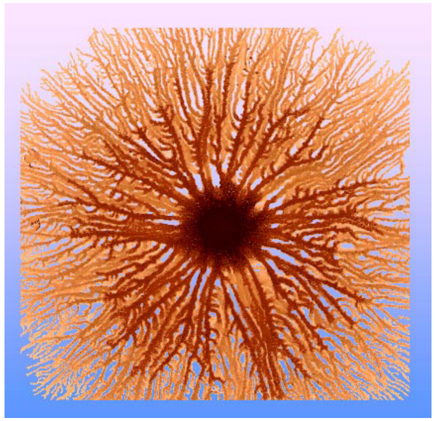
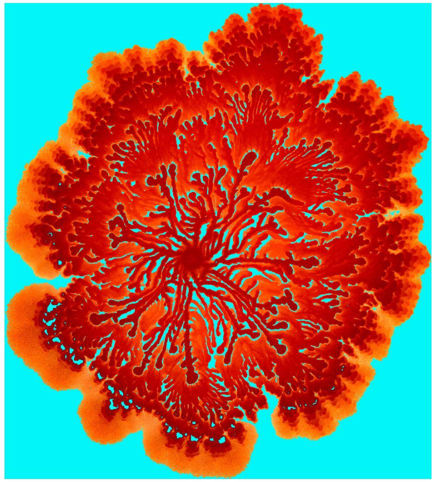
CHEMOTAXIS MODELS : mathematical analysis

Benoît Perthame, ENS, Paris


OUTLINE OF THE LECTURE

I. How and why do cell move

II. Keller-Segel model

III. dentritic bacterial growth

IV. Angiogenesis

V. Hyperbolic and kinetic models

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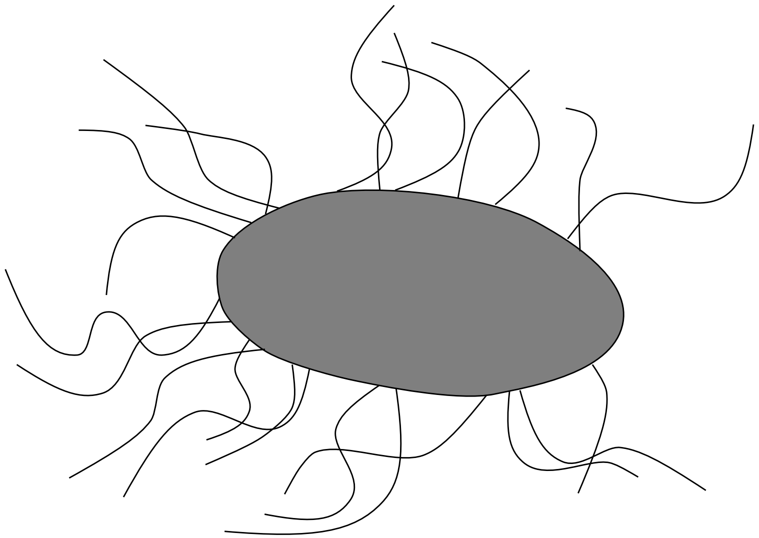
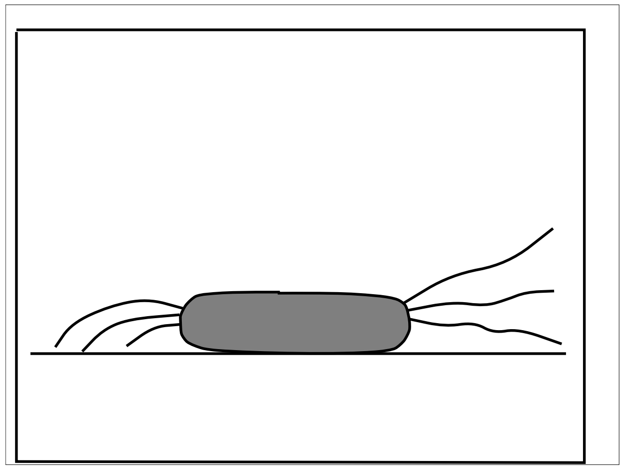
COLLABORATORS

J. Dolbeault, L. Corrias, H. Zaag
F. Chalub, P. Markowich, C. Schmeiser
V.Calvez, F. Filbet, P. Laurencot
A. Marrocco, A. Vasseur

HOW DO CELLS MOVE : bacteria

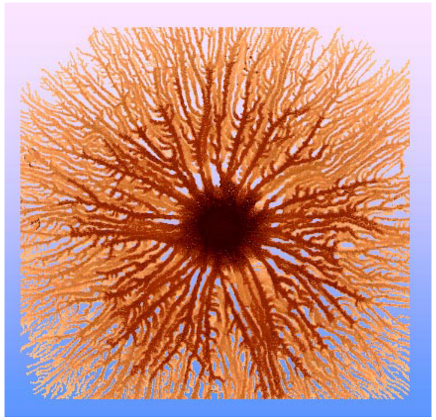


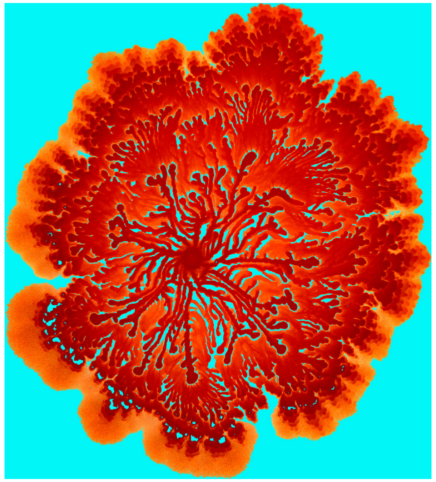


E. Coli and Micrococcus are equipped with external devices ; they emit chemicals and can react to these chemicals

HOW DO CELLS MOVE : bacteria

This creates a collective motion and results in patterns

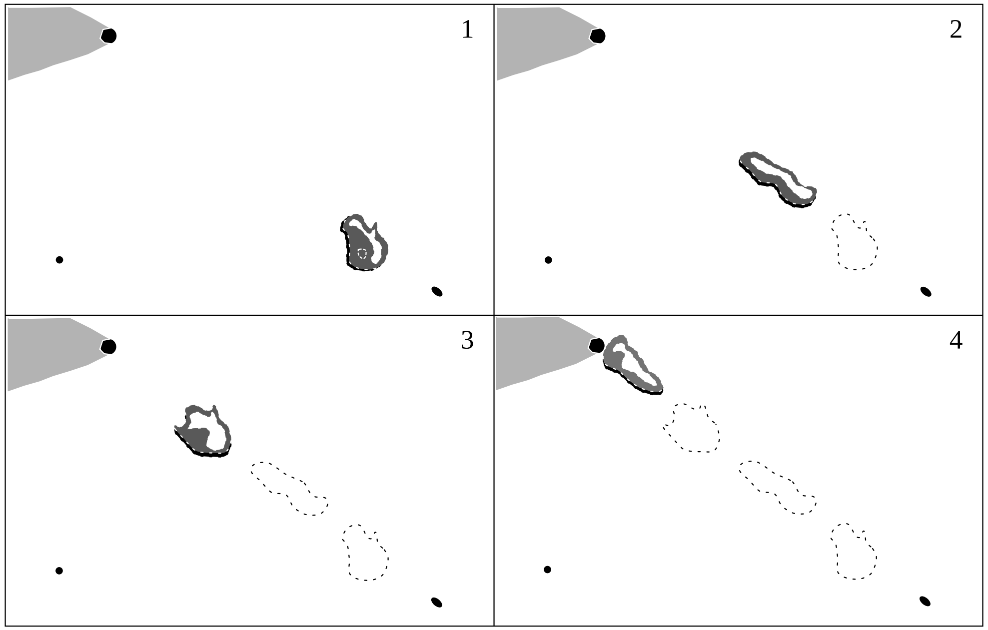




By D. Jukowska, S. Seror, B. Holland (Institut de Génétique et Microbiologie)

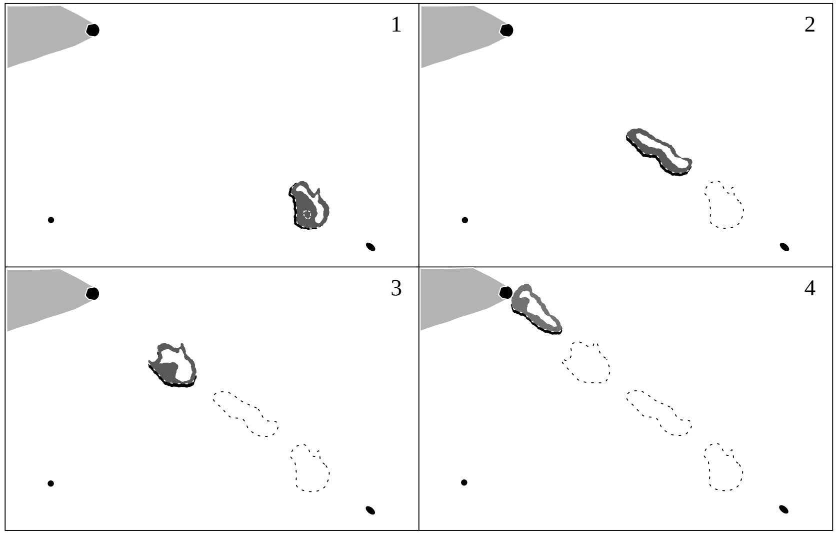
How to characterize these colonies ?

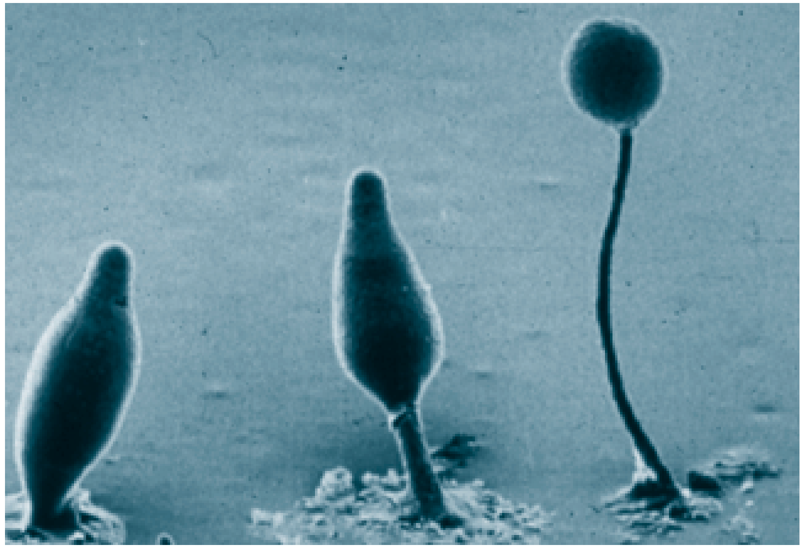
HOW DO CELLS MOVE : amoebia



Dictyostelum Discoideum uses an intenal pseudopod

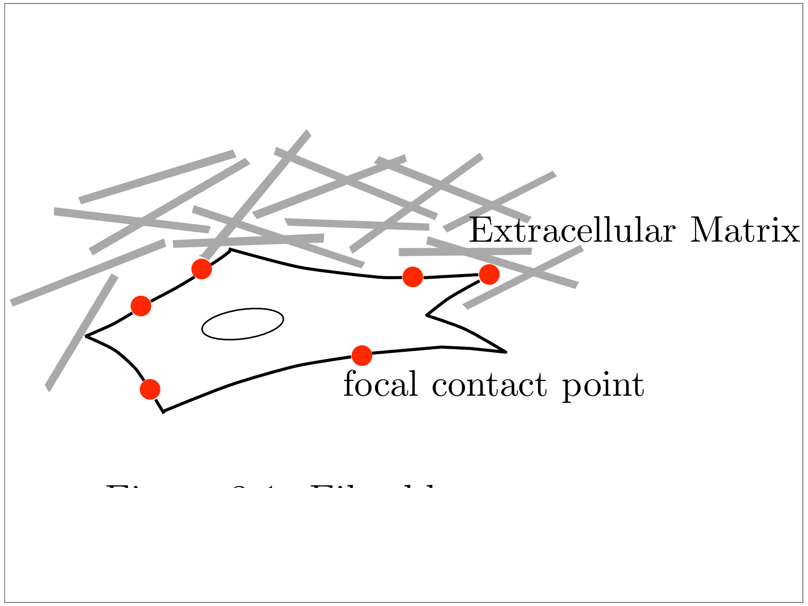
HOW DO CELLS MOVE : amoebia



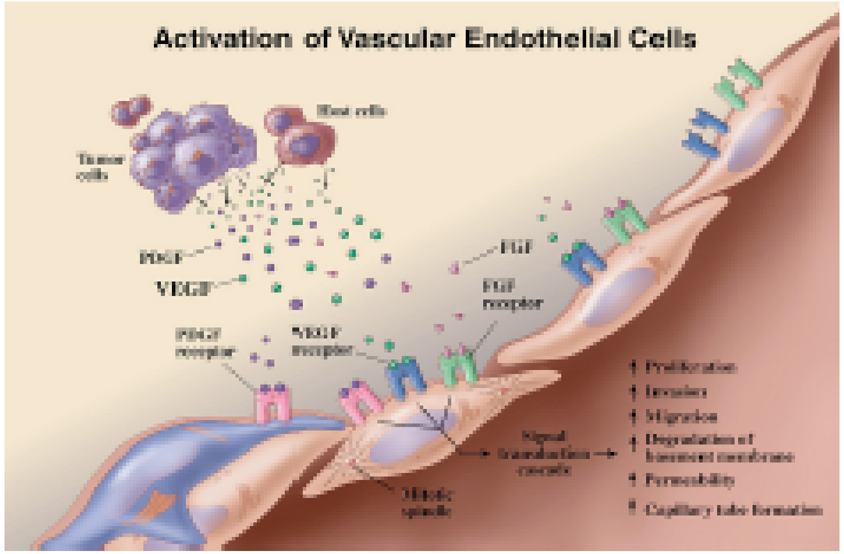


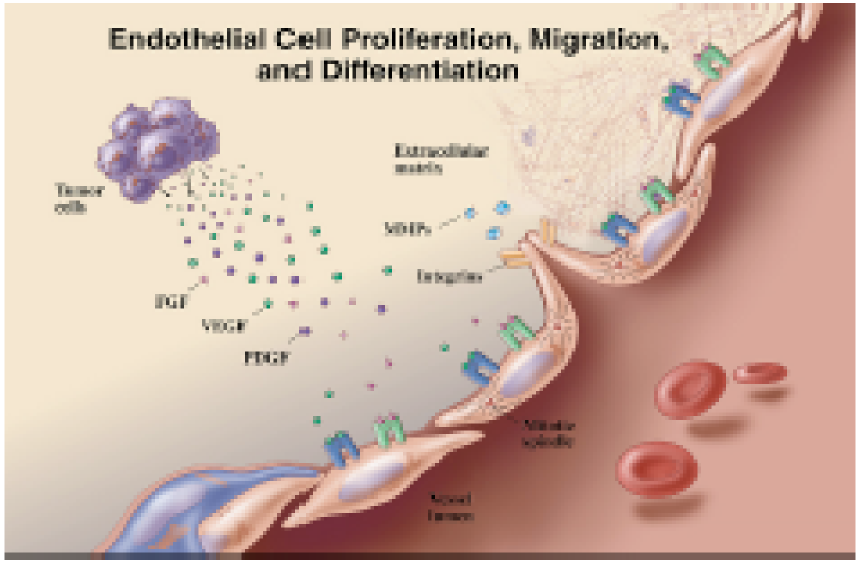
Dictyostelum Dyscoideum can create a fruiting body

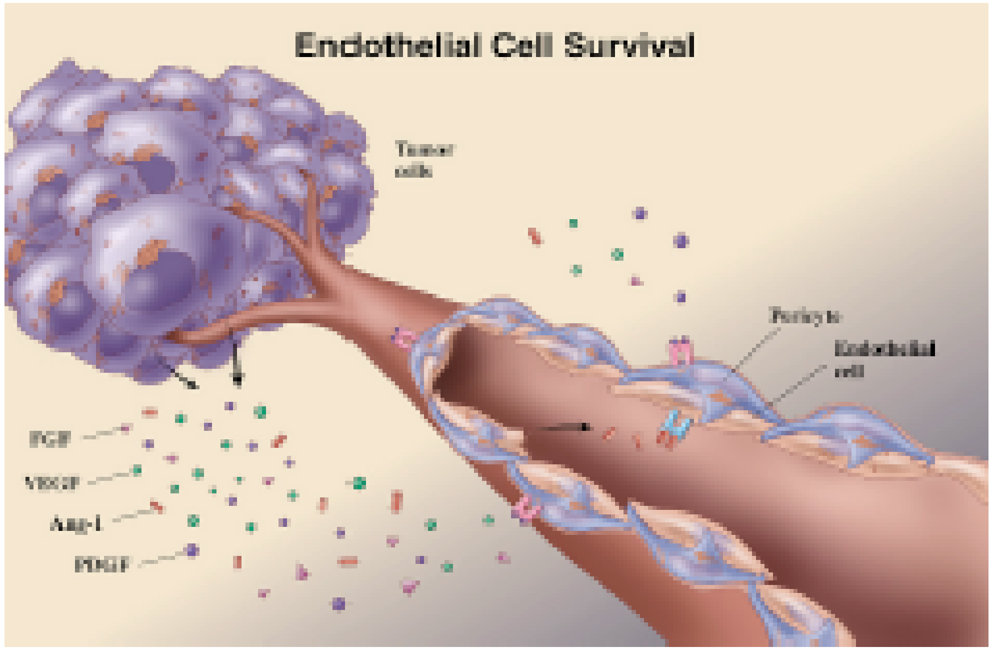
HOW DO CELLS MOVE : fibroblast



In vivo, fibroblast can move within the extracellular matrix


Activation of Vascular Endothelial Cells
Host cells
Tumor cells
PDGF
VEGF
FGF
FGF receptor
PDGF receptor
VEGF receptor
Mitotic spindle


Endothelial Cell Proliferation, Migration, and Differentiation
Extracellular matrix
Tumor cells
MMPs
Integrins
FGF
VEGF
PDGF


Endothelial Cell Survival
Tumor cells
Pericyte
Endothelial cell
FGF
VEGF
Ang-1
PDGF

HOW DO CELLS MOVE : tumor growth

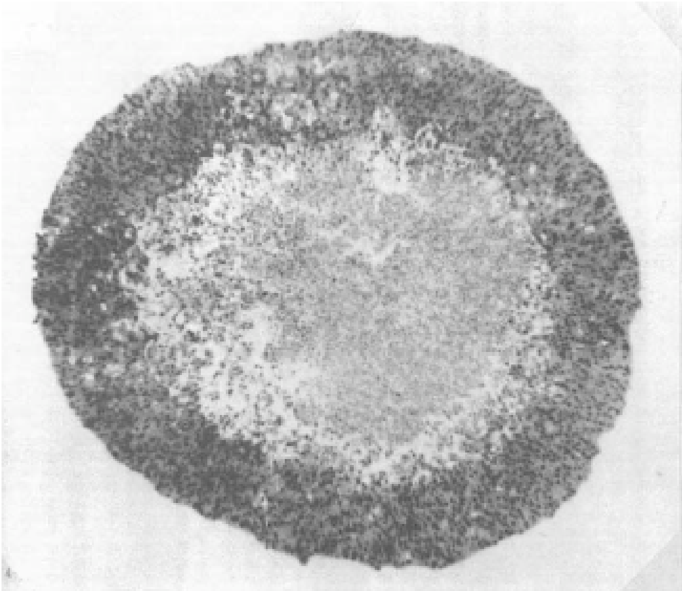
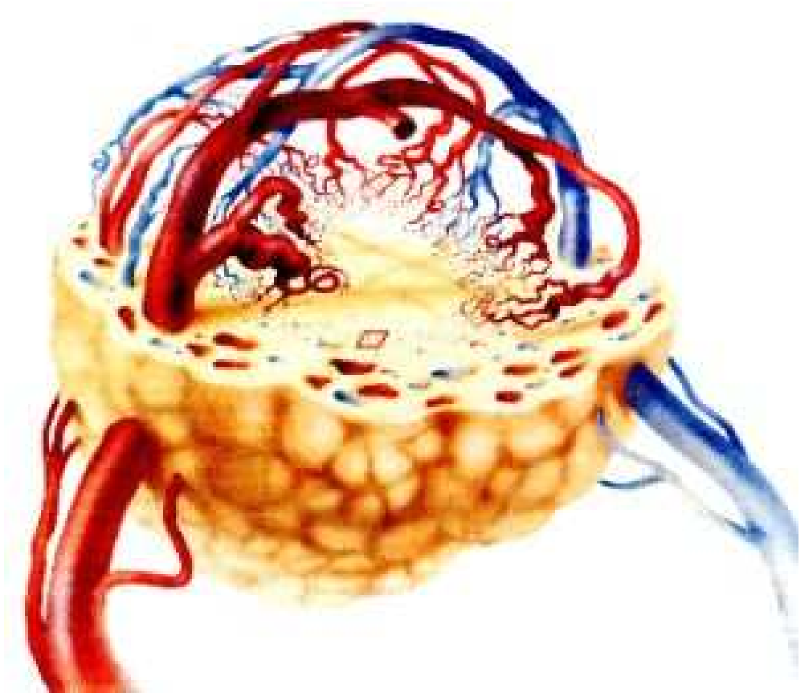


Fig. 1. An illustration of the structure of a multicellular tumour spheroid, with an outer rim of proliferating cells and an inner necrotic core; these are separated by a layer of quiescent cells. The spheroid diameter is 1.4 mm. [Reproduced from Sutherland et al. (Cancer Res.

Tumor spheroid



vascularized tumor through angiogenesis

HOW DO CELLS MOVE : endothelial cells

Animation from M. Mirshahi

(INSERM E 355 faculté de Médecine Paris VI)

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.

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

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

CHEMOTAXIS : Keller-Segel model

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

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 authors.

CHEMOTAXIS : Keller-Segel model

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

-Childress, Percus (84) ; Jäger, Luckhaus (92),
-Rascle, Zitti (95) ; Nagai (95) ; Biler, Nadzieja(93),
-Herrero, Medina, Velazquez (96-04) ;
-Brenner, Constantin, Kadanoff, Schenkel, Venkatarami (98) ;
-Horstmann (00) ; Corrias, Dolbeault, Perthame, Zaag (04) ;

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,

(ii) these small solutions gain L^p regularity,

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

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

CHEMOTAXIS : Keller-Segel model

In dimension 2, for Keller and Segel model :

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

Theorem (dimension d=2) (Method of energy)

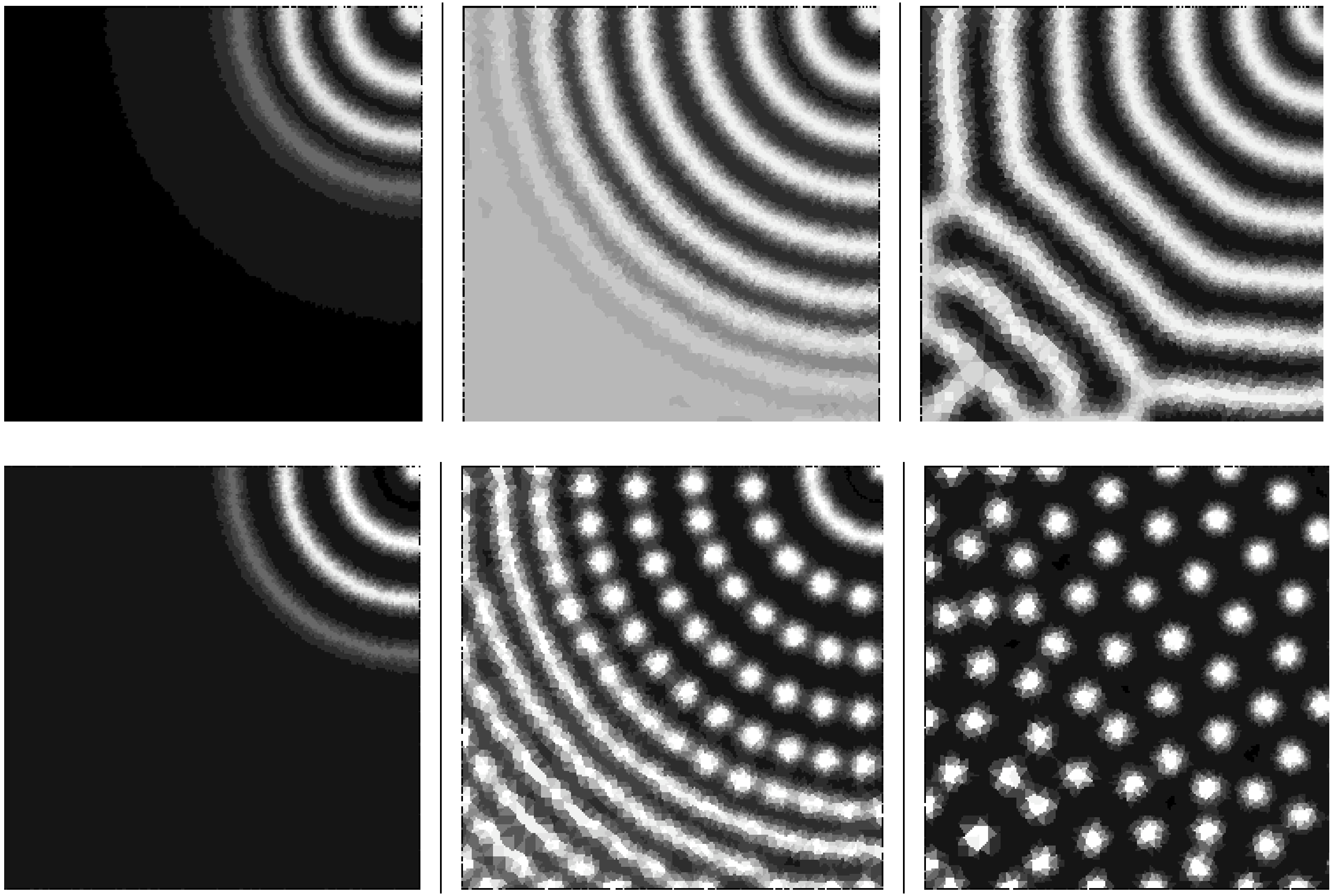
(i) for $\|n^0\|_{L^1(R^2)} < \frac{8\pi}{\chi}$, there are smooth solutions,
(ii) for $\|n^0\|_{L^1(R^2)} > \frac{8\pi}{\chi}$, there is creation of a singular measure (blow-up) in finite time.
(iii) For radially symmetric solutions, blow-up means

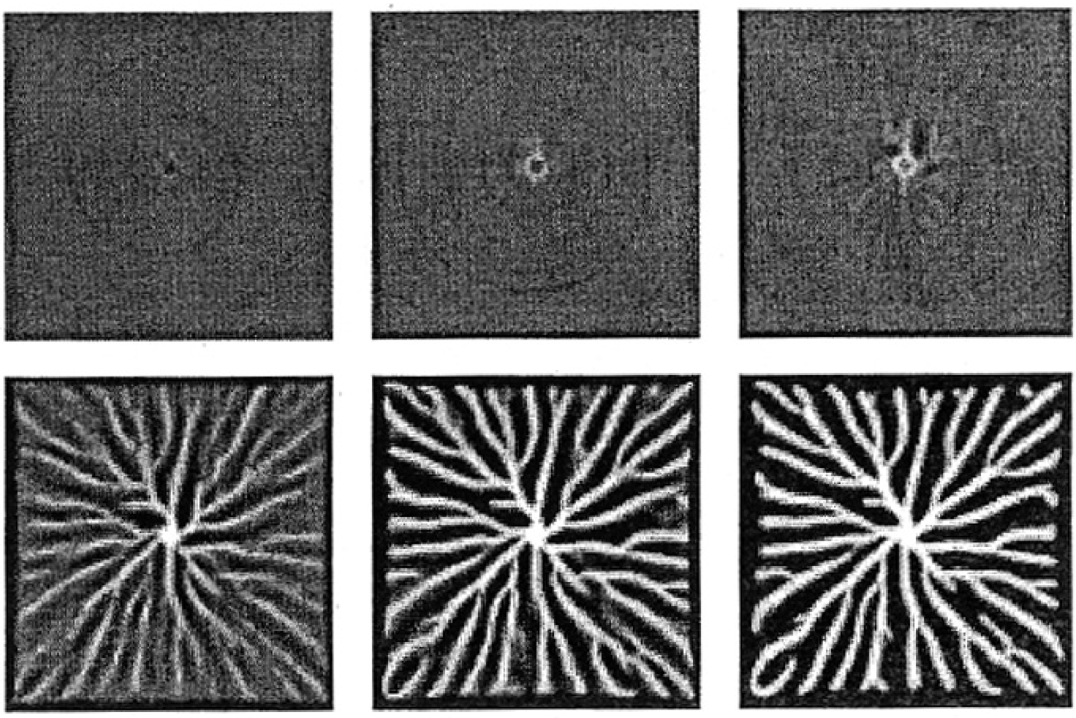
$$n(t) \approx \frac{8\ \pi}{\chi}\delta(x=0) + Rem.$$

CHEMOTAXIS : dimension 2

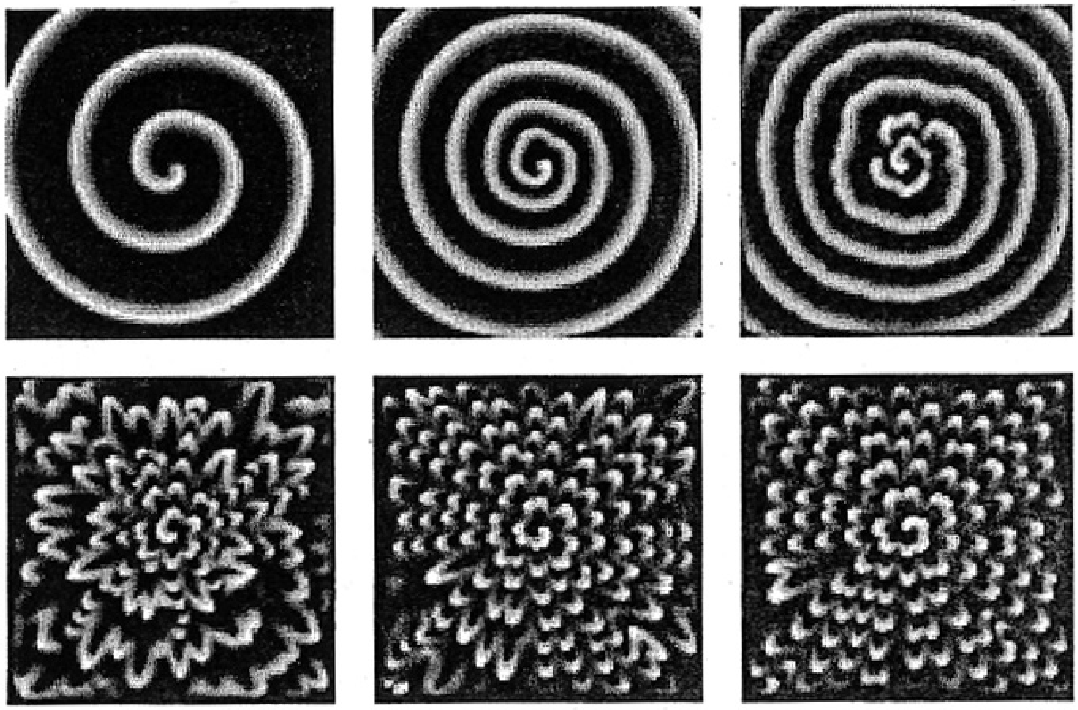
Interest : The Keller-Segel model seems successful to describe aggregation, some 'ring patterns', threshold are observed experimentally.

Mathematically a variety of methods are used ; Sobolev embeddings, energy methods, refined Hardy-Littlewood-Sobolev estimates (from 1994), convolution estimates, DeGiorgi method, asymptotic analysis...etc





(a)



(b)

Dentritic bacterial growth

Is chemotaxis involved in the bacterial movment of *Bacillus Subtilis* and in the development of such colonies ? Another theory is propsed by Mimura

Dentritic bacterial growth

The simplest model is due to Mimura

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) - \Delta n = n\Big(S - \frac{n}{(1+n)(1+S)}\Big), \\ \\ \frac{\partial}{\partial t} S(t,x) - \Delta S = -nS, \\ \\ \frac{\partial}{\partial t} f(t,x) = n \, \frac{n}{(1+n)(1+S)} \end{cases}$$

More elaborated models are due to BenJacob, Kitsunezaki, Shikezada... and are based on the 'nutrient gradient' principle.

ANR Project with Institut de Génétique et Microbiologie (Paris-Sud), Ecole Polytechnique (M. Plapp)

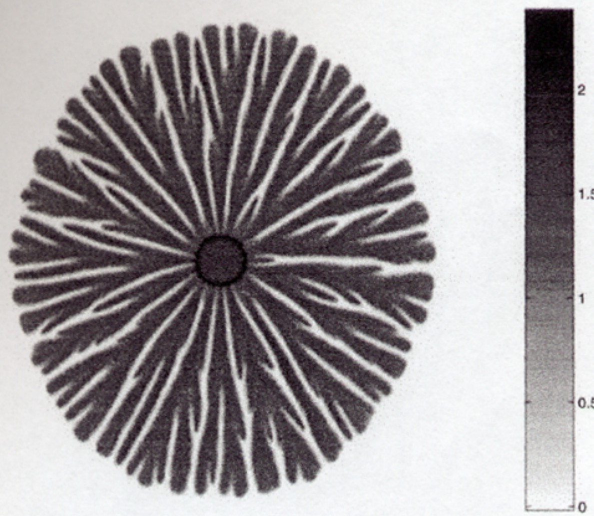


Fig. 28. 2D growth pattern $(b+s)$ of the Kitsunezaki model with repulsive chemotactic signaling included. Parameters are: $\chi_{0r}=1$, $D_r=1$, $\Gamma_r=0.25$, $\Omega_r=0$, $\Lambda_r=0.001$. Other parameters as in Fig. 19.

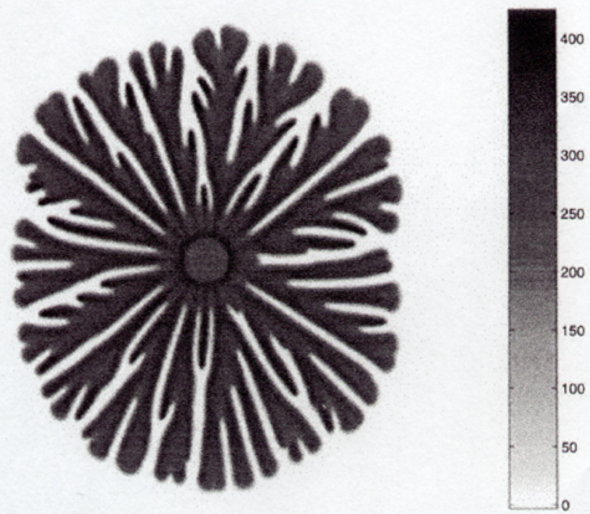
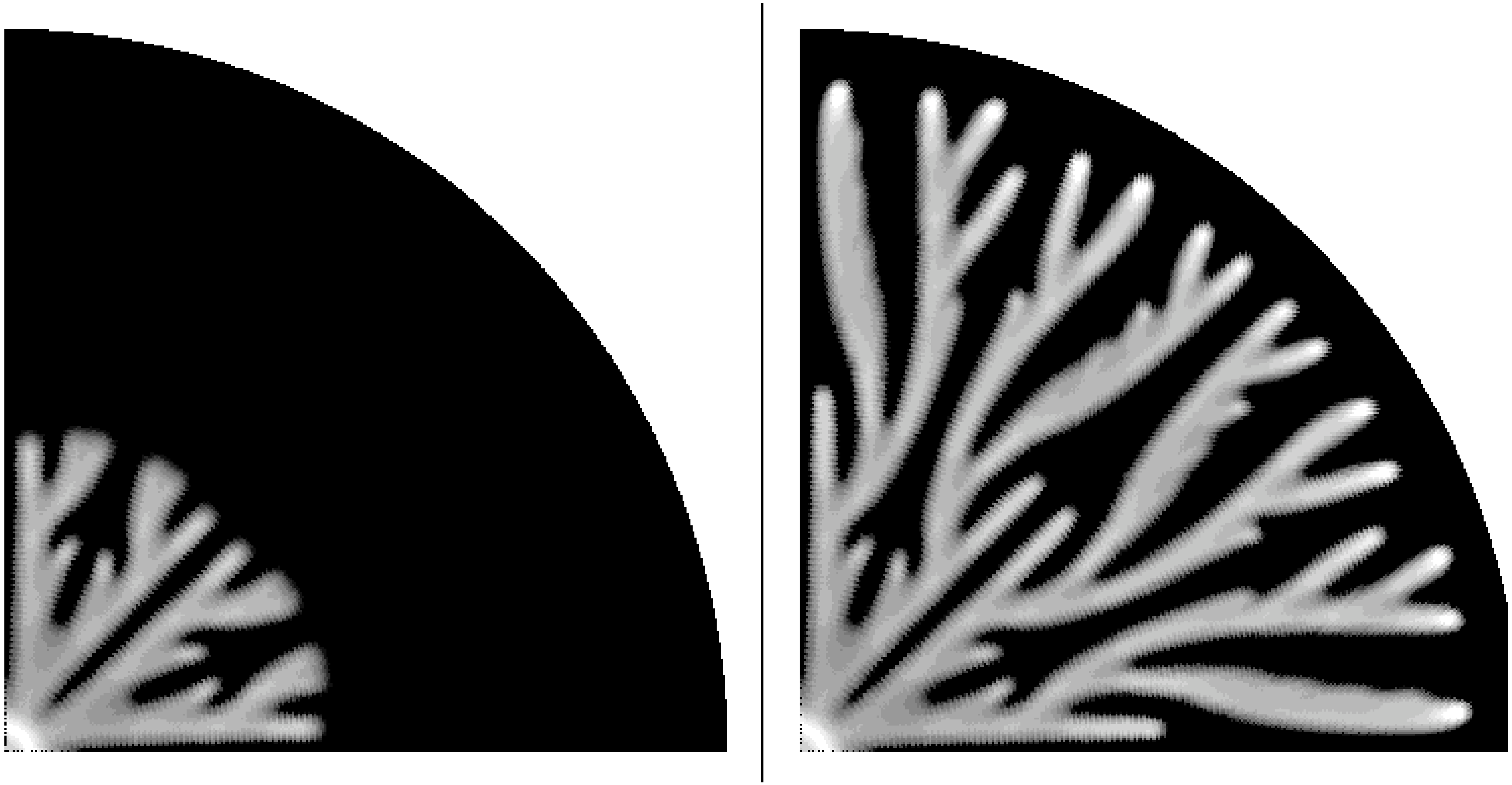
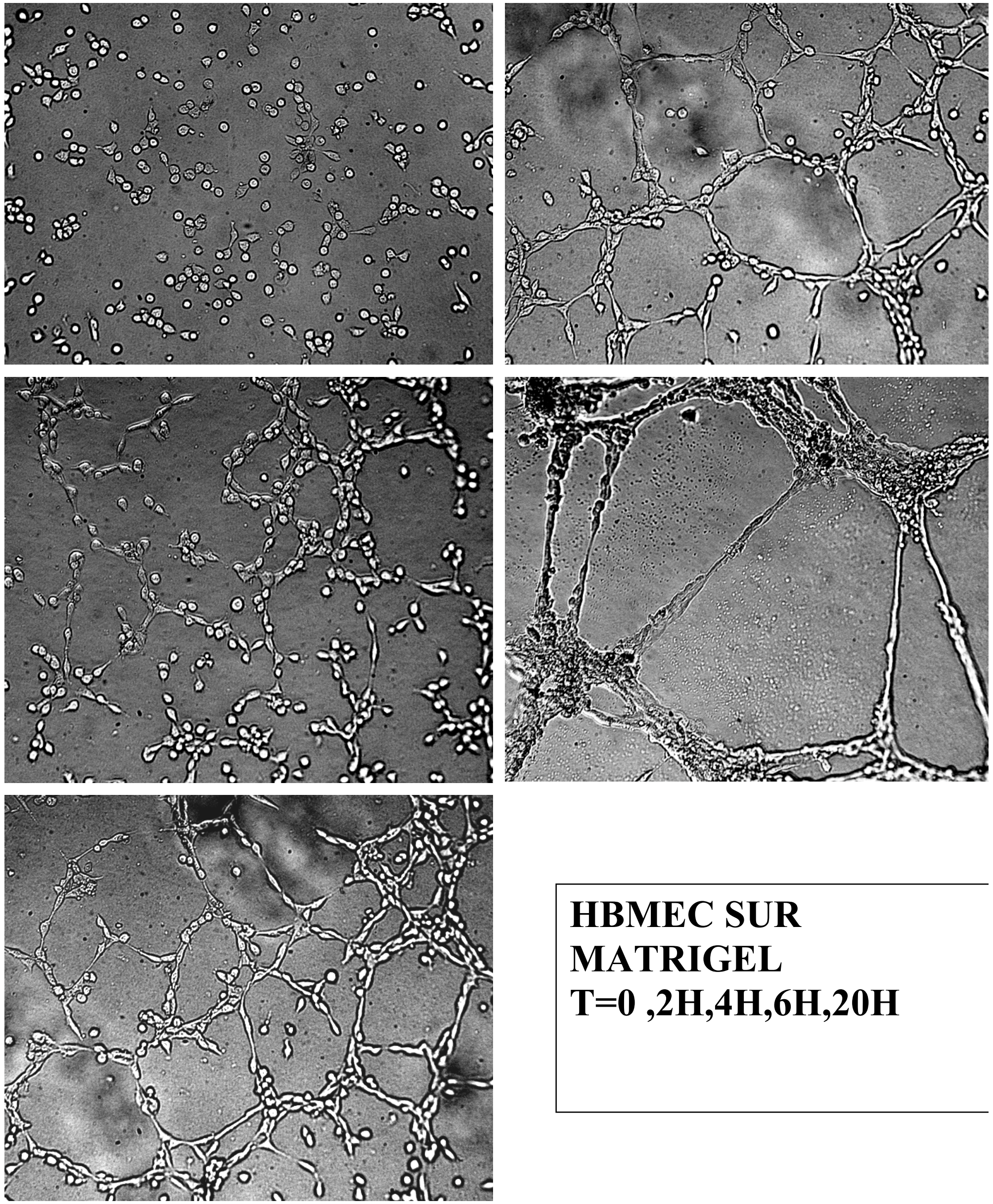


Fig. 29. 2D growth pattern $(b+s)$ of the Mimura et al. model with food chemotaxis included. $\chi_{0f}=0.06$. Other parameters as in Fig. 23a.



Simulation of Mimura’s model by A. Marrocco (inria, bang)

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*

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

Networks and hyperbolic models

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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

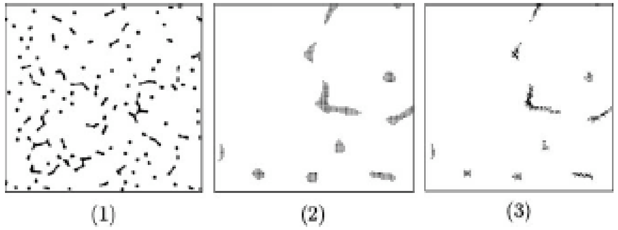


Fig. 4. Formation of network:*(1) density and zoom on the left-bottom corner of (2) the density and (3) velocity field obtained with* 50 $cells/mm^2$.

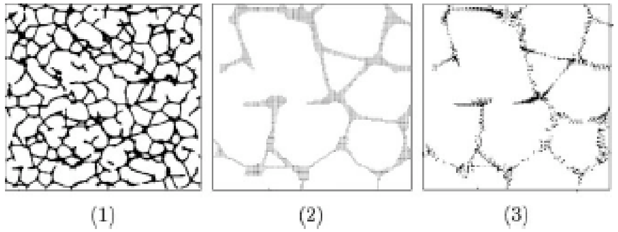
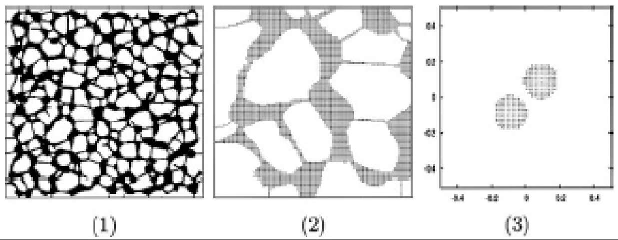
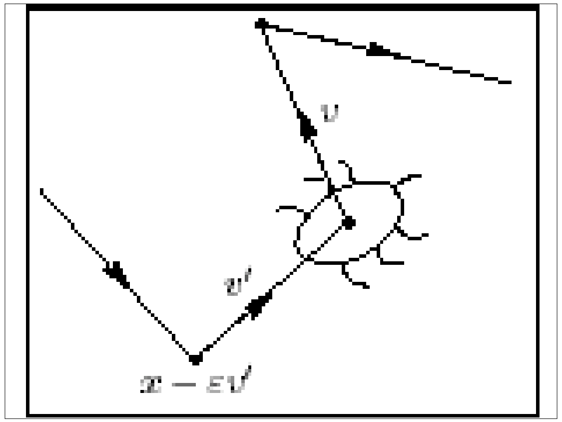


Fig. 5. Formation of network:*(1) density and zoom on the left-bottom corner of (2) the density and (3) velocity field obtained with* 100 $cells/mm^2$.



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.

$x+\varepsilon\xi$ represents a (fundamental) memory term.

KINETIC MODELS

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

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

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

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

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

KINETIC MODELS : diffusion limit

One can perform a parabolic rescaling based on the memory scale

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

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

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

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

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

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.

Conclusion

Several open questions are

-) Is it possible to prove blow-up for

$$\|n^0\|_{L^{d/2}} \quad \text{large (without moment condition)},$$

-) Despite the knowledge of possible blow-up modalities, proofs are not rigorous,

-) More elaborate systems (see V. Calvez, A. Marrocco),

-) Mathematical theory for dentritic growth,

-) Mathematical models for dentritic growth,

-) Modeling : genome, networks, coefficients.