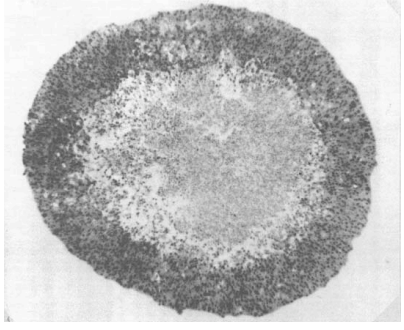
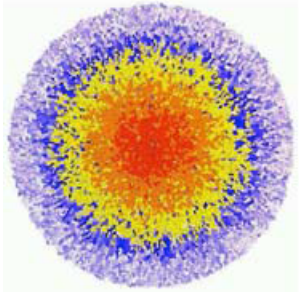
Mathematical aspects of tumor growth and therapy

Benoît Perthame

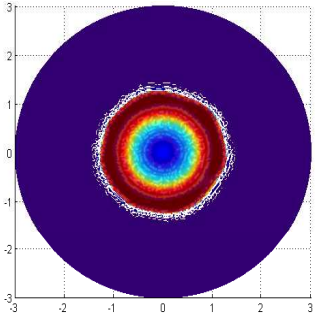


Sherratt-Chaplain JMB 43,

Rotschild et al The lancet,



Byrne-Drasdo JMB,



Tang, Vauchelet

A public health problem

- In 1971, U.S. President Richard Nixon, signed the The National Cancer Act, called 'the war on cancer'

- 1600 Americans die every day from cancer

- since 2004, cancer is the first cause of mortality in France (34% among men, 25% among women)

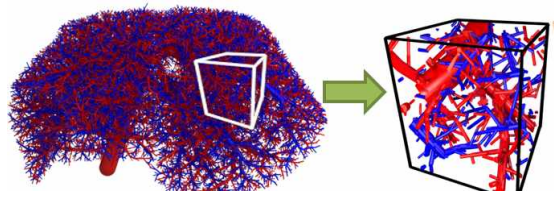
- In developed countries, cancer is the second cause of mortality after hearth deseases

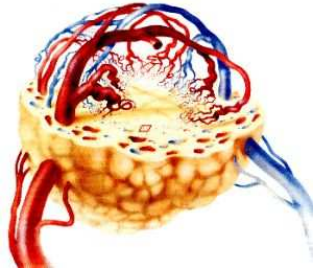
A public health problem

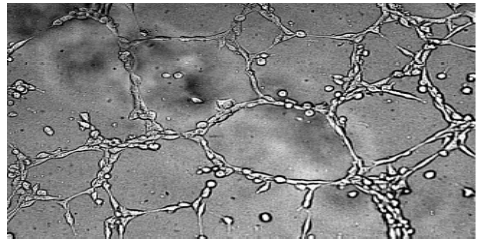
- In 1971, U.S. President Richard Nixon, signed the The National Cancer Act, called 'the war on cancer'
- 1600 Americans die every day from cancer
- since 2004, cancer is the first cause of mortality in France (34% among men, 25% among women)
- In developed countries, cancer is the second cause of mortality after hearth deseases

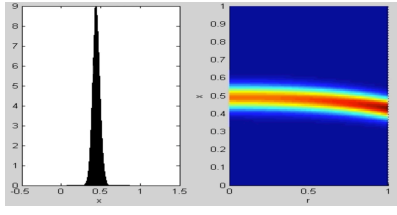
Many faces of the problem

- Solid and liquid tumors
- From molecules to entire organ
- Cell cycle/Circadian rhythms/Chronotherapeutics
- Angiogenesis (new vasculature brings nutrients)
- Immune system
- Metastasis
- Resistance to treatment









Organisation of the talk

1. Cell density models
2. Free boundary problem
3. The Hele-Shaw asymptotics

4. Resistance and Darwinian evolution
5. Dynamic of Dirac concentrations

Models of cell densities

Mechanical only model :

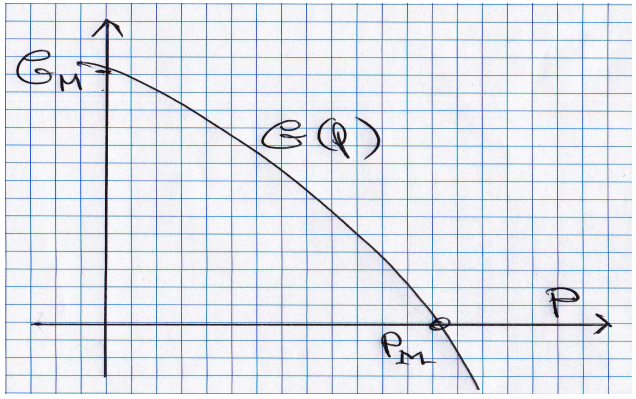
$n(x,t) =$ population density of tumor cells

$$\begin{cases} \frac{\partial}{\partial t} n + \operatorname{div}(nv) = nG\big(p(x,t)\big), & x \in \mathbb{R}^d,\ t \geq 0, \\ v = -\nabla p(x,t), & p(x,t) \equiv \Pi(n) := n^\gamma, \quad \gamma > 1 \end{cases}$$

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

Modeling : Benamar, Byrne, Chaplain, Drasdo, Joanny-Prost-Jülicher...

'homeostatic pressure' p_M



Models of cell densities

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Properties : $e^{-G_M t} n(x,t) \in L^\infty_t(L^1_x)$, $p(x,t) \leq p_M$

$$e^{-G_M t} \frac{\partial n(x,t)}{\partial x_i} \in L^\infty_t(L^1_x),$$

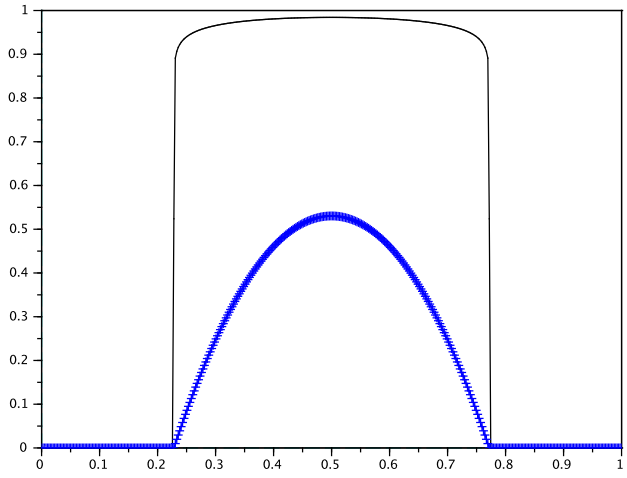
$$\frac{\partial}{\partial t} n^0 \geq 0 \ \Rightarrow\ \frac{\partial}{\partial t} n(t) \geq 0 \qquad (BV \text{ estimate})$$

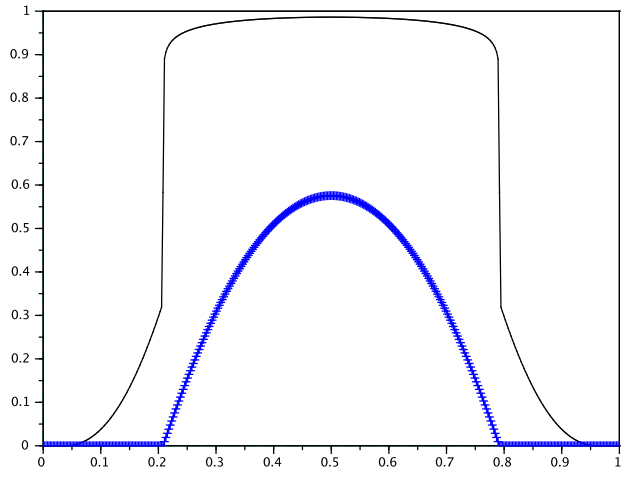
Growing with stability

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

Models of cell densities

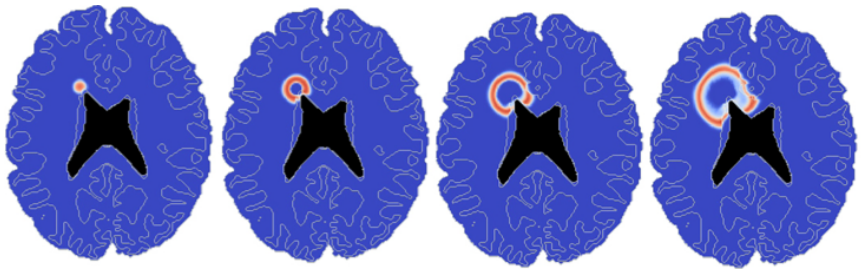
$$\begin{cases} \frac{\partial}{\partial t} n + \operatorname{div}(nv) = nG\big(p(x,t)\big), & x \in \mathbb{R}^d,\ t \geq 0, \\ v = -\nabla p(x,t), & p(x,t) \equiv \Pi(n) := n^\gamma, \quad \gamma > 1 \end{cases}$$



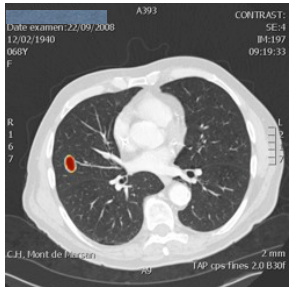


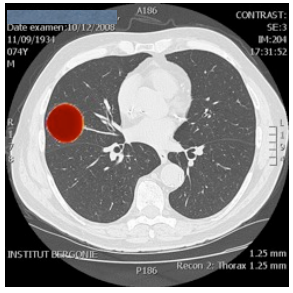
Models of cell densities

- Active cells
- Nutrients
- Quiescent, necrotic cells



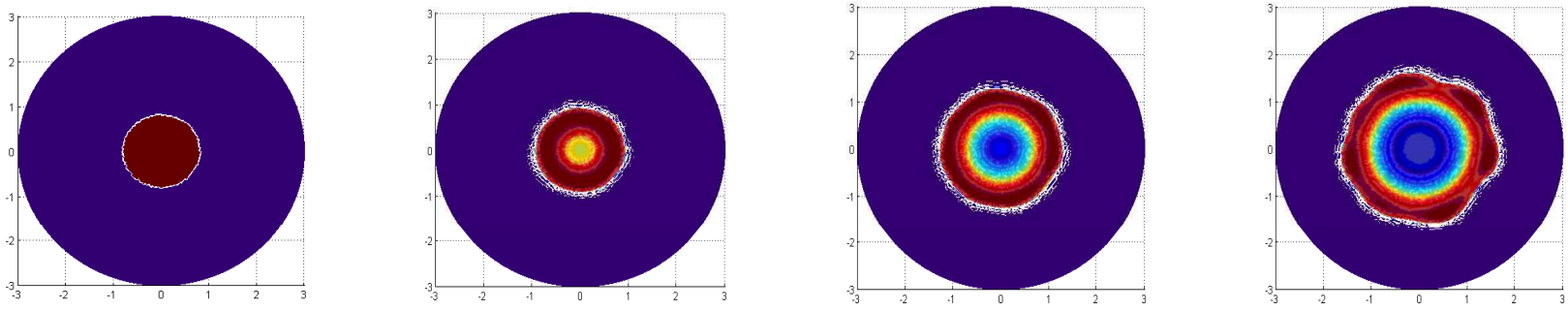
- Models of mixture, multiphase flows (L. Preziosi et al, Titi-Lowengrub-Zhao)
- Healthy cells
- Extra-cellular matrix
- Angiogenesis





Credit for pictures : INRIA team MC2 (Bordeaux)

Models of cell densities



effect of nutrient consumption

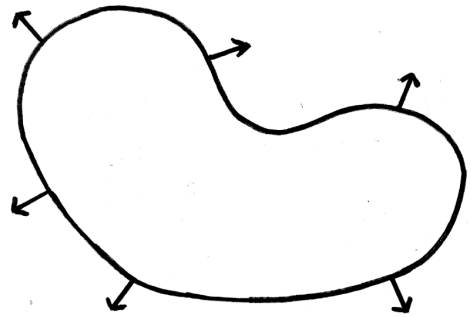
$$\begin{cases} \frac{\partial}{\partial t} n + \operatorname{div}(nv) - \overbrace{\nu \Delta n}^{\text{active movement}} = nG\big(p(x,t), \underbrace{c(x,t)}_{\text{nutrient}}\big), \\ -\nu \Delta v + v = -\nabla p, \qquad \text{visco-elastic fluid}, \\ \frac{\partial}{\partial t} c - \Delta c + \underbrace{R(n)c = c_B}_{\text{nutrient consumption/release}} \end{cases}$$

Necrotic core, instabilities

Incompatible with $\frac{\partial}{\partial t} n(t) \geq 0$

Free boundary models

Spatial 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

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

- Greenspan 1972,
- Lowengrub,..., Cristini, Nonlinearity 2010
- Roose, Maini, Chapman (SIAM review 2007),
- Friedman, DCDS(B) 2004

From cell densities to free boundary

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

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

The Hele-Shaw limit is the limit $\gamma \to \infty$
Stiff pressure law

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

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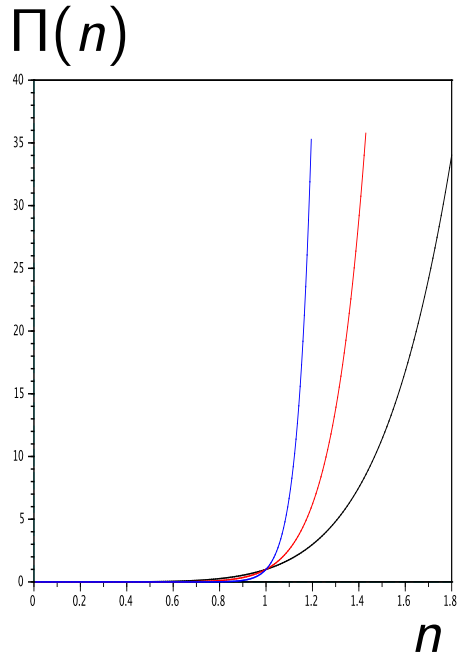
Theorem (Hele-Shaw limit) : As $\gamma \to \infty$

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

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

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



Remarks

1. Unique solution to the equation on n_∞ (Oleinik, Crowley)
2. This is a *weak formulation* of the geometric problem

From cell densities to free boundary

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

Theorem (complementary relation) : We also have

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

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

Remark

1. More difficult to establish, proof uses $\frac{\partial n}{\partial t} \geq 0$
2. However the equation on p_∞ does not predict the set

$$\Omega(t) = \{\ p_\infty(x,t) > 0\} \sim \{\ n_\infty(x,t) = 1\}$$

3. Not an obstacle problem
4. There is a notion of viscosity solution (I. Kim)

From cell densities to free boundary

Proof :

$$\frac{\partial}{\partial t} p_\gamma - n_\gamma p'(n_\gamma) \Delta p_\gamma - |\nabla p_\gamma|^2 = n_\gamma p'(n_\gamma) G\big(p_\gamma(x,t)\big)$$

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

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

(ii) L^2_x estimates for p_γ

(iii) $$|\nabla p_\gamma|^2 \to |\nabla p_\infty|^2 \qquad \text{strongly}$$

is equivalent to establishing the relation

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

This follows from $\frac{\partial}{\partial t} n_\infty \geq 0$.

From cell densities to free boundary

The geometric form of the Hele-Shaw problem follows when

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

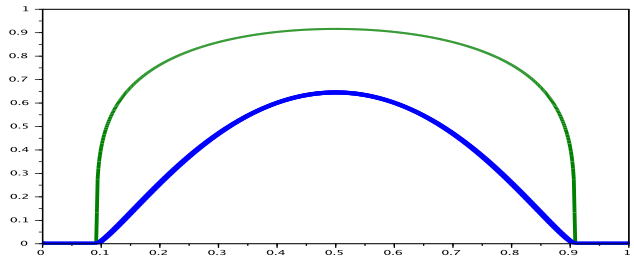
As long as one can define a smooth set $\Omega(t)$ such that

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

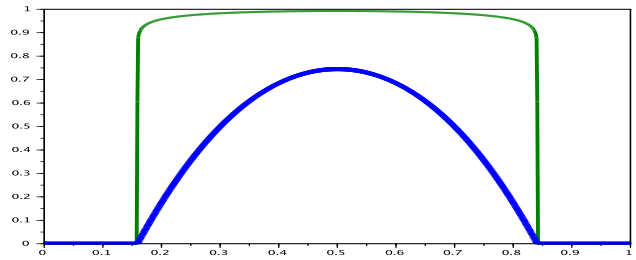
the equation on n_∞ is equivalent to say that $\partial\Omega(t)$ is moving with the normal velocity $v = -\nabla p_\infty$, and

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

From cell densities to free boundary



Left : $\gamma = 4$

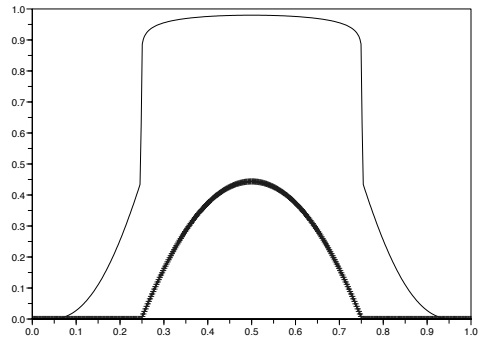


Right : $\gamma = 40$

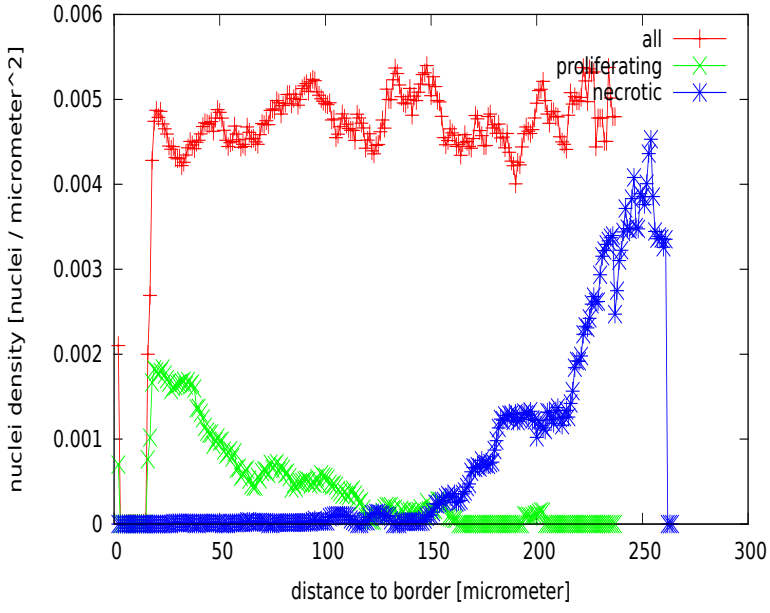
$$\begin{cases} \frac{\partial}{\partial t} n_\infty - \operatorname{div}\left(n_\infty \nabla p_\infty\right) = n_\infty G\left(p_\infty\right), \\ p_\infty = 0 \quad \text{for} \quad n_\infty(x,t) < 1. \end{cases}$$

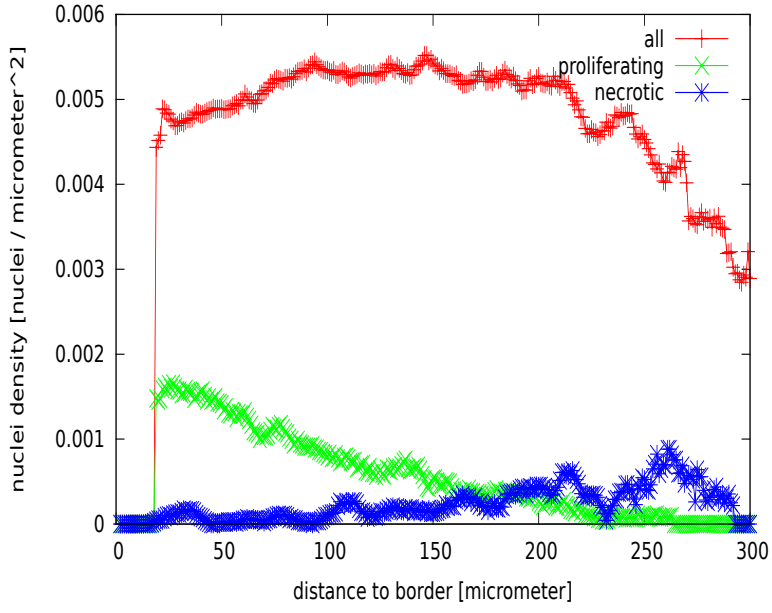
In the region $\{0 < n_\infty < 1\}$, $p_\infty = 0$ and

$$\frac{\partial}{\partial t} n_\infty = n_\infty G(0)$$



From cell densities to free boundary





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

Organisation of the talk

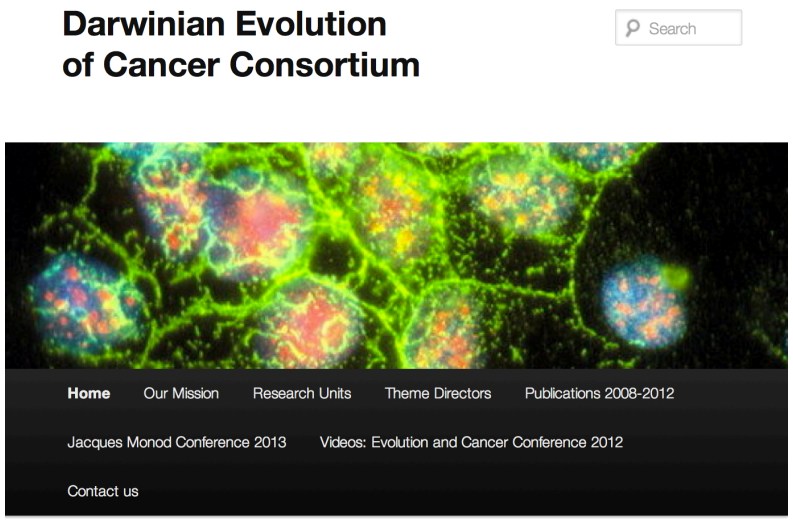
1. Cell density models
2. Free boundary problem
3. The Hele-Shaw asymptotics

4. Resistance and Darwinian evolution

5. Dynamic of Dirac concentrations

Resistance to therapy : Motivations

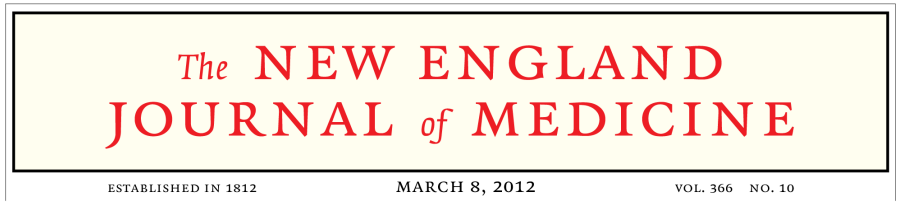
- 40% of cancers escape to therapy
- cells adapt and become resistant to drug(s)
- Tumor as an ecological system



http ://www.darevcan.univ-montp2.

Resistance to therapy : Motivations

Question 1. Heterogeneity Ecological models are compatible with the **'competitive exclusion principle'**



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Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc., Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc., Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc., Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D., Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D., Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.

Question 2. Adaptive therapy ? Use competition to optimize therapy

Resistance to therapy

$$\frac{\partial}{\partial t} n(y,t) = \Big[\overbrace{r(y)}^{\text{reproduction rate}} - \overbrace{d(y)\varrho(t)}^{\text{competition, apoptosis}} - \overbrace{c(t)\mu(y)}^{\text{effect of drug}} \Big] n(y,t)$$

$$\varrho(t) = \int n(y,t)\,dy \qquad \text{total number of cells}$$

- $y =$ genetic expression for a 'resistance phenotype'
- $y = 0$ high proliferation in a normal environment,
- $y = 1$ high resistance (lower reproduction without drug)

$$r' < 0, \qquad d' < 0, \qquad \mu' < 0.$$

$$\frac{\partial}{\partial t} n(y,t) = \Big[\underbrace{\frac{r(y)}{1 + c_S(t)}}_{\text{cytostatic drug}} - d(y)\varrho(t) - \underbrace{c_T(t)\mu(y)}_{\text{cytotoxic drug}} \Big] n(y,t) + \underbrace{\varepsilon \Delta n}_{\text{mutations}}$$

Resistance to therapy

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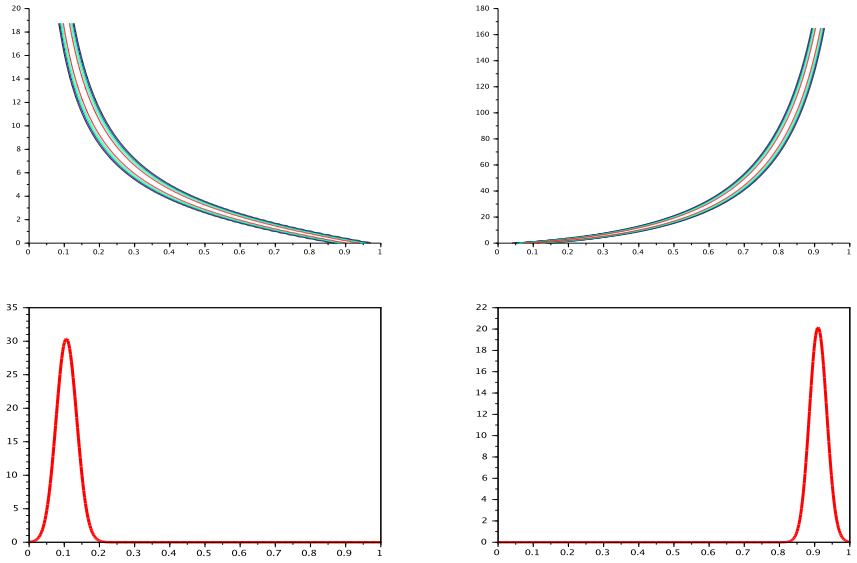
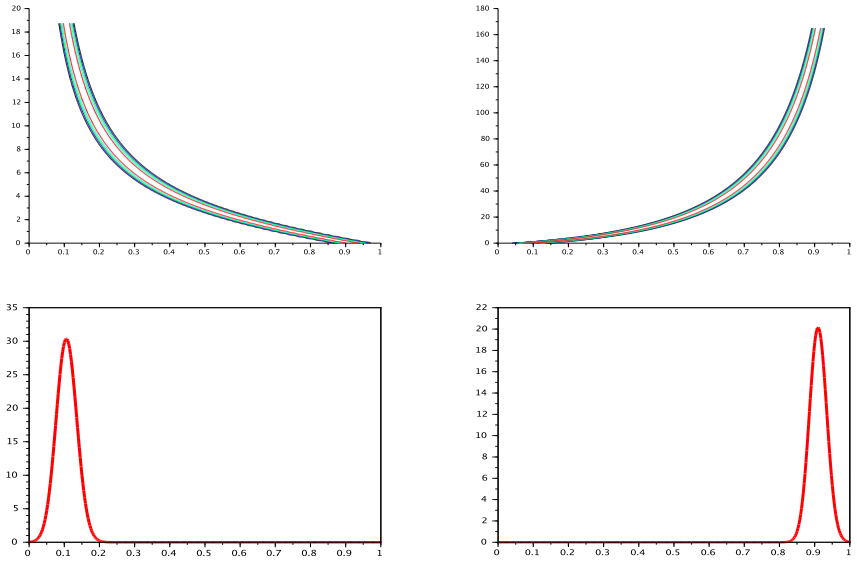
Resistance to therapy



No therapy With Therapy

This is compatible with the competitive exclusion principle

Resistance to therapy



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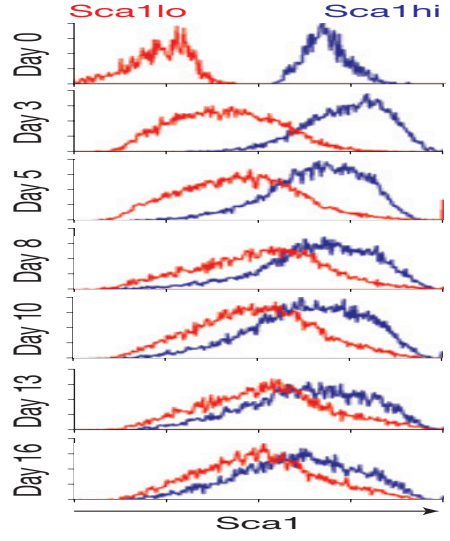
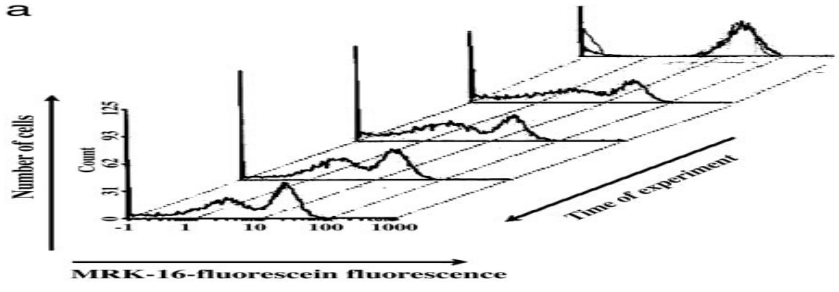


Pina et al, Nature CellBiology 2012



Levchenko et al, PNAS 2005. In vitro. Expression of P-gp measured by fluorescence

Resistance to therapy

To explain this observation we rescale

$$\varepsilon \frac{\partial}{\partial t} n_\varepsilon(y,t) = \left[\frac{r(y)}{1+c_S} - d(y)\varrho_\varepsilon(t) - c_T\, \mu(y) \right] n_\varepsilon(y,t) + \varepsilon^2 \Delta n_\varepsilon$$

Theorem With technical assumptions

$$n_\varepsilon(y,t) \underset{\varepsilon \to 0}{\longrightarrow} \bar{\varrho}(t)\delta\big(y - \bar{y}(t)\big).$$

And there is no easy characterization of $\bar{\varrho}(t),\ \bar{y}(t)$

Method of proof : WKB (Barles, Evans, Fleming, Souganidis, level set : for reaction-diffusion equations)

$$n_\varepsilon(y,t) = e^{\frac{u_\varepsilon(y,t)}{\varepsilon}}$$

Remark Similar to a Gaussian concentrating to a Dirac mass

$$\frac{1}{\sqrt{2\pi}^d}\, e^{-\frac{|y-\bar{y}|^2}{2\varepsilon}} \to \delta(y-\bar{y})$$

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Theorem With technical assumptions and $n^0_\varepsilon \approx \bar\varrho^0 \delta\big(y - \bar y^0\big)$, then

$$n_\varepsilon(y,t) \underset{\varepsilon\to 0}{\longrightarrow} \bar\varrho(t)\delta\big(y-\bar y(t)\big).$$

And there is no easy characterization of $\bar\varrho(t),\ \bar y(t)$

Method of proof : WKB (Barles, Evans, Fleming, Souganidis, level set : for reaction-diffusion equations)

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Resistance to therapy

In the limit $u_\varepsilon \to u$, $\rho_\varepsilon \to \rho$ (uniformly locally) .

We obtain the 'Constrained Hamilton-Jacobi Equation' on (u, ρ)

$$\begin{cases} \dfrac{\partial}{\partial t} u = \dfrac{r(y)}{1 + c_S} - d(y)\varrho(t) - c_T\, \mu(y) + \left|\nabla u\right|^2 \\ \max\limits_y u(y,t) = 0 \end{cases}$$

$$\max_y u(y,t) = 0 = u(\bar{y}(t), t)$$

Remarks

1. $\rho(t)$ is the Lagrange multiplier (belongs to L^∞).

2. The dynamics of $\bar{y}(t)$ depends on the solution u to the constrained Hamilton-Jacobi equation

3. Uniqueness is known for THIS specific case

Resistance to therapy

Conclusion 1. Spatial organization generates heterogeneity

Let $0 < r < 1$ the radius of a spherical tumor

$$\begin{cases} \varepsilon \partial_t n_\varepsilon(r,y,t) = \left[r(y) c_\varepsilon(r,t) - d(y) \varrho_\varepsilon(r,t) - c_T \mu(y) \right] n_\varepsilon(r,y,t) \\ -\Delta_r c_\varepsilon(r,t) + \varrho_\varepsilon(r,t)\, c_\varepsilon(r,t) = 0, \qquad c(r=1,t) = c_B \\ \varrho_\varepsilon(r,t) = \int n_\varepsilon(r,y,t) dy \end{cases}$$

Theorem : As $\varepsilon \to 0$, we have

$$n_\varepsilon(r,y,t) \to \overline{\rho}(r,t) \delta\big(y - \overline{Y}(r,t)\big)$$

Resistance to therapy

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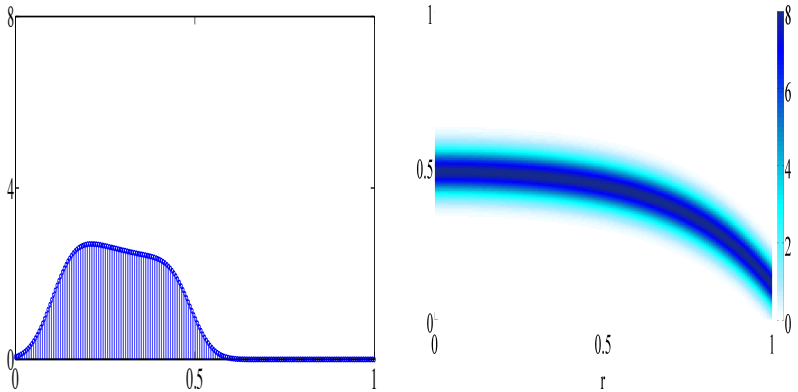
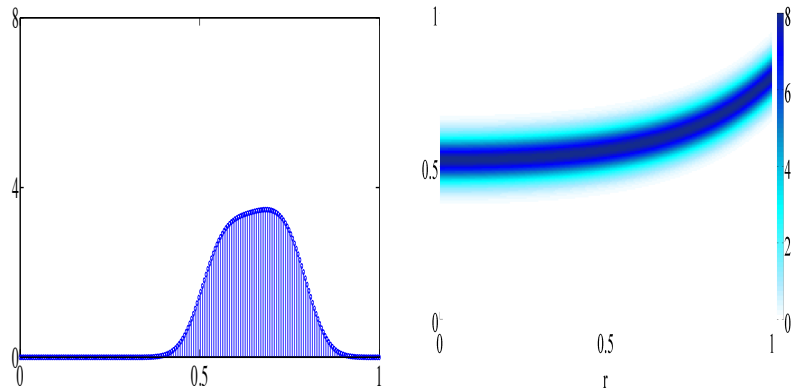


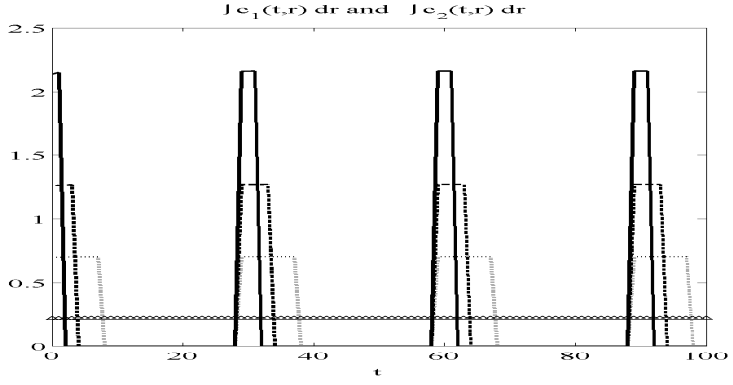
Without therapy
High heterogeneity

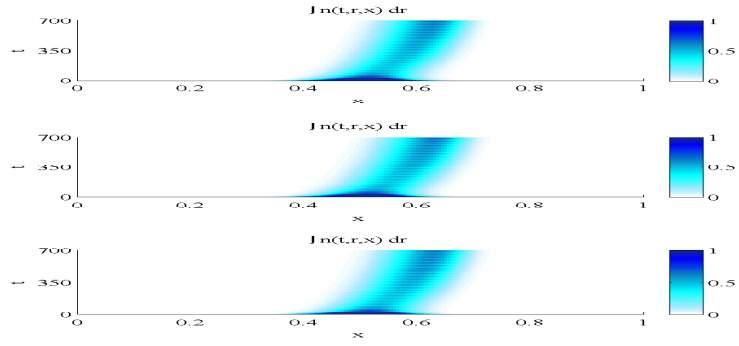


With therapy
Lower heterogeneity

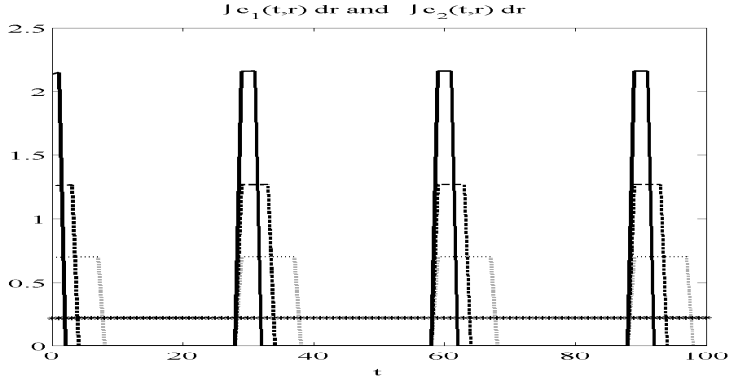
Resistance to therapy

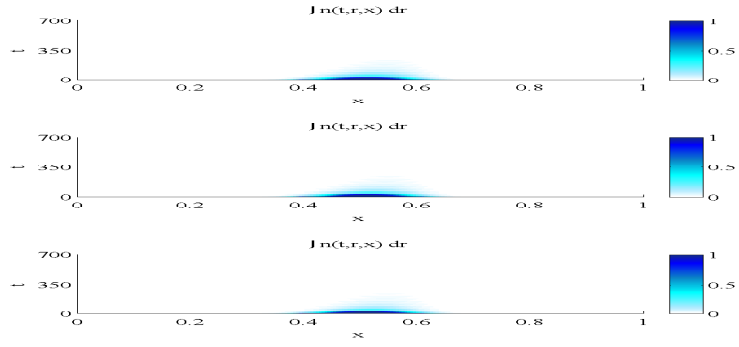
Conclusion 2. Optimal scheduling ?





constant cytotoxic, periodic cytostatic

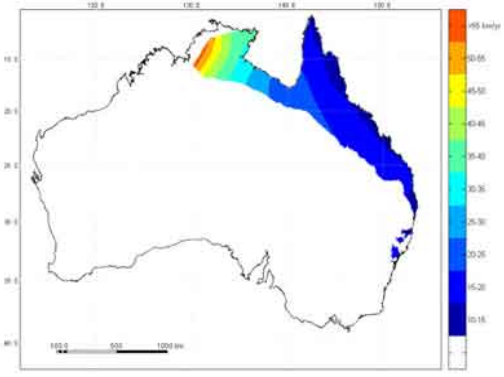




constant cytostatic, periodic cytotoxic

Conclusions

- Sophisticated mathematical models are effectively used in medicine
- They lead to various mathematical questions
- Asymptotic analysis arises naturally because of the many scales
- Directions
  - Systems of PDEs (unstable traveling waves, Hele-Shaw asymptotics)
  - Interaction space/Darwinian evolution ; accelarating fronts (V. Calvez, E. Bouin)



Thanks to my collaborators

F. Quiros, J.-L. Vazquez, M. Tang, N. Vauchelet, D. Drasdo

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Italo Calvino's novel 'Palomar' : ch. 'Il modello dei modelli'

By definition, there is nothing to be changed in a model,
it works to perfection, while as we can see very well,
it is reality where nothing works and all goes to pieces

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THANK YOU