Some models of cell movement

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OUTLINE OF THE LECTURE

I. Why study bacterial colonies growth?
II. Macroscopic models (Keller-Segel)
III. The hyperbolic Keller-Segel models
IV. Proof through the kinetic formulation
V. Movement at a microscopic scale (kinetic models)
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...
Examples of application fields

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

MIMURA's model

\[
\begin{align*}
\frac{\partial}{\partial t} n(t, x) - d_1 \Delta n &= r \ n \left( S - \frac{\mu \ n}{(n_0 + n)(S_0 + S)} \right), \\
\frac{\partial}{\partial t} S(t, x) - d_2 \Delta S &= -r \ n S, \\
\frac{\partial}{\partial t} f(t, x) &= r \ n \ \frac{\mu \ n}{(n_0 + n)(S_0 + S)}
\end{align*}
\]

The dynamics is driven by the source terms, i.e., by bacterial growth.
The mathematical modelling of cell movement goes back to Patlak (1953), E. Keller and L. Segel (70's)

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

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

\[
\begin{align*}
    \frac{\partial}{\partial t} n(t, x) - \Delta n(t, x) + \text{div}(n\chi \nabla c) &= 0, \quad x \in \mathbb{R}^d, \\
    -\Delta c(t, x) &= n(t, x),
\end{align*}
\]

The parameter \( \chi \) is the sensitivity of cells to the chemoattractant.
CHEMOTAXIS : Keller-Segel model

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

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, Laurençon, 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,

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

The existence proof relies on Jäger-Luckhaus argument

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

\[
= -\frac{4}{p} \int |\nabla n^{p/2}|^2 + \chi \int n^{p+1}
\]

parabolic dissipation \hspace{1cm} hyperbolic effect

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

\[
\int n^{p+1} \leq C_{\text{gns}}(d, p) \| \nabla n^{p/2} \|_{L^2}^2 \| n \|_{L^2}^d
\]
**CHEMOTAXIS : Keller-Segel model**

In dimension 2, for Keller and Segel model:

\[
\begin{align*}
  \frac{\partial}{\partial t} n(t, x) - \Delta n(t, x) + \text{div}(n\chi \nabla c) &= 0, \quad x \in \mathbb{R}^2, \\
  -\Delta c(t, x) &= n(t, x),
\end{align*}
\]

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

(i) for \( \|n^0\|_{L^1(\mathbb{R}^2)} < \frac{8\pi}{\chi} \), there are smooth solutions,

(ii) for \( \|n^0\|_{L^1(\mathbb{R}^2)} > \frac{8\pi}{\chi} \), there is creation of a singular measure (blow-up) in finite time.

(iii) For radially symmetric solutions, blow-up means

\[
n(t) \approx \frac{8\pi}{\chi} \delta(x = 0) + \text{Rem}.
\]
Existence part is based on the energy

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

and limit Hardy-Littlewood-Sobolev inequality (Beckner, Carlen-Loss, 96)

\[
\int_{\mathbb{R}^2} f \log f \, dx + \frac{2}{M} \int_{\mathbb{R}^2 \times \mathbb{R}^2} f(x)f(y) \log |x-y| \, dx \, dy \geq M(1 + \log \pi + \log M).
\]

Notice that in \( d = 2 \) we have

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

\[
n \in L^1_{\log} \implies \int nc < \infty.
\]
From A. Marrocco (INRIA, BANG)
Why a need for hyperbolic models

- We see front motion
- The parabolic scale does not explain all the phenomena
- Experiments access to finer scales
The hyperbolic Keller-Segel system (Dolak, Schmeiser)

\[
\begin{aligned}
\quad &\frac{\partial}{\partial t} n(t, x) + \text{div}\left[n(1-n)\nabla c\right] = 0, \quad x \in \mathbb{R}^d, \ t \geq 0, \\
\quad &-\Delta c + c = n, \\
\quad &n(t, x) = n^0(x), \quad 0 \leq n^0(x) \leq 1, \ n^0 \in L^1(\mathbb{R}^d).
\end{aligned}
\]

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 on multiple sclerosis
Hyperbolic Keller-Segel model

\[
\begin{aligned}
\begin{cases}
\frac{\partial}{\partial t}n(t, x) + \text{div}\left[ n(1 - n)\nabla c \right] = 0, & x \in \mathbb{R}^d, t \geq 0, \\
-\Delta c + c = n, \\
n(t, x) = n^0(x), & 0 \leq n^0(x) \leq 1, \quad n^0 \in L^1(\mathbb{R}^d).
\end{cases}
\end{aligned}
\]

Difficulties. All the properties of Scalar Coneservation 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

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

Difficulties. All the properties of Scalar Conservation 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

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

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

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

\[
\begin{aligned}
\begin{cases}
\frac{\partial}{\partial t}n_\varepsilon(t, x) + \text{div}\left[n_\varepsilon(1 - n_\varepsilon)\nabla c_\varepsilon\right] = \varepsilon\Delta n_\varepsilon, & x \in \mathbb{R}^d, t \geq 0, \\
-\Delta c_\varepsilon + c_\varepsilon = n_\varepsilon.
\end{cases}
\end{aligned}
\]
Hyperbolic Keller-Segel model

Related to a problem coming from oil recovery

\[
\begin{aligned}
\frac{\partial}{\partial t}n(t, x) + \text{div}\left[n(1 - n) \ u\right] &= 0, \\
u &= K \nabla p, \\
\text{div} \ u &= 0,
\end{aligned}
\]

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

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

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

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

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

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

for entropy solutions

\[ \partial_t \chi(\xi; n) + a(\xi) \nabla_y \chi(\xi; n) = \partial_\xi m, \quad m \geq 0. \]

because for \( S \) convex

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

\[ \iff \frac{\partial}{\partial t} S(n(t, x)) + \text{div} \eta^S(n) \leq 0, \quad x \in \mathbb{R}^d, \ t \geq 0, \]
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

\[ \partial_t |\chi(\xi; n^1_\varepsilon) - \chi(\xi; n^2_\varepsilon)|^2 + a(\xi) \nabla_y |\chi(\xi; n^1_\varepsilon) - \chi(\xi; n^2_\varepsilon)|^2 \\
= 2 \left( \chi(\xi; n^1_\varepsilon) - \chi(\xi; n^2_\varepsilon) \right) \partial_\xi (m^1_\varepsilon - m^2_\varepsilon) \]

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

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 \(\rho\) 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,
\[
f = f^2, \quad \text{in other words } f = \chi(\xi; n).
\]
Networks and hyperbolic models
A group of Torino Ambrosi, Gamba, Preziosi et al proposed a hydrodynamics model

\[
\begin{align*}
\frac{\partial}{\partial t} n(t, x) + \text{div}(n u) &= 0, \quad x \in \mathbb{R}^2, \\
\frac{\partial}{\partial t} u(t, x) + u(t, x) \cdot \nabla u + \nabla n^\alpha &= \chi \nabla c - \mu u, \\
\frac{\partial}{\partial t} c(t, x) - \Delta c(t, x) + \tau c(t, x) &= n(t, x).
\end{align*}
\]
Networks and hyperbolic models

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

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 56 cells/m².

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/m².
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.
Denote by $f(t, x, \xi)$ the density of cells moving with the velocity $\xi$.

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

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

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

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

Nonlocal, quadratic term on the right hand side for $k_\pm(\cdot, \xi, \xi')$ sublinear.
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 $L^\infty$ when we replace the specific form of $K$ by

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

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

Theorem (Bournaveas, Calvez, Gutierrez, P.)
Assume that
\[ k \left( \nabla c(x - \varepsilon \xi') \right) + k \left( \nabla c(x + \varepsilon \xi) \right). \]
For SMALL initial data, there is a GLOBAL solution to the kinetic model.

Open question Are there cases of blow-up?

Related questions Internal variables (Erban, Othmer, Hwang, Dolak, Schmeiser), quorum sensing type limitations Chalub, Rodriguez)
One can perform a parabolic rescaling based on the memory scale
\[
\frac{\partial}{\partial t} f(t, x, \xi) + \frac{\xi \cdot \nabla_x f}{\varepsilon} = \frac{\mathcal{K}[f]}{\varepsilon^2},
\]
\[
\mathcal{K}[f] = \int K(c; \xi, \xi') f'd\xi' - \int K(c; \xi', \xi) d\xi' \ f,
\]
\[-\Delta c(t, x) = n(t, x) := \int f(t, x, \xi) d\xi,
\]
\[K(c; \xi, \xi') = k_-(c(x - \varepsilon \xi')) + k_+(c(x + \varepsilon \xi)).\]

**Theorem (Chalub, Markowich, P., Schmeiser)** With the same assumptions, as \( \varepsilon \to 0 \), then locally in time,
\[
f_\varepsilon(t, x, \xi) \to n(t, x), \quad c_\varepsilon(t, x) \to c(t, x),
\]
\[
\left\{ \begin{array}{l}
\frac{\partial}{\partial t} n(t, x) - \text{div}[D \nabla n(t, x)] + \text{div}(n \chi \nabla c) = 0, \\
-\Delta c(t, x) = n(t, x).
\end{array} \right.
\]
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 collaborators

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A. Marrocco