Modelling cell-extracellular matrix interactions: From microscopic to macroscopic scale

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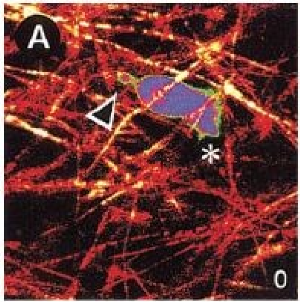
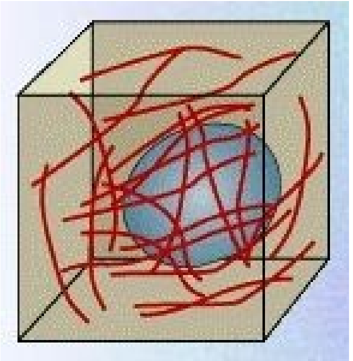
The Extra-Cellular Matrix

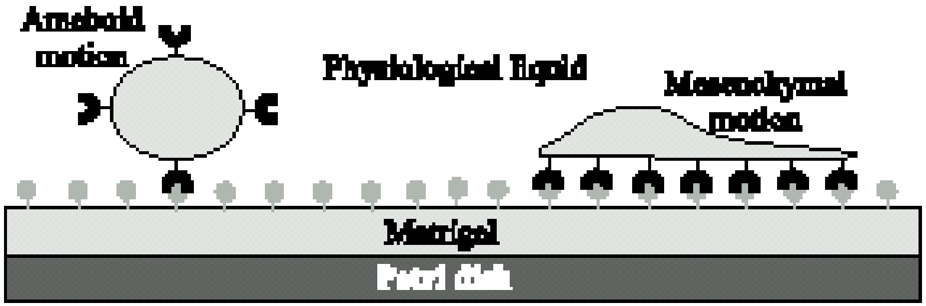
- a complex set of macromolecules, essentially composed by collagen
- a natural complex scaffold cell adhere to
- anisotropic and heterogeneous fibrous medium



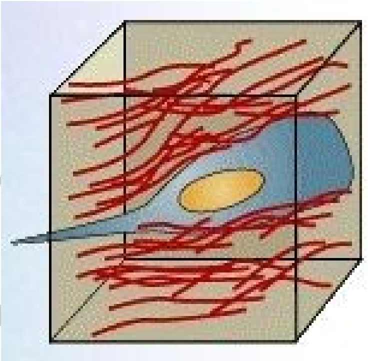
Types of motion:

Ameboid motion:





Mesenchymal motion:



- high deformation of cells
- weak adherence to the surrounding tissue
- no degradation of the ECM
- high migration speed

- strong adherence
- ECM degradation by enzymes (MMP)
- fibers deformation and/or rupture
- low migration speed

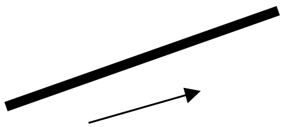
The Kinetic Framework

Two populations

Moving cells

- Fibroblasts
- Leukocytes
- Metastases

Fixed oriented fibers of the ECM



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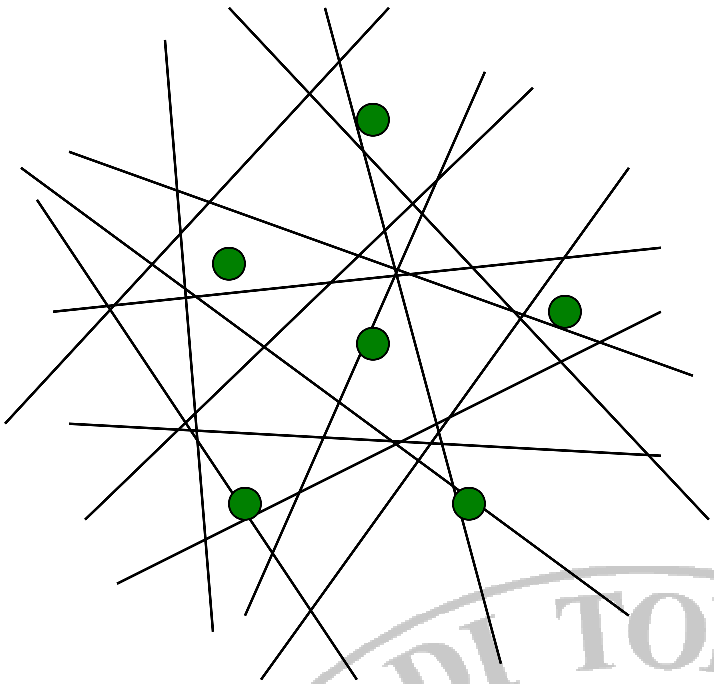
- Collagen
- Elastin
- Fibronectin



Hillen, *J. Math. Biol.*, **53**, 585–616 (2006).
Chauviere, Hillen & Preziosi, *Netw. Heterog. Media*, **22**, 333–357 (2007).

Statistical representation

Cells: Distribution density $p(t, \mathbf{x}, \mathbf{v})$

- Position $\mathbf{x} \in \mathcal{D} \subseteq \mathbb{R}^3$
- Velocity $\mathbf{v} \in V \subseteq \mathbb{R}^3$

Fibers of the network: Distribution density $m(t, \mathbf{x}, \mathbf{n})$

- Non-oriented fiber direction ➡ $\mathbf{n} \in S^2_+$
- $m^e(t, \mathbf{x}, \mathbf{n}) = \begin{cases} m(t, \mathbf{x}, \mathbf{n}) & \text{for } \mathbf{n} \in S^2_+ \\ m(t, \mathbf{x}, -\mathbf{n}) & \text{for } \mathbf{n} \in S^2_- \end{cases}$

The cell movement equation

- Chemotactic effect $\mathbf{f}(\mathcal{C}) \in \mathbb{R}^3$ depending on a chemical profile $\mathcal{C}(t, \mathbf{x})$
  - $\mathbf{f}(\mathcal{C}) = \lambda \nabla_{\mathbf{x}} \mathcal{C}$
- Cell-cell interactions
  - Operator J_c
- Cell-ECM interactions
  - Operator J_m

Mass conservative interactions

- $\int_V J_c \, d\mathbf{v} = 0$
- $\int_V J_m \, d\mathbf{v} = 0.$

Transport equation for cell movement:

$$\frac{\partial p}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} p + \nabla_{\mathbf{v}} \cdot [\mathbf{f}(\mathcal{C}) p] = J_m + J_c$$

Macroscopic quantities

Moments of the distribution function:

Zero-th order: cell number density
$$\rho(t, \mathbf{x}) = \int_V p(t, \mathbf{x}, \mathbf{v})\, d\mathbf{v}$$

First order: momentum
$$\rho(t, \mathbf{x})\mathbf{U}(t, \mathbf{x}) = \int_V p(t, \mathbf{x}, \mathbf{v})\, \mathbf{v}\, d\mathbf{v}$$

Pressure tensor:

$$\mathbb{P}(t, \mathbf{x}) = \int_V p(t, \mathbf{x}, \mathbf{v})\, [\mathbf{v} - \mathbf{U}(t, \mathbf{x})] \otimes [\mathbf{v} - \mathbf{U}(t, \mathbf{x})]\, d\mathbf{v}$$

Macroscopic description of the fiber network

Fiber number density:

- $$M(t,\mathbf{x}) = \int_{S^2_+} m(t,\mathbf{x},\mathbf{n})\, d\mathbf{n} = \frac{1}{2}\int_{S^2} m^e(t,\mathbf{x},\mathbf{n})\, d\mathbf{n}$$

Orientation tensor:

Symmetric and positive tensor

- $$\mathbb{D}(t,\mathbf{x}) = \frac{3}{M(t,\mathbf{x})}\int_{S^2_+} m(t,\mathbf{x},\mathbf{n})\,\mathbf{n}\otimes\mathbf{n}\, d\mathbf{n}$$

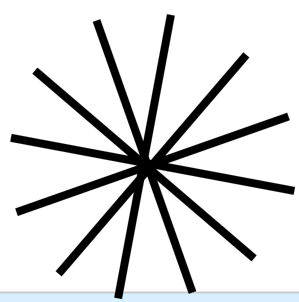
Visualization: By the ellipsoid $\mathbf{x}\cdot\mathbb{D}^{-1}\mathbf{x} = 1$

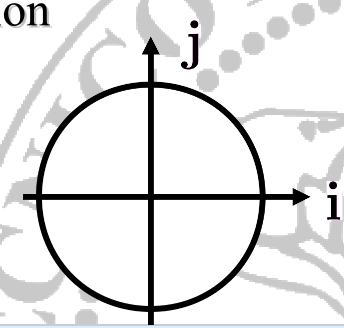
The eigendirection $\mathbf{r}_m$ of the maximum eigenvalue λ_m

$\longrightarrow$ the main fiber network direction

Isotropic case:

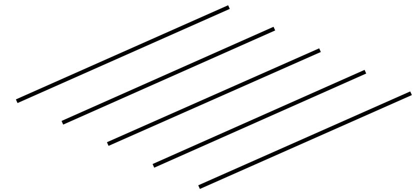
- $m(t,\mathbf{x},\mathbf{n}) = m(t,\mathbf{x})$





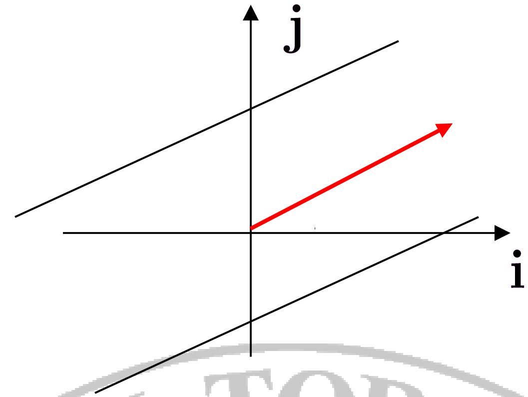
Macroscopic description of the fiber network

One only direction:



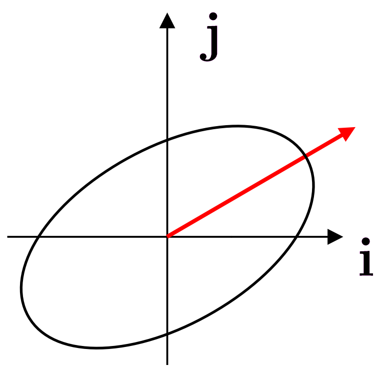
- $m(t, \mathbf{x}, \mathbf{n}) = m(t, \mathbf{x})\delta(\mathbf{n} - \mathbf{n}_0)$

- $\mathbb{D} = 2 \begin{pmatrix} cos^2(\theta) & cos(\theta)sin(\theta) \\ cos(\theta)sin(\theta) & sin^2(\theta) \end{pmatrix}$



- $\lambda_m = 2$
- $\mathbf{r}_m = \mathbf{n}_0$

General case:



Macroscopic description of the fiber network

A particular case for two directions: (typical of arteries)

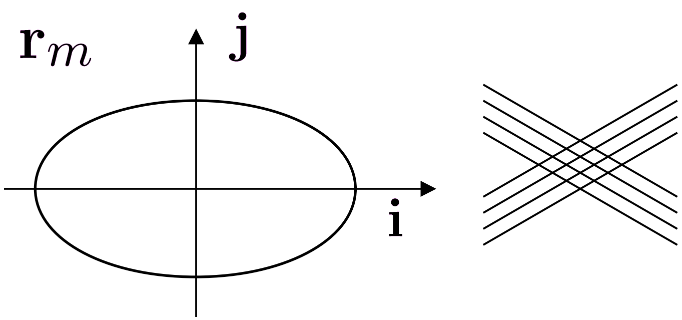
- $m(t, \mathbf{x}, \mathbf{n}) = m(t, \mathbf{x}) \left[\delta(\mathbf{n} - \mathbf{n}_0) + \delta(\mathbf{n} - \mathbf{n}_1) \right]$
- $\theta_0 + \theta_1 = \pi$
- $\mathbb{D} = 2 \begin{pmatrix} cos^2(\theta_0) & 0 \\ 0 & sin^2(\theta_0) \end{pmatrix}$

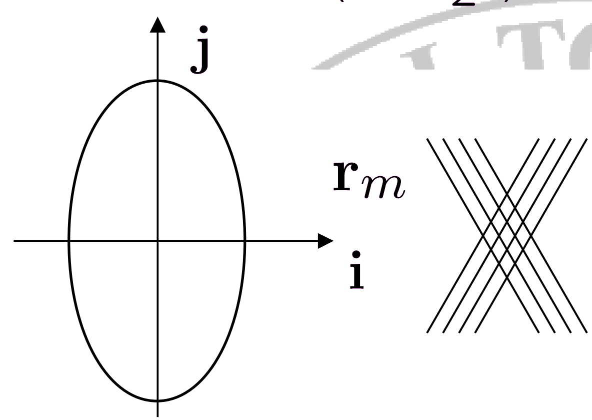
- $\theta_0 = \frac{\pi}{6}$

$$\mathbb{D} = \begin{pmatrix} \frac{3}{2} & 0 \\ 0 & \frac{1}{2} \end{pmatrix}$$

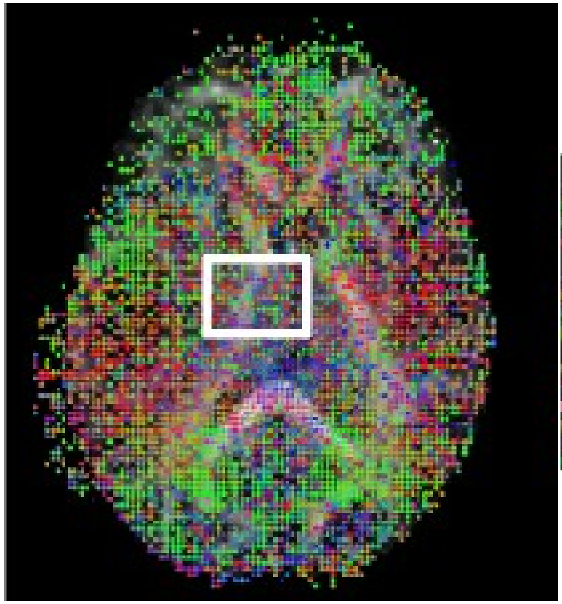
- $\theta_0 = \frac{\pi}{3}$

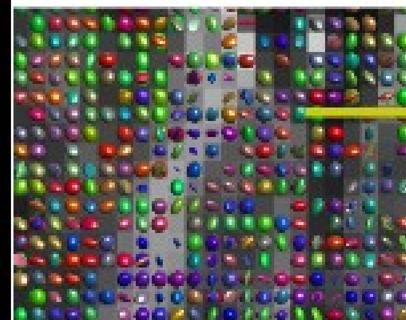
$$\mathbb{D} = \begin{pmatrix} \frac{1}{2} & 0 \\ 0 & \frac{3}{2} \end{pmatrix}$$

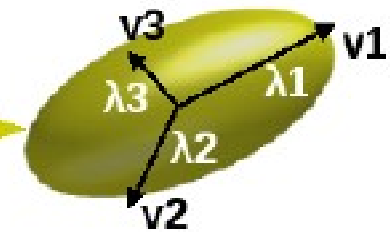




Macroscopic description of the fiber network







Diffusion Ellipsoid
Surface is an isosurface of the probability of diffusion

Jagersand, Murtha, Beaulieu, 200

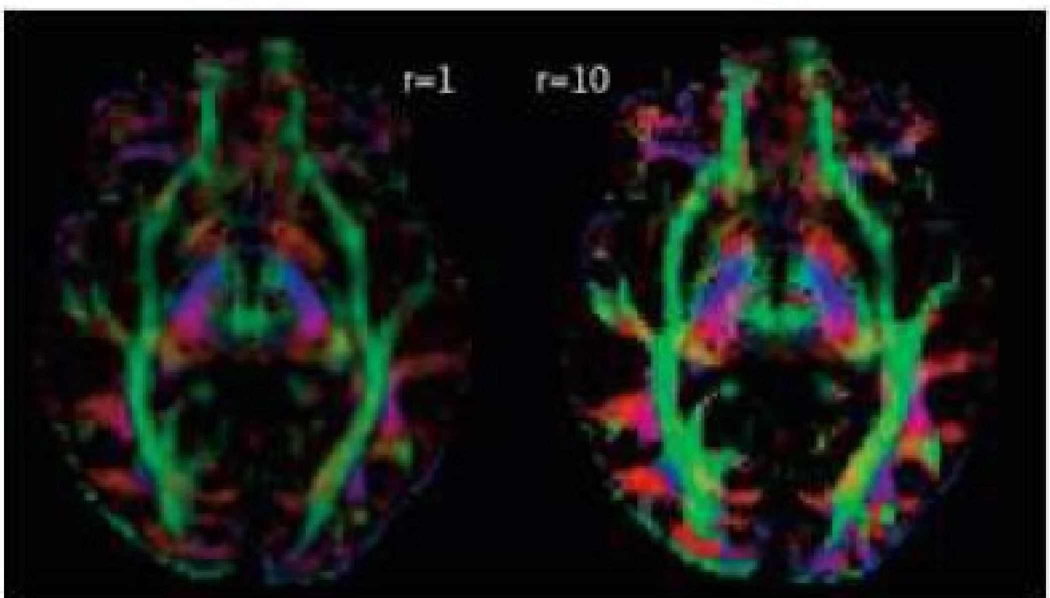


FIG. 1. RGB color maps of the tensor's principal diffusion directions. Left: tensor with no change in tumor cell diffusion anisotropy compared to water anisotropy ($r = 1$). Right: Tensor with change in tumor cell anisotropy ($r = 10$).

Jbabdi et al. 2005

Moment expansions

Integration of the transport equation over V:

$$\int_V \frac{\partial p}{\partial t}\, d\mathbf{v} + \int_V \mathbf{v}\cdot\nabla_{\mathbf{x}} p\, d\mathbf{v} + \underbrace{\int_V \nabla_{\mathbf{v}}\cdot(\mathbf{f}p)\, d\mathbf{v}}_{=0} = \underbrace{\int_V J_m\, d\mathbf{v}}_{=0} + \underbrace{\int_V J_c\, d\mathbf{v}}_{=0}$$

Assumption:

Mass conservative interactions

Mass conservation equation:

$$\frac{\partial \rho}{\partial t} + \nabla_{\mathbf{x}}\cdot(\rho\mathbf{U}) = 0$$

Moment expansions

Integration, over V, of the transport equation multiplied by $\mathbf{v}$:

$$\int_V \frac{\partial}{\partial t}(p\mathbf{v})\,d\mathbf{v} + \int_V [\mathbf{v}\cdot\nabla_{\mathbf{x}} p]\,\mathbf{v}\,d\mathbf{v} + \int_V [\nabla_{\mathbf{v}}\cdot(\mathbf{f}p)]\,\mathbf{v}\,d\mathbf{v} = \mathbf{j}_m + \mathbf{j}_c$$

Cell-ECM interaction force

$$\mathbf{j}_m = \int_V J_m\,\mathbf{v}\,d\mathbf{v}$$

Cell-cell interaction force

$$\mathbf{j}_c = \int_V J_c\,\mathbf{v}\,d\mathbf{v}$$

Using

$$\begin{aligned}[\nabla_{\mathbf{v}}\cdot(\mathbf{f}p)]\mathbf{v} &= \nabla_{\mathbf{v}}\cdot(\mathbf{v}\otimes\mathbf{f}p) - \mathbf{f}p\cdot[\nabla_{\mathbf{v}}\mathbf{v}] \\ &= \nabla_{\mathbf{v}}\cdot(\mathbf{v}\otimes\mathbf{f}p) - \mathbf{f}p\end{aligned}$$

Finally $\int_V [\nabla_{\mathbf{v}}\cdot(\mathbf{f}p)]\,\mathbf{v}\,d\mathbf{v} = \rho\mathbf{f}(c)$

Moment expansions

Integration, over V, of the transport equation multiplied by **v**:

$$\int_V \frac{\partial}{\partial t}(p\mathbf{v})\,d\mathbf{v} + \int_V [\mathbf{v}\cdot\nabla_{\mathbf{x}} p]\,\mathbf{v}\,d\mathbf{v} + \int_V [\nabla_{\mathbf{v}}\cdot(\mathbf{f}p)]\,\mathbf{v}\,d\mathbf{v} = \mathbf{j}_m + \mathbf{j}_c$$

Momentum balance equation

$$\frac{\partial}{\partial t}(\rho\mathbf{U}) + \nabla_{\mathbf{x}}\cdot(\rho\mathbf{U}\otimes\mathbf{U}) = -\nabla_{\mathbf{x}}\cdot\mathbb{P} + \rho\mathbf{f}(c) + \mathbf{j}_m + \mathbf{j}_c$$

and using the mass conservation equation

$$\rho\left(\frac{\partial\mathbf{U}}{\partial t} + \mathbf{U}\cdot\nabla_{\mathbf{x}}\mathbf{U}\right) = -\nabla_{\mathbf{x}}\cdot\mathbb{P} + \rho\mathbf{f}(c) + \mathbf{j}_m + \mathbf{j}_c$$

Cell-cell interaction modeling

Main hypothesis:

The transition probability density does not depend on the incoming velocities

$$\psi_c((\mathbf{v}', \mathbf{v}'_*) \to \mathbf{v}) \equiv \psi_c(\mathbf{v}) = \frac{1}{4\pi}\bar{\psi}_c(v)$$

Collision operator:

$$J_c = \eta_c \psi_c(\mathbf{v}) \int_V \int_V p(\mathbf{v}')p(\mathbf{v}'_*)\, d\mathbf{v}'\, d\mathbf{v}'_* - \eta_c p(\mathbf{v}) \int_V p(\mathbf{v}'_*)\, d\mathbf{v}'_*$$
$$= \eta_c \rho [\rho \psi_c(\mathbf{v}) - p(\mathbf{v})]\,,$$

Mass preserved:

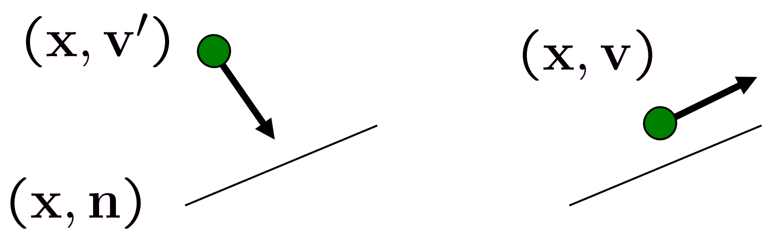
$$\int_V J_c\, d\mathbf{v} = \eta_c \rho \int_V [\rho \psi_c(\mathbf{v}) - p(\mathbf{v})]\, d\mathbf{v} = 0$$

Momentum contribution is a drag:

$$\mathbf{j}_c = \int_V J_c\, \mathbf{v}\, d\mathbf{v} = \eta_c \rho \int_V [\rho \psi_c(\mathbf{v})\, \mathbf{v} - p(\mathbf{v})\, \mathbf{v}]\, d\mathbf{v}$$
$$= -\eta_c \rho^2 \mathbf{U}\,,$$

Cell-ECM Interaction

Before interaction   After interaction



Main hypothesis:
indipendently of the incoming velocities

$$\psi_m((\mathbf{v}',\mathbf{n}')\to\mathbf{v})\equiv\psi_m(\mathbf{n}';\mathbf{v})=\psi_m(v)\,\frac{1}{2}[\delta(\mathbf{n}'-\hat{\mathbf{v}})+\delta(\mathbf{n}'+\hat{\mathbf{v}})]$$

Collision operator: $$J_m=\eta_m\left[\frac{1}{2}\rho\psi_m(v)m^e(\hat{\mathbf{v}})-Mp(\mathbf{v})\right]$$

Mass preserved: $$\int_V J_m\,d\mathbf{v}=\eta_m\rho\left[\int_{\mathbb{R}_+}\psi_m(v)v^2\,dv\cdot\frac{1}{2}\int_{S^2}m^e(\hat{\mathbf{v}})\,d\hat{\mathbf{v}}-M\right]=0$$

Momentum contribution is a drag: $$\mathbf{j}_m=\int_V J_m\,\mathbf{v}\,d\mathbf{v}=-\eta_m M\rho\mathbf{U}$$

Transport equation and moment expansion

$$\frac{\partial p}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} p + \nabla_{\mathbf{v}} \cdot (\mathbf{f} p) = \eta_c \rho [\rho \psi_c(\mathbf{v}) - p(\mathbf{v})] + \eta_m \left[\frac{1}{2} \rho \psi_m(v) m^e(\hat{\mathbf{v}}) - M p(\mathbf{v}) \right]$$

Mass conservation equation: $$\frac{\partial \rho}{\partial t} + \nabla_{\mathbf{x}} \cdot (\rho \mathbf{U}) = 0$$

Momentum balance equation:

$$\rho \left(\frac{\partial \mathbf{U}}{\partial t} + \mathbf{U} \cdot \nabla_{\mathbf{x}} \mathbf{U} \right) = \underbrace{-\nabla_{\mathbf{x}} \cdot \mathbb{P}}_{\text{Pressure tensor}} + \rho \mathbf{f}(\mathcal{C}) \underbrace{- (\eta_m M + \eta_c \rho) \rho \mathbf{U}}_{\text{Drag forces}}$$

Pressure tensor

Drag forces due to:

- Cell-cell interaction
- Cell-ECM interaction

System not closed:

The pressure tensor depends on the distribution

Diffusion limit

Parabolic scaling: $\tau = \varepsilon^2 t \quad \xi = \varepsilon \mathbf{x} \quad \mathbf{f} = \varepsilon \hat{\mathbf{f}}$

$$\Rightarrow \quad \varepsilon^2 \frac{\partial p}{\partial \tau} + \varepsilon \nabla_\xi \cdot (p\mathbf{v}) + \varepsilon \nabla_{\mathbf{v}} \cdot (\hat{\mathbf{f}} p) = J_m + J_c$$

Hibert expansion: $p_\varepsilon = p_0 + \varepsilon p_1 + \mathcal{O}(\varepsilon^2)$

- ε^0 : $J_m + J_c = 0 \quad \Rightarrow$ Equilibrium: $p_0 = p_0(\tau, \xi, \mathbf{v}; \rho_0)$

$$0 = \eta_m \left[\frac{1}{2} \rho_0 \psi_m(v) m^e(\hat{\mathbf{v}}) - M p_0(\mathbf{v}) \right] + \eta_c \rho_0 \left[\rho_0 \psi_c(\mathbf{v}) - p_0(\mathbf{v}) \right]$$

$$p_0(\mathbf{v}) = \frac{\rho_0}{\eta_m M + \eta_c \rho_0} \left[\frac{\eta_m}{2} \psi_m(v) m^e(\hat{\mathbf{v}}) + \eta_c \rho_0 \psi_c(\mathbf{v}) \right]$$

$$\rho_0 = \int_V p_0(\mathbf{v})\, d\mathbf{v}$$

$$\mathrm{U}_0 = \frac{1}{\rho_0} \int_V p_0(\mathbf{v})\, \mathbf{v}\, d\mathbf{v} = \mathbf{0}$$

Diffusion limit

ε^1 :

$$\nabla_\xi \cdot [p_0(\mathbf{v})\mathbf{v}] + \nabla_\mathbf{v} \cdot \left[\hat{\mathbf{f}} p_0(\mathbf{v})\right] = \eta_m \left[\frac{1}{2}\rho_1 \psi_m(v) m^e(\hat{\mathbf{v}}) - M p_1(\mathbf{v})\right] + \eta_c \left[\rho_1 \left(2\rho_0 \psi_c(\mathbf{v}) - p_0(\mathbf{v})\right) - \rho_0 p_1(\mathbf{v})\right]$$

$$p_1(\mathbf{v}) = \frac{1}{\eta_m M + \eta_c \rho_0} \left[-\nabla_\xi \cdot [p_0(\mathbf{v})\mathbf{v}] - \nabla_\mathbf{v} \cdot \left[\hat{\mathbf{f}} p_0(\mathbf{v})\right] + \rho_1 \left(\frac{\eta_m}{2} \psi_m(v) m^e(\hat{\mathbf{v}}) + \eta_c [2\rho_0 \psi_c(\mathbf{v}) - p_0(\mathbf{v})] \right) \right]$$

$$\int_V p_1(\mathbf{v})\, \mathbf{v}\, d\mathbf{v} = \frac{1}{\eta_m M + \eta_c \rho_0} \left[-\nabla_\xi \cdot \int_V p_0(\mathbf{v})\, \mathbf{v} \otimes \mathbf{v}\, d\mathbf{v} + \rho_0 \hat{\mathbf{f}} \right]$$

Pressure tensor at the equilibrium

$$\frac{\partial \rho_0}{\partial \tau} + \nabla_\xi \cdot \int_V p_1(\mathbf{v})\,\mathbf{v}\,d\mathbf{v} = 0$$

$$\frac{\partial \rho_0}{\partial \tau} = \nabla_\xi \cdot \left[\frac{\nabla_\xi \cdot \mathbb{P}_0 - \rho_0 \hat{\mathbf{f}}}{\eta_m M + \eta_c \rho_0} \right]$$

$$\mathbb{P}_0 = \frac{\rho_0}{\eta_m M + \eta_c \rho_0} \left(\eta_m \sigma_m M \mathbb{D} + \eta_c \sigma_c \rho_0 \mathbb{I} \right)$$

- $\sigma_m,\ \sigma_c$: macroscopic coefficients (variance)

Assumption:

The intensity of after-interaction velocities does not depend on the interaction type

$$\sigma_m = \sigma_c \equiv \sigma$$

$$\mathbb{P}_0 = \sigma \rho_0 \mathbb{I} + \frac{\eta_m \sigma M}{\eta_m M + \eta_c \rho_0} (\mathbb{D} - \mathbb{I}) \rho_0$$

Dimensionless Equation

$$\frac{\partial \rho}{\partial t} + \mathcal{P}_e \nabla_{\mathbf{x}} \cdot \left[\frac{\rho \mathbf{f}(c)}{M + \alpha\rho} \right] = \nabla_{\mathbf{x}} \cdot \left[\frac{\nabla_{\mathbf{x}}(\rho)}{M + \alpha\rho} \right]$$

Chemotactic advection — Isotropic spatially varying diffusion

$$+ \nabla_{\mathbf{x}} \cdot \left[\frac{1}{M + \alpha\rho} \nabla_{\mathbf{x}} \cdot \left(\frac{M(\mathbb{D} - \mathbb{I})\rho}{M + \alpha\rho} \right) \right]$$

Anisotropic spatially varying diffusion due to the fibers direction

Parameters of the model:

- Peclet number $\mathcal{P}_e = FL/\sigma$
- $\alpha = \eta_c/\eta_m$

External data:

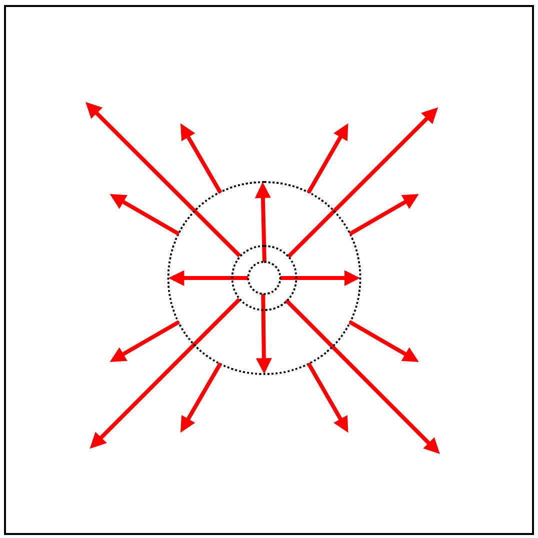
- the chemotactic force $\mathbf{f}$
- the description of the ECM

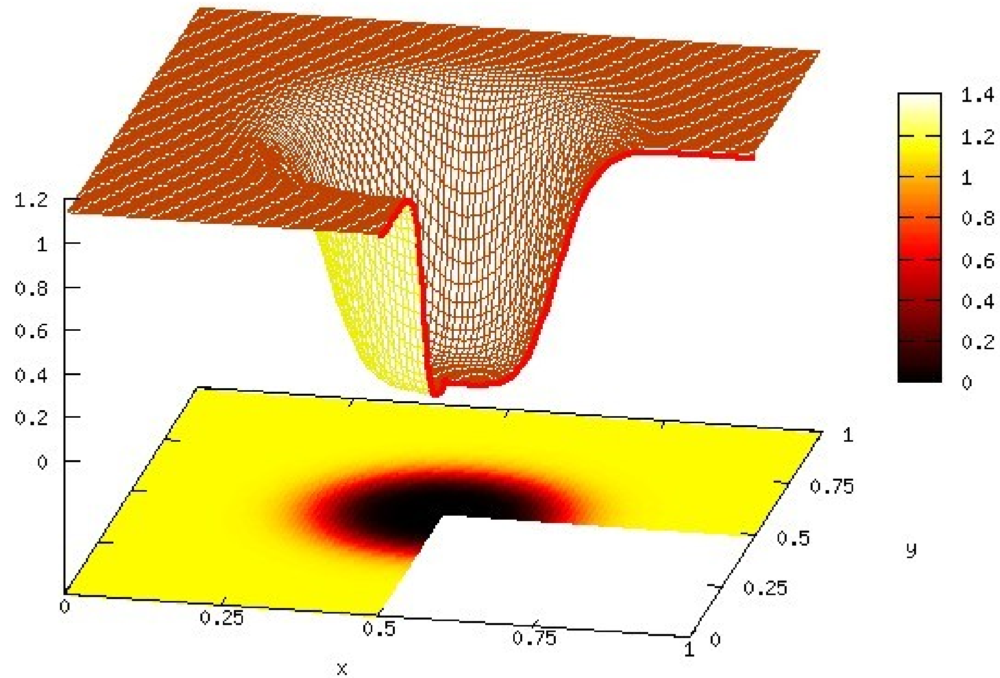
M → Heterogeneity

$\mathbb{D}$ → Anisotropy

The stationary solution

- Configuration: a radial chemo-repellent force





Exercise: stationary configuration

$$\mathcal{P}_e \nabla_{\mathbf{x}} \cdot \left[\frac{\rho \mathbf{f}(c)}{M + \alpha\rho} \right] = \nabla_{\mathbf{x}} \cdot \left[\frac{\nabla_{\mathbf{x}}(\rho)}{M + \alpha\rho} \right]$$

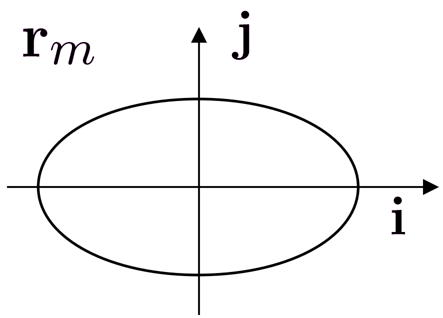
The heterogeneous case

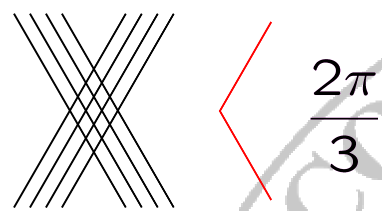
- Case 1 : Example with symmetry
  - uniform initial condition $\rho(t=0,\mathbf{x}) \equiv C$
  - homogeneous $M(\mathbf{x}) \equiv C$
  - isotropic $\mathbb{D}(\mathbf{x}) \equiv \mathbb{I}$
  - short time
  - long time
- Case 2 :
  - uniform initial condition $\rho(t=0,\mathbf{x}) \equiv C$
  - inhomogeneous $M(\mathbf{x}) \neq C$
  - isotropic $\mathbb{D}(\mathbf{x}) \equiv \mathbb{I}$
  - short time
  - long time
- Case 3 :
  - non uniform initial condition $\rho(t=0,\mathbf{x}) \neq C$
  - homogeneous $M(\mathbf{x}) \equiv C$
  - isotropic $\mathbb{D}(\mathbf{x}) \equiv \mathbb{I}$
  - short time
  - long time

The anisotropic case

- uniform initial condition $\rho(t=0,\mathbf{x}) \equiv C$
- homogeneous $M(\mathbf{x}) \equiv C$
- anisotropic $\mathbb{D}(\mathbf{x}) \neq \mathbb{I}$

$$\mathbb{D}(\mathbf{x}) = Cste = \begin{pmatrix} \frac{1}{2} & 0 \\ 0 & \frac{3}{2} \end{pmatrix}$$



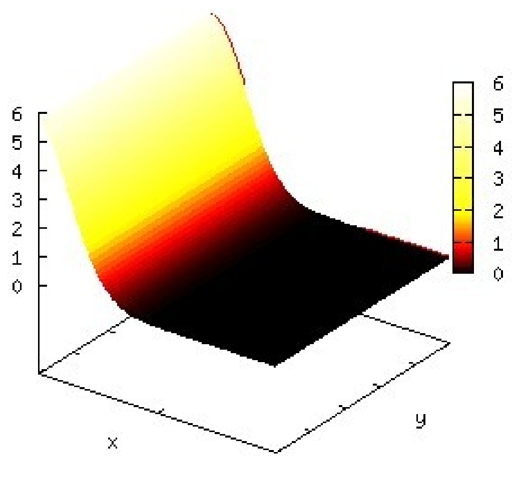


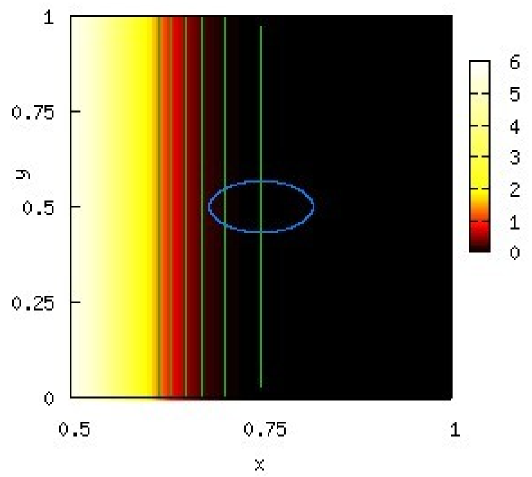
- movie

Heterogeneous ECM

- Parameters $\begin{cases} \mathcal{P}_e = 50 \\ \alpha = 1 \end{cases}$

$t = 0.$

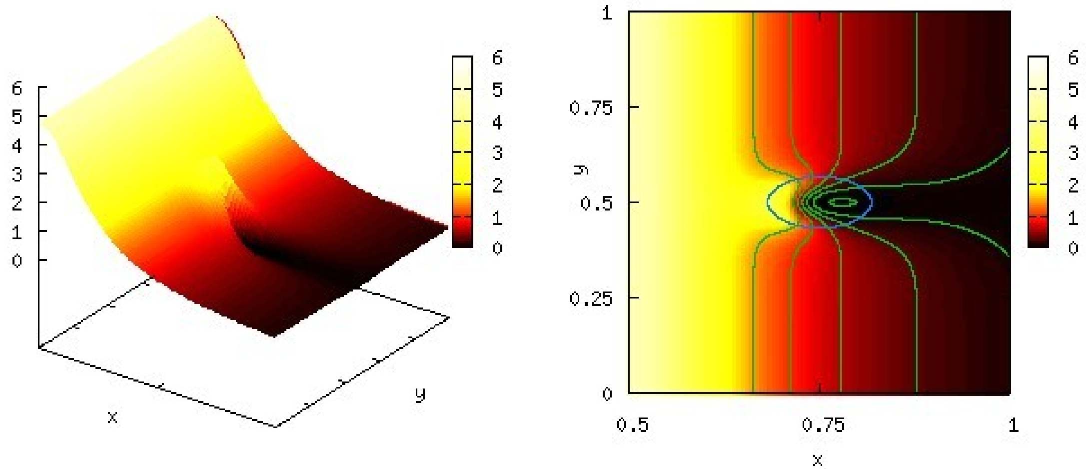




Heterogeneous ECM

- Parameters $\begin{cases} \mathcal{P}_e = 50 \\ \alpha = 1 \end{cases}$

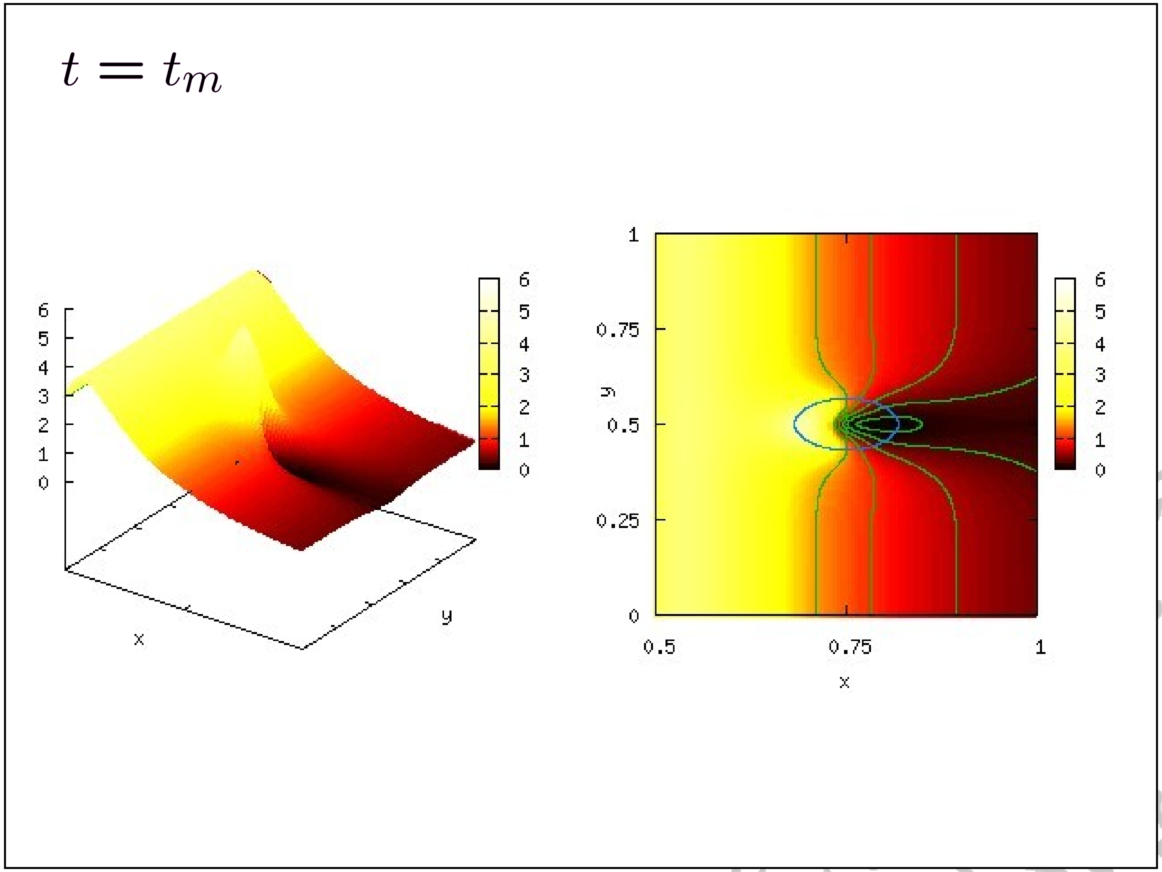
$$t = \frac{1}{2} t_m$$



Heterogeneous ECM

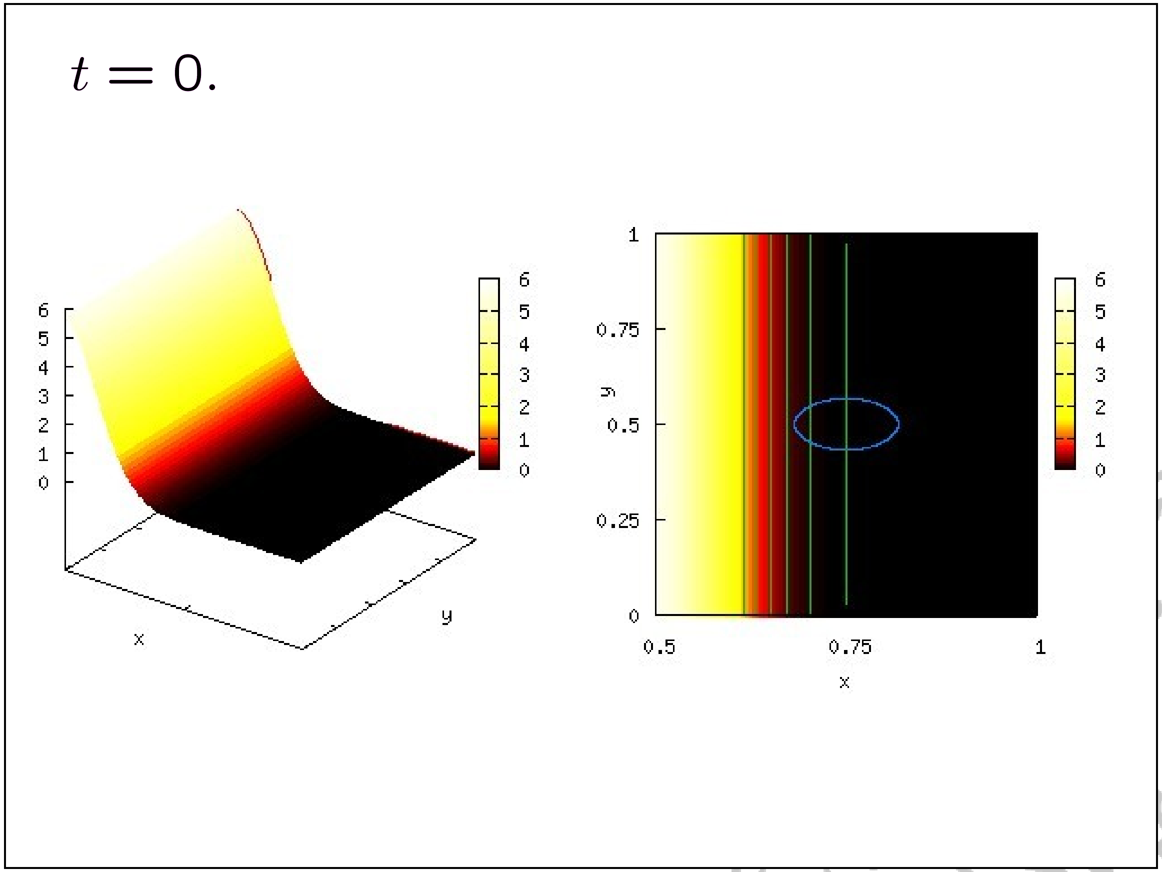
- Parameters $\begin{cases} \mathcal{P}_e = 50 \\ \alpha = 1 \end{cases}$

movie



Heterogeneous ECM

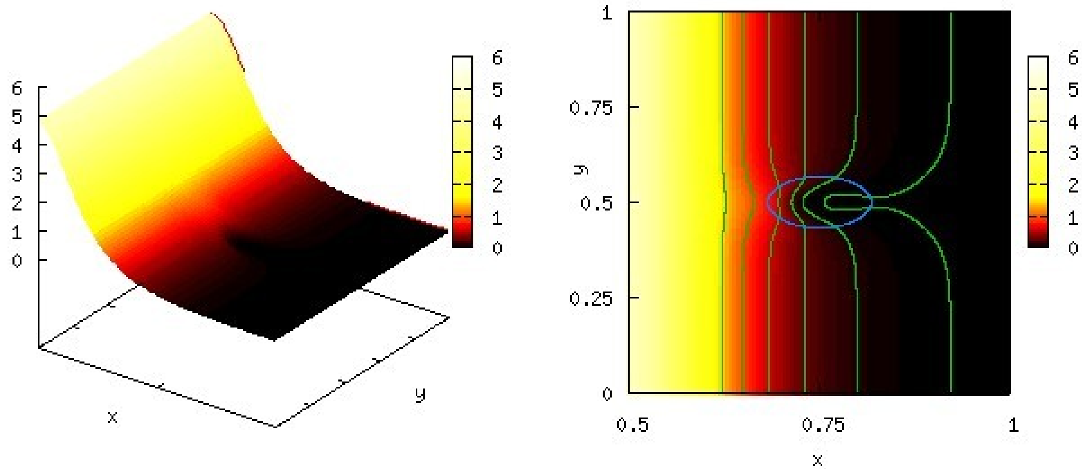
- Parameters $\begin{cases} \mathcal{P}_e = 0.02 \\ \alpha = 1 \end{cases}$



Heterogeneous ECM

- Parameters $\begin{cases} \mathcal{P}_e = 0.02 \\ \alpha = 1 \end{cases}$

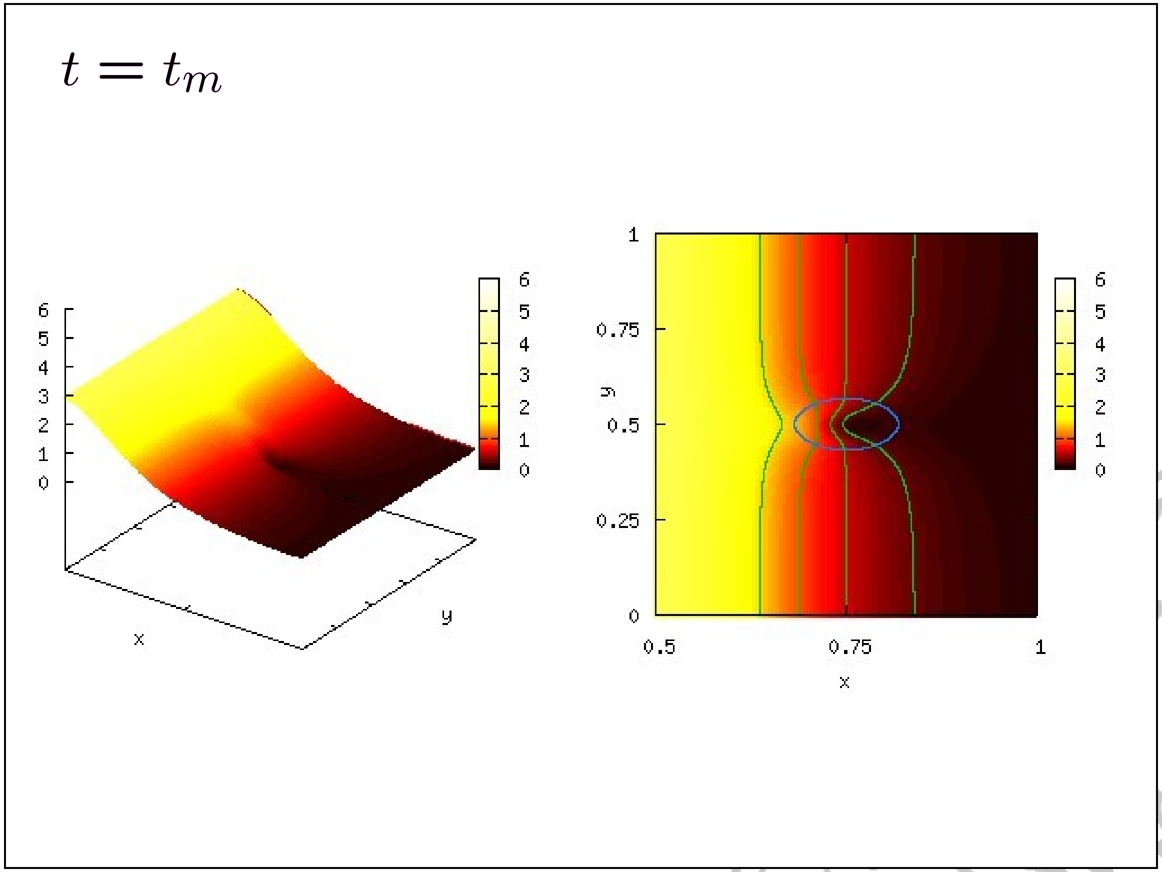
$$t = \frac{1}{4} t_m$$



Heterogeneous ECM

- Parameters $\begin{cases} \mathcal{P}_e = 0.02 \\ \alpha = 1 \end{cases}$

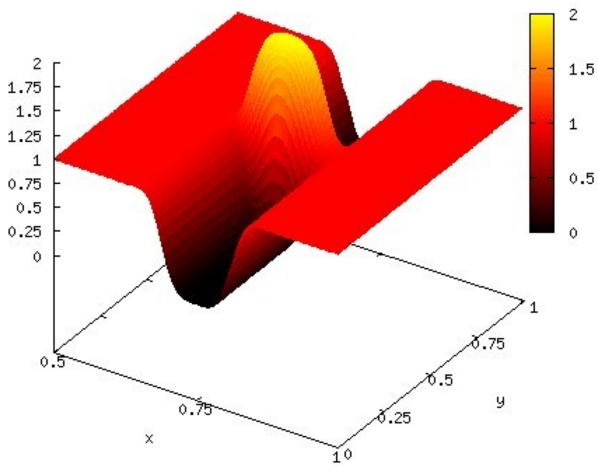
movie



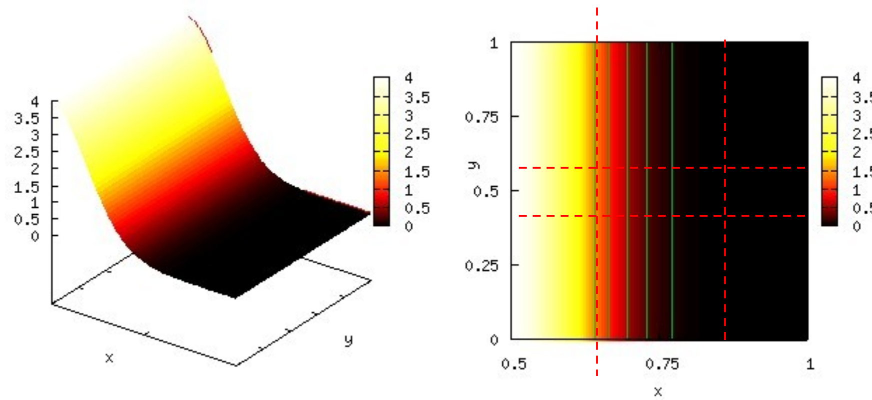
Anisotropic ECM

- Parameters $\begin{cases} \mathcal{P}_e = 1 \\ \alpha = 0.5 \end{cases}$

$D(x,y)$



$t = 0.$

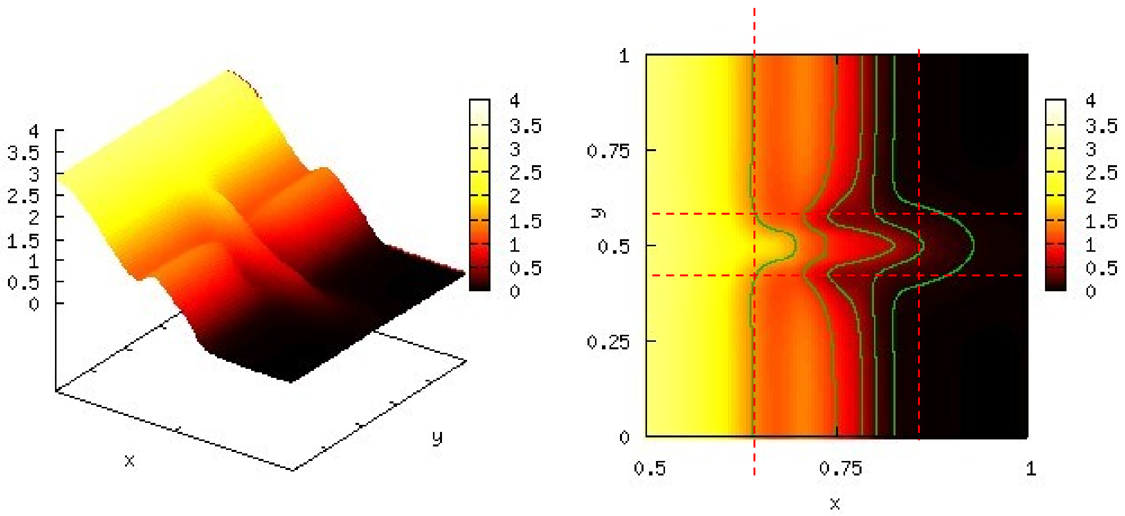


- $\mathbb{D}(\mathbf{x}) = \begin{pmatrix} D(x,y) & 0 \\ 0 & 2 - D(x,y) \end{pmatrix}$

Anisotropic ECM

- Parameters $\begin{cases} \mathcal{P}_e = 1 \\ \alpha = 0.5 \end{cases}$

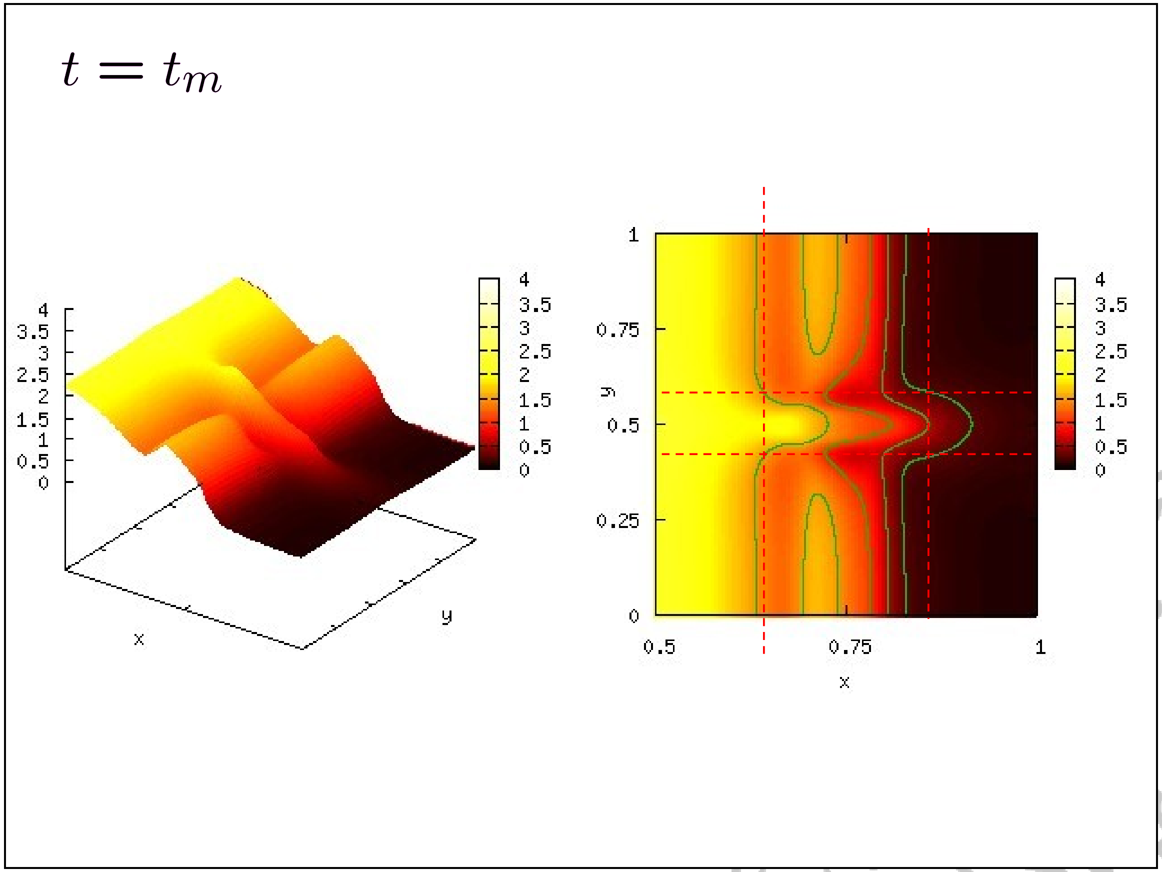
$$t = \frac{1}{2} t_m$$



Anisotropic ECM

movie

- Parameters $\begin{cases} \mathcal{P}_e = 1 \\ \alpha = 0.5 \end{cases}$



Biased interactions

$$J_m^{\mathcal{B}}(t, \mathbf{x}, \mathbf{v}) = \eta_m M(\mathbf{x}) \left(\rho(t, \mathbf{x}) \psi(v) \frac{m^e(\mathbf{x}, \hat{\mathbf{v}})}{2M(\mathbf{x})} [1 + \mathcal{B}(t, \mathbf{x}, \hat{\mathbf{v}})] - p(t, \mathbf{x}, \mathbf{v}) \right)$$

$$J_c^{\mathcal{B}}(t, \mathbf{x}, \mathbf{v}) = \eta_c \rho(t, \mathbf{x}) \left(\rho(t, \mathbf{x}) \frac{\psi(v)}{\mathcal{V}_d} [1 + \mathcal{B}(t, \mathbf{x}, \hat{\mathbf{v}})] - p(t, \mathbf{x}, \mathbf{v}) \right)$$

$$\mathcal{B}(t, \mathbf{x}, \hat{\mathbf{v}}) = \pm \Gamma \frac{\nabla \mathcal{S}(t, \mathbf{x}) \cdot \hat{\mathbf{v}}}{\beta_{\mathcal{S}} + \mathcal{S}(t, \mathbf{x})}$$

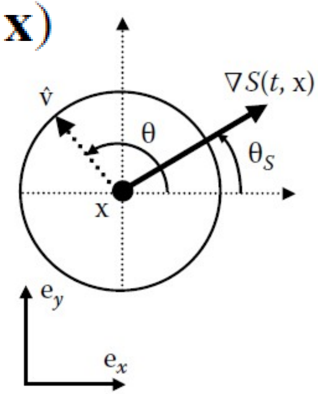
$$\frac{\partial \rho^{(0)}}{\partial t} \pm \kappa \nabla \cdot \left[\rho^{(0)} \frac{\mathbb{T}^{(0)} \nabla \mathcal{S}}{\beta_{\mathcal{S}} + \mathcal{S}} \right] = \sigma \nabla \cdot \left[\frac{\nabla \cdot [\mathbb{T}^{(0)} \rho^{(0)}]}{M + \alpha \rho^{(0)}} \right]$$

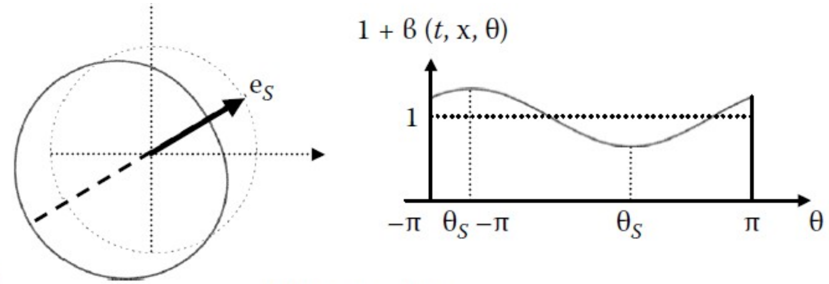
Biased interactions

$$J_m^{\mathcal{B}}(t, \mathbf{x}, \mathbf{v}) = \eta_m M(\mathbf{x}) \left(\rho(t, \mathbf{x}) \psi(v) \frac{m^e(\mathbf{x}, \hat{\mathbf{v}})}{2M(\mathbf{x})} [1 + \mathcal{B}(t, \mathbf{x}, \hat{\mathbf{v}})] - p(t, \mathbf{x}, \mathbf{v}) \right)$$

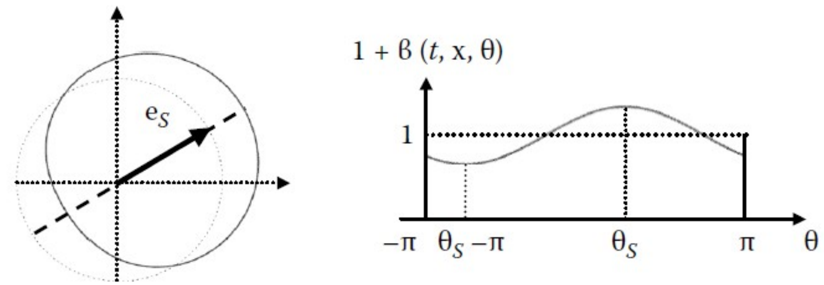
$$J_c^{\mathcal{B}}(t, \mathbf{x}, \mathbf{v}) = \eta_c \rho(t, \mathbf{x}) \left(\rho(t, \mathbf{x}) \frac{\psi(v)}{\mathcal{V}_d} [1 + \mathcal{B}(t, \mathbf{x}, \hat{\mathbf{v}})] - p(t, \mathbf{x}, \mathbf{v}) \right)$$

$$\mathcal{B}(t, \mathbf{x}, \hat{\mathbf{v}}) = \pm \Gamma \frac{\nabla \mathcal{S}(t, \mathbf{x}) \cdot \hat{\mathbf{v}}}{\beta_{\mathcal{S}} + \mathcal{S}(t, \mathbf{x})}$$



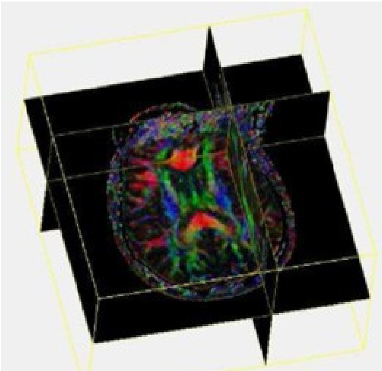


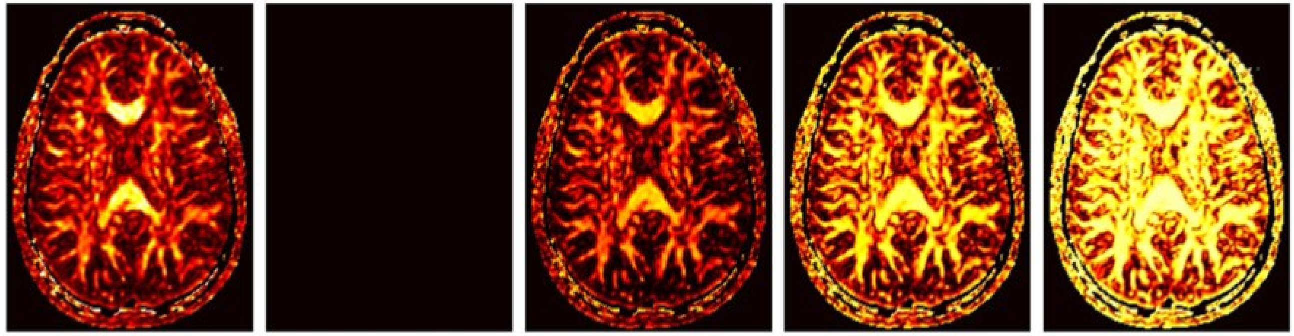
(a) Repellent bias



(b) Attractive bias

Glioblastoma





k=0 k=5 k=10 k=20

k = sensitivity of the cell to directional cues

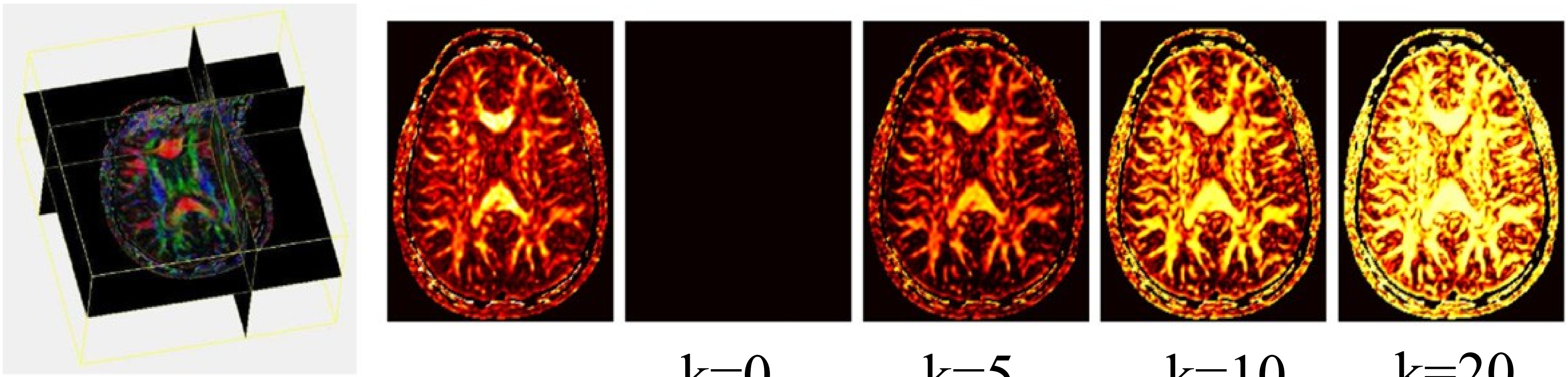
δ = ratio of random turning

φ = eigendirection

$$D_C(\mathbf{x}) = \frac{s^2}{3\mu}\left[\left(\delta + (1-\delta)\left(\frac{\coth k}{k} - \frac{1}{k^2}\right)\right)\square + (1-\delta)\left(1 - \frac{3\coth k}{k} + \frac{3}{k^2}\right)\varphi_1\varphi_1^T\right].$$

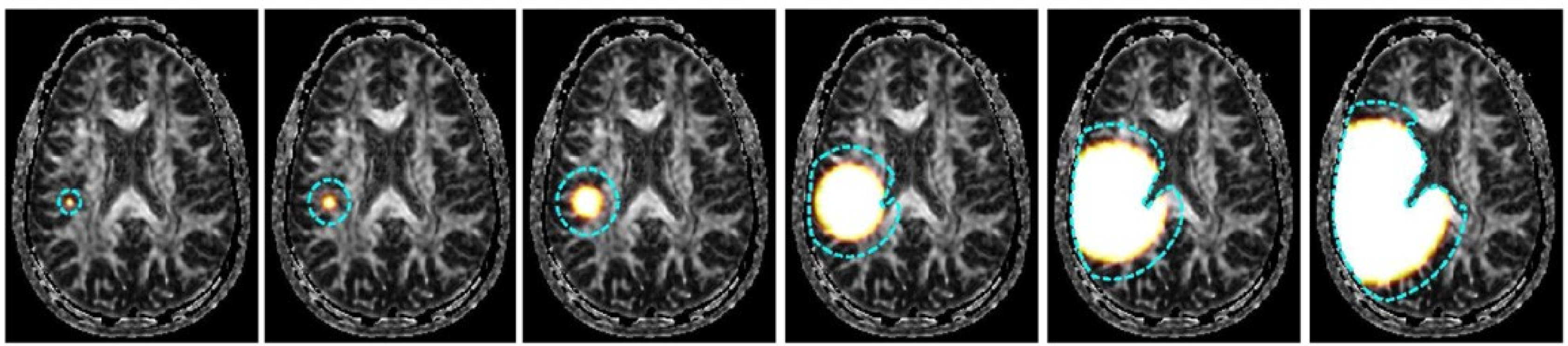
Painter & Hillen, J. Theor. Biol., 323, 25-39 (2013)

Glioblastoma



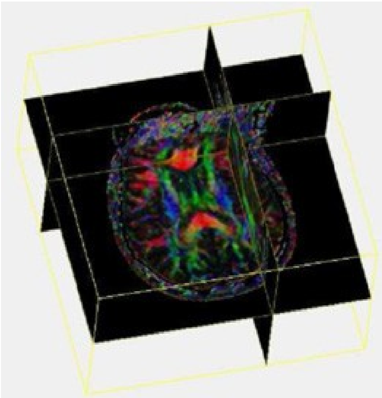
k=0 k=5 k=10 k=20

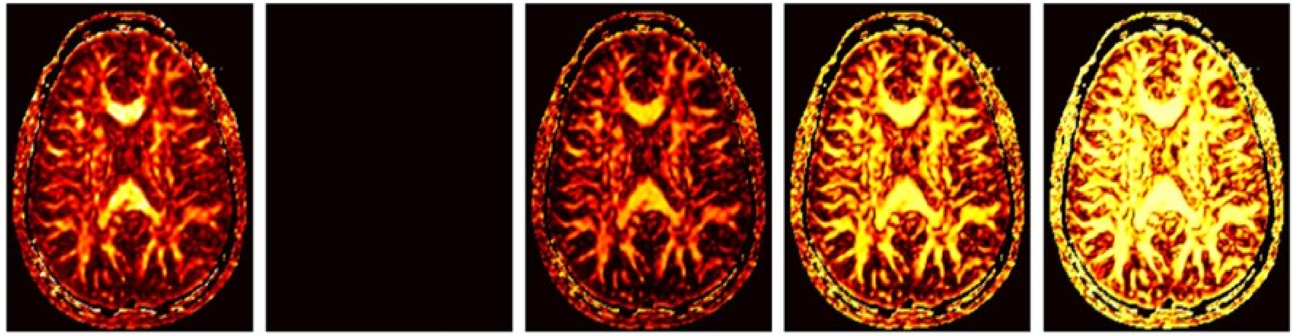
k=0



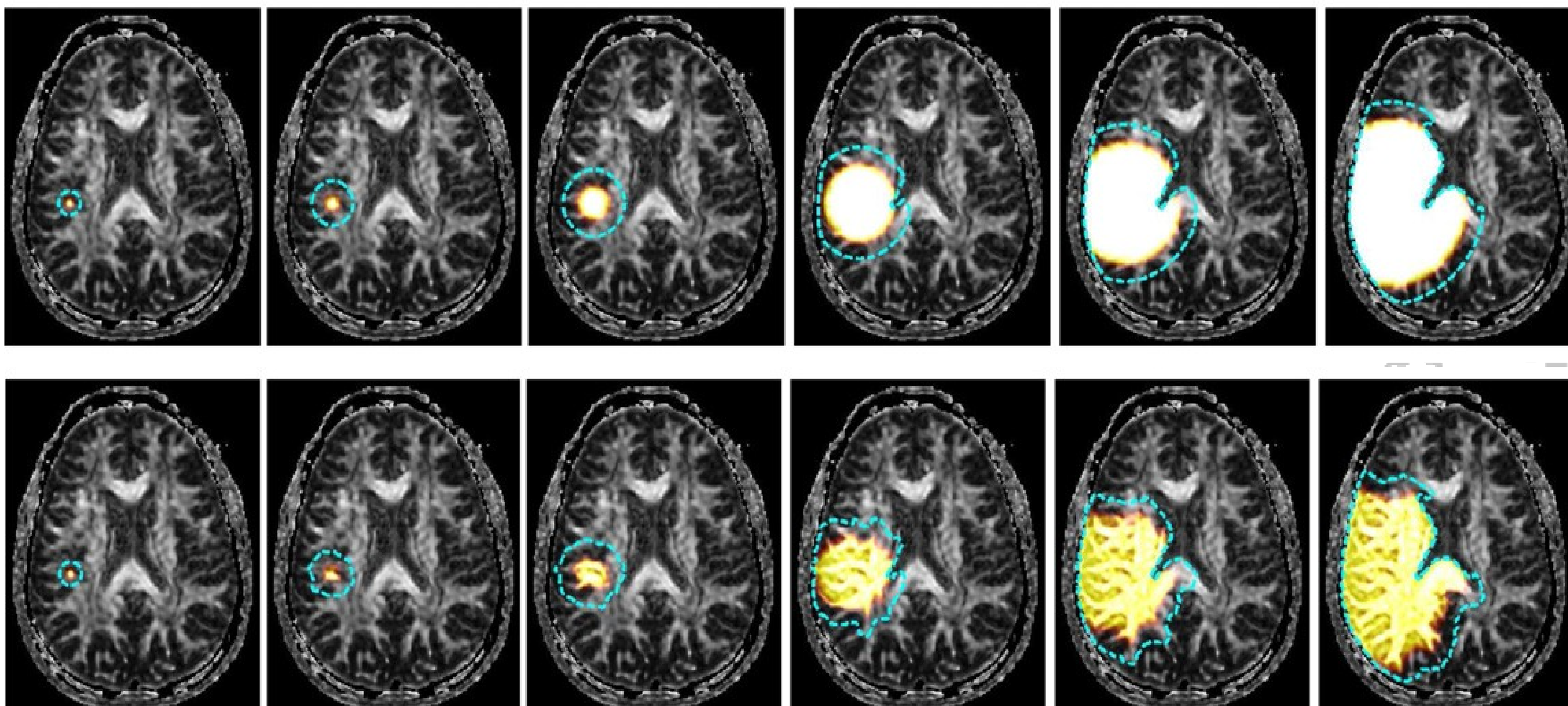
Painter & Hillen, J. Theor. Biol., 323, 25-39 (2013)

Glioblastoma





k=0 k=5 k=10 k=20



k=0

k=20

ECM Remodelling

- Fibers don't move
- They are degraded by the interaction with the cells

$$\frac{\partial m}{\partial t}(t,\mathbf{x},\mathbf{n}) = -\mathcal{L}_m\left(p(t,\mathbf{x},\mathbf{v}),\mathbf{n}\right)\left(m(t,\mathbf{x},\mathbf{n}) - m_0(\mathbf{x},\mathbf{n})\right)$$

$$\mathcal{L}_m \equiv \mathcal{L}_m(t,\mathbf{x},\mathbf{n}) = \int_V \eta_m K(\mathbf{v},\mathbf{n})\, p(t,\mathbf{x},\mathbf{v})\, d\mathbf{v}$$

- If fibers on the way of the cells are cut and those along the direction of cell motion are not, e.g.,

$$\bar{K}(|\hat{\mathbf{v}}\cdot\mathbf{n}|) = \mu(1 - |\hat{\mathbf{v}}\cdot\mathbf{n}|^{\beta})$$

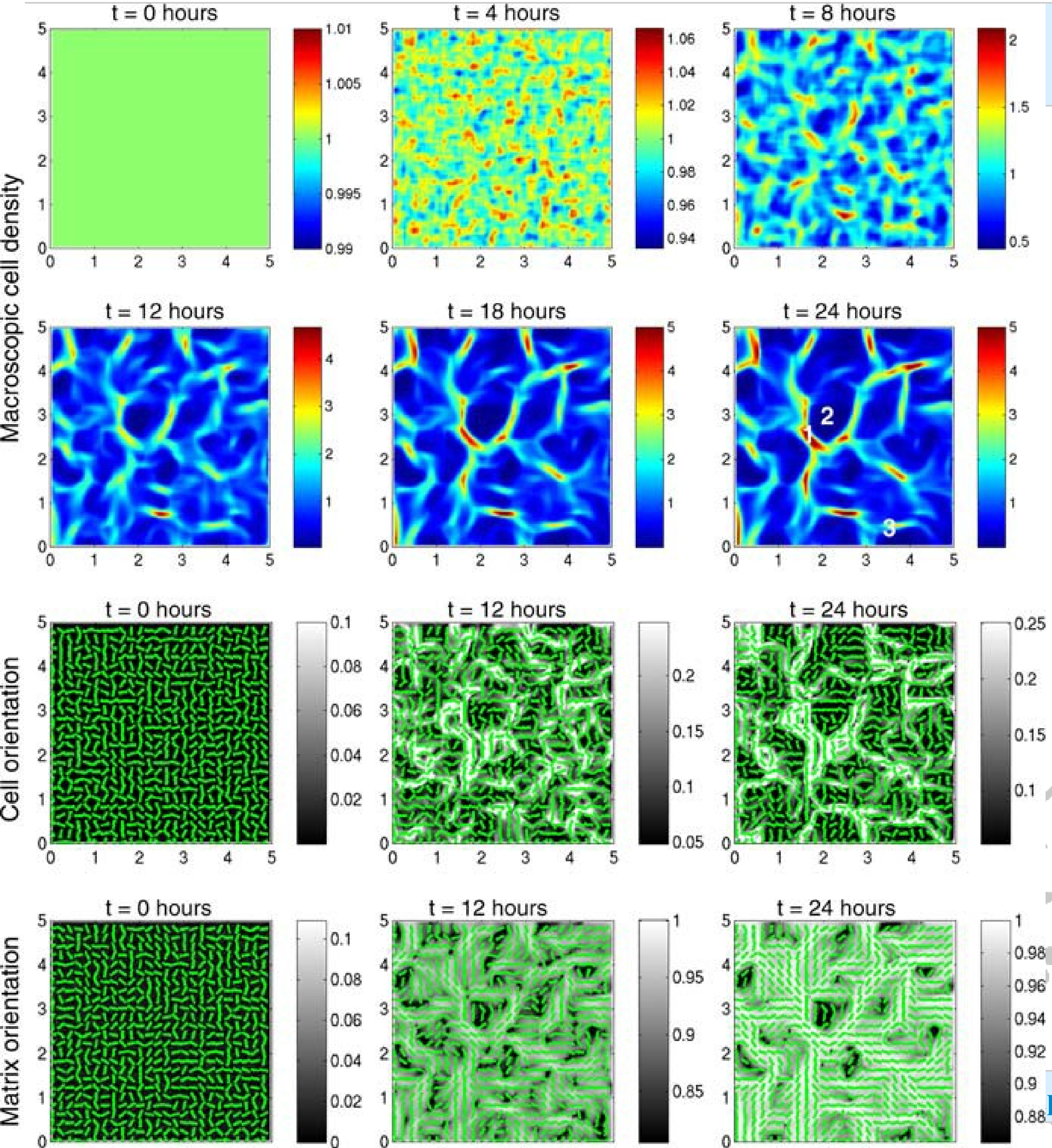
ECM Remodelling

$$c(\mathbf{x},\theta,t)_t + s_0\nabla\cdot c(\mathbf{x},\theta,t)(\cos\theta,\sin\theta)$$
$$= -\mu c(\mathbf{x},\theta,t) + \mu\int^{\pi} T(\theta,\theta')c(\mathbf{x},\theta',t)\,\mathrm{d}\theta'$$

$$m(\mathbf{x},\phi,t)_t = -\delta\left(\int_{-\pi}^{\pi}(1-\psi\,|\cos(\theta-\phi)|)\,c(\mathbf{x},\theta,t)\,\mathrm{d}\theta\right)m(\mathbf{x},\phi,t).$$

$$T(\theta,\theta') = \begin{cases} \dfrac{1-b}{2\pi} + b\dfrac{m(\theta)}{2\overline{m}} & \text{if } \theta\in(-\pi,0] \\ \dfrac{1-b}{2\pi} + b\dfrac{m(\theta-\pi)}{2\overline{m}} & \text{if } \theta\in(0,\pi] \end{cases}$$

Painter, *J. Math. Biol.*, **58**,511–543, (2009)



Painter, *J. Math. Biol.*, **58**,511–543, (2009)