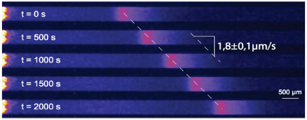
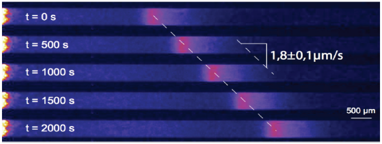
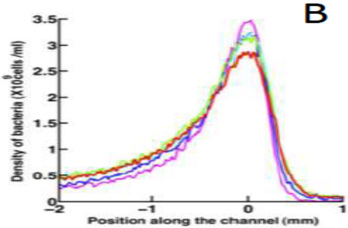
Bacterial movement by run and tumble : models, patterns, pathways, scales

Benoît Perthame



FLKS : Why ?





- Adler's famous experiment for E. Coli (1966)
- Curie institute : Buguin, Saragosti, Silberzan,
- Explained by the Flux Limited Keller-Segel system

FLKS : Why ?

Robust traveling pulses have been explained using the Flux-Limited-Keller-Segel system

$$\begin{cases} \frac{\partial n(x,t)}{\partial t} - \Delta n + \mathrm{div}(n\phi(|\nabla c|)\,\nabla c) = 0, \quad x \in \mathbb{R}^d,\ t > 0, \\ \tau \frac{\partial c(x,t)}{\partial t} = \Delta c + n - \alpha c. \end{cases}$$

$$\phi(|\nabla c|) \approx \frac{1}{\sqrt{1 + \delta |\nabla c|^2}}$$

Saragosti-Calvez et al, Calvez-Schmeiser,...

Dolak-Schmeiser, Erban-Othmer, Chertock et al., Bellomo-Winkler, Emako et al., James-Vauchelet, BP-Vauchelet-Wang

FLKS : Why ?

We consider the chemotactic background is imposed.

$$\frac{\partial n(x,t)}{\partial t} - \Delta n + \mathrm{div}(n\phi(|\nabla c|)\,\nabla c) = 0, \quad x \in \mathbb{R}^d,\ t > 0,$$

$$\phi(|\nabla c|)\,|\nabla c| \leq \mathsf{Cst}$$

Existence and uniform bounds follow from Nash-Alikakos iterations.

Interest is more about relations to run and tumble

Method

1. Cell scale. Boltzman's kinetic theory describes run-tumble phenomena at individual cell scale

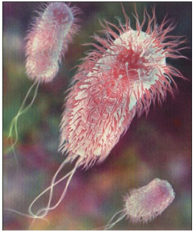
2. Multiscale analysis. Derive FLKS macroscopic from mesoscopic

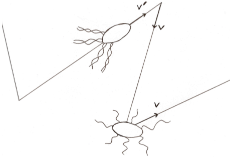
3. Pattern formation ability. Stiffness-related instabillities for FLKS model

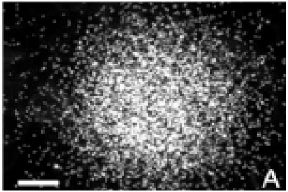
4. Biochemical pathways. Explain the cell behaviour

Kinetic models

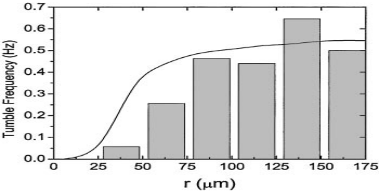
E. Coli is known (since the 80's) to move by run and tumble Alt, Dunbar, Othmer, Stevens, Hillen...





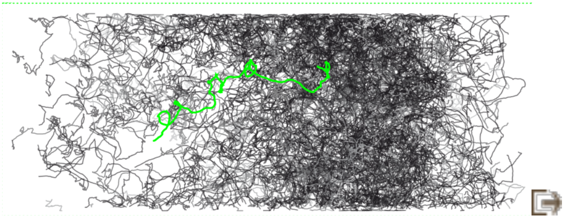


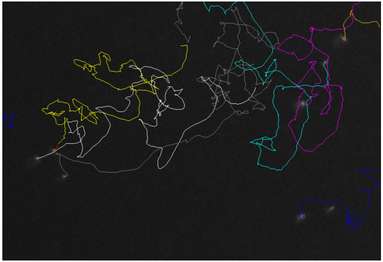
Mittal et al Cluster of bacteria



Tumbling frequency/function of cell position

A beautiful example of multiscale motion





Kinetic models

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

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

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

- Boltzmann formalism for molecular collisions/scattering ;
- There are now TWO variables x, ξ (difficult to compute)
- Used to derive macroscopic models (Boltzmann $\rightarrow$ Navier-Stokes)

Kinetic models

Simplest example of tumbling kernel

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

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

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

Related to linear scattering with a changing background.

Kinetic models : diffusion limit

Multiscale analysis based on the memory time scale

$$\begin{cases} \frac{\partial}{\partial t} f(t,x,\xi) + \frac{\xi \cdot \nabla_x f}{\varepsilon} = \frac{\mathcal{K}[c,f]}{\varepsilon^2}, \\ \mathcal{K}[f] = \int K(c;\xi,\xi') f' d\xi' - \int K(c;\xi',\xi) d\xi' \; f, \\ K(c;\xi,\xi') = \; k_-\big(c(x-\varepsilon\xi')\big) + \; k_+\big(c(x+\varepsilon\xi)\big). \end{cases}$$

Theorem As $\varepsilon \to 0$, then for short times,

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

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

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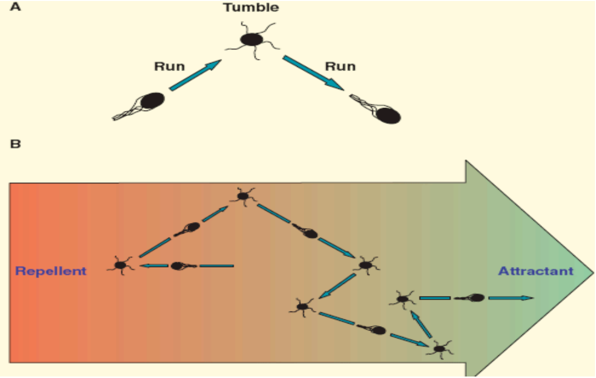
$$f_\varepsilon(t,x,\xi) \to n(t,x),$$

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

$$D(c) = D_0 \, \frac{1}{k_-(c)+k_+(c)}, \quad \chi(c) = \chi_0 \, \frac{k'_-(c)+k'_+(c)}{k_-(c)+k_+(c)} \, .$$

Pulse waves



When c increases, jumps are longer

Pulse waves

$$\frac{\partial}{\partial t} f(t,x,\xi) + \xi \cdot \nabla_x f = \int K(c;\xi') f(\xi') d\xi' - \int K(c;\xi) d\xi' \ f(\xi)$$

This leads Dolak and Schmeiser to choose

$$K(c;\xi') = \mathbf{K}\Big(\underbrace{\frac{\partial c}{\partial t} + \xi' . \nabla c}_{D_t c} \Big)$$

With

$$\mathbf{K}(\cdot) \text{ decreasing and stiff}$$

Pulse waves

$$\frac{\partial}{\partial t} f(t,x,\xi) + \xi \cdot \nabla_x f = \int K(c;\xi') f(\xi') d\xi' - \int K(c;\xi) d\xi' \ f(\xi)$$

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Example (very stiff)

$$\mathbf{K}(D_t c) = \begin{cases} k_- & \text{for } D_t c < 0, \\ k_+ < k_- & \text{for } D_t c > 0. \end{cases}$$

Singuler hyperbolic limit (James-Vauchelet)

Kinetic models : diffusion limit

$$\frac{\partial}{\partial t} f(t,x,\xi) + \xi \cdot \nabla_x f = \int K(c;\xi') f(\xi') d\xi' - \int K(c;\xi) d\xi' \; f(\xi)$$

With

$$K(c;\xi,\xi') = \mathbf{K}_\varepsilon \Big(\underbrace{\frac{\partial c}{\partial t} + \xi' . \nabla c}_{D_t c} \Big)$$

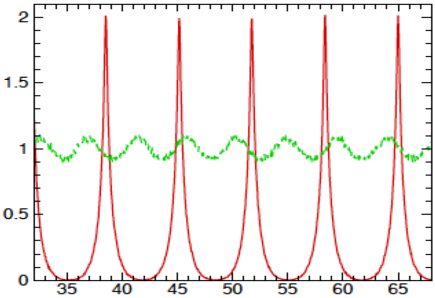
the diffusion limit is the Flux Limited Keller-Segel system (BP, Vauchelet and Z. A. Wang

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) - \Delta n(t,x) + \mathrm{div}(nU) = 0, \\ U = \phi(|\nabla c|) \, \nabla c \end{cases}$$

and $\phi(|\nabla c|)$ is smooth

FLKS : instability

$$\frac{\partial}{\partial t} f(t,x,\xi) + \underbrace{\xi \cdot \nabla_x f}_{\text{run}} = \underbrace{\mathcal{K}_\delta[c,f]}_{\text{tumble}} + \underbrace{r(1-n(x,t))f(t,x,\xi)}_{\text{cell division/death}},$$

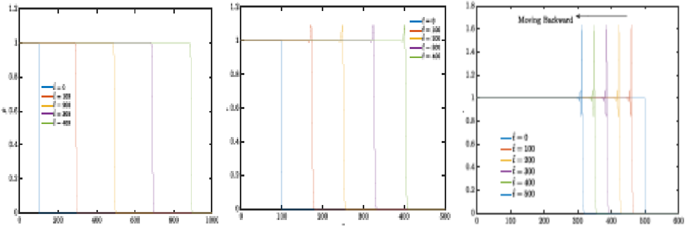


Numerical observation with a Monte-Carlo code (S. Yasuda)

The steady state $n \equiv 1$ is not obeserved

FLKS : instability

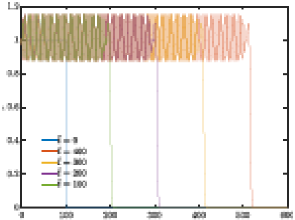
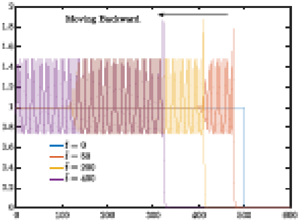
$$\begin{cases} \frac{\partial}{\partial t} n(t,x) - \Delta n(t,x) + \mathrm{div}(n U_\delta) = r(1-n)n, \\ U_\delta = \phi_\delta(|\nabla c|)\, \nabla c, \qquad -\Delta c + \alpha c = n, \end{cases}$$



Numerical observation : forward left-center, backward-right

FLKS : instability

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) - \Delta n(t,x) + \mathrm{div}(n U_\delta) = r(1-n)n, \\ U_\delta = \phi_\delta(|\nabla c|)\, \nabla c, \qquad -\Delta c + \alpha c = n, \end{cases}$$

Numerical observation : forward-left, backward-right

Competition between

- Fisher-KPP type of wave (propagating in the empty region)
- attraction where cells emit the chemoattractant

FLKS : instability

$$\frac{\partial}{\partial t} f(t,x,\xi) + \underbrace{\xi \cdot \nabla_x f}_{\textbf{run}} = \underbrace{\mathcal{K}_\delta[c,f]}_{\textbf{tumble}} + \underbrace{r(1-n(x,t))f(t,x,\xi)}_{\textbf{cell division/death}},$$

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Theorem (BP, S. Yasuda)

- Both for the kinetic and FLKS models,
- for stiff response (δ small)

we have

- the steady state $n \equiv 1$ is linearly unstable
- in the sense of Turing (only bounded wave length)

FLKS : instability

Proof

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) - \Delta n(t,x) + \mathrm{div}(n\phi_\delta(|\nabla c|)\,\nabla c) = r(1-n)n, \\ -\Delta c + \alpha c = n, \end{cases}$$

Consider a perturbation

$$n = 1 + \delta_n e^{ix.k} e^{\lambda t}, \qquad c = 1 + \delta_c e^{ix.k} e^{\lambda t}$$

FLKS : instability

Proof

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) - \Delta n(t,x) + \mathrm{div}\big(n\phi_\delta(|\nabla c|)\,\nabla c\big) = r(1-n)n, \\ -\Delta c + \alpha c = n, \end{cases}$$

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One finds

$$\begin{cases} \lambda \delta_n + |k|^2 \delta_n - \phi(0)|k|^2 \delta_c = -r\delta_n \\ |k|^2 \delta_c + \alpha \delta_c = \delta_n \end{cases}$$

Proof

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) - \Delta n(t,x) + \mathrm{div}(n\phi_\delta(|\nabla c|)\,\nabla c) = r(1-n)n, \\ -\Delta c + \alpha c = n, \end{cases}$$

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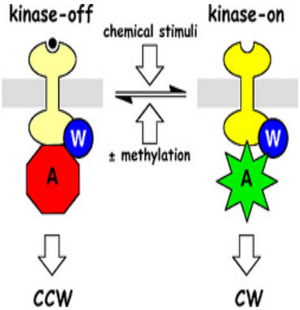
$$\lambda = -(|k|^2 + r) + \phi(0)\frac{|k|^2}{\alpha + |k|^2} > 0 \quad \text{for } |k| \text{ moderate, } \phi(0) \text{ large}$$

Biochemical pathways

Can one explain the tumbling rate

$$K(c;\xi,\xi') = \mathbf{K}\left(\frac{\partial c}{\partial t} + \xi'.\nabla c\right)?$$



Extracellular medium

———membrane———

Cytosol

Biochemical pathways

Can one explain the tumbling rate

$$K(c;\xi,\xi') = \mathbf{K}\Big(\frac{\partial c}{\partial t} + \xi'.\nabla c\Big)?$$

Use the internal biochemical pathway controling tumbling,

$f(t,x,\xi,m)$ m= receptor methylation level (internal state)

c = external concentration

See Erban-Othmer, Dolak-Schmeiser, Zhu *et al*, Jiang *et al*

Biochemical pathways

$$\frac{\partial}{\partial t} f(t,x,\xi,m) + \xi \cdot \nabla_x f \underbrace{+ \frac{\partial}{\partial m}[R(m,c)f] =}_{\text{Change in methylation level}} \mathcal{K}[m,c][f]$$

$$\mathcal{K}[m,c][f] = \int \left[K(m,c,\xi,\xi')f(t,x,\xi',m) - K(m,c,\xi',\xi)f(t,x,\xi,m)\right] d\xi'$$

Question : Can it be related to the tumbling kernel

$$K(c;\xi,\xi') = \mathbf{K}\left(\frac{\partial c}{\partial t} + \xi'.\nabla c\right)$$

Biochemical pathways

$$\frac{\partial}{\partial t} f(t,x,\xi,m) + \xi \cdot \nabla_x f + \frac{1}{\varepsilon} \frac{\partial}{\partial m} [\bar{R}(m - M(c))f] = \mathcal{K}_\varepsilon[m,c][f]$$

(fast adaptation)

$$\mathcal{K}_\varepsilon[m,c][f] = \int_{\xi'} \left[K\left(\frac{m - M(c)}{\varepsilon}, \xi, \xi'\right) f(t,x,\xi',m) - K(\dots,\xi',\xi) f(t,x,\xi,m) \right]$$

(stiff response)

Theorem : As $\varepsilon \to 0$, $\quad f_\varepsilon(t,x,\xi,m) \to \bar{f}(t,x,\xi)\, \delta\big(m - M(c)\big)$

and the tumbling kernel for $\bar{f}(t,x,\xi)$ is $\mathbf{K}\big(\frac{\partial c}{\partial t} + \xi'.\nabla c\big)$.

Biochemical pathways

$$\frac{\partial}{\partial t} f(t,x,\xi,m) + \xi \cdot \nabla_x f + \frac{1}{\varepsilon} \frac{\partial}{\partial m} [R(m,c) f] =$$

$$\int \left[K\left(\frac{m - M(c)}{\varepsilon}, \xi, \xi'\right) f(t,x,\xi',m) - K(\ldots, \xi', \xi) f(t,x,\xi,m) \right] d\xi'$$

Biochemical pathways

$$\frac{\partial}{\partial t} f(t,x,\xi,m) + \xi \cdot \nabla_x f + \frac{1}{\varepsilon} \frac{\partial}{\partial m}[R(m,c)f] =$$

$$\int \left[K\left(\frac{m-M(c)}{\varepsilon},\xi,\xi'\right) f(t,x,\xi',m) - K(\dots,\xi',\xi) f(t,x,\xi,m)\right] d\xi'$$

$$f(t,x,\xi,m) = \varepsilon q\left(t,x,\xi,\frac{m-M(c)}{\varepsilon}\right), \qquad y = \frac{m-M(c)}{\varepsilon}$$

Biochemical pathways

$$\frac{\partial}{\partial t}f(t,x,\xi,m)+\xi\cdot\nabla_x f+\frac{1}{\varepsilon}\frac{\partial}{\partial m}[R(m,c)f]=$$

$$\int\left[K\left(\frac{m-M(c)}{\varepsilon},\xi,\xi'\right)f(t,x,\xi',m)-K(\ldots,\xi',\xi)f(t,x,\xi,m)\right]d\xi'$$

$$f(t,x,\xi,m)=\varepsilon q\left(t,x,\xi,\frac{m-M(c)}{\varepsilon}\right),\qquad y=\frac{m-M(c)}{\varepsilon}$$

$$\frac{\partial}{\partial t}q(t,x,\xi,y)+\xi\cdot\nabla_x f+\frac{1}{\varepsilon}\frac{\partial}{\partial y}[yG(y)-D_tM]q=$$

$$\int\left[K(y,,\xi,\xi')q(t,x,\xi',y)-K(y,\xi',\xi)q(t,x,\xi,y)\right]d\xi'$$

Biochemical pathways

$$\frac{\partial}{\partial t} f(t,x,\xi,m) + \xi \cdot \nabla_x f + \frac{1}{\varepsilon}\frac{\partial}{\partial m}[R(m,c)f] =$$

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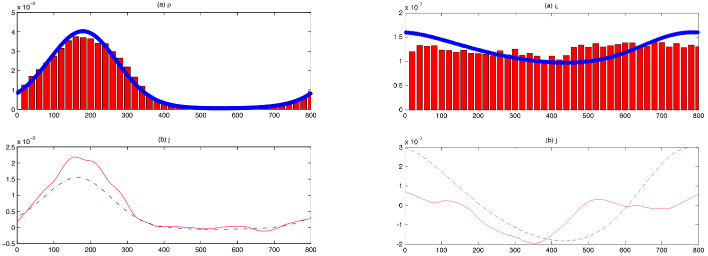
$$f(t,x,\xi,m) = \varepsilon q(t,x,\xi,\frac{m-M(c)}{\varepsilon}), \qquad y = \frac{m-M(c)}{\varepsilon}$$

$$\frac{\partial}{\partial t} q(t,x,\xi,y) + \xi \cdot \nabla_x f + \frac{1}{\varepsilon}\frac{\partial}{\partial y}[yG(y) - D_t M]q =$$

$$\int \left[K(y,,\xi,\xi')q(t,x,\xi',y) - K(y,\xi',\xi)q(t,x,\xi,y)\right] d\xi'$$

Forces $q \longrightarrow \delta(y - \frac{D_t M}{G(0)})$

Biochemical pathways



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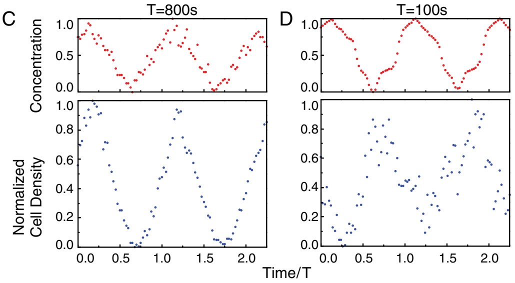

Biochemical pathways and FLKS

$$\varepsilon^2 \frac{\partial}{\partial t} f(t,x,\xi,m) + \varepsilon \xi \cdot \nabla_x f + \varepsilon \frac{\partial}{\partial m}[m - \xi \nabla c] f =$$

$$K(m) \int \left[f(t,x,\xi',m) - f(t,x,\xi,m) \right] d\xi'$$

Theorem. With this scaling, f converges and we obtain the FLKS system.

Abnormal diffusions

nature COMMUNICATIONS

ARTICLE

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Swarming bacteria migrate by Lévy Walk

Gil Ariel[1], Amit Rabani[2], Sivan Benisty[2], Jonathan D. Partridge[3], Rasika M. Harshey[3] & Avraham Be'er[2]

$$\varepsilon^{1+\mu}\frac{\partial}{\partial t}g(t,x,\xi,m)+\varepsilon\xi\cdot\nabla_x g+\varepsilon^s\Delta_m g=\mathcal{K}[m][g]$$

When $\mathcal{K}[m][g]$ degenerates,

$$\mathcal{K}[m][g]\approx 0 \quad \text{as} \quad m\to\infty,$$

the limiting behaviour is Fractional Laplacian

$$\frac{\partial n}{\partial t}-\Delta^\alpha n=0$$

Conclusion

- The FLKS is a macroscopic model founded on the individual behaviour of *E. coli*

- The FLKS exhibits robust traveling band solutions (inherited from the kinetic)

- Pattern formation ability and instabilities are observed, even when including division/death terms

Conclusion

Thanks to :

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THANK YOU