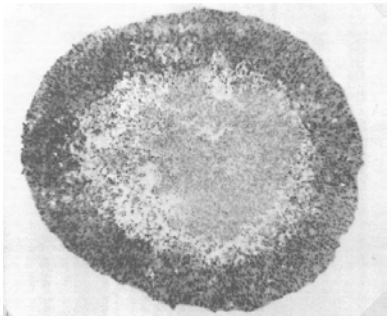
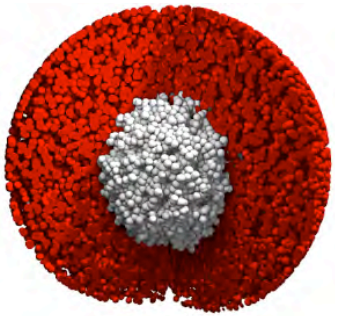
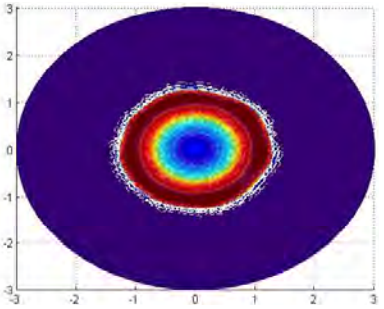
Mathematical aspects of tumor growth and therapy

Benoît Perthame



A public heath problem

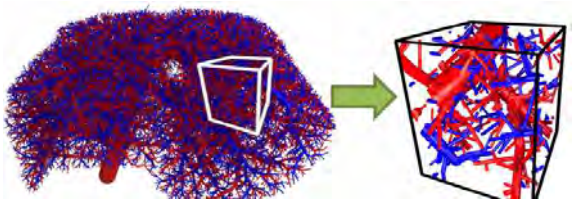
• In 1971, U.S. President Richard Nixon, signed the The National Cancer Act, called 'the war on cancer'

• 1500 Americans die every day from cancer

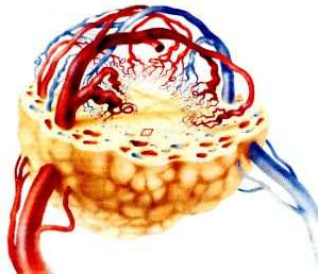
• since 2004, cancer is the first cause of mortality in France (34% among men, 25% among women)

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

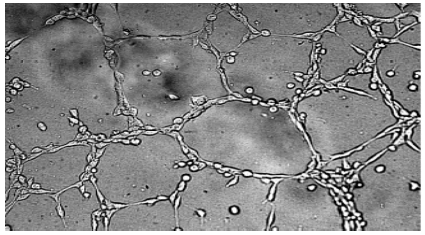
Many faces of the problem



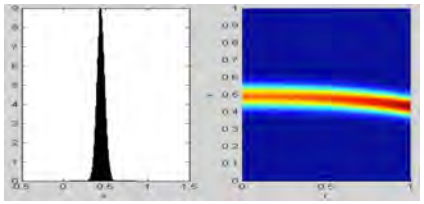
- Solid and liquid tumors
- From molecules to entire organ



- Cell cycle/Circadian rhythms/Chronotherapeutics
- Angiogenesis (new vasculature brings nutrients)



- Immune system
- 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

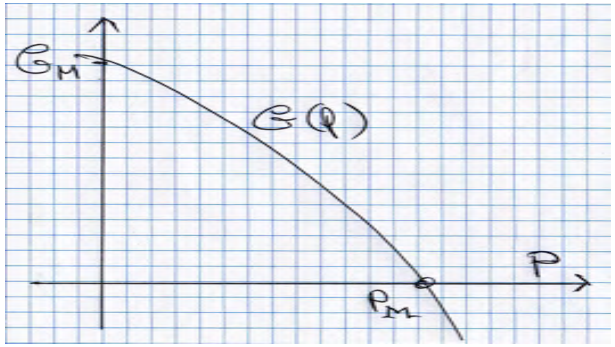
The purely mechanical model

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

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

Byrne, Chaplain, Benamar, Colin-Saut, Drasdo, Joanny-Prost-Jülicher...

'homeostatic pressure'



Models of cell densities

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

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

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

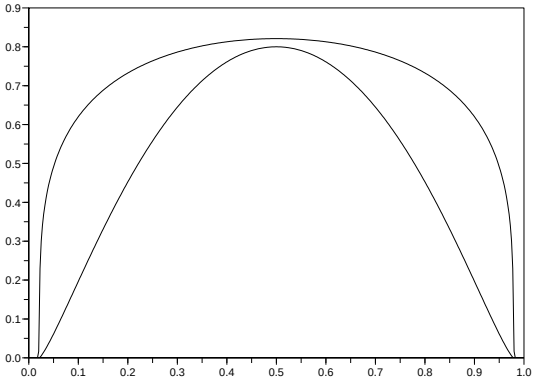
$$\frac{\partial}{\partial t} n^0 \geq 0 \ \Rightarrow\ \frac{\partial}{\partial t} n(t) \geq 0$$

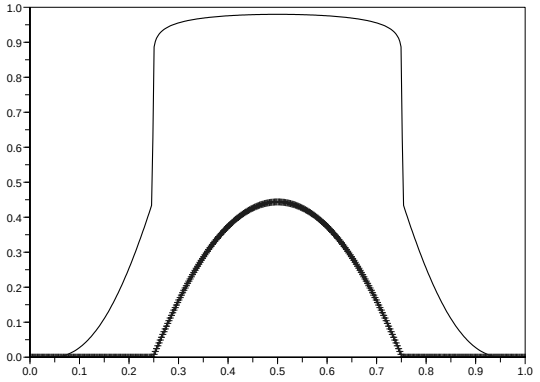
No necrotic core (early stage)

Stable

Models of cell densities

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



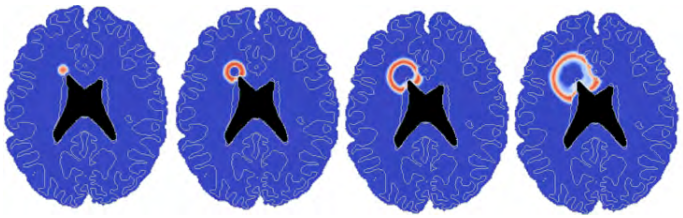


Models of cell densities

2. Active cells

3. Nutrients

4. Quiescent cells

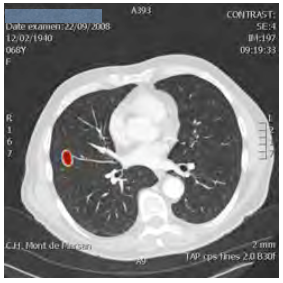


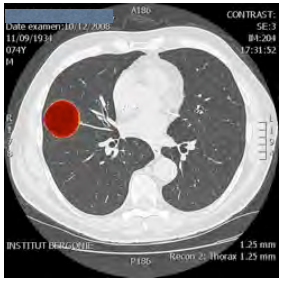
5. Models of mixture, multiphase flows (L. Peziosi-A. Tosin..., Titi-Lowengrub-Zhao)

5. Healthy cells

7. Extra-cellular matrix

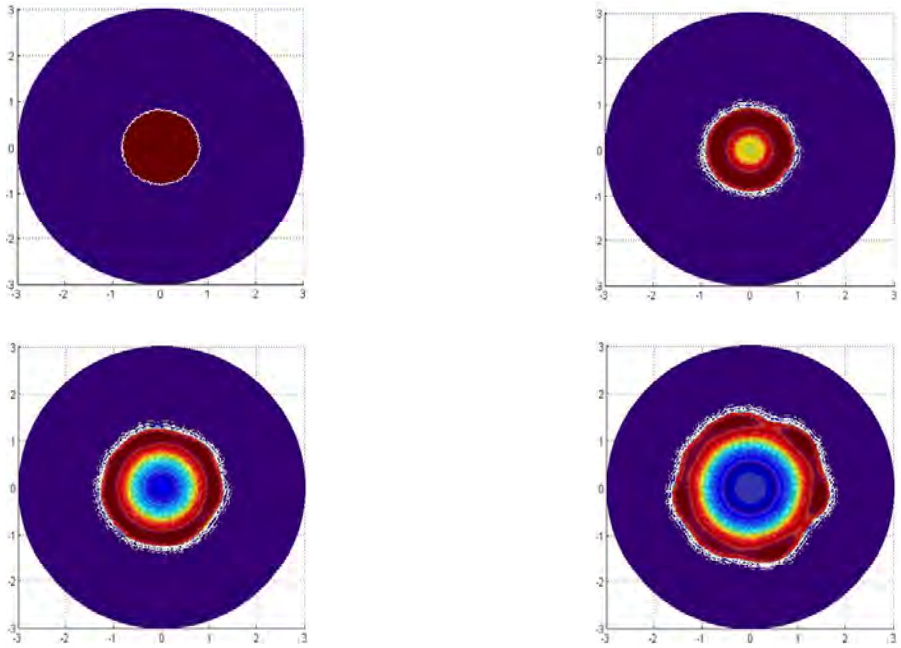
8. Angiogenesis





Credit for pictures : INRIA team MC2 (Bordeaux)

Models of cell densities

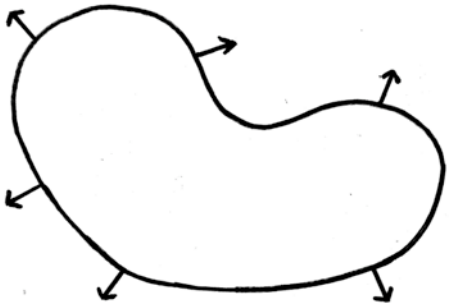


Effects of nutrients

$$\begin{cases} \frac{\partial}{\partial t} n + \mathrm{div}\big(nv\big) = nG\big(p(x,t), c(x,t)\big), \\ \frac{\partial}{\partial t} c - \Delta c + R(n)c = c_b \end{cases}$$

Free boundary models

Spatial domain $\Omega(t)$



Compute the pressure as

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

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

Free boundary models

Compute the pressure as

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

and Darcy's law

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

The tumor grows with the normal velocity

$$\dot{X}(t) = v\Big(X(t),t\Big), \qquad X(t) \in \partial\Omega(t).$$

Often, surface tension is included with κ the mean curvature

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

From cell densities to free boundary

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

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

The Hele-Shaw limit is the limit $\gamma \to \infty$
Stiif equation of state

Benilan, Caffarelli-Friedman, Gil, Quiros, Vazquez...etc

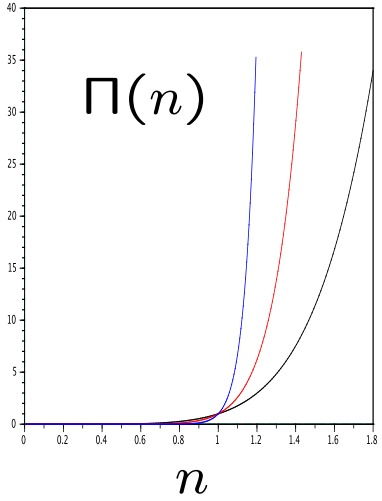
From cell densities to free boundary

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

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

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

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



Remarks

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

From cell densities to free boundary

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

Let us define $\Omega(t) = \{x \; s.\, t.\, p_\infty(x,t) > 0\}$. Then, we have

$$n_\infty(x,t) = 1 \quad \forall x \in \Omega(t),$$

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

Remark

1. However the equation on p_∞ does not predict the set $\Omega(t)$
2. Not an obstacle problem
3. There is a notion of viscosity solution (I. Kim)

From cell densities to free boundary

This establishes the standard Hele-Shaw problem when

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

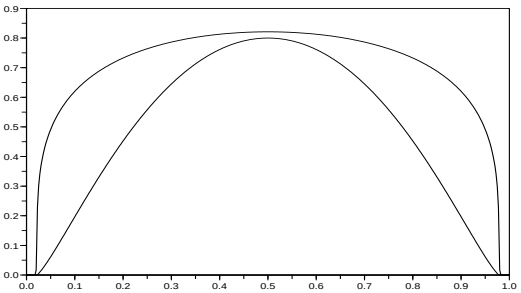
then for all times

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

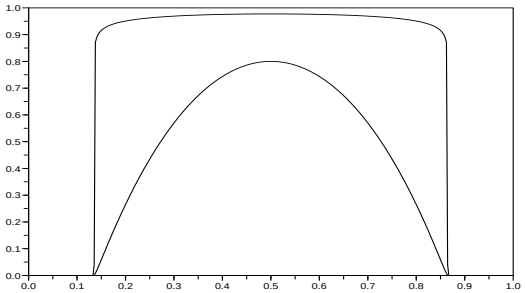
and the equation on n_∞ is equivalent to say that $\Omega(t)$ is moving with the normal velocity $v = -\nabla p_\infty$, that is the free boundary problem and

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

From cell densities to free boundary



Left : $\gamma = 5$

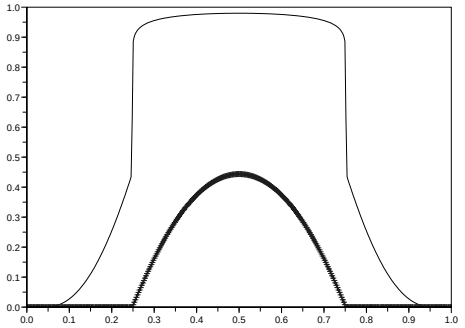


Right : $\gamma = 50$

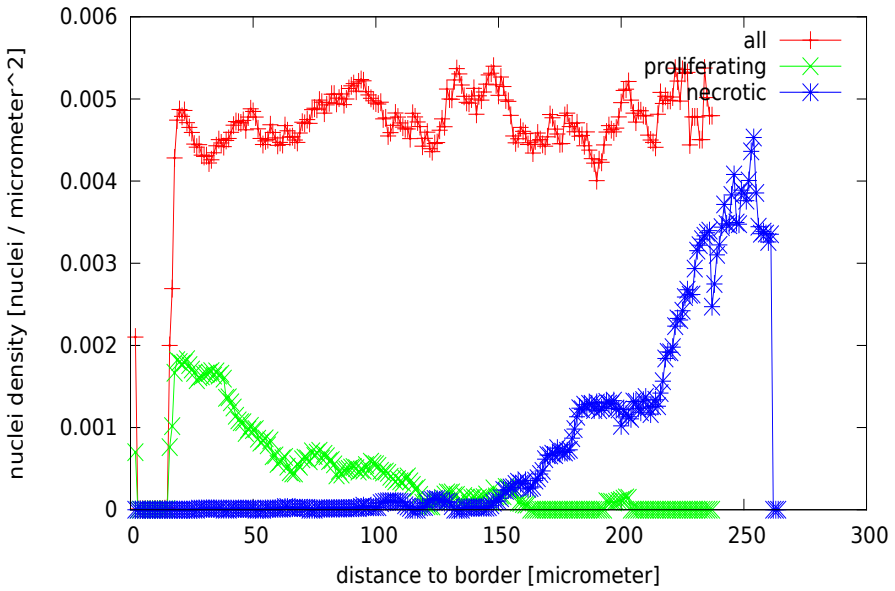
$$\begin{cases} \frac{\partial}{\partial t} n_\infty - \text{div}\Big(n_\infty \nabla p_\infty\Big) = n_\infty G\Big(p_\infty\Big), \\ p_\infty = 0 \quad \text{for} \quad n_\infty(x,t) < 1. \end{cases}$$

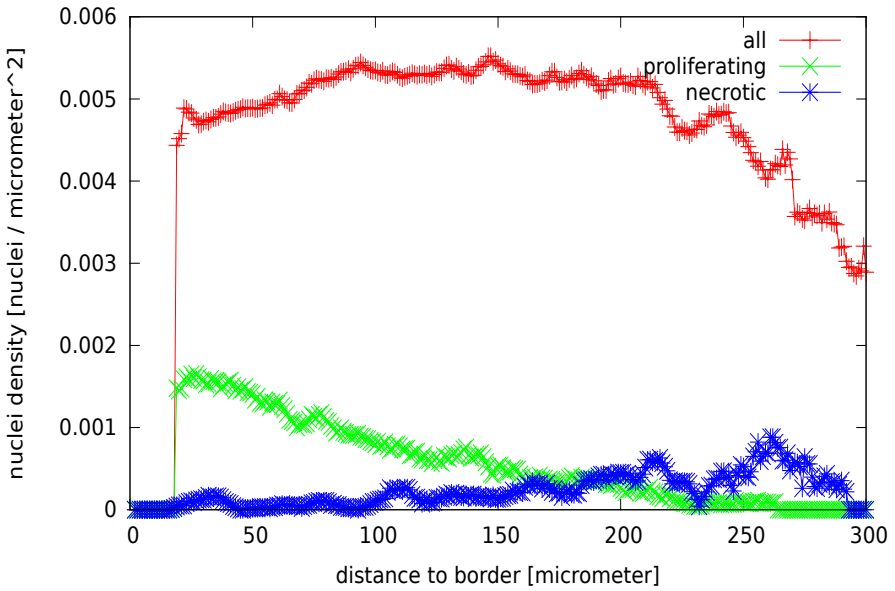
In the region $\{0 < n_\infty < 1\}$, $p_\infty = 0$ and

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



From cell densities to free boundary





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

From cell densities to free boundary

Proof : Based on L^∞, BV estimates and

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

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

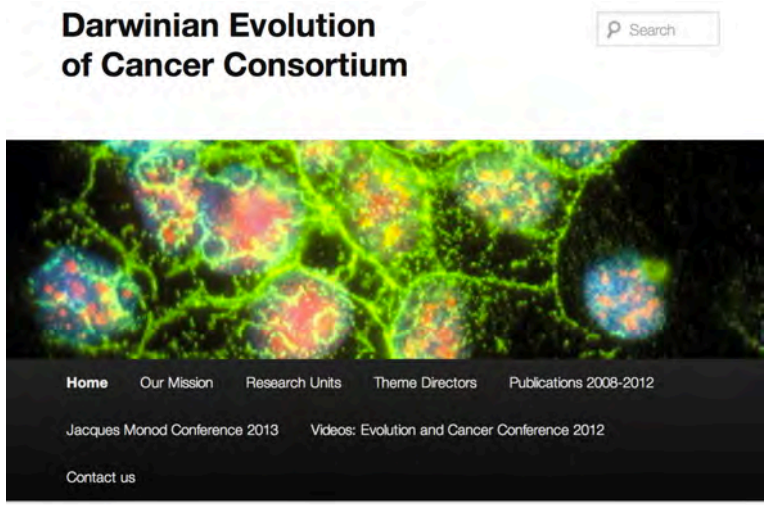
Lefthandside is a bounded measure. Difficulties :

(i) Estimates on p_γ do not give much on n_γ.

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

Resistance to therapy : Motivations

- 40% of cancers escape to therapy
- cells adapt and become resistance 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 ? Play competition to optimize therapy

Resistance to therapy

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

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

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

$$\frac{\partial}{\partial t}n(x,t) = \Big[\underbrace{\frac{r(x)}{1+c_S(t)}} - d(x)\varrho(t) - \underbrace{c_T(t)\mu(x)} \Big] n(x,t)$$

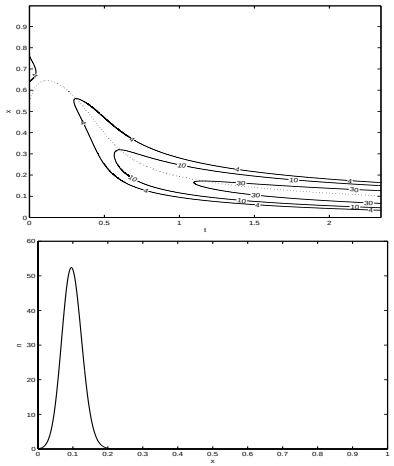
Resistance to therapy

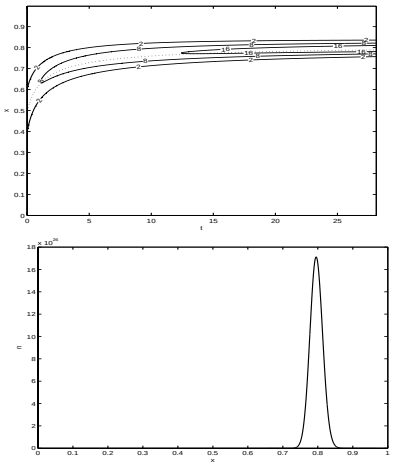
$$\frac{\partial}{\partial t}n(x,t) = \Big[\overbrace{r(x)}^{\text{reproduction rate}} - \overbrace{d(x)\varrho(t)}^{\text{competition, apoptosis}} - \overbrace{c(t)\mu(x)}^{\text{effect of drug}} \Big] n(x,t)$$

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

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

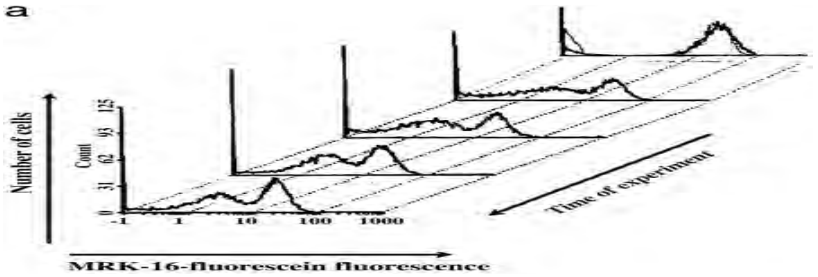
$$\frac{\partial}{\partial t}n(x,t) = \Big[\underbrace{\frac{r(x)}{1+c_S(t)}}_{\text{cytostatic drug}} - d(x)\varrho(t) - \underbrace{c_T(t)\mu(x)}_{\text{cytotoxic drug}} \Big] n(x,t)$$





No therapy With Therapy

This is compatible with the competitive exclusion principle



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

Resistance to therapy

A simple explanation of this observation is after rescalling

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

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

In the limit we obtain the 'Constrained Hamilton-Jacobi Equation'

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

Resistance to therapy

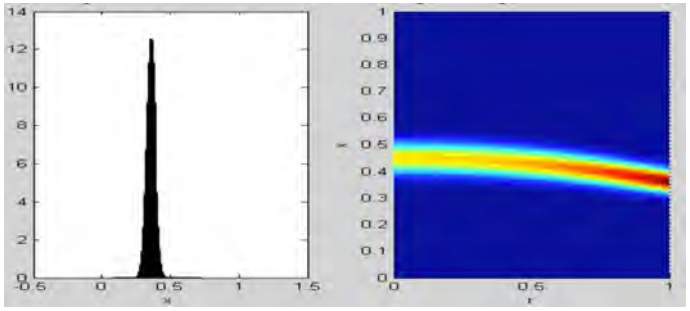
Theorem

$$n_\varepsilon(x,t) \underset{\varepsilon\to 0}{\longrightarrow} \bar{\varrho}(t)\delta\Big(x-\bar{x}(t)\Big)$$

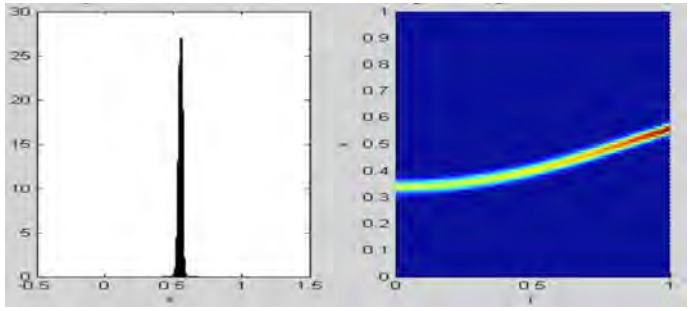
and there is no easy chracterization of $\bar{\varrho}(t)$, $\bar{x}(t)$

$$\max_x u(x,t) = 0 = u(\bar{x}(t),t)$$

Conclusion 1. Heterogeneity comes from spatial organization



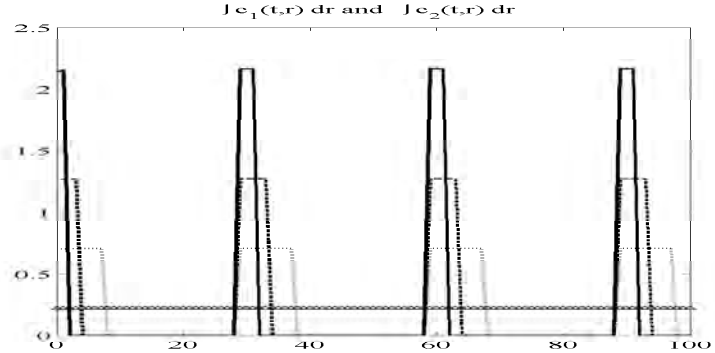
Without therapy

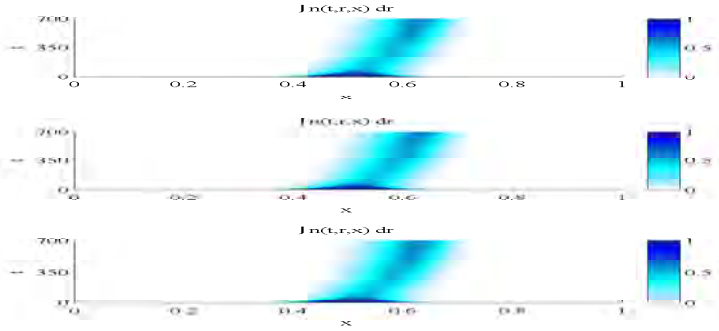


With therapy

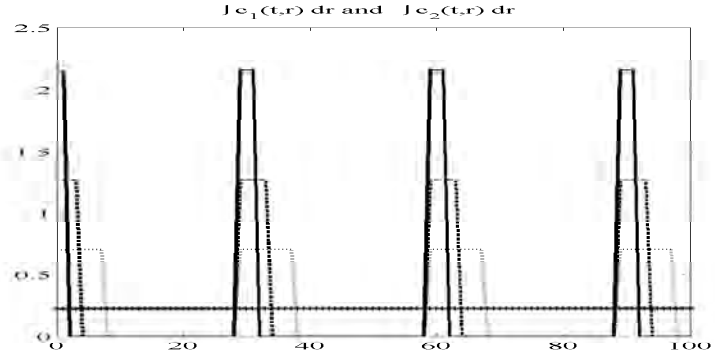
Resistance to therapy

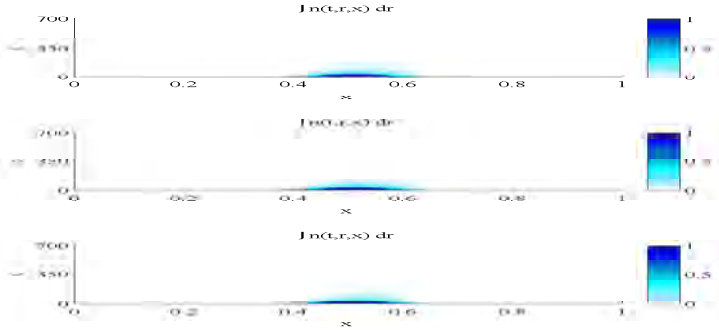
Conclusion 2. Optimal scheduling ?





constant cytotoxic, periodic cytostatic





constant cytostatic, periodic cytotoxic

Conlusions - Perspectives

- Very different questions from biology and medicine ; very different mathematics
- Asymptotic analysis arises naturally because of the scales
- Many open mathematical questions
    - Hele-Shaw asymptotics for systems of PDEs
    - Interaction of space and Darwinian evolution

Thanks to my collaborators

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