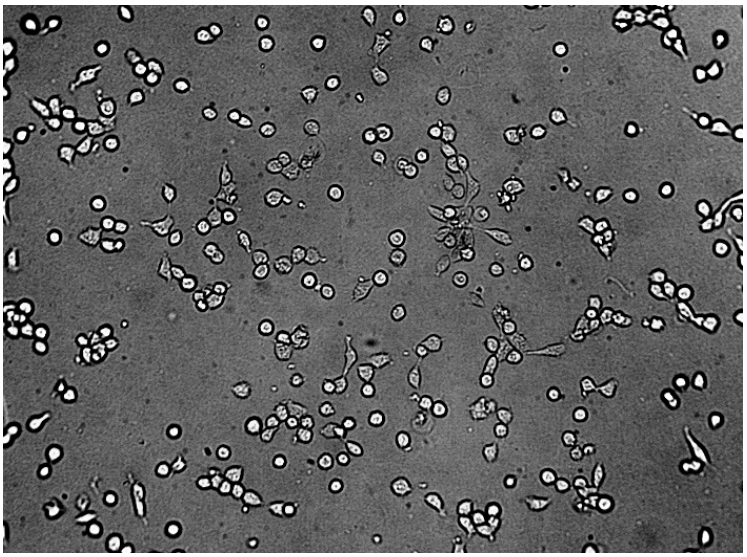
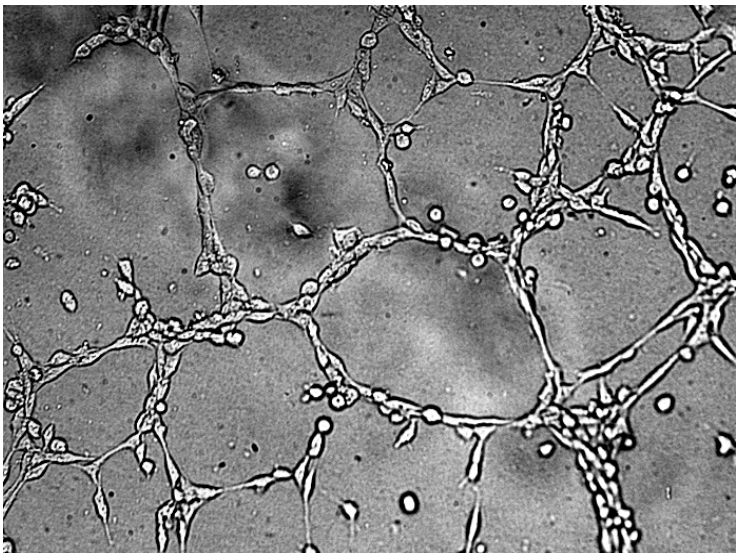
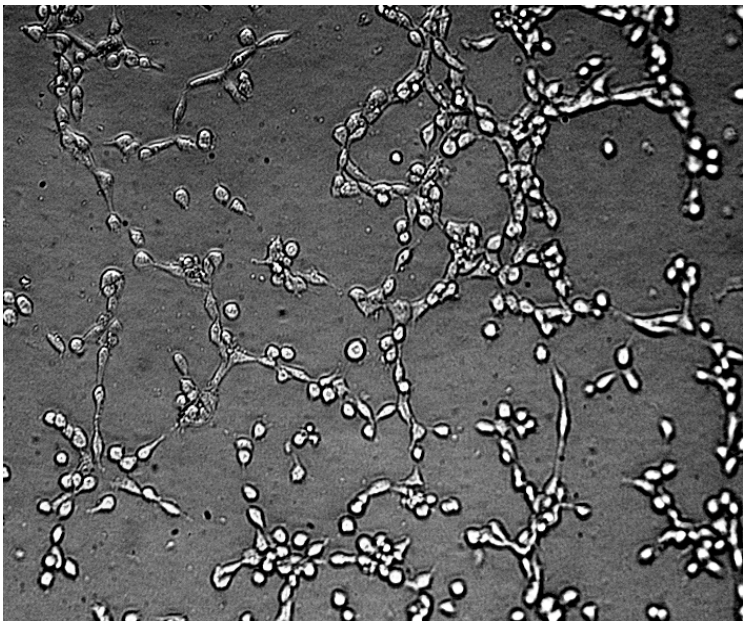
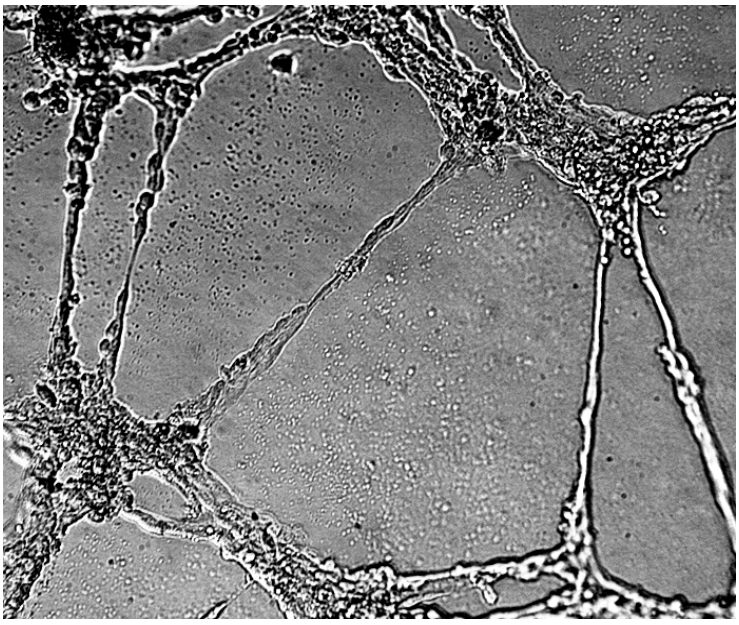
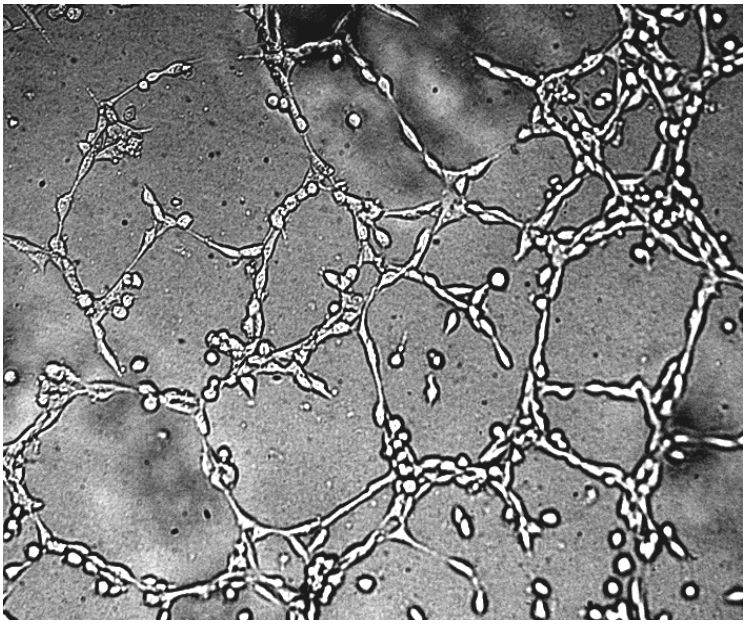
Initiation of angiogenesis

When considering human endothelial cells, the pattern formed is quite different and cannot be explained by the parabolic model.

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

Initiation of angiogenesis

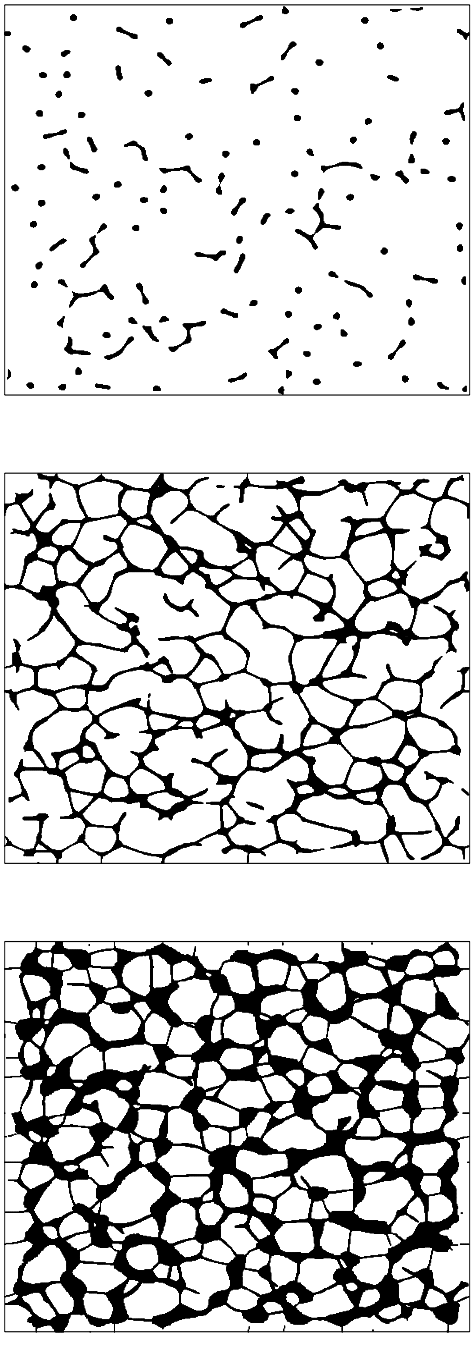
A group of Torino Ambrosi, Gamba, Preziosi et al proposed a *hydrodynamics model*

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

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

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

is neglected.



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Formation of network with hydrodynamic model: density obtained with 50, 100, 400 $cells/mm^2$.

Kinetic picture: motivation

There are three mitivations for a kinetic picture

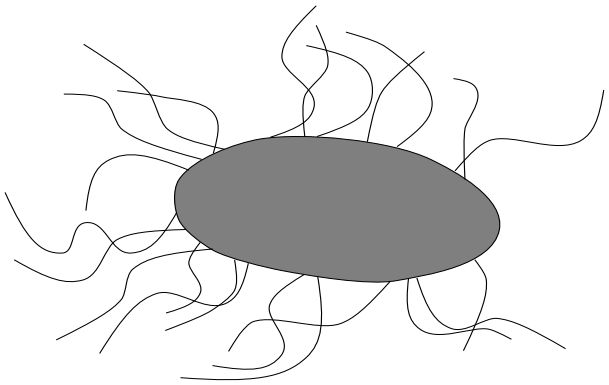
Some experiments go in these direction

Unify the two previous models

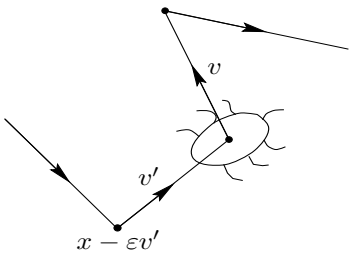
Being given that an individual can only measure a concentration of chemoattractant (but not a gradient, neither compare two concentrations at two different times)... How is it possible to move in the direction of higher concentration?

The bacterium E. Coli can do that by 'run and tumble', where the tumble frequency depends upon a chemoattractant concentration.

Does this really work?



For E. Coli, it has been reported in the 80's that the motion is not regular. The bacteria run straight for approximately one second and then turn and choose a new direction.



Run and tumble movement for E. Coli.

This has lead Alt, Dunbar, Othmer, Stevens, to propose a kinetic model for the motion

Kinetic picture: equation

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

They are subject to run and tumble with a rate depending on the chemoattractant concentration $c(t, x)$.

Kinetic picture: equation

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

They are subject to run and tumble with a rate depending on the chemoattractant concentration $c(t,x)$.

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

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

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

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

This memory effect is fundamental.

Kinetic picture: equation

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

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

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

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

Theorem (Chalub, Markowich, P., Schmeiser)
Assume that $0 \leq k(c;\xi,\xi') \leq C(1+c)$ 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 w replace the specific form of K by

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

Kinetic picture: diffusive scaling

The physical time scale ε allows one to rescale in space and time the system

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

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

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

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

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

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

and (n,c) satisfies the Keller-Segel model

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

Kinetic picture: diffusive scaling

The transport coefficients are given by

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

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

The mathematical interpretation is as follows
-) the diffusion D comes from the turning frequency
-) the drift χ comes from the memory effect

If one decides to turn according only to the present concentration (the higher it is the higher is the rate of turning) then one does not move towards the higher concentration.

The delay is fundamental.

Kinetic picture: diffusive scaling

An idea of the proof is as follows. Decompose $K(c;\xi,\xi')$ in a symmetric and antisymmetric part

$$K(c;\xi,\xi') = K^S(c;\xi,\xi') + \varepsilon K^A(c;\xi,\xi'),$$

$$K^S(c;\xi,\xi') = K^S(c;\xi',\xi),$$

What is the L^2 bound ?

$$\frac{\partial}{\partial t}\int (f_\varepsilon)^2 \;\; dx\, d\xi + \int \frac{K^S}{\varepsilon^2}\,(f-f')^2 dx\, d\xi$$

$$= \int \frac{K^A}{\varepsilon}\,(f-f')(f+f')dx\, d\xi$$

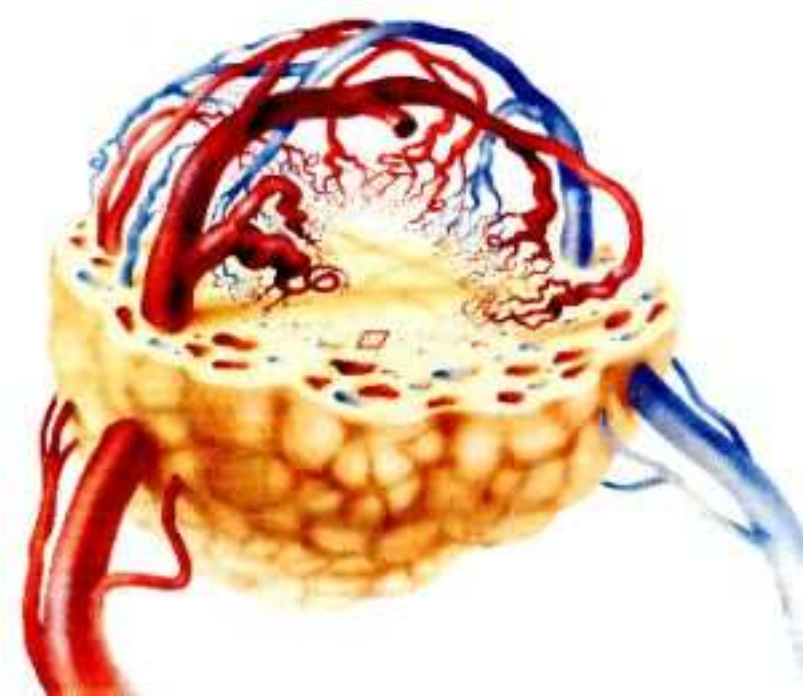
$$\leq \int \frac{K^S}{\varepsilon^2}\,(f-f')^2 dx\, d\xi + \int \frac{(K^A)^2}{K^S}\, f^2 dx\, d\xi$$

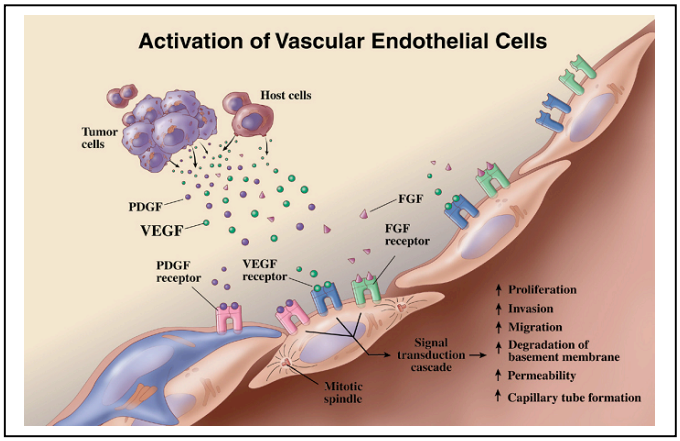
and Gronwall argument proves a local L^2 bounds (because K depends on c_ε and thus on f_ε itself) .

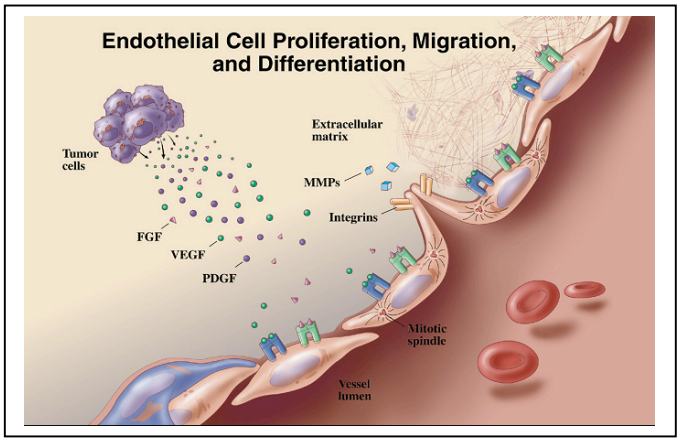
And K^S is roughly $k(c_\varepsilon)$, while K^A converges to $k'(c_\varepsilon)(\xi-\xi')$.

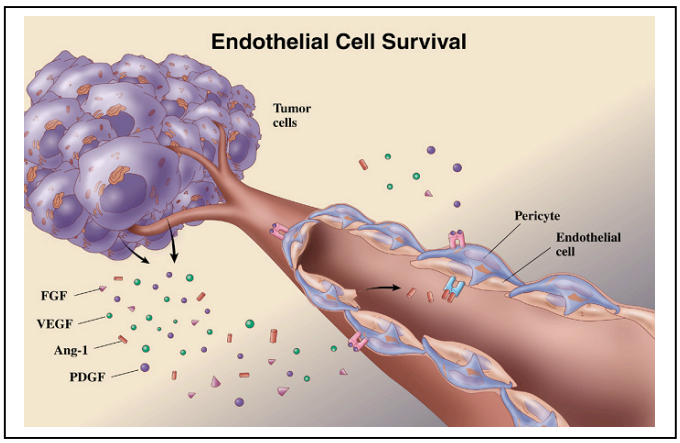
Angiogenesis

Angiogenesis describes the development of capillary blood vessels leading to a vascularized tumor.




Activation of Vascular Endothelial Cells
Host cells
Tumor cells
PDGF
VEGF
FGF
FGF receptor
PDGF receptor
VEGF receptor
Proliferation
Invasion
Migration
Degradation of basement membrane
Permeability
Capillary tube formation
Signal transduction cascade
Mitotic spindle


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


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

Angiogenesis: mathematical model

Chaplain, Levine, Sleeman proposed models which simpler version is:

-) $n(t,x)$ is the density of capillary blood vessels

-) $c(t,x)$ is the concentration of chemoattactant

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

This is close to Keller-Segel model for chemotaxis but this models makes two major differences:

1) the chemoattractant is no longer emited but consumed

Angiogenesis: mathematical model

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

2) This model has a positive energy

$$\mathcal{E}(t) = \int_\Omega [n \ln(n) + n|\nabla c|^2] \leq \mathcal{E}^0,$$

while Keller-Segel model admits the energy

$$\mathcal{E}(t) = \int_\Omega [n \ln(n) - nc] \leq \mathcal{E}^0,$$

and this quantity has no sign, allowing for blow-up in L^p.

Angiogenesis: mathematical model

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

2) This model has a positive energy

$$\mathcal{E}(t) = \int_\Omega [n \ln(n) + n|\nabla c|^2] \leq \mathcal{E}^0,$$

As a consequence we have

Theorem (Corrias-Perthame-Zaag)

(i) For $c^0 \leq K$ with finite initial energy and $n^0 \ln(1 + |x|^{d+1}) \in L^1(R^d)$, then there is a weak solution with finite energy (and the nonlinearities are well defined).

(ii) For $\|n^0\|_{L^{d/2}}$ small there is a strong solution (that propagates all L^q norms).

Movement of cells: CONCLUSION

Movment of cells is a important phenomenon related to tumor developments. It rises several types of questions in terms of

-) Mathematics: variety of models, the theory is not complete, especially in 3D,

-) Scientific computation: do the models reproduce the patterns expected?

-) Modelling: this can assert some biological observations and lead to simple models