MODELING THE MOTION OF A CELL POPULATION IN THE EXTRACELLULAR MATRIX

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Abstract. The paper aims at describing the motion of cells in fibrous tissues taking into account of the interaction with the network fibers and among cells, of chemotaxis, and of contact guidance from network fibers. Both a kinetic model and its continuum limit are described.

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 mechanics 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 [9, 10, 11, 21]. From the modeling point of view, the anisotropy of the ECM has been modelled at the macroscopic scale by Barocas and Tranquillo [3] while transport models of cell migration including contact guidance can be found in [7, 8]. Interesting applications considering cell-substratum interactions can also be found in [17, 18, 20] 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 proper 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 [13, 19], and in particular, on the kinetic model described in [6]. In [19] 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 [13], a transport equation for moving cells was derived which includes cell-ECM interactions but does not include forces and cell-cell interactions.

Here we start from the development of a kinetic model for mesenchymal cell motion in fibrous tissues, including chemotaxis, contact guidance from network fibers, cell-ECM and cell-cell interactions. However, with respect to [6] 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 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. The moment closure method is a fast and easy method to obtain a closed moment system. It is significantly based on the moment closure assumption that is used. Generally, there are many ways to close a moment system. From a modeling point of view it is sensible to assume that the pressure term is dominated by the equilibrium distribution of the system, which is the assumption used here. Other moment closure techniques use entropy or energy minimization approaches to justify the moment closure (see, for example, [12] or [15]). In another paper [6] we will compare the moment method used here with scaling methods known as parabolic scaling, for example.

Finally, numerical simulations are presented in order to emphasize the influence of an inhomogeneous fiber network on the cell motion and of the presence of an exogenous chemoattrattant 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 on a substratum ($d = 2$).

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

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

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

$\mathbf{U}$ being here the mean cellular velocity. As classically in the kinetic theory, we also define the pressure tensor as

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

and observe that

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

Similarly, the density and orientation of the fiber network is given by the distribution density function $q = q(\mathbf{x}, \mathbf{n})$ where $\mathbf{n}$ denotes the direction. Since fibers are not oriented, 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

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

Then the quantity

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

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

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

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

- There is a given chemical stationary field $c(\mathbf{x})$ 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 λ 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 corresponding linear cell-ECM interaction operator is denoted by $J_m[p, q]$ and will be shorten as J_m;
- Cells also interact with cells and the corresponding quadratic cell-cell interaction operator is denoted by $J_c[p, p]$, also shorten as J_c;
- We will not require that momentum and energy are conserved during both interactions and, in fact, in general they will not. On the contrary mass is preserved, which as we shall see in Eq.(11) classically requires

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

Then the Boltzmann transport equation (see [5]) for cell movement is

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

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 ρ and momentum $\rho \mathbf{U}$. Integrating Eq.(9) over the domain velocity V gives

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

Now, under the assumption that p vanishes on the boundary ∂V, the last integral on the l.h.s. vanishes due to the divergence theorem, while the r.h.s. vanishes due to the mass conservation assumption (8). Hence one obtains the mass conservation equation

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

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

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

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

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

Note that, as usual in kinetic theories, even after specifying the interaction operators 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 Operators.** Following [6] the interaction operators can be written as

$$J_c = \int_V \int_V \eta_c(\mathbf{v}', \mathbf{v}'_*)\psi_c((\mathbf{v}', \mathbf{v}'_*) \to \mathbf{v})p(t, \mathbf{x}, \mathbf{v}')p(t, \mathbf{x}, \mathbf{v}'_*)\,d\mathbf{v}'\,d\mathbf{v}'_*$$
$$- p(t, \mathbf{x}, \mathbf{v}) \int_V \eta_c(\mathbf{v}, \mathbf{v}'_*)p(t, \mathbf{x}, \mathbf{v}'_*)\,d\mathbf{v}'_*\,, \tag{14}$$

and

$$J_m = \int_V \int_{S^{d-1}_+} \eta_m(\mathbf{v}', \mathbf{n}')\psi_m((\mathbf{v}', \mathbf{n}') \to \mathbf{v})p(t, \mathbf{x}, \mathbf{v}')q(\mathbf{x}, \mathbf{n}')\,d\mathbf{v}'\,d\mathbf{n}'$$
$$- p(t, \mathbf{x}, \mathbf{v}) \int_{S^{d-1}_+} \eta_m(\mathbf{v}, \mathbf{n}')q(\mathbf{x}, \mathbf{n}')\,d\mathbf{n}'\,. \tag{15}$$

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 $\psi_c((\mathbf{v}', \mathbf{v}'_*) \to \mathbf{v})$ 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 $\psi_m((\mathbf{v}', \mathbf{n}') \to \mathbf{v})$ 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

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

We now consider that during the interactions cells have no memory of the velocity they had before encountering. This is due to the fact that cells strongly deform in an inelastic way, and the interactions may take a non-negligible time (non modelled here) during which the cytoskeleton rearranges. Then we assume that the transition probability densities define the possible range of outgoing velocity regardless of the incoming velocity. In addition, as we do not account for directional persistence in the motion, as done in [1, 19, 20], the direction of one cell after having interacted with another one is then chosen at random. That leads to the following basic hypothesis:

- The transition probability densities ψ_c and ψ_m do not depend on the particular incoming velocities;
- The transition probability density ψ_c depends only on the outgoing velocity modulus.

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

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

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

Finally, as interactions between living entities are very far from the classical collisions between matter particles, and keeping in mind the aim of describing biological events, we assume as a simplification to be further developed that the encounter rates η_c and η_m are constant.

The interaction terms can then be written as

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

and

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

It is trivial to check the validity of (8). One can then explicitly compute the momentum dissipation due to cell-cell interaction

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

where the first term under the integral vanishing because the function ψ_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

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

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

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

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 corresponds to $J_c + J_m = 0$, e.g.

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

Following [14] one can perform a diffusion limit and prove (see [6] for more details) that the flux term in the mass balance equation (11) can be substituted by

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

where

$$\mathbb{P} = \frac{\rho(\eta_m Q \mathbb{D}_m + \eta_c \rho \mathbb{D}_c)}{\eta_m Q + \eta_c \rho}, \qquad (25)$$

$$\mathbb{D}_m = \frac{1}{Q} \int_{S_+^{d-1}} q(\mathbf{n}') \left(\int_V \psi_m(\mathbf{n}'; \mathbf{v}) \mathbf{v} \otimes \mathbf{v} \, d\mathbf{v} \right) d\mathbf{n}', \qquad (26)$$

and

$$\mathbb{D}_c = \int_V \psi_c(\mathbf{v}) \mathbf{v} \otimes \mathbf{v} \, d\mathbf{v}. \qquad (27)$$

Therefore Eq.(11) can be rewritten as

$$\frac{\partial \rho}{\partial t} = \nabla_{\mathbf{x}} \cdot \left[\frac{\nabla_{\mathbf{x}} \cdot \mathbb{P} - \rho \mathbf{f}(c)}{\eta_m Q + \eta_c \rho} \right]. \qquad (28)$$

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

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

We observe that the tensors $\mathbb{D}_m$ and $\mathbb{D}_c$ can be computed once and for all when the interaction kernels and the fiber distribution are given. Furthermore, due to the independence of the function ψ_c on the velocity direction, the tensor $\mathbb{D}_c$ is diagonal and is written $\mathbb{D}_c = D_c \mathbb{I}$.

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.

In order to describe some qualitative properties of the solution we consider the case in which D_m is constant, which, for instance occurs if the substratum is isotropic and the cells align with the fibers after the interaction (i.e., $\hat{\mathbf{v}} = \pm \mathbf{n}$), independently from the particular incoming velocity, e.g.

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

where the δ are Dirac's deltas and v is the modulus of $\mathbf{v}$.

Independently on whether the substratum is homogeneous or not, assuming $c(x)$ integrable and $D_m = D_c = \sigma$, the stationary state is then given by

$$\lambda\rho\frac{\partial c}{\partial x} = \sigma\frac{\partial\rho}{\partial x}\,, \tag{31}$$

which can be solved to give

$$\rho(x) = C\exp\left[\frac{\lambda}{\sigma}c(x)\right]\,, \tag{32}$$

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

$$\rho(x) = \frac{\exp\left[\frac{\lambda}{\sigma}c(x)\right]}{\int_{\mathcal{D}}\exp\left[\frac{\lambda}{\sigma}c(s)\right]ds}\,, \tag{33}$$

that will be compared to the numerical stationary solution.

A symmetric splitting operator scheme of order two has been used to solve equation (29). 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 [16].

In the simulation we scale distances with the dimension L of the domain, times with $\eta_m L^2/\sigma$, and concentrations with its maximum. The first simulation in Fig. 2 shows how the solution tends to the 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. It can be noticed that in both cases the simulation tends toward the analytical stationary configuration as shown on Fig. 2.
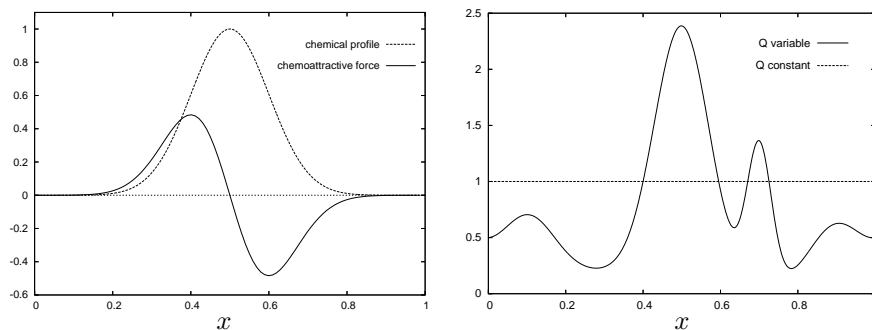

FIGURE 1. Chemoattractive force $f(x)$ induced by the chemical stationary profile $c(x)$ as well as the zero-value in dotted line (left) and fiber densities $Q(x)$ (right) related to the simulation shown in Fig. 2 in the domain $\mathcal{D} = [0, 1]$.

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 $f(x) = f_0$ due to a constant chemical gradient c_{max}/L. The two curves presented on Fig. 3 show the evolution of the same initial gaussian-like distribution
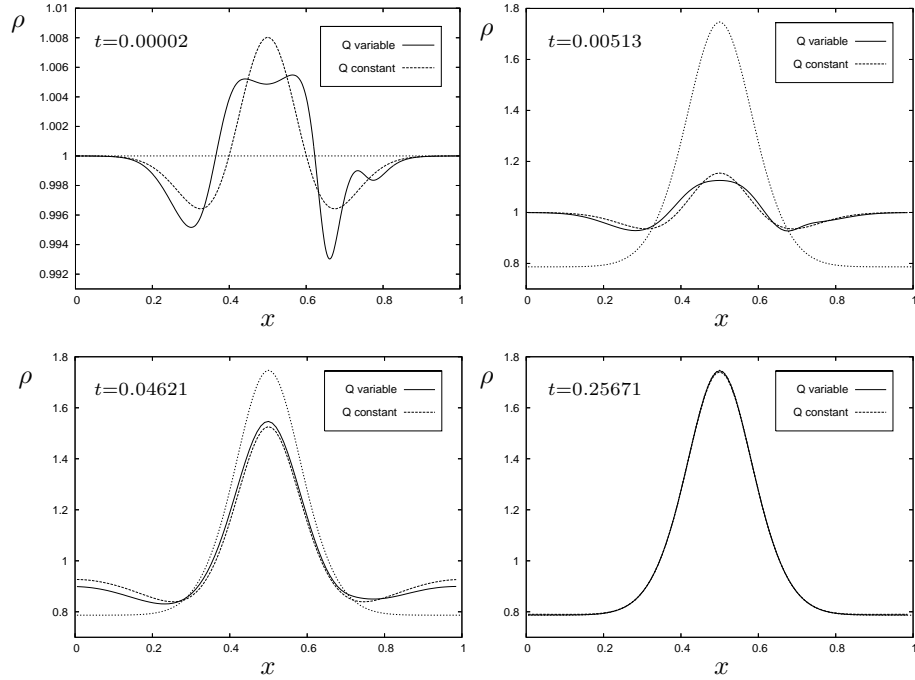
FIGURE 2. Evolution of the cell densities toward the stationary solution (the dotted line in the second and third figure, no longer evident in the last figure because of superposition with the solutions) in the homogeneous (dashed line) and inhomogeneous (full line) situations, from a constant initial condition (the dotted line in the first figure). To be read from left to right while going down. Parameters are $\eta_m = \eta_c$ and $\lambda c_{max}/\sigma = 0.8$.

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 full line corresponds to an inhomogeneous case 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.
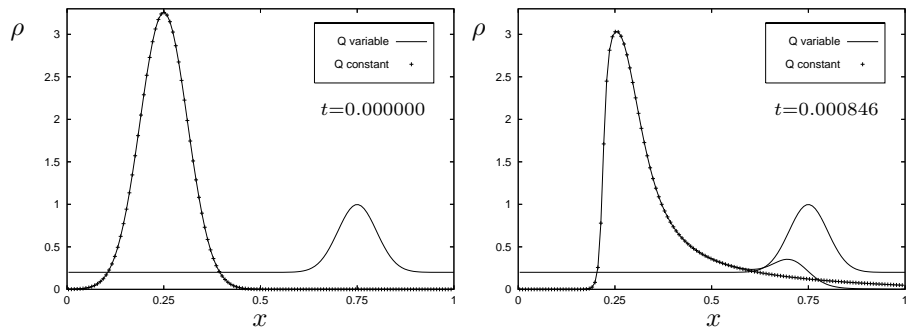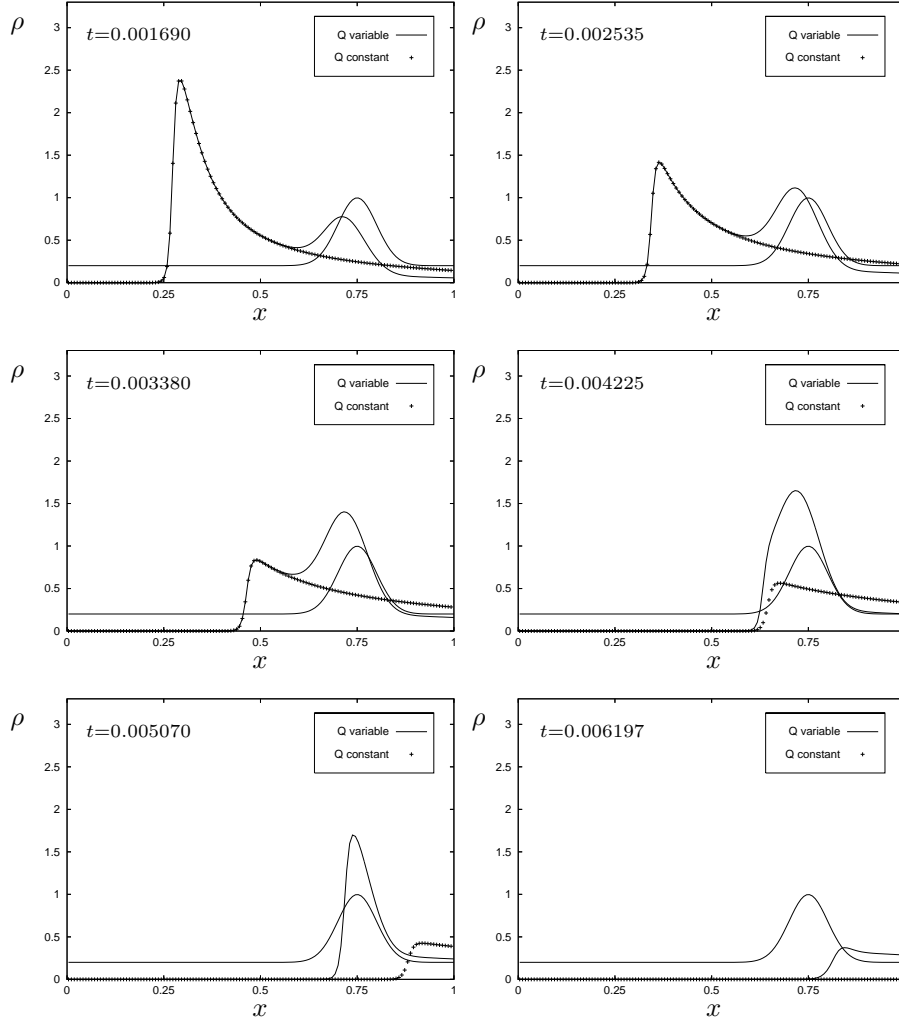
FIGURE 3. Motion slowed down by the inhomogeneities of the fibrous network (the resting full line gives the fixed fiber distribution). To be read from left to right while going down. Parameters are $\eta_m = \eta_c$ and $\lambda c_{max}/\sigma = 100$.

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.

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 [6, 13].

REFERENCES

[1] D. Ambrosi, F. Bussolino and L. Preziosi, *A review of vasculogenesis models*, J. Theor. Med. 6 (2005), 1–19.

[2] D. S. Bale, R. J. Leveque, S. Mitran and J. A. Rossmanith, *A wave propagation method for conservation laws and balance laws with spatially varying flux functions*, SIAM J. Sci. Comput. 24(3) (2002), 955–978.

[3] V. H. Barocas and R. T. Tranquillo, *An anisotropic biphasic theory of tissue-equivalent mechanics: The interplay among cell traction, fibrillar network deformation, fibril alignment and cell contact guidance*, J. Biomechanical Eng. 119(2) (1997), 137–145.

[4] M. Brandner and S. Mika, *Finite volume methods for balance laws with spatially-varying flux functions*, Preprint UWB (2003).

[5] C. Cercignani, "Theory and application of the Boltzmann equation", Elsevier, New York (1975).

[6] A. Chauviere, T. Hillen and L. Preziosi, *Continuum model for mesenchymal motion in a fibrous network*, Networks and Heterogeneous Media (2007).

[7] R. B. Dickinson, *A generalized transport model for biased cell migration in an anisotropic environment*, J. Math. Biol. 40 (2000), 97–135.

[8] R. B. Dickinson, *A model for cell migration by contact guidance*, in W. Alt, A. Deutsch and G. Dunn editors, "Dynamics of Cell and Tissue Motion", Basel, Birkhauser (1997), 149–158.

[9] P. Friedl, *Prespecification and plasticity: shifting mechanisms of cell migration*, Curr. Opin. Cell. Biol. 16 (2004), 14–23.

[10] P. Friedl and E. B. Bröcker, *The biology of cell locomotion within three dimensional extracellular matrix*, Cell Motility Life Sci. 57 (2000), 41–64.

[11] P. Friedl and K. Wolf, *Tumour-cell invasion and migration: diversity and escape mechanisms*, Nature Rev. 3 (2003), 362–374.

[12] T. Hillen, *On the L^2-closure of transport equations: The general case*, Discr. Cont. Dyn. Syst. B 5 (2005), 299-318.

[13] T. Hillen, *(M5) Mesoscopic and macroscopic models for mesenchymal motion*, J. Math. Biol. 53(4) (2006), 585–616.

[14] T. Hillen and H. G. Othmer, *The diffusion limit of transport equations derived from velocity jump processes*, SIAM J. Appl. Math. 61(3) (2000), 751–775.

[15] C. D. Levermore, *Moment closure hierarchies for kinetic theories*, J. Stat. Phys. 83 (1996), 1021–1065.

[16] R. B. Lowrie, *A comparison of implicit time integration methods for nonlinear relaxation and diffusion*, J. Computational Physics 196 (2004), 566–590.

[17] D. Manoussaki, S. R. Lubkin, R. B. Vernon and J. D. Murray, *A mechanical model for the formation of vascular networks in vitro*, Acta Biotheoretica 44 (1996), 271–282.

[18] P. Namy, J. Ohayon and P. Traqui, *Critical conditions for pattern formation and in vitro tubulogenesis driven by cellular traction fields*, J. Theor. Biol. 227 (2004), 103–120.

[19] G. Serini, D. Ambrosi, E. Giraudo, A. Gamba, L. Preziosi and F. Bussolino, *Modeling the early stages of vascular network assembly*, EMBO J. 22 (2003), 1771–1779.

[20] A. Tosin, D. Ambrosi and L. Preziosi, *Mechanics and chemotaxis in the morphogenesis of vascular networks*, to appear in Bull. Math. Biol. 68(7) (2006), 1819–1836.

[21] K. Wolf, I. Mazo, H. Leung, K. Engelke, U. H. von Andrian, E. I. Deryugina, A. Y. Strongin, E. B. Bröcker and P. Friedl, *Compensation mechanism in tumor cell migration: mesenchymal–ameboid transition after blocking of pericellular proteolysis*, J. Cell. Biol. 160 (2003), 267–277.

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