# *Kinetic modelling of cell migration in the ECM.*

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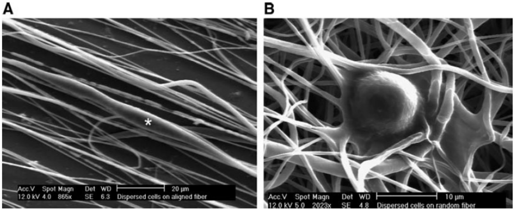
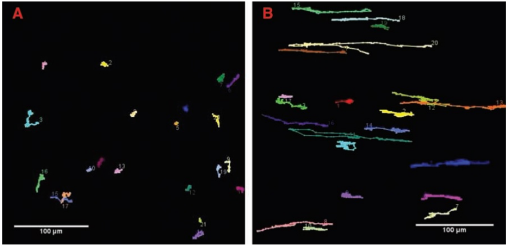
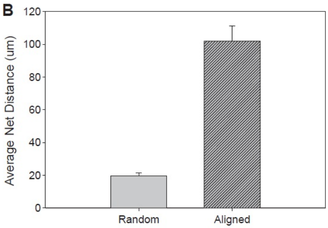
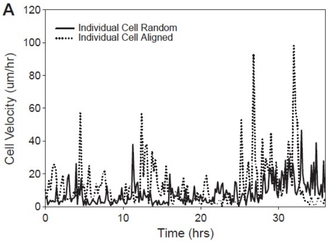


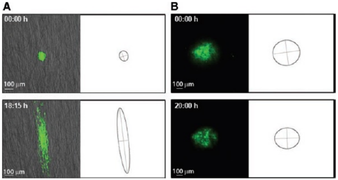

Jed Johnson, M. Oskar Nowicki, Carol H. Lee, E. Antonio Chiocca, Mariano S. Viapiano, Sean E. Lawler, and John J. Lannutti *Quantitative Analysis of Complex Glioma Cell Migration on Electrospun Polycaprolactone Using Time-Lapse Microscopy*,TISSUE ENGINEERING: Part C Volume 15, Number 4, 2009



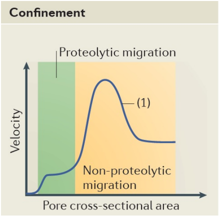
B
Average Net Distance (um)
0
20
40
60
80
100
120
Random
Aligned

A
Individual Cell Random
Individual Cell Aligned
Cell Velocity (um/hr)
0
20
40
60
80
100
120
0
10
20
30
Time (hrs)

A
B
00:00 h
18:15 h
00:00 h
20:00 h
100 µm

Confinement
Proteolytic migration
(1)
Velocity
Non-proteolytic migration
Pore cross-sectional area

### *Cells population*

$p = p(t, \mathbf{x}, \mathbf{v}),\ \ t \geq 0,\ \mathbf{x} \in \Omega \subset \mathbb{R}^n,\ \ \mathbf{v} = \hat{\mathbf{v}} v, (\hat{\mathbf{v}}, v) \in V = \mathbb{S}_+^{n-1} \times [-U, U].$

Macroscopic quantities (per unit volume)

* Density

$$\rho(\mathbf{x}, t) = \int_V p(\mathbf{x}, v, \hat{\mathbf{v}}, t)\, dv d\hat{\mathbf{v}}.$$

* Momentum

$$\rho(\mathbf{x}, t)\mathbf{U}(\mathbf{x}, t) = \int_V v\hat{\mathbf{v}} p(\mathbf{x}, v, \hat{\mathbf{v}}, t)\, dv d\hat{\mathbf{v}}.$$

* Mean velocity

$$\mathbf{U}(\mathbf{x}, t) = \frac{\displaystyle\int_V v\hat{\mathbf{v}} p(\mathbf{x}, v, \hat{\mathbf{v}}, t)\, dv d\hat{\mathbf{v}}}{\displaystyle\int_V p(\mathbf{x}, v, \hat{\mathbf{v}}, t)\, dv d\hat{\mathbf{v}}}.$$

* Pressure tensor

$$\mathbb{D} = \int_V (v\hat{\mathbf{v}} - \mathbf{U}) \otimes (v\hat{\mathbf{v}} - \mathbf{U}) p dv d\hat{\mathbf{v}}.$$

## *Matrix*

$$m = m(\mathbf{x}, \mathbf{n}), \quad \mathbf{x} \in \Omega, \, \mathbf{n} \in \mathbb{S}_{+}^{n-1}$$

* Matrix density

$$M(\mathbf{x}) = \int_{\mathbb{S}_{n-1}^{+}} m(\mathbf{x}, \mathbf{n}) d\mathbf{n}.$$

* Matrix mean direction

$$\hat{\mathbf{U}}_M = \int_{\mathbb{S}_{n-1}^{+}} \frac{m(\mathbf{x}, \mathbf{n})}{M(\mathbf{x})} \mathbf{n} d\mathbf{n}$$

* Matrix diffusion tensor

$$\mathbb{D}_m = \frac{n}{M(\mathbf{x})} \int_{\mathbb{S}_{n-1}^{+}} \mathbf{n} \otimes \mathbf{n} m(\mathbf{x}, \mathbf{n}) d\mathbf{n}.$$

## *Anisotropy index*

$$FA = \frac{n}{2} \frac{\sqrt{\sum_{i=1}^{n} (\lambda_i - \bar{\lambda})}}{\sum_{i=1}^{n} \lambda_i}$$

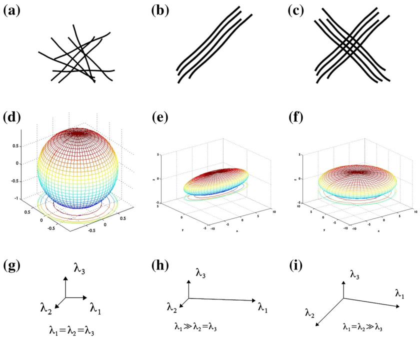



***Figure:*** Surulescu et Al.

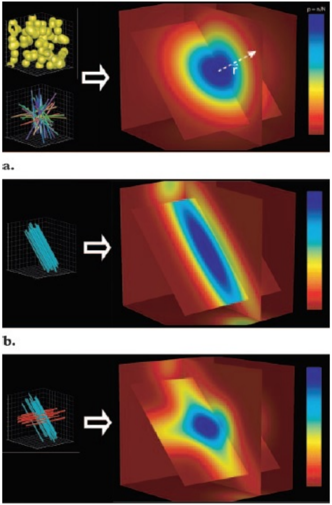



***Figure:*** Hagmann et Al.

**The model**

$$\frac{\partial p}{\partial t}(t,\mathbf{x},\mathbf{v}) + \mathbf{v}\cdot\nabla_{\mathbf{x}} p(t,\mathbf{x},\mathbf{v}) = \mathcal{J}_m[p](t,\mathbf{x},\mathbf{v})) + \mathcal{J}_c[p](t,\mathbf{x},\mathbf{v}))$$

$$\mathcal{J}_m[p](t,\mathbf{x},\mathbf{v})) = \mu_m(t,\mathbf{x})(\rho(t,\mathbf{x})\psi_m(v)\frac{m(\mathbf{x},\hat{\mathbf{v}})}{M(\mathbf{x})} - p(t,\mathbf{x},\mathbf{v})), \quad \mu_m(t,\mathbf{x}) = (1-d(t,\mathbf{x}))f(M)$$

$$\mathcal{J}_c[p](t,\mathbf{x},\mathbf{v}) = \mu_c(t,\mathbf{x})(\rho(t,\mathbf{x}) \overbrace{\psi_c(\mathbf{v})}^{=\psi_m(v)\frac{m(\mathbf{x},\hat{\mathbf{v}})}{M(\mathbf{x})}} - p(t,\mathbf{x},\mathbf{v})), \quad \mu_c(t,\mathbf{x}) = \eta_c(t,\mathbf{x})\rho(t,\mathbf{x})$$

Hillen '05, Chauviere, Hillen, Preziosi '10

***H Theorem (Lods, Toscani, Bisi)***

$\forall p(0,\mathbf{x},\cdot)$ in $L_1(\Omega)\times L_2(V)$ with finite mass and energy,

$$\| \, p - (\mu_c\psi_c + \mu_m\psi_m\frac{m}{M}) \, \|_{L^2(V)} \to 0$$

as $t\to\infty$ for $a.e.$ $\mathbf{x}$ in $V$.

### *Index of directional persistence*

$$\psi_d = sgn(\bar{U}_M v')\hat{\mathbf{U}}_M \cdot \hat{\mathbf{v}}' = \begin{cases} \pm 1 & \textit{if} \quad \mathbf{v}' \parallel \hat{\mathbf{U}}_M \\ 0 & \textit{if} \quad \mathbf{v}' \perp \hat{\mathbf{U}}_M \end{cases}$$

### *Mean squared displacement (Alt, Othmer '88)*

$$\mathcal{D}(t) = \begin{cases} \dfrac{2D}{\mu(1-\psi_d)}\left[t - \dfrac{1}{\mu(1-\psi_d)}(1 - e^{-\mu(1-\psi_d)t}\right] & \textit{if} \quad \psi_d \neq 1 \\ Dt^2 \quad \textit{if} \quad \psi_d = 1 \end{cases}$$

### *Momentum of the cells population*

'Momentum' of the matrix/mean velocity of cells

$$\mathbf{U}_M = U_M \hat{\mathbf{U}}_M$$

Mean post-collision velocity

$$\mathbf{U}_c = \int_V \psi_c d\mathbf{n} dv$$

$$\mathbf{U}(\mathbf{x},t) \leq \mathbf{U}^0 \exp(-(\mu_m+\mu_c)t) + (\mathbf{U}_M+\mathbf{U}_c)[1-\exp(-(\mu_m+\mu_c)t)] \to (\mathbf{U}_M+\mathbf{U}_c) \;\; a.e.$$

### *Diffusion tensor*

$$\mathbb{D}_c = \int_V (\mathbf{v}-\mathbf{U}) \otimes (\mathbf{v}-\mathbf{U}) \psi_c(\mathbf{v}) dv d\hat{\mathbf{v}}$$

$$\mathbb{D}_M = \int_V (\mathbf{v}-\mathbf{U}) \otimes (\mathbf{v}-\mathbf{U}) \psi_m(v) \frac{m}{M} dv d\hat{\mathbf{v}}$$

**Properties of $\psi_m$**

$\psi_m(v|\hat{\mathbf{v}}) : [-U, U] \to \mathbb{R}_+$

* $\int_{-U}^{U} \psi_m(v)dv = 1$
* $\int_{-U}^{U} \psi_m(v)v dv = U_M$
* $\int_{-U}^{U} \psi_m(v)v^2 dv = D_M$

- $\psi_m$ even: diffusion case;
- $\psi_m$ not even: drift case.

## Macroscopic models

- parabolic scaling: $\tau = \epsilon^2 t, \hat{x} = \epsilon x \to$ diffusion case ;
- hyperbolic scaling: $\tau = \epsilon t, \hat{x} = \epsilon x \ \to$ drift case;
- moments closure.

## *Nondimensionalization*

- $V_m$ mean velocity, $X$ macroscopic length
- $l_c^0, \mu_c^0$ mean free path/ frequency for cells binary collisions
- $l_m^0 = \frac{d^0 X}{1-d^0}$, $\mu_m^0$ mean free path/frequency for cell-fiber interaction
- $\epsilon = \frac{l_c^0}{X}$: Knudsen number.
- $\mu_c^0 = \frac{V_m}{l_0}$
- $\mu_m^0 = \frac{V_m}{l_m^0}$

$\rightarrow \mu_m^0 l_m^0 = \mu_c^0 l_c^0$

$$V_m = d_0 X f(M_0).$$

$$\hat{\mathbf{x}} = \frac{\mathbf{x}}{X}, \quad \hat{\mathbf{v}} = \frac{\mathbf{v}}{V_m}, \quad \hat{t} = \frac{t}{\tau}, \quad \hat{\rho} = \frac{\rho}{\rho_0}, \quad \hat{p} = \frac{p}{\frac{\rho_0}{V_m^n}}, \quad \hat{\psi} = \psi U^n, \quad \hat{m} = \frac{m}{M_0}, \quad \hat{M} = \frac{M}{M_0}$$

## *Macroscopic time scales*

$T_{drift} = \frac{X}{V_m} = \frac{1}{\mu_c^0 \epsilon}$.

$D = \frac{V_m^2 \mu_m^0}{1-d_0} \rightarrow T_{diff} = \frac{X^2}{D} = \frac{\mu_m^0 (1-d_0)}{\epsilon^2 {\mu_c^0}^2}$

## *Parabolic scaling - Diffusive limit*

$$\epsilon^2 \frac{\partial p}{\partial t}(t,\mathbf{x},\mathbf{v}) + \epsilon\alpha \mathbf{v}\cdot\nabla_{\mathbf{x}} p(t,\mathbf{x},\mathbf{v}) = \alpha^2 \mathcal{J}_m[p] + \alpha \mathcal{J}_c[p]$$

$\alpha = \frac{\mu_m^0}{\mu_c^0}$

## *Diffusion dominated equation*

$$\frac{\partial \rho_0}{\partial t} - \alpha \nabla_{\mathbf{x}} \cdot \frac{1}{\alpha\mu_m + \mu_c} \cdot [\nabla_{\mathbf{x}} \cdot \left(\rho_0 \frac{\mu_c \mathbb{D}_c + \alpha\mu_m \mathbb{D}_M}{\alpha\mu_m + \mu_c}\right)] = 0$$

Covergence: Hillen 00.

**Hyperbolic scaling - Chapman Enskog**

$$\epsilon\frac{\partial p}{\partial t}(t,\mathbf{x},\mathbf{v})+\epsilon\alpha(1-d_0)\mathbf{v}\cdot\nabla_{\mathbf{x}}p(t,\mathbf{x},\mathbf{v})=\mathcal{J}_m[p]+\mathcal{J}_c[p]$$

**Drift dominated equation**

$$\frac{\partial \rho_0}{\partial t}+\nabla_{\mathbf{x}}\cdot\left(\rho_0\frac{1}{\alpha\mu_m+\mu_c}(\alpha\mu_m\mathbf{U}_M+\mu_c\mathbf{U}_c)\right)=0,$$

**Loss of details!!**

Spatially homogeneous case: $\frac{\partial \rho}{\partial t} = 0$

$\Downarrow$

**Microscopic approach**

Parallelism between microscopic approach and velocity jump approach.

## *Microscopic collision approach-2D, spatially homogeneous*

$$f = f(\tau, \theta, v), \quad m = m(\theta_n), \quad \theta, \theta_n \in [0, \pi), v \ \in [-U, U]$$

$$\theta' - \theta = \epsilon(\theta_n - \theta) + \sqrt{\epsilon}\Theta\sqrt{(D_\theta - \theta_M^2)}$$

$$v' - v = \epsilon(U_M - v) + \sqrt{\epsilon}\Theta\sqrt{(D_v - U_M^2)}$$

$$\frac{d}{d\tau}\int_0^\pi \int_{-U}^U \varphi(\theta, v) f(\tau, \theta, v) d\theta dv =$$
$$\langle \int_0^\pi \int_0^\pi \int_{-U}^U \left(\varphi(\theta', v') - \varphi(\theta, v)\right) f(\tau, \theta, v) m(\theta_n) d\theta_n d\theta dv \rangle$$

Scaling: $t = \Delta t \tau, \quad p(t,\theta,v) = f(\tau,\theta,v)$

### *Quasi-invariant limit*

$$\frac{\partial f(t,\theta,v)}{\partial t} =$$
$$\partial_\theta[f(\theta_M - \theta)] + \partial_v[f(U_M - v)]$$
$$+\partial^2_{\theta\theta}[f(D_\theta - \theta_M^2)] + 2\partial^2_{\theta v}[f\sqrt{D_\theta - \theta_M^2}\sqrt{D_v - U_M^2}] + \partial^2_{vv}[f(D_v - U_M^2)]$$

### *Stationary state $U_M$ constant*

$$f = \rho c \left( \frac{1}{((U_M - v)^2 + D_v^2)} \frac{1}{((\theta_M - \theta)^2 + D_\theta^2)} \right)^2$$

L.Pareschi, M.Zanella *Structure preserving schemes for nonlinear Fokker-Planck equations and applications*, Journal of Scientific Computing

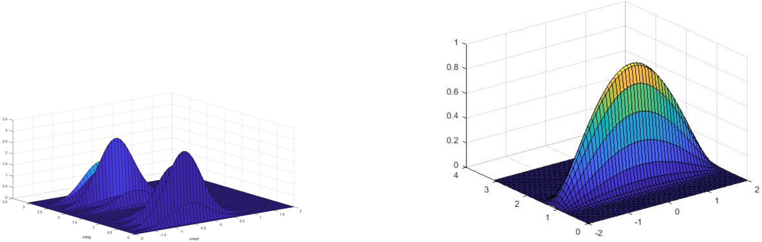



***Figure:*** Random initial cells, aligned fibers $\theta = 3\pi/8, ,\ U_M = 0$


***Figure:*** Random initial cells, aligned fibers $\theta = 3\pi/8, ,\ U_M = 0.5$

***Figure:*** Random initial cells, aligned fibers $\theta = 3\pi/8, ,\ U_M = 0$

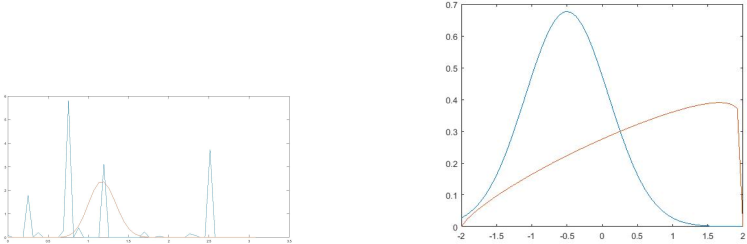



***Figure:*** Random initial cells, aligned fibers $\theta = 3\pi/8, ,\ U_M = 0.5$

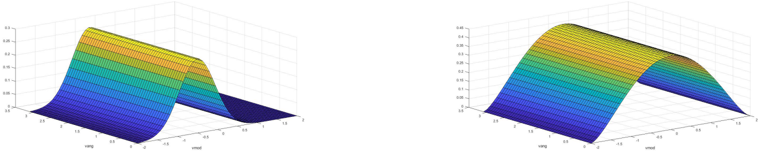



***Figure:*** Uniform fibers, $U_M = 0$

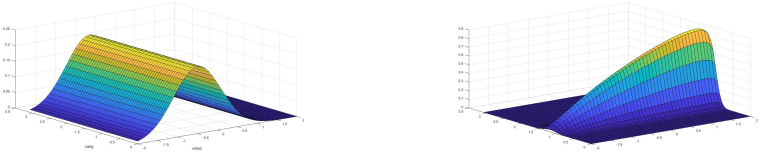



***Figure:*** Aligned fibers $\theta = 3\pi/8, ,\ U_M = 0.5$

Thank you for your attention!