(p_\gamma(x,t)\big), \qquad p = n^\gamma$$

Compactness of ∇p_γ

$$\frac{\partial}{\partial t} n_\gamma - \mathrm{div}\big(n_\gamma \nabla p_\gamma\big) = n_\gamma G\big(p_\gamma(x,t)\big), \qquad p = n^\gamma$$

$$\frac{\partial}{\partial t} n_\gamma - \frac{\gamma}{\gamma+1} \Delta n_\gamma^{\gamma+1} = n_\gamma G\big(p_\gamma(x,t)\big), \qquad p = n^\gamma$$

$$\frac{\partial}{\partial t} n_\infty - \Delta p_\infty = ...$$

$$(\frac{\gamma}{\gamma+1} p_\gamma - p_\infty)\frac{\partial}{\partial t}(n_\gamma - n_\infty) - (\frac{\gamma}{\gamma+1} p_\gamma - p_\infty)\Delta(\frac{\gamma}{\gamma+1} p_\gamma - p_\infty) = ...$$

$$\int |\nabla(\frac{\gamma}{\gamma+1} p_\gamma - p_\infty)|^2 + ... = 4 \text{ terms}$$

Compactness of ∇p_γ

$$\left(\frac{\gamma}{\gamma+1}p_\gamma - p_\infty\right)\frac{\partial}{\partial t}(n_\gamma - n_\infty) - \left(\frac{\gamma}{\gamma+1}p_\gamma - p_\infty\right)\Delta\left(\frac{\gamma}{\gamma+1}p_\gamma - p_\infty\right) = ...$$

$$\int \left|\nabla\left(\frac{\gamma}{\gamma+1}p_\gamma - p_\infty\right)\right|^2 + ... = 4 \text{ terms} + ...$$

$$p_\gamma \frac{\partial}{\partial t} n_\gamma = \frac{1}{\gamma+1}\frac{\partial}{\partial t} n_\gamma^{\gamma+1} \to 0$$

$$p_\infty \frac{\partial}{\partial t}(n_\gamma - n_\infty) \to 0 \qquad \text{enough to use weak CV of } \nabla p_\gamma$$

$$p_\gamma \frac{\partial}{\partial t} n_\infty \to p_\infty \frac{\partial}{\partial t} n_\infty = 0 \qquad \text{weak CV enough}$$

Organisation of the talk

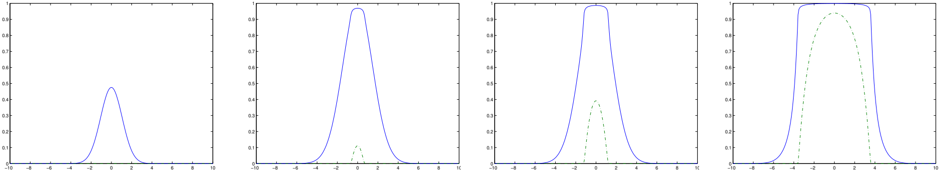
1. Single equation
2. Nutrients, chemotaxis
3. Multispecies
4. **Related problems**

Model with active movment

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

Hele-Shaw limit : We still have

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

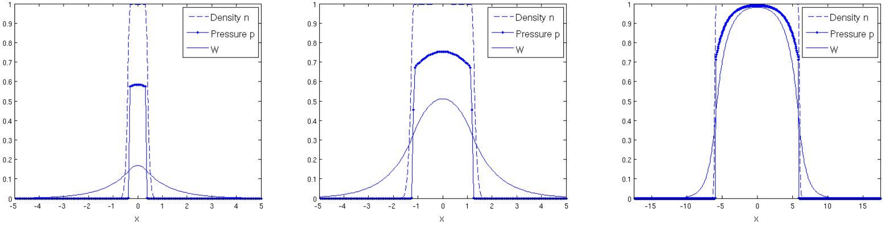


Effect of active movement (cell density is smooth)

Effect of viscosity

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

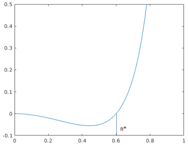
visco-elastic fluid



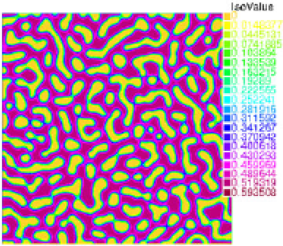
Multiphase models (Cahn-Hilliard)

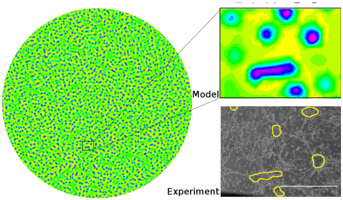
$$c = \frac{n_1}{n_1 + n_2} \qquad \text{(concentration)}$$

$$\begin{cases} \frac{\partial c}{\partial t} - \mathrm{div}\big(c(1-c)^2 \nabla p\big) = c(1-c)G(\ldots), \\ p = W'(c) - \delta \Delta c \end{cases}$$



Wise, Lowengrub, Miranville, Poulain, Benamar, Agosti, Ciarletta, Graselli, Garke, Roger, Lam, Rocca...





Computations by Agosti, Ciarletta et al (Poli. Milano)

Conclusions

- Modeling of tissue growth is an interdisciplinary subject
- Recent progresses on the incompressible limit of porous media flow
- Systems of PDEs (unstability)
- Multiphase Cahn-Hilliard approach under investigation

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