

## MODELING THE MOTION OF A CELL POPULATION IN THE EXTRACELLULAR MATRIX

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**Abstract. DA FARE !**

**1. Introduction.** Cells that move through tissues (like cancer metastases, or fibroblasts) interact with the tissue matrix (the Extra-Cellular Matrix, usually shortened as ECM) as well as with other cells. Recently, much attention has been devoted to the description of the mechanisms of motions of cells as a result of their interaction with the ECM. A detailed description of the physiological mechanisms is given by Friedl and coworkers [8, 9, 10, 18]. From the modeling point of view we can cite the work by Barocas and Tranquillo [3], and by Dickinson [6, 7]. Interesting application considering cell-substratum interactions can also be found in [14, 15, 17] and in the review article [1].

In this paper we want to look closer at the interaction mechanisms and deduce the continuum model as a limit of a kinetic one. The model deduced includes external forces acting on the cells and obtains drag forces in the continuum model as a result of the interactions among cells and between cells and the ECM.

This work is based on earlier models by the Authors [11, 16], and in particular, on the kinetic model described in [5]. In [16] mass and momentum balance for cell motion are joined with diffusion equations for the chemical factors influencing motion to describe network formation of endothelial cells. In the  $M^5$ -model proposed in [11], a transport equation for moving cells was derived which includes cell-ECM interactions but does not include forces and cell-cell collisions.

Here we start from the development of a kinetic model for mesenchymal cell motion in fibrous tissues, including chemotactic forces, contact guidance from network fibers, cell-ECM and cell-cell interactions. However, with respect to [5] we do not include the degradation of the surrounding tissue by proteases released by moving cells. On the other hand, we work in a general  $d$ -dimensional space having in mind two- and three-dimensional experimental set-ups, and consider more general interaction kernels.

The paper is structured as followed. Starting from the mesoscopic description and the kinetic model deduced in Section 2, we derive in Section 3 the system of

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moment equations for mass and momentum at the macroscopic scale. By modeling the interactions between cells and the fibers of the tissue at the microscopic level, in Section 4 we derive the terms appearing in the system of moment equations. In Section 5 we investigate the moments system, and apply a moment closure technique to derive a continuum model. Finally, numerical simulations are presented in order to emphasize the influence of an inhomogeneous isotropic fiber network over the cell motion and of the presence of an exogenous chemoattractant field.

**2. The Kinetic Model.** We consider a cell population moving in the ensemble of tiny fibers constituting the ECM. We assume that the cells neither deform, nor degrade/produce the ECM, so that the fiber network acts as a passive substratum. We assume that the statistical description of the cells is given by the distribution density function  $p = p(t, \mathbf{x}, \mathbf{v})$ , where  $t > 0$  is the time,  $\mathbf{x} \in \mathcal{D} \subseteq \mathbb{R}^d$  denotes the position and  $\mathbf{v} \in V \subseteq \mathbb{R}^d$  the velocity. In particular,  $p$  is normalized with respect to the total number of cells, so that  $\int_{\mathcal{D}} \int_V p(t=0, \mathbf{x}, \mathbf{v}) d\mathbf{x} d\mathbf{v} = 1$ . Often the velocity vector will be written as  $\mathbf{v} = v\hat{\mathbf{v}}$  where  $\hat{\mathbf{v}}$  defines the velocity direction and  $v = |\mathbf{v}|$  its modulus. The general case  $\mathbb{R}^d$  is presented with the aim to describe *in vivo* motion ( $d = 3$ ) or *in vitro* motion over a substratum ( $d = 2$ ).

We denote by  $\rho$  and  $\rho\mathbf{U}$ , the cell (number) density and momentum, respectively, where

$$\rho(t, \mathbf{x}) = \int_V p(t, \mathbf{x}, \mathbf{v}) d\mathbf{v}, \quad (1)$$

$$\rho(t, \mathbf{x})\mathbf{U}(t, \mathbf{x}) = \int_V p(t, \mathbf{x}, \mathbf{v}) \mathbf{v} d\mathbf{v}. \quad (2)$$

We also define the pressure tensor as

$$\mathbb{P}(t, \mathbf{x}) = \int_V p(t, \mathbf{x}, \mathbf{v}) [\mathbf{v} - \mathbf{U}(t, \mathbf{x})] \otimes [\mathbf{v} - \mathbf{U}(t, \mathbf{x})] d\mathbf{v}, \quad (3)$$

and observe that

$$\int_V p(t, \mathbf{x}, \mathbf{v}) \mathbf{v} \otimes \mathbf{v} d\mathbf{v} = \mathbb{P}(t, \mathbf{x}) + \rho(t, \mathbf{x})\mathbf{U}(t, \mathbf{x}) \otimes \mathbf{U}(t, \mathbf{x}). \quad (4)$$

Similarly, the density and orientation of the fiber network is given by the distribution density function  $q = q(\mathbf{x}, \mathbf{n})$  where  $\mathbf{n}$  is the angle of fibers. Since fibers have no preferred direction, to characterize how their are distributed it is enough to define  $q$  over half of the unit sphere  $S_+^{d-1}$ , or to extend  $q$  over the entire sphere as an even function of  $\mathbf{n}$ , e.g. using

$$q^e(\mathbf{x}, \mathbf{n}) = \begin{cases} q(\mathbf{x}, \mathbf{n}) & \text{for } \mathbf{n} \in S_+^{d-1}, \\ q(\mathbf{x}, -\mathbf{n}) & \text{for } \mathbf{n} \in S_-^{d-1}. \end{cases} \quad (5)$$

Then the quantity

$$Q(\mathbf{x}) = \int_{S_+^{d-1}} q(\mathbf{x}, \mathbf{n}) d\mathbf{n} = \frac{1}{2} \int_{S^{d-1}} q^e(\mathbf{x}, \mathbf{n}) d\mathbf{n}, \quad (6)$$

denotes the network fiber density, while the orientation of the network can be described by the symmetric and positive definite tensor

$$\mathbb{D}(\mathbf{x}) = \frac{d}{Q(\mathbf{x})} \int_{S_+^{d-1}} q(\mathbf{x}, \mathbf{n}) \mathbf{n} \otimes \mathbf{n} d\mathbf{n}. \quad (7)$$

In order to visualize it, it is useful to refer to the ellipsoid  $\mathbf{x} \cdot \mathbb{D} \mathbf{x} = 1$  which has the axes identified by the eigenvectors of the tensor  $\mathbb{D}$  and gives the principal directions of the orientation of the network. In particular, in the isotropic case the tensor is diagonal and all eigenvalues are equal. On the contrary, in the anisotropic case, the direction of the eigenvector corresponding to the maximum eigenvalue (e.g. the smallest axis of the ellipsoid) gives the main fiber direction. In the limit case in which the fibers are all aligned along the orientation  $\mathbf{N}$ , then  $\mathbb{D} = d\mathbf{N} \otimes \mathbf{N}$ , the eigenvalues are 1 and 0 corresponding, respectively, to the eigenvector  $\mathbf{N}$  and to any orthogonal eigendirection. The ellipsoid is given by  $(\mathbf{x} \cdot \mathbf{N})^2 = 1/d$ , e.g., if  $\mathbf{N} = \mathbf{e}_x$ , it degenerates into the domain  $x = \pm 1/\sqrt{d}$ . It is also useful to observe that  $\text{tr}(\mathbb{D}) = d$ .

To derive a kinetic model for cell movement we make the following assumptions:

- There is a chemical field  $c$  that induces by internal mechanism an influence on cells, treated here as an external force  $\mathbf{f}(c) \in \mathbb{R}^d$ , e.g.  $\mathbf{f}(c) = \lambda \nabla_{\mathbf{x}} c$  where  $\lambda$  can depend on  $c$ . This force is assumed to model chemotactic and haptotactic phenomena;
- Cells interact mechanically with the extra-cellular matrix and use fibers for contact guidance. The collision operator of cells and ECM is denoted by  $J_m$ ;
- Cells also interact with cells and the corresponding cell-cell collision operator is denoted by  $J_c$ .
- During both interactions mass is preserved, e.g.

$$\int_V J_m d\mathbf{v} = 0, \quad \text{and} \quad \int_V J_c d\mathbf{v} = 0. \quad (8)$$

On the other hand we will not impose that the collision kernels satisfy neither momentum, nor energy conservation.

Then the transport equation for cell movement is

$$\frac{\partial p}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} p + \nabla_{\mathbf{v}} \cdot [\mathbf{f}(c)p] = J_m + J_c, \quad (9)$$

and it will be the starting point to develop the macroscopic model by using the moment expansion method.

**3. Moment Expansions.** The aim of this section is to obtain dynamic equations for the population density  $\rho$  and momentum  $\rho \mathbf{U}$ . Integrating Eq.(9) over the domain velocity  $V$  gives

$$\int_V \frac{\partial p}{\partial t} d\mathbf{v} + \int_V \mathbf{v} \cdot \nabla_{\mathbf{x}} p d\mathbf{v} + \int_V \nabla_{\mathbf{v}} \cdot (\mathbf{f}p) d\mathbf{v} = \int_V J_m d\mathbf{v} + \int_V J_c d\mathbf{v}. \quad (10)$$

Now, under the assumption that  $p$  vanishes on the boundary  $\partial V$ ,  $\int_V \nabla_{\mathbf{v}} \cdot (\mathbf{f}p) d\mathbf{v} = 0$  due to the divergence theorem, and the r.h.s. vanishes due to the mass conservation assumptions (8). Hence one obtains the mass conservation equation

$$\frac{\partial \rho}{\partial t} + \nabla_{\mathbf{x}} \cdot (\rho \mathbf{U}) = 0. \quad (11)$$

The integration of the transport equation (9), multiplied by  $\mathbf{v}$  this time, gives

$$\begin{aligned} \int_V \frac{\partial}{\partial t} (p\mathbf{v}) d\mathbf{v} + \int_V [\mathbf{v} \cdot \nabla_{\mathbf{x}} p] \mathbf{v} d\mathbf{v} + \int_V [\nabla_{\mathbf{v}} \cdot (\mathbf{f}p)] \mathbf{v} d\mathbf{v} \\ = \int_V J_m \mathbf{v} d\mathbf{v} + \int_V J_c \mathbf{v} d\mathbf{v}. \end{aligned} \quad (12)$$

Writing the identity

$$\nabla_{\mathbf{v}} \cdot (\mathbf{v} \otimes \mathbf{f}p) = \mathbf{f}p \cdot [\nabla_{\mathbf{v}} \mathbf{v}] + [\nabla_{\mathbf{v}} \cdot (\mathbf{f}p)] \mathbf{v},$$

and observing that  $\nabla_{\mathbf{v}} \mathbf{v} = \mathbb{I}$ , where  $\mathbb{I}$  is the identity matrix, one can write

$$[\nabla_{\mathbf{v}} \cdot (\mathbf{f}p)] \mathbf{v} = \nabla_{\mathbf{v}} \cdot (\mathbf{v} \otimes \mathbf{f}p) - \mathbf{f}p.$$

Again because of the divergence theorem, we obtain  $\int_V \nabla_{\mathbf{v}} \cdot (\mathbf{v} \otimes \mathbf{f}p) d\mathbf{v} = \mathbf{0}$ , and since  $\mathbf{f} = \mathbf{f}(c)$ , then  $\int_V \mathbf{f}(c)p d\mathbf{v} = \rho \mathbf{f}(c)$ , so that Eq.(12) can then be written as

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

where  $\mathbf{j}_m$  and  $\mathbf{j}_c$  are related to momentum dissipation and are defined by

$$\mathbf{j}_m = \int_V J_m \mathbf{v} d\mathbf{v}, \quad \text{and} \quad \mathbf{j}_c = \int_V J_c \mathbf{v} d\mathbf{v}.$$

Finally, recalling the expression (4) of the pressure tensor one has

$$\frac{\partial}{\partial t}(\rho \mathbf{U}) + \nabla_{\mathbf{x}} \cdot (\rho \mathbf{U} \otimes \mathbf{U}) = -\nabla_{\mathbf{x}} \cdot \mathbb{P} + \rho \mathbf{f}(c) + \mathbf{j}_m + \mathbf{j}_c. \quad (13)$$

Note that, as usual in kinetic theories, even after specifying the collision kernels the system of equations for  $(\rho, \rho \mathbf{U})$  is not closed since the distribution  $p(t, \mathbf{x}, \mathbf{v})$  is used in the pressure tensor  $\mathbb{P}$ . The closure of the system (11),(13) will be done in Section 5.

**4. Interaction Kernels.** Following [5] the collision kernels can be written as

$$\begin{aligned} J_c &= \int_V \int_V \eta_c(\mathbf{v}', \mathbf{v}'_*) \psi_c((\mathbf{v}', \mathbf{v}'_*) \rightarrow \mathbf{v}) p(\mathbf{v}') p(\mathbf{v}'_*) d\mathbf{v}' d\mathbf{v}'_* \\ &\quad - p(\mathbf{v}) \int_V \eta_c(\mathbf{v}, \mathbf{v}'_*) p(\mathbf{v}'_*) d\mathbf{v}'_*, \end{aligned} \quad (14)$$

and

$$\begin{aligned} J_m &= \int_V \int_{S_+^{d-1}} \eta_m(\mathbf{v}', \mathbf{n}') \psi_m((\mathbf{v}', \mathbf{n}') \rightarrow \mathbf{v}) p(\mathbf{v}') q(\mathbf{n}') d\mathbf{v}' d\mathbf{n}' \\ &\quad - p(\mathbf{v}) \int_{S_+^{d-1}} \eta_m(\mathbf{v}, \mathbf{n}') q(\mathbf{n}') d\mathbf{n}'. \end{aligned} \quad (15)$$

where the encounter rate  $\eta_c(\mathbf{v}', \mathbf{v}'_*)$  denotes the number of encounters per unit volume and unit time between cell pair with velocities  $\mathbf{v}'$  and  $\mathbf{v}'_*$  and  $\eta_m(\mathbf{v}', \mathbf{n}')$  the one of a cell with velocity  $\mathbf{v}'$  with a fiber whose orientation is  $\mathbf{n}'$ . The notation  $\psi_c((\mathbf{v}', \mathbf{v}'_*) \rightarrow \mathbf{v})$  denotes the transition probability of a cell having a velocity  $\mathbf{v}'$  before the encounter, to continue its motion with the velocity  $\mathbf{v}$  after having interacted with another cell with velocity  $\mathbf{v}'_*$ , while  $\psi_m((\mathbf{v}', \mathbf{n}') \rightarrow \mathbf{v})$  denotes the transition probability of a cell having a velocity  $\mathbf{v}'$  before the encounter, to continue its motion with the velocity  $\mathbf{v}$  after having interacted with a fiber oriented along  $\mathbf{n}'$ .

Since cells are conserved during interactions, we have the natural conditions

$$\int_V \psi_c((\mathbf{v}', \mathbf{v}'_*) \rightarrow \mathbf{v}) d\mathbf{v} = 1, \quad \text{and} \quad \int_V \psi_m((\mathbf{v}', \mathbf{n}') \rightarrow \mathbf{v}) d\mathbf{v} = 1. \quad (16)$$

We now introduce the following basic hypothesis:

- The encounter rates  $\eta_c$  and  $\eta_m$  are constant and the transition probability densities  $\psi_c$  and  $\psi_m$  do not depend on the particular incoming velocities;

- The transition probability density  $\psi_c$  depends only on the outgoing velocity modulus.

This means that during the interactions cells have no memory of the velocity they had before encountering, so that the transition probability densities define the possible range of outgoing velocity regardless of the incoming velocity. As we do not account for directional persistence in the motion, the direction of one cell after having interacted with another one is then chosen at random.

In addition, the fact that ECM fibers are not directional implies that  $\psi_m$  is an even function of its arguments (i.e. the fiber direction and the outgoing velocity). Hence,

$$\int_{S^{d-1}} \psi_m(\mathbf{n}'; \mathbf{v}) \mathbf{n}' d\mathbf{n}' = \mathbf{0}, \quad \text{and} \quad \int_{S^{d-1}} \psi_m(\mathbf{n}'; \mathbf{v}) \hat{\mathbf{v}} d\hat{\mathbf{v}} = \mathbf{0}, \quad (17)$$

where  $\hat{\mathbf{v}}$  is the direction of  $\mathbf{v}$ .

The interaction terms can then be written as

$$\begin{aligned} J_c &= \eta_c \psi_c(\mathbf{v}) \int_V \int_V p(\mathbf{v}') p(\mathbf{v}'_*) d\mathbf{v}' d\mathbf{v}'_* - \eta_c p(\mathbf{v}) \int_V p(\mathbf{v}'_*) d\mathbf{v}'_* \\ &= \eta_c \rho [\rho \psi_c(\mathbf{v}) - p(\mathbf{v})], \end{aligned} \quad (18)$$

and

$$J_m = \eta_m \rho \int_{S_+^{d-1}} \psi_m(\mathbf{n}'; \mathbf{v}) q(\mathbf{n}') d\mathbf{n}' - \eta_m Q p(\mathbf{v}). \quad (19)$$

It is trivial to check the validity of (8), and one can explicitly compute the momentum dissipation due to cell-cell interaction

$$\begin{aligned} \mathbf{j}_c &= \int_V J_c \mathbf{v} d\mathbf{v} = \eta_c \rho \int_V [\rho \psi_c(\mathbf{v}) \mathbf{v} - p(\mathbf{v}) \mathbf{v}] d\mathbf{v} \\ &= -\eta_c \rho^2 \mathbf{U}, \end{aligned} \quad (20)$$

the first term under the integral vanishing because the function  $\psi_c$  depends only on the velocity modulus.

On the other hand, thanks to Eq.(17), one also obtains the momentum dissipation due to the cell-ECM interaction

$$\begin{aligned} \mathbf{j}_m &= \int_V J_m \mathbf{v} d\mathbf{v} = \eta_m \rho \int_{S_+^{d-1}} q(\mathbf{n}') \left( \int_V \psi_m(\mathbf{n}'; \mathbf{v}) \mathbf{v} d\mathbf{v} \right) d\mathbf{n}' - \eta_m Q \rho \mathbf{U} \\ &= -\eta_m Q \rho \mathbf{U}. \end{aligned} \quad (21)$$

Expressions (20) and (21) allow to write the momentum balance equation (13) as

$$\frac{\partial}{\partial t}(\rho \mathbf{U}) + \nabla_{\mathbf{x}} \cdot (\rho \mathbf{U} \otimes \mathbf{U}) = -\nabla_{\mathbf{x}} \cdot \mathbb{P} + \rho \mathbf{f}(c) - (\eta_m Q + \eta_c \rho) \rho \mathbf{U}, \quad (22)$$

where the last term can be identified as the drag forces due to the cell interaction with the ECM and the other cells.

As already mentioned, the system of equations (11) and (22) is not closed, since the pressure tensor  $\mathbb{P}$  depends fully on the distribution  $p(t, \mathbf{x}, \mathbf{v})$ . In the next section we will derive a closed system for mass and momentum.

**5. Moment Closure.** A fundamental role in the closure of the system of conservation equations is played by the equilibrium distribution for the transport equation, which can be determined setting  $J_c + J_m = 0$ , e.g.

$$p(\mathbf{v}) \equiv p_\infty(\mathbf{v}) = \frac{\rho}{\eta_c \rho + \eta_m Q} \left[ \eta_m \int_{S_+^{d-1}} \psi_m(\mathbf{n}'; \mathbf{v}) q(\mathbf{n}') d\mathbf{n}' + \eta_c \rho \psi_c(\mathbf{v}) \right]. \quad (23)$$

Following [12] and [5], one can perform a diffusion limit and prove that the flux term in the mass balance equation can be substituted by

$$\rho \mathbf{U} = \frac{-\nabla_{\mathbf{x}} \cdot \mathbb{P} + \rho \mathbf{f}(c)}{\eta_c \rho + \eta_m Q}. \quad (24)$$

Therefore, one has that

$$\frac{\partial \rho}{\partial t} = \nabla_{\mathbf{x}} \cdot \left[ \frac{\nabla_{\mathbf{x}} \cdot \mathbb{P} - \rho \mathbf{f}(c)}{\eta_c \rho + \eta_m Q} \right], \quad (25)$$

where

$$\mathbb{P} = \frac{\rho(\eta_m Q \mathbb{D}_m + \eta_c \rho \mathbb{D}_c)}{\eta_c \rho + \eta_m Q}, \quad (26)$$

$$\mathbb{D}_m = \frac{1}{Q} \int_{S_+^{d-1}} q(\mathbf{n}') \left( \int_V \psi_m(\mathbf{n}'; \mathbf{v}) \mathbf{v} \otimes \mathbf{v} d\mathbf{v} \right) d\mathbf{n}', \quad (27)$$

and

$$\mathbb{D}_c = \int_V \psi_c(\mathbf{v}) \mathbf{v} \otimes \mathbf{v} d\mathbf{v}. \quad (28)$$

Taking  $\mathbf{f}(c) = \lambda \nabla_{\mathbf{x}} c$ , leads finally to the evolution equation for the cell density

$$\frac{\partial \rho}{\partial t} + \nabla_{\mathbf{x}} \cdot \left[ \frac{\rho \lambda \nabla_{\mathbf{x}} c}{\eta_c \rho + \eta_m Q} \right] = \nabla_{\mathbf{x}} \cdot \left[ \frac{1}{\eta_c \rho + \eta_m Q} \nabla_{\mathbf{x}} \cdot \left( \frac{\rho(\eta_m Q \mathbb{D}_m + \eta_c \rho \mathbb{D}_c)}{\eta_c \rho + \eta_m Q} \right) \right]. \quad (29)$$

We observe that the tensors  $\mathbb{D}_m$  and  $\mathbb{D}_c$  can be computed ones for all when the interaction kernels and the fiber distribution are given. Furthermore, due to the independence of the function  $\psi_c$  on the velocity direction, the tensor  $\mathbb{D}_c$  is diagonal. Finally, we assume that after the interaction with a fiber oriented along a direction  $\mathbf{n}$  the cell aligns with it ( $\hat{\mathbf{v}} = \pm \mathbf{n}$ ), independently from the particular incoming velocity, e.g.

$$\psi_m(\mathbf{n}'; \mathbf{v}) \equiv \psi_m(v) \frac{1}{2} [\delta(\mathbf{n}' - \hat{\mathbf{v}}) + \delta(\mathbf{n}' + \hat{\mathbf{v}})], \quad (30)$$

where the  $\delta$  are Dirac's deltas.

In this case, the tensors  $\mathbb{D}_m$  and  $\mathbb{D}_c$  become

$$\mathbb{D}_m = \sigma_m \mathbb{D}, \quad \text{and} \quad \mathbb{D}_c = \sigma_c \mathbb{I}, \quad (31)$$

where  $\mathbb{D}$  is defined by (7) and

$$\sigma_m = \frac{1}{d} \int_{\mathbb{R}_+} \psi_m(v) v^{d+1} dv, \quad \sigma_c = \frac{2\pi(d-1)}{d} \int_{\mathbb{R}_+} \psi_c(v) v^{d+1} dv. \quad (32)$$

We will consider an isotropic situation, so that the tensor  $\mathbb{D}$  reduces to the identity. If in addition  $\sigma_c = \sigma_m$ , which means that the random velocity after an encounter does not depend on the kind of encounter, equation (29) then simplifies to

$$\frac{\partial \rho}{\partial t} + \nabla_{\mathbf{x}} \cdot \left[ \frac{\lambda \rho \nabla_{\mathbf{x}} c}{\eta_c \rho + \eta_m Q} \right] = \nabla_{\mathbf{x}} \cdot \left[ \frac{\nabla_{\mathbf{x}}(\sigma \rho)}{\eta_c \rho + \eta_m Q} \right]. \quad (33)$$

**6. Numerical simulations.** As a first step in the validation of the model, the one-dimensional configuration is considered which of course does not allow to take into account any anisotropy of the fibrous network.

Independently on whether the substratum is homogeneous or not, assuming  $c(x)$  integrable, the stationary state is given by

$$\lambda\rho\frac{\partial c}{\partial x} = \sigma\frac{\partial\rho}{\partial x}, \quad (34)$$

which can be solved to give

$$\rho(x) = C \exp\left[\frac{\lambda}{\sigma}c(x)\right], \quad (35)$$

where the constant is determined by the constant total number of cells. Hence one has

$$\rho(x) = \frac{\exp\left[\frac{\lambda}{\sigma}c(x)\right]}{\int_{\mathcal{D}} \exp\left[\frac{\lambda}{\sigma}c(s)\right] ds}, \quad (36)$$

that will be compared to the numerical stationary solution.

A symmetric splitting operator scheme of order two has been used to solve equation (33). For each part of the equation, we used the finite volume method with a specific scheme related to the type of operator. A high resolution wave-propagation algorithm for spatially varying flux (see [2, 4]) has been implemented for the non-linear hyperbolic part. The non-linear parabolic part is solved using a Crank-Nicholson scheme, in which the implicit non-linear term is treated by a Beam and Warming scheme, whose high accuracy has been studied in [13].

The first simulation in Fig. 2 shows how the solution tends to the analytic stationary configuration in a homogeneous and in an inhomogeneous situation, starting from a uniform initial distribution. The corresponding homogenous ( $Q$  constant) and inhomogeneous ( $Q$  variable) fiber densities are shown on Fig. 1 as well as the chemical profile  $c$  that induces the attractive force  $\mathbf{f} = f(x)\mathbf{e}_x$ , where  $f(x) = \lambda\frac{\partial c}{\partial x}$ . It can be noticed that in both cases the simulation tends toward the analytical stationary configuration.

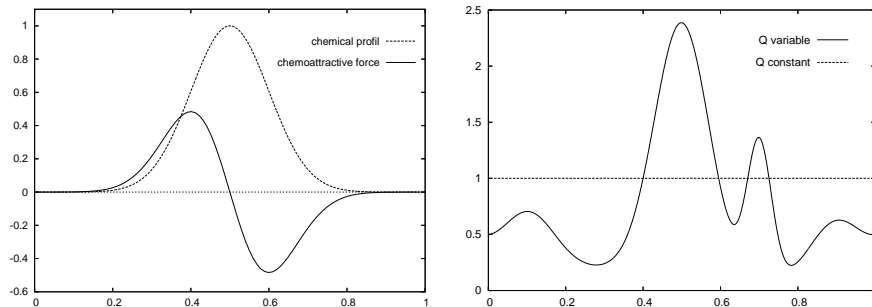


FIGURE 1. Chemoattractive force  $f(x)$  induced by the chemical stationary profile  $c(x)$  (left) and fiber densities  $Q(x)$  (right) related to the simulation shown in Fig. 2 in the domain  $\mathcal{D} = [0, 1]$ .

In order to evaluate the ability of the model to mimic the phenomena observed during cell motion, we present the simulations of motion induced by a constant external force  $f(x) = f_0$ . The two curves presented on Fig. 3 show the evolution of

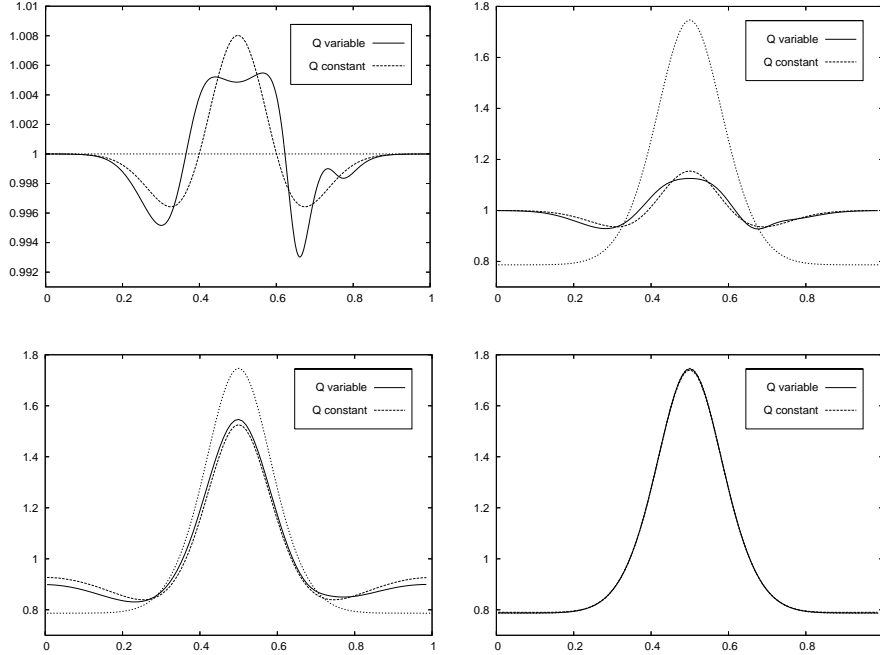
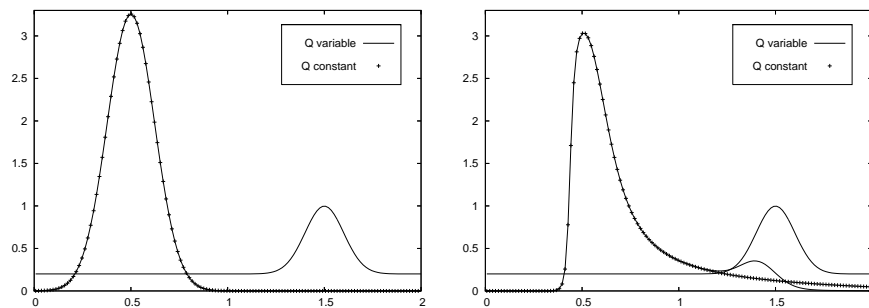


FIGURE 2. Evolution of the cell densities toward the stationary solution in the homogeneous and inhomogeneous situations at time  $t = 0.0002$ ,  $t = 0.0513$ ,  $t = 0.4621$  and  $t = 2.5671$  (to be read from left to right while going down). Parameters are  $\eta_m = \eta_c = 1$ ,  $\sigma = 0.1$  and  $\lambda = 0.08$ .

the same initial gaussian-like distribution of cells attracted by a chemoattractant located outside the domain to the right. The curve with the crosses corresponds to a constant density of fibers, while the line-style one corresponds to  $Q$  variable due to a local increase of the fiber density (also shown on the graphs). In both cases, one can first observe a rarefaction-like wave at the beginning of the motion. Then, while the cell motion continues without disturbance in the  $Q$ -constant case, a local accumulation of cells due to the higher fiber density is observed in the other case. Once this obstacle is passed over, the disturbed motion turns back to normal.





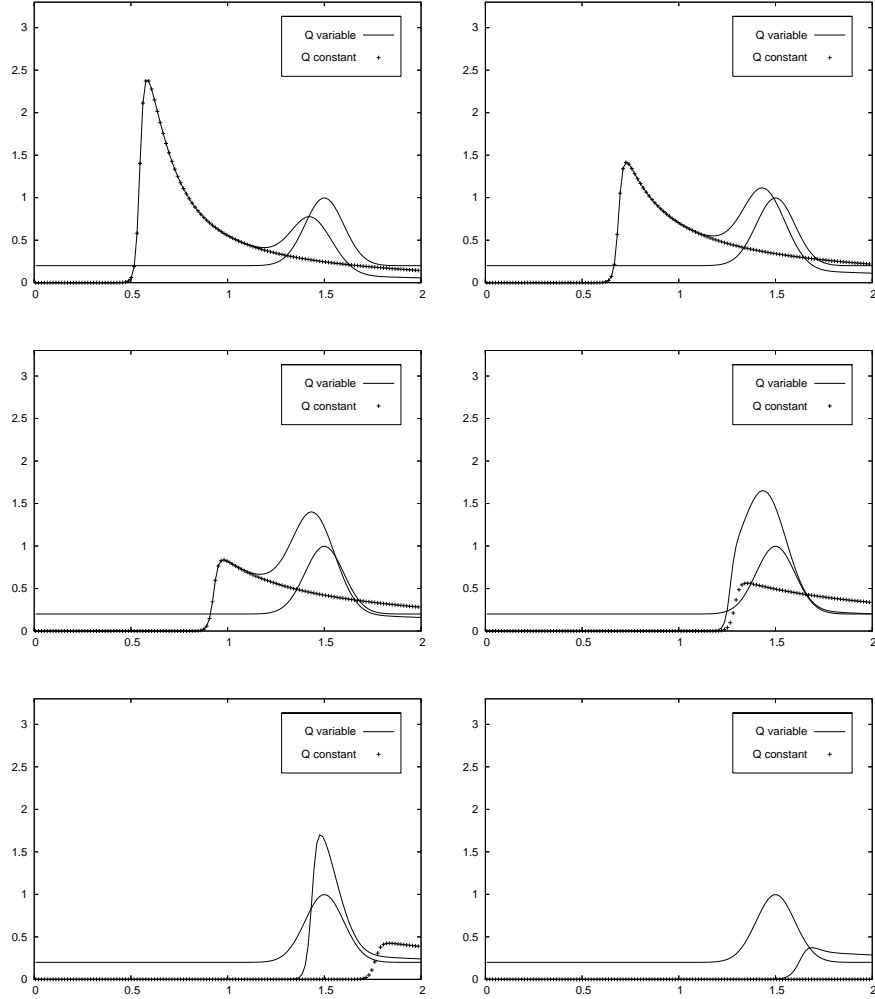


FIGURE 3. Motion slowed down by the inhomogeneities of an isotropic fibrous network (to be read from left to right while going down). The solutions are shown at time  $t = 0.0000$ ,  $t = 0.0676$ ,  $t = 0.1352$ ,  $t = 0.2028$ ,  $t = 0.2704$ ,  $t = 0.3380$ ,  $t = 0.4056$  and  $t = 0.4958$ . Parameters are  $\eta_m = \eta_c = 10$ ,  $\sigma = 0.5$  and  $f_0 = 50$ .

Before the model may be validated from an experimental point of view, the numerical simulations have to be extended to the two- and three-dimensional configuration so that possible anisotropies of the ECM may also be taken into account. That is one of the main goal of the model. It is also worth mentioning that the next step in the development of this work is the description of the degradation of the tissue by proteases released by the cells, either by altering the tissue or by cutting the fibers.

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