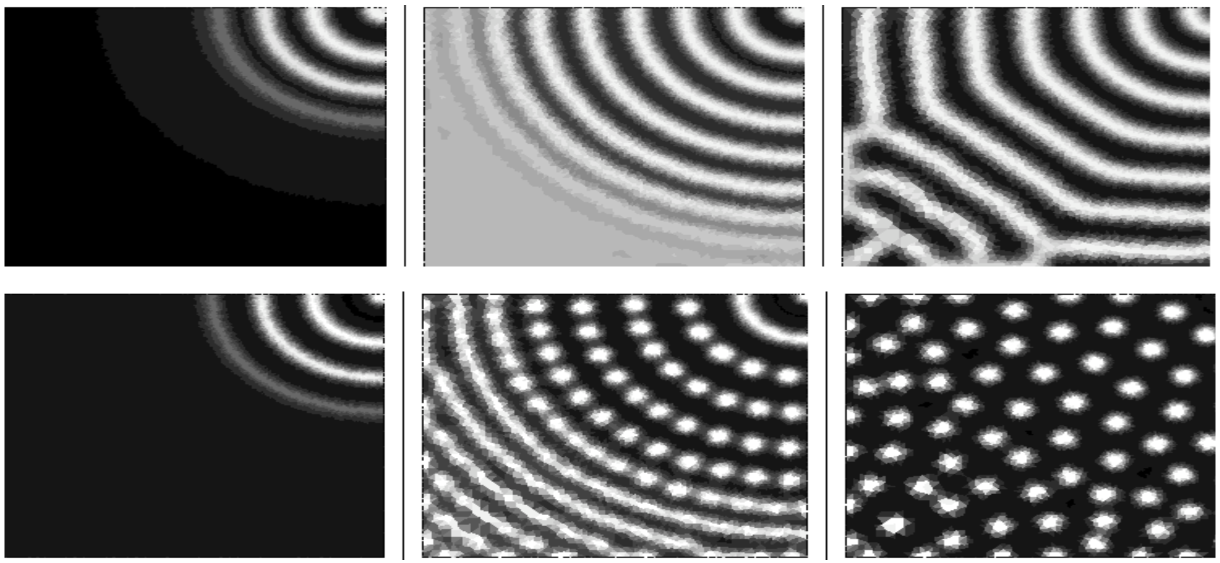
Some models of cell movement

Benoît Perthame



OUTLINE OF THE LECTURE

I. Why study bacterial colonies growth ?

II. Macroscopic models (parabolic)

III. The hyperbolic Keller-Segel models

IV. Proof through the kinetic formulation

V. Movement at a microscopic scale (kinetic models)

WHY

Bacterial colonies. Top S. Serror (CNRS). Bottom K. Ben Jacob (Tel Aviv Univ.)

WHY

Biologist can now access to

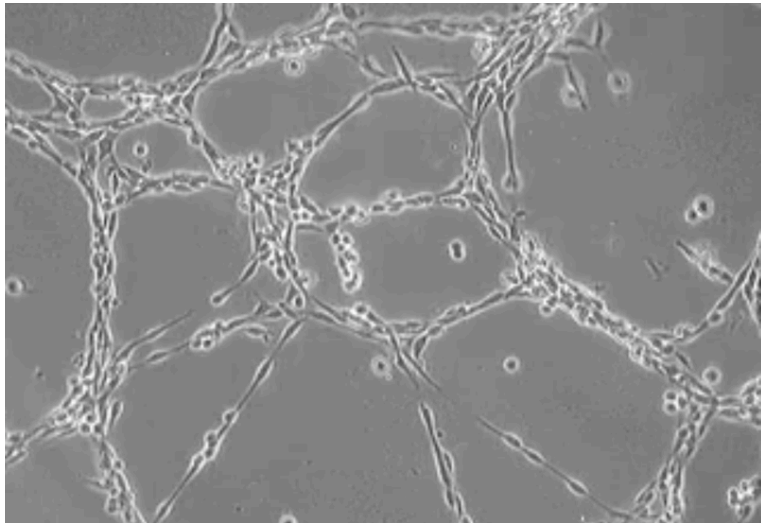
- Individual cell motion
- Molecular content in some proteins
- They act on the genes controlling these proteins

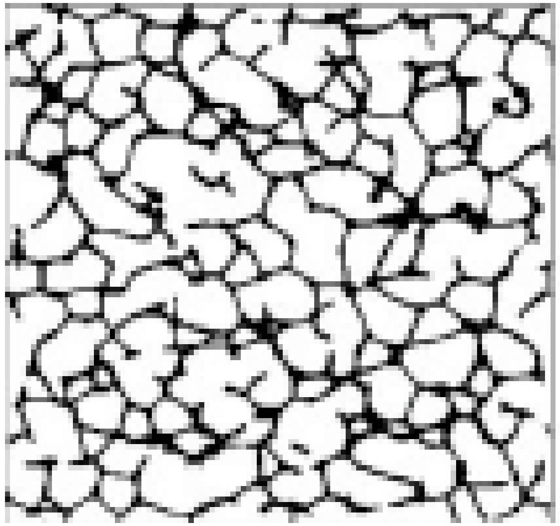
But the global effects are still to explain : nutrients, chemoattraction, chemorepulsion, response to light, effectivity of propulsion, effects of surfactants, cell-to-cell interactions and exchanges, metabolic control loops...

WHY

Examples of application fields

- Ecology : bioreactors, biofilms
- Health : biofilms, cancer therapy





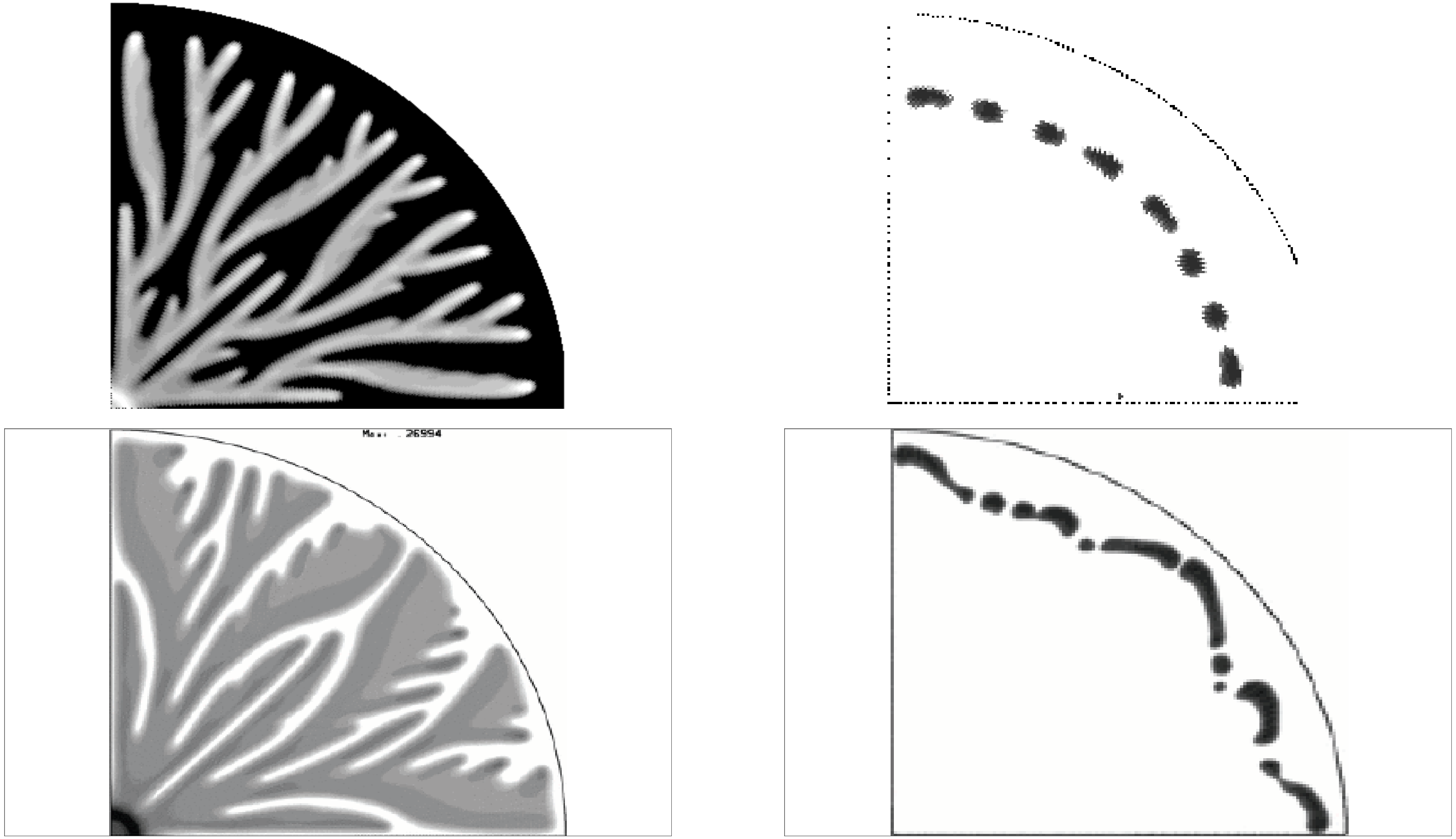
MACROSCOPIC MODELS

MIMURA's model

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) - d_1 \Delta n = r\ n\Big(S - \frac{\mu\ n}{(n_0+n)(S_0+S)}\Big), \\ \\ \frac{\partial}{\partial t} S(t,x) - d_2 \Delta S = -r\ nS, \\ \\ \frac{\partial}{\partial t} f(t,x) = r\ n\ \frac{\mu\ n}{(n_0+n)(S_0+S)} \end{cases}$$

The dynamics is driven by the source terms, i.e., by bacterial growth.

MACROSCOPIC MODELS



CHEMOTAXIS : Keller-Segel model

The mathematical modelling of cell movement goes back to Patlak (1953), E. Keller and L. Segel (70's)

$$
\begin{aligned}
n(t,x) &= \text{ density of cells at time t and position } x, \\
c(t,x) &= \text{concentration of chemoattractant,}
\end{aligned}
$$

In a collective motion, the chemoattractant is emited by the cells that react according to biased random walk.

$$
\begin{cases}
\frac{\partial}{\partial t} n(t,x) - \Delta n(t,x) + \mathrm{div}(n \chi \nabla c) = 0, \quad x \in R^d, \\
\varepsilon \frac{\partial c}{\partial t} - \Delta c(t,x) + \tau c(t,x) = n(t,x),
\end{cases}
$$

The parameter χ is the sensitivity of cells to the chemoattractant.

CHEMOTAXIS : Keller-Segel model

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) - \Delta n(t,x) + \text{div}(n \chi \nabla c) = 0, \qquad x \in R^d, \\ \\ -\Delta c(t,x) = n(t,x), \end{cases}$$

This model, although very simple, exhibits a deep mathematical structure and mostly only dimension 2 is understood, especially "chemotactic collapse".

This is the reason why it has attracted a number of mathematicians Jäger-Luckhaus, Biler *et al*, Herrero- Velazquez, Suzuki-Nagai, Brenner *et al*, Laurençot, Corrias.

CHEMOTAXIS : Keller-Segel model

Theorem (dimensions $d \geq 2$) - (method of Sobolev inequalities)

(i) for $\|n^0\|_{L^{d/2}(R^d)}$ small, then there are global weak solutions,

(ia) they gain L^p regularity,

(ib) and $\|n(t)\|_{L^\infty(R^d)} \to 0$ with the rate of the heat equation,

(ii) for $\left(\int |x|^2 n^0\right)^{(d-2)} < C\|n^0\|^d_{L^1(R^d)}$ with C small, there is blow-up in a finite time T^*.

CHEMOTAXIS : Keller-Segel model

The existence proof relies on Jäger-Luckhaus argument

$$\frac{d}{dt}\int n(t,x)^p \;=-\frac{4}{p}\int |\nabla\, n^{p/2}|^2 + \underbrace{\int p\nabla n^{p-1}\, n\, \chi\, \nabla c}_{\chi\int \nabla n^p\cdot\nabla c=-\chi\int n\Delta c}$$

$$= \underbrace{-\frac{4}{p}\int |\nabla n^{p/2}|^2}_{\text{parabolic dissipation}} + \underbrace{\chi\int n^{p+1}}_{\text{hyperbolic effect}}$$

Using Gagliardo-Nirenberg-Sobolev ineq. on the quantity $u(x) = n^{p/2}$, we obtain

$$\int n^{p+1} \le C_{\text{gns}}(d,p)\|\nabla n^{p/2}\|^2_{L^2}\, \|n\|_{L^{\frac{d}{2}}}$$

CHEMOTAXIS : Keller-Segel model

In dimension 2, for Keller and Segel model :

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) - \Delta n(t,x) + \mathrm{div}(n\chi \nabla c) = 0, \quad x \in R^2, \\ -\Delta c(t,x) = n(t,x), \end{cases}$$

Theorem (d=2) (Method of energy) (Blanchet, Dolbeault, BP)

(i) for $\|n^0\|_{L^1(R^2)} < \frac{8\pi}{\chi}$, there are smooth solutions,
(ii) for $\|n^0\|_{L^1(R^2)} > \frac{8\pi}{\chi}$, there is creation of a singular measure (blow-up) in finite time.
(iii) For radially symmetric solutions, blow-up means

$$n(t) \approx \frac{8\ \pi}{\chi} \delta(x=0) + Rem.$$

CHEMOTAXIS : dimension 2

Existence part is based on the energy

$$\frac{d}{dt}\left[\int_{R^2} n \log n \, dx - \frac{\chi}{2}\int_{R^2} n\, c\, dx\right] = -\int_{R^2}\left|\nabla\sqrt{n} - \chi\nabla c\right|^2 dx \, .$$

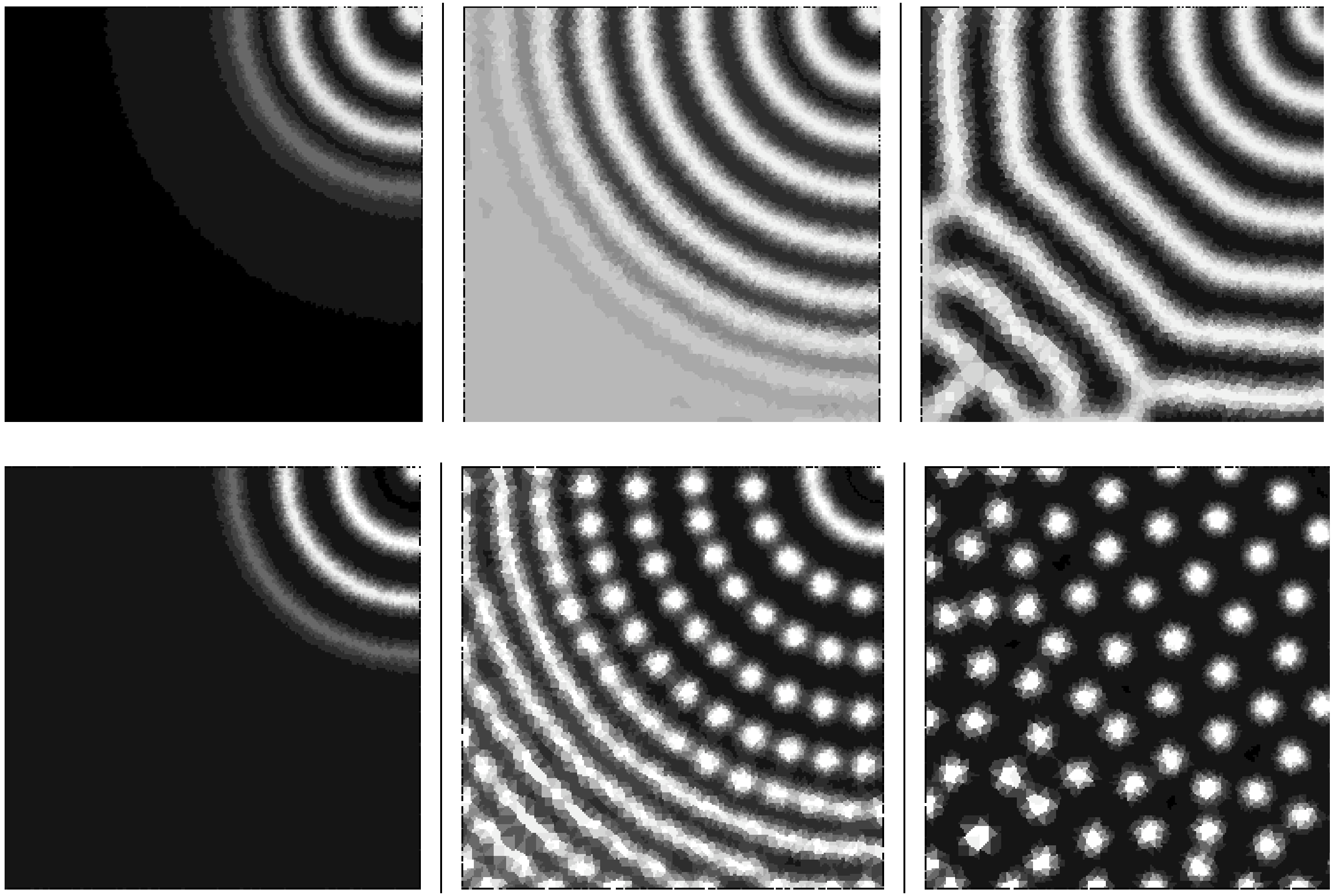
and limit Hardy-Littlewood-Sobolev inequality (Beckner, Carlen-Loss, 96), for $M = \int u(x)dx, \; u > 0$,

$$\int_{R^2} u \log u \, dx + \frac{2}{M}\int\int_{R^2\times R^2} u(x)u(y)\log|x-y| \, dx\, dy \geq M(1 + \log\pi + \log M) \, .$$

Notice that in $d = 2$ we have

$$-\Delta c = n, \qquad c(t,x) = \frac{-1}{2\pi}\int n(t,y)\log|x-y| \, dy$$

$$n \in L^1_{log} \Longrightarrow \int nc < \infty.$$



From A. Marrocco (INRIA, BANG)

Hyperbolic Keller-Segel model

Why a need for hyperbolic models

- We see front motion
- The parabolic scale does not explain all the patterns
- Experiments access to finer scales

Hyperbolic Keller-Segel model

The hyperbolic Keller-Segel system (Dolak, Schmeiser)

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) + \mathrm{div}\Big[n(1-n)\nabla c\Big] = 0, \qquad x \in \mathbb{R}^d,\ t \geq 0, \\ -\Delta c + c = n, \\ n(t,x) = n^0(x), \qquad 0 \leq n^0(x) \leq 1, \quad n^0 \in L^1(\mathbb{R}^d). \end{cases}$$

Interpretation

-) $n(t,x) =$ bacterial density ,

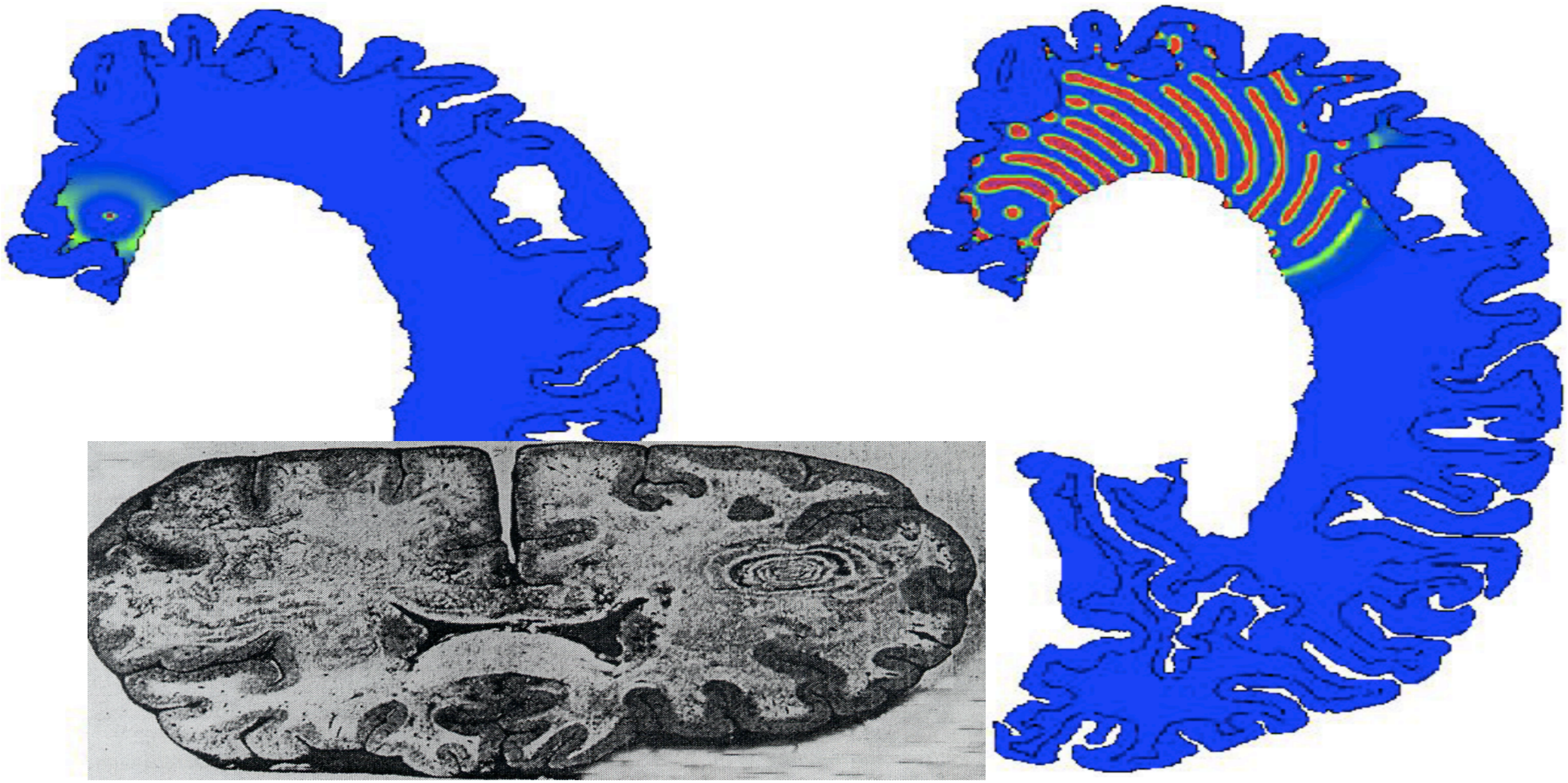
-) $c(t,x) =$ chemical signalling (chemoattraction),

-) $n(1-n)$ represents quorum sensing,

-) random motion of bacterials is neglected (but exists)

Hyperbolic Keller-Segel model : applications

By V. Calvez, B. Desjardins, H. Khonsari on multiple sclerosis



Hyperbolic Keller-Segel model

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Difficulties. All the properties of Scalar Consevation Laws are lost

-) TV property is wrong (except in dimension $d = 1$),
-) Contraction is wrong,
-) Regularizing effects are wrong (except in dimension $d = 1$),

Hyperbolic Keller-Segel model

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) + \mathrm{div}\Big[n(1-n)\nabla c\Big] = 0, & x \in \mathbb{R}^d,\ t \geq 0, \\ -\Delta c + c = n, & \\ n(t,x) = n^0(x), \qquad 0 \leq n^0(x) \leq 1, & n^0 \in L^1(\mathbb{R}^d). \end{cases}$$

Difficulties. All the properties of Scalar Consevation Laws are lost

-) TV property is wrong (except in dimension $d = 1$),
-) Contraction is wrong,
-) Regularizing effects are wrong (except in dimension $d = 1$),
-) Good news : A priori estimate $0 \leq n(t,x) \leq 1$.

Hyperbolic Keller-Segel model

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) + \text{div}\Big[n(1-n)\nabla c\Big] = 0, \qquad x \in \mathbb{R}^d,\ t \geq 0, \\ -\Delta c + c = n. \end{cases}$$

Theorem (A.-L. Dalibar, B. P.) There exist a solution $n \in L^\infty\Big(\mathbb{R}^+; L^1 \cap L^\infty(\mathbb{R}^d)\Big)$ in the weak sense.

It is the strong limit of the same eq. with a small diffusion.

$$\begin{cases} \frac{\partial}{\partial t} n_\varepsilon(t,x) + \text{div}\Big[n_\varepsilon(1-n_\varepsilon)\nabla c_\varepsilon\Big] = \varepsilon \Delta n_\varepsilon, \qquad x \in \mathbb{R}^d,\ t \geq 0, \\ -\Delta c_\varepsilon + c_\varepsilon = n_\varepsilon. \end{cases}$$

Hyperbolic Keller-Segel model

Related to a problem coming from oil recovery

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) + \text{div}\Big[n(1-n)\ u\Big] = 0, & x \in \mathbb{R}^d,\ t \geq 0, \\ u = K(n).\nabla p, \\ \text{div}\ u = 0, \end{cases}$$

which is still open.

Hyperbolic Keller-Segel model

Idea of the proof It is based on the kinetic formulation. In the present case, with $A(n) = n(1-n)$, $a = A'$, it is

$$\begin{cases} \frac{\partial \chi(\xi;n)}{\partial t} + a(\xi)\nabla_y c \cdot \nabla_y \chi(\xi;n) + (\xi - c)A(\xi)\frac{\partial \chi(\xi;n)}{\partial \xi} = \frac{\partial m}{\partial \xi}, \\ m(t,x,\xi) \text{ a nonnegative measure}, \\ D^2 c \in L^p([0,T]\times\mathbb{R}^d), \qquad 1 < p < \infty, \end{cases}$$

$$\chi(\xi,u) = \begin{cases} +1 & \text{for } 0 \le \xi \le u, \\ -1 & \text{for } u \le \xi \le 0, \\ 0 & \text{otherwise.} \end{cases}$$

Hyperbolic Keller-Segel model

With a small diffusion, the function $\chi(\xi; n_\varepsilon)$ satisfies a similar kinetic equation.

Then one can pass to the weak limit and the problem comes from the 'nonlinear' term in the kinetic formulation

$$\frac{\partial \chi(\xi;n)}{\partial t} + a(\xi) \underbrace{\nabla_y c \cdot \nabla_y \chi(\xi;n)}_{=\text{div}[\nabla_y c\ \chi(\xi;n)] - \Delta c\ \chi(\xi;n)} + (\xi - c)A(\xi)\frac{\partial \chi(\xi;n)}{\partial \xi} = \frac{\partial m}{\partial \xi},$$

One obtains

$$\partial_t f + a(\xi)\nabla_y c \cdot \nabla_y f + a(\xi)(\rho - nf) + (\xi - c)A(\xi)\partial_\xi f = \partial_\xi m.$$

Recalling the standard case

$$\frac{\partial}{\partial t}n(t,x) + \text{div}A(n) = 0, \qquad x \in \mathbb{R}^d,\ t \geq 0,$$

for entropy solutions

$$\partial_t \chi(\xi;n) + a(\xi)\nabla_y \chi(\xi;n) = \partial_\xi m, \qquad m \geq 0.$$

because for S convex

$$\partial_t \int S'(\xi)\chi(\xi;n)d\xi + \text{div} \int S'(\xi)a(\xi)\chi(\xi;n)d\xi = \int S'(\xi)\partial_\xi m d\xi.$$

$$\Longleftrightarrow \frac{\partial}{\partial t}S\Big(n(t,x)\Big) + \text{div}\eta^S(n) \leq 0, \qquad x \in \mathbb{R}^d,\ t \geq 0,$$

Recalling the standard case

Uniqueness follows in three steps

1st step. Convolution

$$\partial_t \chi(\xi; n) *_{(t,x)} \omega_\varepsilon + a(\xi)\nabla_y \chi(\xi; n) *_{(t,x)} \omega_\varepsilon = \partial_\xi m *_{(t,x)} \omega_\varepsilon,$$

2nd step. L^2 linear uniqueness

$$\partial_t |\chi(\xi; n^1)_\varepsilon - \chi(\xi; n^2)_\varepsilon|^2 + a(\xi)\nabla_y |\chi(\xi; n^1)_\varepsilon - \chi(\xi; n^2)_\varepsilon|^2$$

$$= 2\left(\chi(\xi; n^1)_\varepsilon - \chi(\xi; n^2)_\varepsilon\right) \partial_\xi (m^1_\varepsilon - m^2_\varepsilon)$$

$$\partial_t \int |\chi(\xi; n^1)_\varepsilon - \chi(\xi; n^2)_\varepsilon|^2 dx d\xi = 2\left(\delta(\xi = n^1)_\varepsilon - \delta(\xi = n^2)_\varepsilon\right)\left(m^1_\varepsilon - m^2_\varepsilon\right)$$

3rd step. Limit as $\varepsilon \to 0$

$$\frac{d}{dt}\int |\chi(\xi; n^1) - \chi(\xi; n^2)|^2 dx d\xi = 0+ \leq 0 + 0+ \leq 0$$

Hyperbolic Keller-Segel model

Back to the HKS, one have obtained

$$\partial_t f + a(\xi)\nabla_y c \cdot \nabla_y f + a(\xi)(\rho - nf) + (\xi - c)A(\xi)\partial_\xi f = \partial_\xi m.$$

From the properties of the weak limit ρ one can prove that

$$|a(\xi)(\rho - nf)| \ \leq C(f - f^2).$$

Therefore

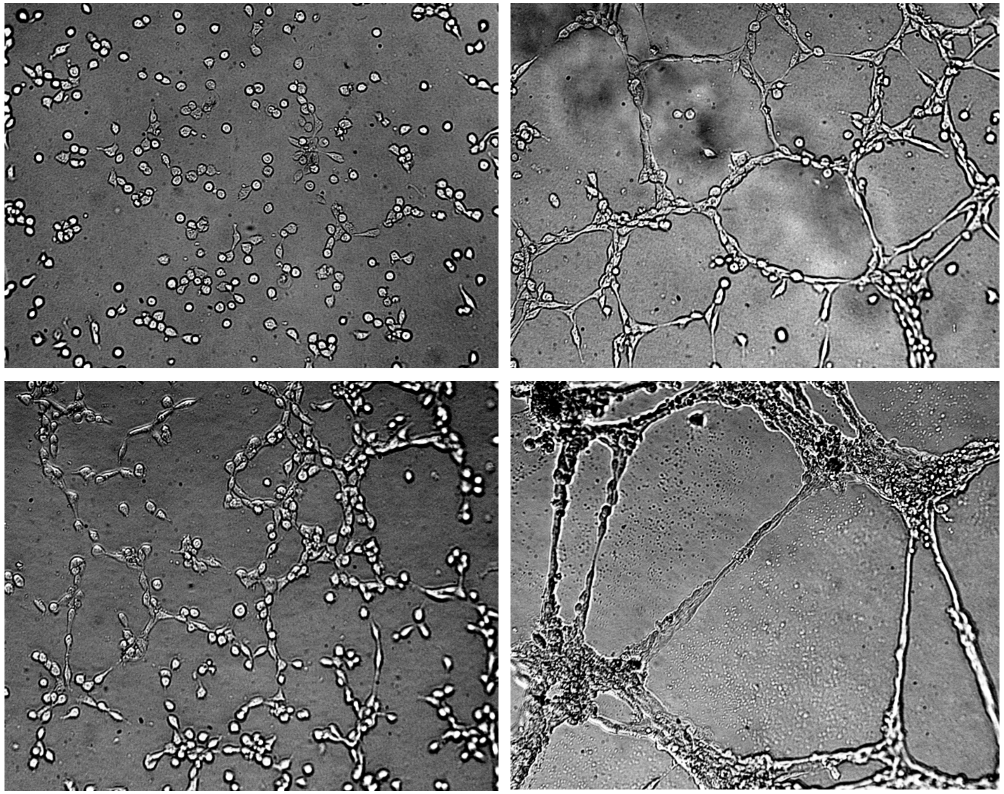
$$\partial_t f^2 + a(\xi)\nabla_y c \cdot \nabla_y f^2 + f a(\xi)(\rho - nf) \ \ +(\xi - c)A(\xi)\partial_\xi f^2$$

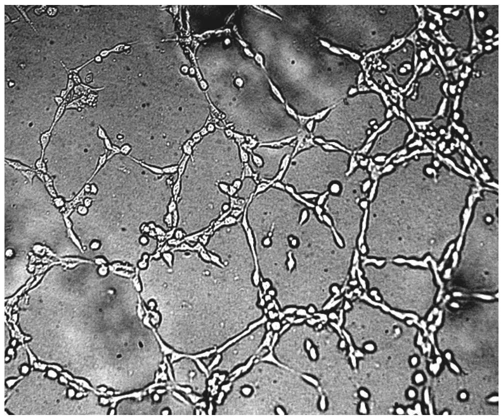
$$\geq 2\partial_\xi(fm) - C(f - f^2).$$

This implies, by Gronwall lemma,

$$f = f^2, \qquad \text{in other words } f = \chi(\xi; n).$$

Networks and hyperbolic models





HBMEC SUR MATRIGEL
T=0 ,2H,4H,6H,20H

Networks and hyperbolic models

A group of Torino Ambrosi, Gamba, Preziosi et al proposed a *hydrodynamics model*

$$
\begin{cases}
\frac{\partial}{\partial t} n(t,x) + \mathrm{div}(n\ u) = 0, \quad x \in R^2, \\
\frac{\partial}{\partial t} u(t,x) + u(t,x) \cdot \nabla u + \nabla n^{\alpha} = \chi\ \nabla c - \mu u, \\
\frac{\partial}{\partial t} c(t,x) - \Delta c(t,x) + \tau c(t,x) = n(t,x).
\end{cases}
$$

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Keller-Segel model can be viewed as a special case where the acceleration term is neglected

$$\frac{\partial}{\partial t} u(t,x) + u(t,x) \cdot \nabla u = 0.$$

Networks and hyperbolic models

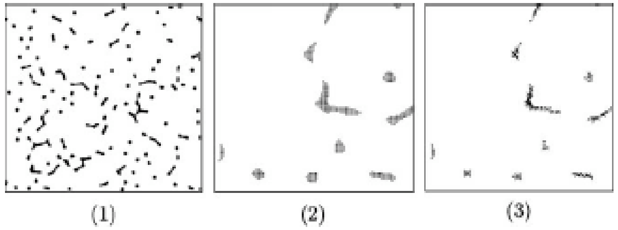


Fig. 4. Formation of network:*(1) density and zoom on the left-bottom corner of (2) the density and (3) velocity field obtained with* 50 $cells/mm^2$.

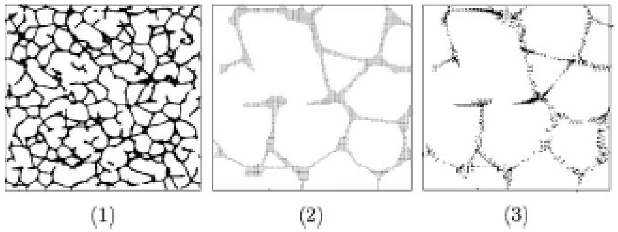
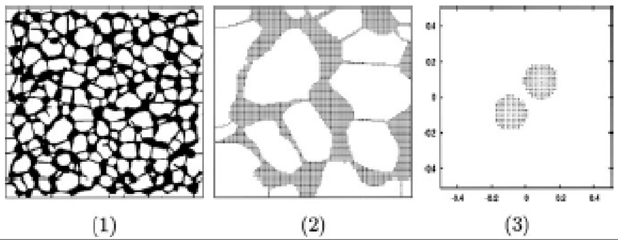
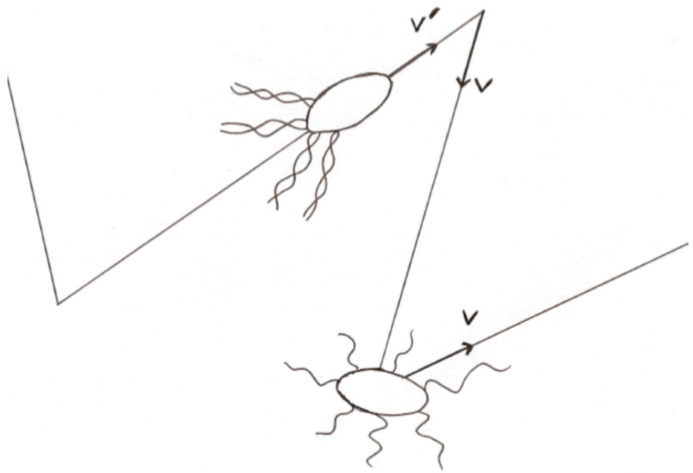


Fig. 5. Formation of network:*(1) density and zoom on the left-bottom corner of (2) the density and (3) velocity field obtained with* 100 $cells/mm^2$.



KINETIC MODELS

E. Coli is known (since the 80's) to move by run and tumble depending on the coordination of motors that control the flagella



See Alt, Dunbar, Othmer, Stevens.

KINETIC MODELS

Denote by $f(t,x,\xi)$ the density of cells moving with the velocity ξ.

$$\frac{\partial}{\partial t} f(t,x,\xi) + \underbrace{\xi \cdot \nabla_x f}_{\textbf{run}} = \underbrace{\mathcal{K}[f]}_{\textbf{tumble}},$$

$$\mathcal{K}[f] = \int K(c;\xi,\xi') f(\xi') d\xi' - \int K(c;\xi',\xi) d\xi' \; f,$$

$$-\Delta c(t,x) = n(t,x) := \int f(t,x,\xi) d\xi,$$

$$K(c;\xi,\xi') = k_-(c(x-\varepsilon\xi')) + \; k_+(c(x+\varepsilon\xi)).$$

Nonlocal, quadratic term on the right hand side for $k_\pm(\cdot,\xi,\xi')$ sublinear.

KINETIC MODELS

Theorem (Chalub, Markowich, P., Schmeiser)
Assume that $0 \leq k_{\pm}(c;\xi,\xi') \leq C(1+c)$ then there is a GLOBAL solution to the kinetic model and

$$\|f(t)\|_{L^\infty} \leq C(t)[\ \|f^0\|_{L^1} + \|f^0\|_{L^\infty}]$$

-) Open question : Is it possible to prove a bound in L^∞ when we replace the specific form of K by

$$0 \leq K(c;\xi,\xi') \leq \|c(t)\|_{L^\infty_{\text{loc}}} \ ?$$

-) Hwang, Kang, Stevens : $k\Big(\nabla c(x-\varepsilon\xi')\Big)$ or $k\Big(\nabla c(x+\varepsilon\xi)\Big)$

KINETIC MODELS

Theorem (Bournaveas, Calvez, Gutierrez, P.)
Assume that

$$k\Big(\nabla c(x - \varepsilon\xi')\Big) + k\Big(\nabla c(x + \varepsilon\xi)\Big).$$

For SMALL initial data, there is a GLOBAL solution to the kinetic model.

Long standing question There are cases of blow-up (Bournaveas, Calvez)

Related questions Internal variables (Erban, Othmer, Hwang, Dolak, Schmeiser), quorum sensing, mesenchymal (Hillen)

KINETIC MODELS : diffusion limit

One can perform a parabolic rescaling based on the memory scale

$$\frac{\partial}{\partial t} f(t,x,\xi) + \frac{\xi \cdot \nabla_x f}{\varepsilon} = \frac{\mathcal{K}[f]}{\varepsilon^2},$$

$$\mathcal{K}[f] = \int K(c;\xi,\xi') f' d\xi' - \int K(c;\xi',\xi) d\xi' \, f,$$
$$-\Delta c(t,x) = n(t,x) := \int f(t,x,\xi) d\xi,$$
$$K(c;\xi,\xi') = \; k_-\Big(c(x-\varepsilon\xi')\Big) + \; k_+\Big(c(x+\varepsilon\xi)\Big).$$

Theorem (Chalub, Markowich, P., Schmeiser) With the same assumptions, as $\varepsilon \to 0$, then locally in time,

$$f_\varepsilon(t,x,\xi) \to n(t,x), \qquad c_\varepsilon(t,x) \to c(t,x),$$

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) - \text{div}[D\nabla n(t,x)] + \text{div}(n\chi\nabla c) = 0, \\ -\Delta c(t,x) = n(t,x). \end{cases}$$

and the transport coefficients are given by

$$D(n,c) = D_0 \, \frac{1}{k_-(c) + k_+(c)} \, ,$$

$$\chi(n,c) = \chi_0 \, \frac{k'_-(c) + k'_+(c)}{k_-(c) + k_+(c)} \, .$$

The drift (sensibility) term $\chi(n,c)$ comes from the memory term.

Interpretation in terms of random walk : memory is fundamental.

Thanks to my coolaborators

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