Mathematical models for cell motility with nonlocal repulsion from saturated areas.

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Cell motility importance

Cellular movements are critical for a wide number of biological processes:

- embryogenesis,
- tissue formation,
- wound healing,
- defense against infection,
- control cancer metastasis and birth defects, among other.

Hence, the cellular motion has become an *increasingly interesting topic within biomedical research*.

It is well known that if cells get too close to each other, they *repulse* , while if they get too far away from each other, they *attract*.
On the other hand, they also exhibit certain *random movement*.

Saturation and repulsion prevent to occur high accumulations at narrow zones or single points.

Non-local operators

From a mathematical point of view, *nonlocal operators are crucial* to understand the immense majority of biological processes, by their *ability to taking into account the effect of the surrounding environment* to describe what happens at certain point, in contrast to local differential operators.

Non-local advection is a mechanism present in the mathematical modelling of a wide range of biological phenomena. Animals explore their surroundings to find prey, avoid predators or aggregate in colonies, herds or swarms.

This non-local sensing, which in animals is due mainly to using smell, hearing or sight, it also occurs at cellular level, through the extension of *long thin protrusions*.

Armstrong-Painter-Sherrat model

They consider one *single population of cells* moving (in 1d) responding to a natural random motion and also due to adhesive forces between the cells.

The forces acting on the cells define a *conservative system*, where no cell birth or death is supposed to occur:

$$\frac{\partial u}{\partial t}(x,t) = \frac{\partial J}{\partial x}(x,t),$$

where $u(x,t)$ is the density of cells at position x and time t.
J is the sum of the diffusive and adhesion fluxes, $J = J_d + J_a$.
For simplicity, the authors take the following diffusive flux

$$J_d(x,t) = \frac{\partial u}{\partial x}(x,t),$$

'the results reported in this paper are the consequence of the adhesion term and could be obtained even without a diffusion term in the model'

N. J. Armstrong, K. J. Painter, & J. A. Sherratt, A continuum approach to modelling cell adhesion, J. Theoret. Biol., 2006.

Armstrong-Painter-Sherrat model

Regarding the *adhesive flux*, it is proposed to be *proportional to the density of the cells and the forces* between them are *inversely proportional to cell size*

$$J_a(x,t) = \frac{\nu}{R} u(x,t) F(x,t),$$

where $\nu > 0$ is a viscosity coefficient and $R > 0$ *the sensing radius*.
The total force is the nonlocal gradient

$$\begin{aligned} F(x,t) = (\nabla_{NL} u)(x,t) &:= \mathcal{G}^+ u(x,t) - \mathcal{G}^- u(x,t) \\ &= \int_x^{x+R} u(y,t)\omega(y-x)dy - \int_{x-R}^{x} u(y,t)\omega(x-y)dy. \end{aligned}$$

After adimensionalization, they get the evolution equation

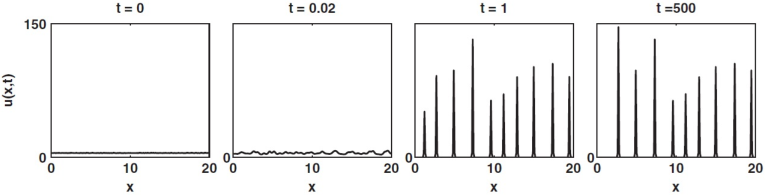
$$u_t(x,t) = u_{xx} - \gamma \frac{\partial}{\partial x}\Big(u(x,t)(\nabla_{NL} u)(x,t) \Big),$$

subject to *periodic boundary conditions*. Here $\gamma > 0$ *is the strength of the adhesion*

Armstrong-Painter-Sherrat model

Simulations of this model are performed, taking $R = 1$, $\omega(x) \equiv 1$ and $\gamma = 10$, on a domain of length 20 discretized into 200 mesh points.

The population of cells is *initially* assumed to be *uniformly distributed, perturbed by a small amount of noise*.



Over time the population develops a number of peaks in cell density. As time progresses, these *peaks are seen to coarsen*, becoming steeper and more widely spaced.

Review on APS model

Carrillo et al focus on APS model, to avoid high accumulations. With a *porous media* diffusion they consider

$$J_a(x,t) = (1-u(x,t))u(x,t)\int_0^R \Big(u(x+r,t)-u(x-r,t)\Big)\omega(r)dr,$$

where the crowding capacity has been rescaled to $M=1$, taking also the initial data below one.

In fact, the variable u of this model can be interpreted as the *volume fraction of cells*.

The factor $(1-u(x,t))$ reduces their velocity as the area becomes gradually more crowded at x, producing *saturation effect*.

Further *repulsion effects* could be included through ω *taking negative values*, but depending on the distance between cells.

J. A. Carrillo, H. Murakawa, M. Sato, H. Togashi, & O. Trush, A population dynamics model of cell-cell adhesion incorporating population pressure and density saturation, J. Theoret. Biol. 2019

Questions about the previuos models

- Is it feasible to include *repulsion effects, depending on the density of population as part of the drift term*?
- Is it possible to compute the *relative importance between diffusion and interaction processes*?
- How does the dynamics evolve in *confinement*?
  There exist types of cells that are spontaneously motile only in confinement.

  R.J. Hawkins, M. Piel, G. Faure-Andre, A. M. Lennon-Dumenil, J. F. Joanny, J. Prost, & R. Voituriez, Pushing off the walls: A mechanism of cell motility in confinement, Phys. Rev. Lett., 2009.

Description of a discrete model

Let $\{1, \cdots, N\}$ be the cells.

At time $t = 0$ we assign a real number $x_i(0) \in \overline{\Omega} = [-L, L]$, representing the *initial position* of the cell $i \in \{1, \cdots, N\}$.

Let us subdivide the interval $[-L, L]$ in $\{I_j\}, j \in \{1, \cdots, M\}$, a family of intervals of length h.

Denote as

$$s_j(t) = \frac{\#\{i : x_i(t) \in I_j\}}{N}, \quad j \in \{1, \cdots, M\},$$

the proportion of cells with position within the interval I_j, for $j \in \{1, \cdots, M\}$.

Description of a discrete model

Fix the *characteristic time step* Δt. Then, for $j = 1, \cdots, M$

$$s_j(t+\Delta t) = s_j(t) + \Delta t \left[Q^h_{\text{diff}} \Big(G_{\text{diff}}(j,t) - L_{\text{diff}}(j,t) \Big) + Q^h_{\text{int}} \Big(G_{\text{int}}(j,t) - L_{\text{int}}(j,t) \Big) \right],$$

- $G_{\text{diff}}(j,t), G_{\text{int}}(j,t)$ stand for probability *gain terms*,
- $L_{\text{diff}}(j,t), L_{\text{int}}(j,t)$ represent *loss terms*,

due both to diffusion and interaction effects, respectively.

- The coefficients Q^h_{diff} and Q^h_{int} account for the *frequency of diffusion and interaction processes*, respectively, per unit of time.
- *The dynamics is isolated*.

Random motion

Assuming that the jump of a cell is of length h, the proportion of cells arriving to I_j due to diffusion comes from adjacent intervals.

The transition probabilities to interval I_j are

$$P_{I_{j+1}\to I_j} = p/2 = P_{I_{j-1}\to I_j},$$

while the probability of remaining at I_j is $1-p$. Namely,

$$G_{\text{diff}}(t,j) = s_{j+1}(t)P_{I_{j+1}\to I_j} + s_{j-1}P_{I_{j-1}\to I_j} = \frac{p}{2}s_{j+1}(t) + \frac{p}{2}s_{j-1}(t).$$

On the other hand, the cells in I_j will leave it to travel to either I_{j-1} or I_{j+1} with respective probabilities

$$P_{I_j\to I_{j-1}} = p/2 = P_{I_j\to I_{j+1}}.$$

Thus, the proportion of cells leaving I_j is

$$L_{\text{diff}}(t,j) = s_j(t)(P_{I_j\to I_{j-1}} + P_{I_j\to I_{j+1}}) = p\,s_j(t).$$

Finding the underlaying PDE

To this end, we introduce $u_h(x,t) : [-L, L] \times [0, \infty) \to \mathbb{R}_0^+$ such that

$$s_j(t) = \int_{I_j} u_h(x,t)dx = h\, u_h(x_j, t) + O(h^3),$$

being x_j the midpoint of each I_j.

In other words, u_h *restricted to the interval* I_j *behaves as* $s_j(t)/h$.

We rewrite the gain and loss in terms of the density u_h.

Assuming that

$$u_h \to u \text{ as } h \to 0 \text{ (in some sense)}$$

our aim is to deduce (formally) the *PDEs verified by* u.

Diffusive motion

We write the previous balance in terms of the density u_h,

$$G_{\text{diff}}(t,j) - L_{\text{diff}}(t,j) = \frac{p}{2} s_{j+1}(t) + \frac{p}{2} s_{j-1}(t) - p\, s_j(t)$$

$$= h\frac{p}{2}\Big[(u_h(x_{j+1},t) - u_h(x_j,t)) + (u_h(x_{j-1},t) - u_h(x_j,t))\Big]$$

$$= h^3\frac{p}{2}\Big[\Delta_h u_h(x_j)\Big],$$

where

$$\Delta_h v(x) = \frac{v(x+h) - 2v(x) + v(x-h)}{h^2}$$

is the discrete Laplacian.

Aggregation through nonlocal gradient

The proportion of cells arriving to I_j are

$$G_{\text{int}}(t,j) = s_{j+1}(t)P_{I_{j+1}\to I_j}(t) + s_{j-1}(t)P_{I_{j-1}\to I_j}(t),$$

where the *transition probabilities* are given by

$$P_{I_{j+1}\to I_j}(t) = \sum_{i=j-r}^{j} s_i(t)w((j+1-i)h),\ P_{I_{j-1}\to I_j}(t) = \sum_{i=j}^{j+r} s_i(t)w((i-(j-1))h).$$

On the other hand, *the proportion of cells leaving I_j* are

$$L_{\text{int}}(t,j) = s_j(t)\Big[P_{I_j\to I_{j-1}}(t) + P_{I_j\to I_{j+1}}(t)\Big],$$

being

$$P_{I_j\to I_{j-1}}(t) = \sum_{i=j-1-r}^{j-1} s_i(t)w((j-i)h) \qquad P_{I_j\to I_{j+1}}(t) = \sum_{i=j+1}^{j+1+r} s_i(t)w((i-j)h).$$

The number $r = r(h) = [R/h]$.

Aggregation through nonlocal gradient

We bring together the following terms

$$\text{Left} := s_{j+1}(t)P_{I_{j+1}\to I_j}(t) - s_j(t)P_{I_j\to I_{j-1}},$$

$$\text{Right} := s_{j-1}(t)P_{I_{j-1}\to I_j}(t) - s_j(t)P_{I_j\to I_{j+1}}.$$

By the definition of u_h, one has

$$s_i(t)w(|j+1-i|h) = \int_{I_i} u_h(y,t)w(|x_{j+1}-y|)dy + O(h^3),$$

hence, from

$$P_{I_{j+1}\to I_j}(t) = \int_{\bigcup_{i=j-r}^{j} I_i} u_h(y,t)w(x_{j+1}-y)dy + O(h^2) = \mathcal{G}^- u_h(x_{j+1},t) + O(h^2)$$

Similarly,

$$P_{I_{j-1}\to I_j}(t) = \int_{\bigcup_{i=j}^{j+r} I_i} u_h(y,t)w(y-x_{j-1})dy + O(h^2) = \mathcal{G}^+ u_h(x_{j-1},t) + O(h^2).$$

Aggregation through nonlocal gradient

One arrives then to

$$
\begin{aligned}
\text{Left} &= \Big[h u_h(x_{j+1}), t)\Big]\Big[\mathcal{G}^- u_h(x_{j+1}, t) + O(h^2)\Big] \\
&\quad - \Big[h u_h(x_j, t)\Big]\Big[\mathcal{G}^- u_h(x_j, t) + O(h^2)\Big] \\
&= h^2 \left[\frac{u_h(x_{j+1}, t)\mathcal{G}^- u_h(x_{j+1}, t) - u_h(x_j, t)\mathcal{G}^- u_h(x_j, t)}{h}\right] + O(h^3)
\end{aligned}
$$

and

$$
\text{Right} = -h^2 \left[\frac{u_h(x_j, t)\mathcal{G}^+ u_h(x_j, t) - u_h(x_{j-1}, t)\mathcal{G}^+ u_h(x_{j-1}, t)}{h}\right] + O(h^3)
$$

Aggregation through nonlocal gradient

Summing up, we have shown that

$$G_{\text{int}}(t,j) - L_{\text{int}}(t,j) = -h^2\Big[\mathcal{T}^h_{aps}(x_j,t) + O(h)\Big],$$

where

$$\mathcal{T}^h_{aps}(x_j,t) := \partial_h^-\Big[u_h(x_j,t)\mathcal{G}^+u_h(x_j,t)\Big] - \partial_h^+\Big[u_h(x_j,t)\mathcal{G}^-u_h(x_j,t)\Big].$$

Hence $\lim_{h\to 0}\mathcal{T}^h_{aps}(x_j,t) = \dfrac{\partial}{\partial x}\Big(u(x,t)(\nabla_{NL}u)(x,t)\Big).$

where recall that

$$\begin{aligned}(\nabla_{NL}u)(x,t) &:= \mathcal{G}^+u(x,t) - \mathcal{G}^-u(x,t)\\ &= \int_x^{x+R} u(y,t)\omega(y-x)dy - \int_{x-R}^{x} u(y,t)\omega(x-y)dy.\end{aligned}$$

Aggregation through nonlocal gradient

The master equation reads as

$$\left[h\frac{u_h(x_j,t+\Delta t)-u_h(x_j,t)}{\Delta t}\right]= Q^h_{\text{diff}}h^3\mathcal{T}^h_{diff}(x_j,t)-Q^h_{\text{int}}h^2[\mathcal{T}^h_{aps}(x_j,t)+O(h)],$$

where $\quad \lim_{h\to 0}\mathcal{T}^h_{diff}(x_j,t)=\frac{p}{2}\Delta u(x,t).$

Aggregation through nonlocal gradient

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where $\lim_{h\to 0}\mathcal{T}^h_{diff}(x_j,t)=\frac{p}{2}\Delta u(x,t).$

To preserve all of the effects in the limit PDE, we find the constrains

$$\lim_{h\to 0} h^2 Q^h_{\text{diff}}=\alpha_{\text{diff}},\quad \lim_{h\to 0} hQ^h_{\text{int}}=\alpha_{\text{int}}.$$

Aggregation through nonlocal gradient

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To preserve all of the effects in the limit PDE, we find the constrains

$$\lim_{h\to 0} h^2 Q^h_{\text{diff}}=\alpha_{\text{diff}},\quad \lim_{h\to 0} hQ^h_{\text{int}}=\alpha_{\text{int}}.$$

This yields the following nonlocal PDE

$$u_t(x,t)=u_{xx}(x,t)-\gamma\frac{\partial}{\partial x}\Big(u(x,t)(\nabla_{NL}u)(x,t)\Big)$$

and isolated boundary conditions

$$u_x(L,t)+\gamma u(L,t)\int_0^R u(L-r,t)w(r)dr=0$$

$$-u_x(-L,t)+\gamma u(-L,t)\int_0^R u(-L+r,t)w(r)dr=0.$$

Lagrangian perspective

Again, consider a population of N cells randomly distributed in $[-L, L]$, at initial positions $x_i(0)$, $i = 1, \cdots, N$.
Select an arbitrary particle at $x_i(0)$ and follow its trajectory, $x_i(t)$.

The following system of stochastic differential equations describes *how the position of each of the N cells evolves along time*:

$$dx_i(t) = \frac{1}{N} \sum_{j \neq i} \mathcal{F}(x_i(t), x_j(t), S_a(x_i))dt + \sqrt{2}\, \varepsilon\, B_t^i, \quad i = 1, \cdots, N,\ t > 0.$$

Here, $\mathcal{F}(x_i(t), x_j(t), S_a(x_i)) = S_a(x_i) F(|x_i - x_j|)$ represents the action of the particle j interfering on the trajectory of the particle i.

The coefficient $S_a(x_i)$ models the saturation or repulsion mechanisms.

The terms B_t^i, $\quad i = 1, \cdots, N$ *are independent Brownian motion*.

Lagrangian perspective

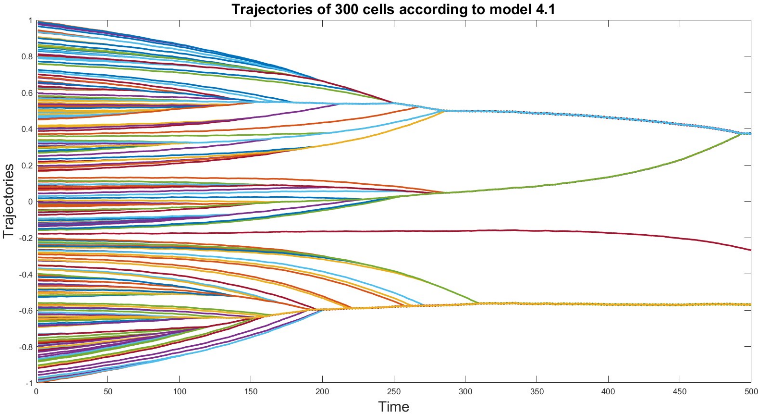
Let $\varphi : [-L, L] \to \mathbb{R}$ be an observable function and μ_t^N the empirical measure of the system of N cells:

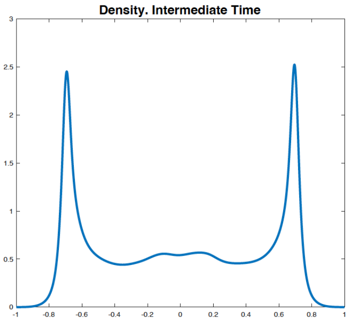
$$\mu_t^N = \frac{1}{N} \sum_{i=1}^{N} \delta_{x_i(t)},$$

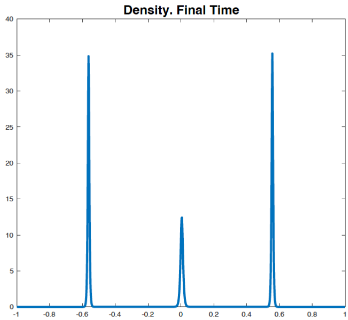
where δ_x is the Dirac mass on $x \in \mathbb{R}$.

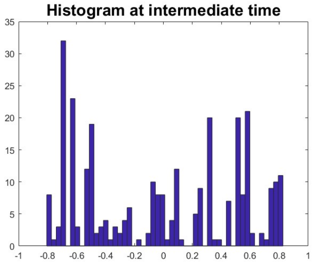
$$\langle \varphi, \delta_{x_i(t)} \rangle - \langle \varphi, \delta_{x_i(0)} \rangle = \sqrt{2}\varepsilon \int_0^t \frac{d\varphi}{dx}(x_i(s)) dB_s^i$$

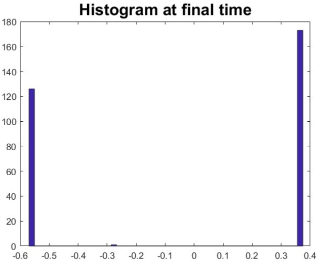
$$+ \int_0^t \left[S_a(x_i(s)) \frac{1}{N} \sum_{j \neq i} F(x_i(s), x_j(s)) \frac{d\varphi}{dx}(x_i(s)) + \varepsilon^2 \frac{d^2\varphi}{dx^2}(x_i(s)) \right] ds.$$

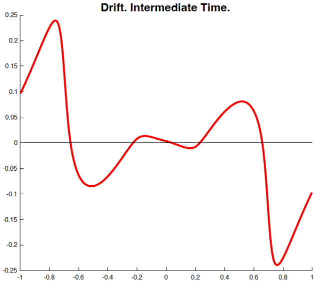

Trajectories of 300 cells according to model 4.1
Trajectories
Time
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
0
50
100
150
200
250
300
350
400
450
500

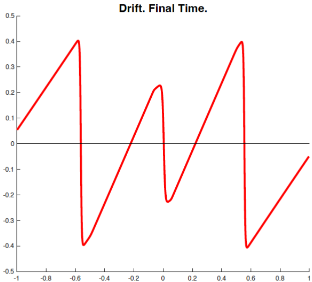

Density. Intermediate Time
0
0.5
1
1.5
2
2.5
3
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

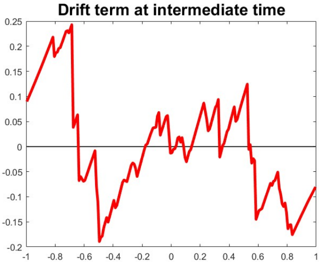

Density. Final Time
0
5
10
15
20
25
30
35
40
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

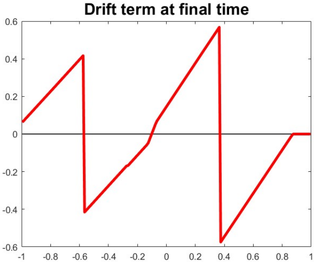

Histogram at intermediate time
0
5
10
15
20
25
30
35
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1


Histogram at final time
0
20
40
60
80
100
120
140
160
180
-0.6
-0.5
-0.4
-0.3
-0.2
-0.1
0
0.1
0.2
0.3
0.4


Drift. Intermediate Time.


Drift. Final Time.


Drift term at intermediate time


Drift term at final time

Lagrangian perspective: Local Saturation Model

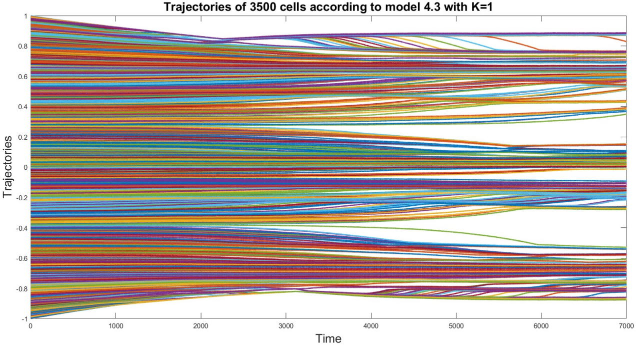
Take $a = a(N) \to 0$ as $N \to \infty$ and define

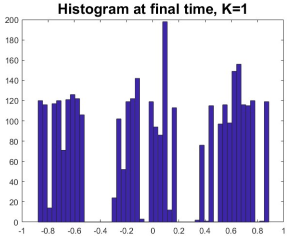
$$S_a(x_i(t)) = 1 - \frac{1}{2a}\langle \mathbb{1}_{|z-x_i(t)|<a}, \mu_t^N \rangle = 1 - \frac{1}{2a}\int_{x_i(t)-a}^{x_i(t)+a} d\mu_t^N(z).$$

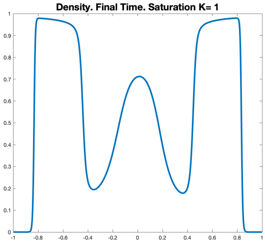
The measure μ_t^N is the empirical measure of the system of particles.

The coefficient $S_a(x_i(t))$ approaches to the local coefficient $1-u$ as $N \to \infty$ in the PDE

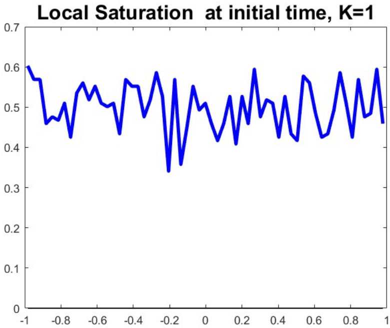
$$u_t(x,t) = u_{xx}(x,t) - \gamma(1-u(x,t))\frac{\partial}{\partial x}\Big(u(x,t)(\nabla_{NL}u)(x,t)\Big)$$

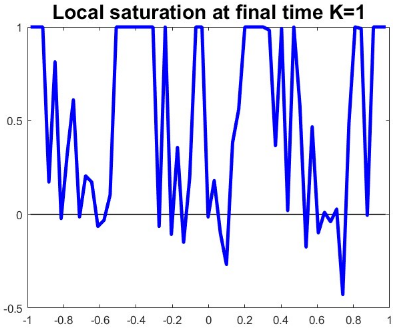

Trajectories of 3500 cells according to model 4.3 with K=1
Trajectories
Time


Histogram at final time, K=1


Density. Final Time. Saturation K= 1


Drift. Intermediate Time. Saturation K= 1
Drift. Final Time. Saturation K= 1
Drift term at intermediate time, K=1
Drift term at final time, K=1
0.25
0.2
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
-0.2
-0.25
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1


Local Saturation at initial time, K=1
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1


Local saturation at final time K=1
1
0.5
0
-0.5
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

A nonlocal aggregation/ repulsion coefficient

In the spirit of avoiding large accumulations, we propose to take a nonlocal saturation coefficient choosing $a = R$ the sensing radius. Namely,

$$\mathcal{F}(x_i, x_j, S_R(x_i)) = \left(1 - \frac{1}{2RK}\langle \mathbb{1}_{|z-x_i(t)|<R}, \mu_t^N\rangle\right) F(|x_i - x_j|),$$

for some value of the crowding capacity $0 < K \leqslant 1$.

Taking $N \to \infty$ it yields the PDE

$$u_t(x,t) = u_{xx}(x,t) - \gamma\left(1 - \frac{1}{K}\int_{x-R}^{x+R} u(y,t)\mathbb{1}_\Omega(y)dy\right)\frac{\partial}{\partial x}\Big(u(x,t)(\nabla_{NL}u)(x,t)\Big).$$

A nonlocal aggregation/ repulsion coefficient.

We analyze this new coefficient, which under the Euler perspective reads as

$$1 - \frac{1}{K} \sum_{i=j-l}^{j+l} s_i(t),$$

for some $K \in (0, 1]$.

It can take negative values, How could we then to define the transition probabilities among the intervals...?

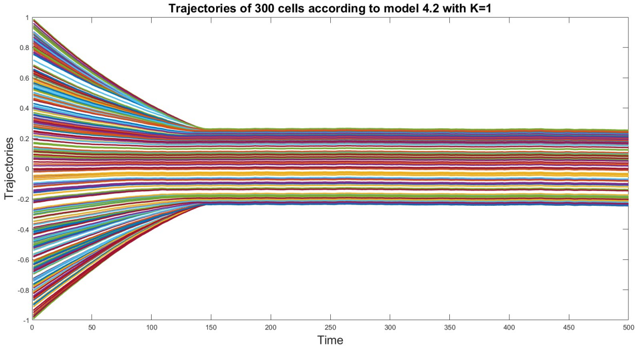
A nonlocal aggregation/ repulsion coefficient.

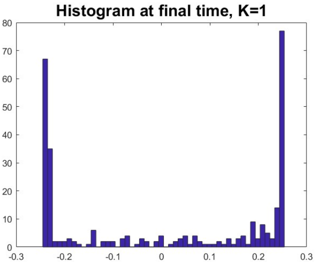
$$P_{I_{j+1}\to I_j}(t) = -\left(K - \sum_{i=j+1-l}^{j+1+l} s_i(t)\right)_{-} \sum_{i=j+2}^{j+2+r} s_i(t) w((i-(j+1))h) \text{ (repulsion term)}$$
$$+\left(K - \sum_{i=j+1-l}^{j+1+l} s_i(t)\right)_{+} \sum_{i=j-r}^{j} s_i(t) w((j+1-i)h) \text{ (aggregation term)}$$

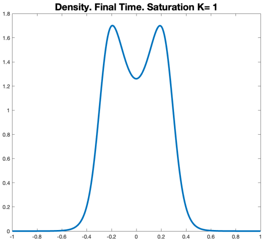
A nonlocal aggregation/ repulsion coefficient.

$$P_{I_{j+1}\to I_j}(t) = -\left(K - \sum_{i=j+1-l}^{j+1+l} s_i(t)\right)_- \sum_{i=j+2}^{j+2+r} s_i(t)w((i-(j+1))h)\ \text{(repulsion term)}$$
$$+\left(K - \sum_{i=j+1-l}^{j+1+l} s_i(t)\right)_+ \sum_{i=j-r}^{j} s_i(t)w((j+1-i)h)\ \text{(aggregation term)}$$

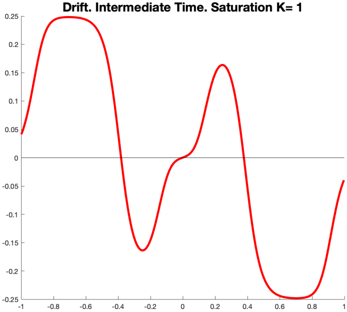
$$P_{I_{j-1}\to I_j}(t) = -\left(K - \sum_{i=j-1-l}^{j-1+l} s_i(t)\right)_- \sum_{i=j-2-r}^{j-2} s_i(t)w((j-1-i)h)\ \text{(repulsion term)}$$
$$+\left(K - \sum_{i=j-1-l}^{j-1+l} s_i(t)\right)_+ \sum_{i=j}^{j+r} s_i(t)w((i-(j-1))h)\ \text{(aggregation term)}$$

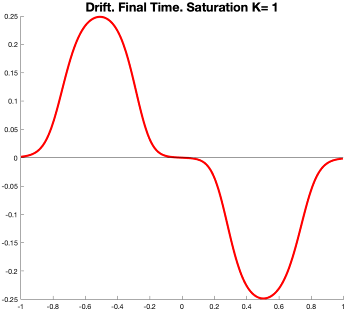

Trajectories of 300 cells according to model 4.2 with K=1
Trajectories
Time
0
50
100
150
200
250
300
350
400
450
500
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

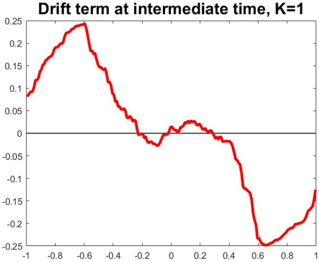

Histogram at final time, K=1
80
70
60
50
40
30
20
10
0
-0.3
-0.2
-0.1
0
0.1
0.2
0.3

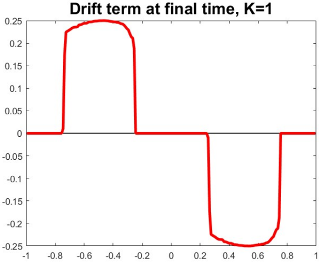

Density. Final Time. Saturation K= 1
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

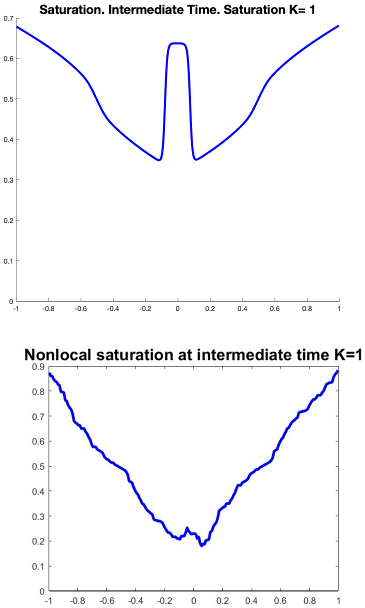
$K = 1$, $w \equiv 1$

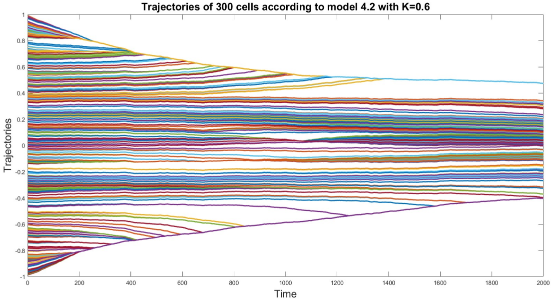

Drift. Intermediate Time. Saturation K= 1
0.25
0.2
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
-0.2
-0.25
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

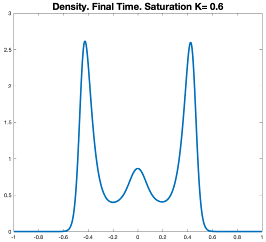

Drift. Final Time. Saturation K= 1
0.25
0.2
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
-0.2
-0.25
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

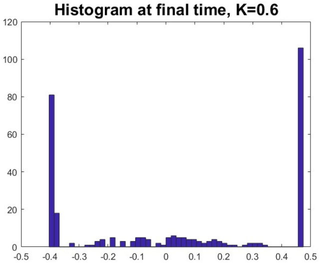

Drift term at intermediate time, K=1
0.25
0.2
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
-0.2
-0.25
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

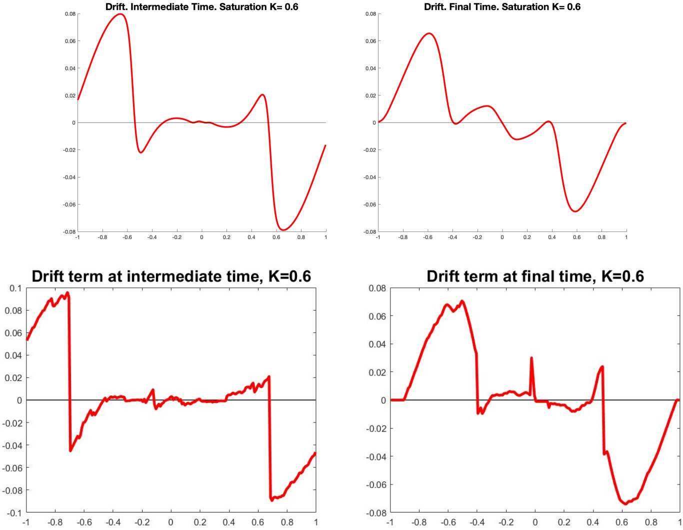

Drift term at final time, K=1
0.25
0.2
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
-0.2
-0.25
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

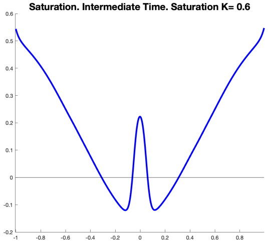

Saturation. Intermediate Time. Saturation K= 1
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1
Saturation. Final Time. Saturation K= 1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1
Nonlocal saturation at intermediate time K=1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1
Nonlocal saturation at final time, K=1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

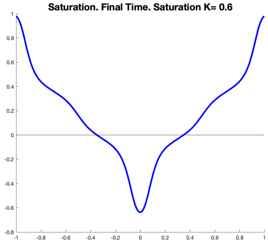

Trajectories of 300 cells according to model 4.2 with K=0.6
Trajectories
Time
0
200
400
600
800
1000
1200
1400
1600
1800
2000
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1

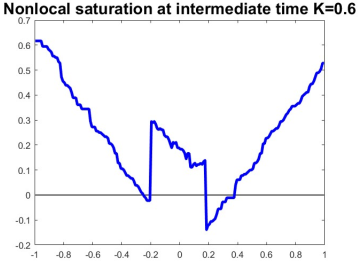

Density. Final Time. Saturation K= 0.6
3
2.5
2
1.5
1
0.5
0
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

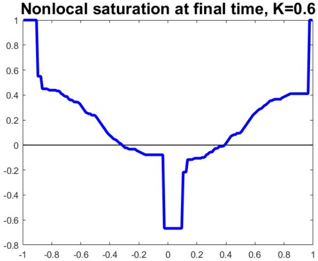

Histogram at final time, K=0.6
120
100
80
60
40
20
0
-0.5
-0.4
-0.3
-0.2
-0.1
0
0.1
0.2
0.3
0.4
0.5

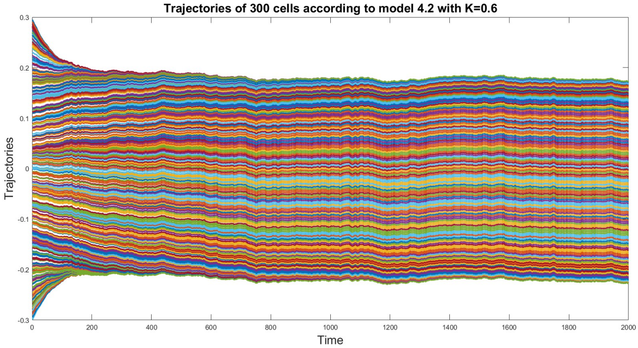

Drift. Intermediate Time. Saturation K= 0.6
Drift. Final Time. Saturation K= 0.6
Drift term at intermediate time, K=0.6
Drift term at final time, K=0.6

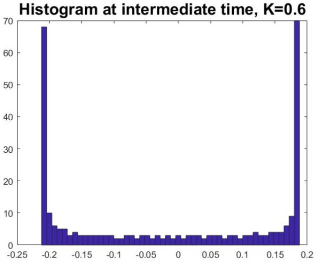

Saturation. Intermediate Time. Saturation K= 0.6

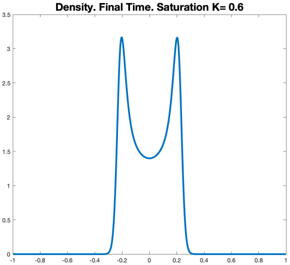

Saturation. Final Time. Saturation K= 0.6

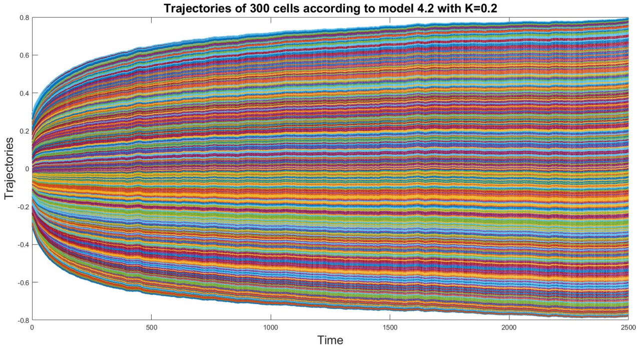

Nonlocal saturation at intermediate time K=0.6

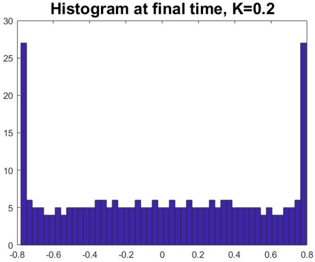

Nonlocal saturation at final time, K=0.6

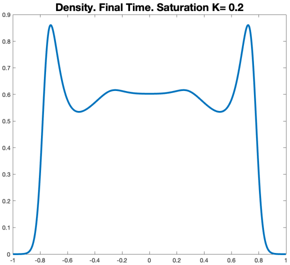

Trajectories of 300 cells according to model 4.2 with K=0.6
Trajectories
Time
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
0
200
400
600
800
1000
1200
1400
1600
1800
2000


Histogram at intermediate time, K=0.6
70
60
50
40
30
20
10
0
-0.25
-0.2
-0.15
-0.1
-0.05
0
0.05
0.1
0.15
0.2


Density. Final Time. Saturation K= 0.6
3.5
3
2.5
2
1.5
1
0.5
0
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1


Trajectories of 300 cells according to model 4.2 with K=0.2
Trajectories
Time
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
0
500
1000
1500
2000
2500


Histogram at final time, K=0.2
30
25
20
15
10
5
0
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8


Density. Final Time. Saturation K= 0.2
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

Present and future goals

- Consider a long range diffusion of nonlocal nature: Let $J(x, y)$ represent the probability of jumping from position x to y and $u(x, t)$ the density of cells as usual. If there is no other mechanisms than diffusion, the density evolution follows

$$u_t(x,t) = \int_{\text{supp}(J(x,\cdot))} J(x,y)u(y,t)dy - \int_{\text{supp}(J(\cdot,x))} J(y,x)dyu(x,t).$$

  - Scaling of a long range process with a differential process: trajectories no longer differential.
  - Protected/Preferred zones.
  - Response to external cues, rugosity of the surface, magnetic fields, etc
- Analysis of the sorting of two populations of cells with the different models.
- Modelling systems of Cell-Chemoattractant Substance.

Thank you !!! Happy sixties for Kisko and Manolo !!!!