

## A CONTINUUM MODEL FOR CELL MOTION IN NETWORK TISSUES

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**Abstract.** DA FARE!

**1. Introduction.** From recent experimental studies, much has been learned about cell movement in tissues (see Friedl and Bröcher [4]). Cells that move through tissues (like cancer metastases, or leukocytes) interact with the tissue matrix (Extra-Cellular Matrix) as well as with other cells. Many different biological and physical processes interact in a complicated way.

In this paper we choose the framework of transport equations and correlated random walks to derive a continuum model for mass and momentum. We include forces that are generated by friction or by chemotaxis as well as momentum dissipation due to interactions with the Extra-Cellular Matrix (ECM) and due to cell-cell interactions.

This work generalizes earlier models by Preziosi and al. [7], [9] and Hillen [5]. Continuum models for cell movement were used to describe network formation of cells by Preziosi and al.. In the  $M^3$ -model proposed by Hillen, a transport equation for moving cells was derived which includes cell-ECM interactions but does not include forces and cell-cell collisions.

Thus we describe in the next section our most general transport model for mesenchymal cell movement in tissues, including chemotactic forces, contact guidance from network fibers, drag forces, cell-ECM and cell-cell interactions, but excluding the degradation of the surrounding tissue by proteases released by moving cells.

Then starting from this mesoscopic description, we derive the system of moment equations for mass  $\rho$ , and momentum  $\rho\mathbf{U}$  at the macroscopic scale.

By modeling the interactions between cells and the fibers of the tissue at the microscopic level, we can derive the terms appearing in the system of moment equations.

Finally, we investigate the moments system, and apply a moment closure technique to derive a continuum model for this specific mesenchymal motion.

Numerical simulations are presented in order to emphasize the influence of an inhomogeneous isotropic fiber network over the cell motion.

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**2. The Cell Movement Equation.** As the extension of the  $M^5$ -model of Hillen, the system is constituted by two interacting entities: the cell population and the ECM fiber network. 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,  $\mathbf{x} \in \mathcal{D} \subseteq \mathbb{R}^n$  denotes the position and  $\mathbf{v} \in V \subseteq \mathbb{R}^n$  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  $\mathbb{R}^n$  is presented with the aim to describe *in vivo* motion ( $n = 3$ ). The two-dimensional case ( $n = 2$ ) corresponding to the *in vitro* motion over a substratum can also be worked out in a similar fashion.

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  $q = q(t, \mathbf{x}, \mathbf{n})$  where  $\mathbf{n}$  is the angle of fibers defined over the half unit sphere, e.g.  $\mathbf{n} \in S_+^{n-1}$ . The function  $q$  is also normalized with respect to the total number of cells. The definition of  $q$  over the half sphere corresponds to the observation that fibers of the extra-cellular matrix are not directional. Therefore, giving the distribution of fibers over half of the sphere completely characterizes how the fibers are placed. In the following, however, it will be useful to extend  $q$  over the entire sphere as an even function of  $\mathbf{n}$ , e.g. using

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

Then the quantity

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

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

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

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 give the principal directions of the orientation of the network. In particular, the direction of the eigenvector corresponding to the maximum eigenvalue gives the main fiber direction. On the contrary, the isotropic configuration corresponds to equal eigenvalues, so that the ellipsoid reduces to a sphere.

For the following it is useful to observe that  $\text{tr}(\mathbb{D}) = n$ , and that one has

$$\int_{S^{n-1}} q^e(t, \mathbf{x}, \mathbf{n}) \mathbf{n} d\mathbf{n} = \mathbf{0}, \quad (8)$$

thanks to the symmetry of the distribution function  $q^e$ . In addition and for simplicity, we will drop in the following the  $(t, \mathbf{x})$  dependency of the distribution functions and of the macroscopic variables.

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

- There is a chemotactic or haptotactic force  $\mathbf{f}(c) \in \mathbb{R}^n$ , depending on a given chemical profile  $c(t, \mathbf{x})$ . As a particular example, we may consider  $\mathbf{f}(c) = \lambda \nabla c$ ;
- Cells interact mechanically with the extra-cellular matrix and use fibers for contact guidance. The collision operator of cells and ECM is denoted by  $J_m$  and we assume the mass conservation  $\int_V J_m d\mathbf{v} = 0$ ;
- Cells interact with cells in the way where mass is conserved during collisions. The cell-cell collision operator is denoted by  $J_c$  and we assume  $\int_V J_c d\mathbf{v} = 0$  for mass conservation.

Since we model active moving cells, which are deformable and capable to change trajectory by their own, we will not assume momentum conservation for the interactions neither with the ECM nor with the other cells.

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  $V$  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  $\int_V J_m d\mathbf{v} = \int_V J_c d\mathbf{v} = 0$  due to the mass conservation assumptions. 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

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

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

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

To summarize, we derived equations for mass conservation (11) and momentum balance (13). Note that 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  $\mathbb{P}$ . Moreover, appropriate collision terms need to be studied to find expressions for  $\mathbf{j}_m$  and  $\mathbf{j}_c$ . This will be done in the following section.

**4. Interaction Kernels.** As we assume that interactions are dominated by pair-interactions, the general form of the cell-cell collision operator can be written as

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

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  $\mathbf{v}'_*$ . The notation  $\psi_c((\mathbf{v}', \mathbf{v}'_*) \rightarrow \mathbf{v})$  denotes as for it 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  $\mathbf{v}'_*$ .

Similarly, the cell-ECM collision operator can be written as

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

where  $\eta_m(\mathbf{v}', \mathbf{n}')$  is the encounter rate of a cell with velocity  $\mathbf{v}'$  with a fiber whose orientation is  $\mathbf{n}'$ , and  $\psi_m((\mathbf{v}', \mathbf{n}') \rightarrow \mathbf{v})$  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

$$\int_V \psi_c((\mathbf{v}', \mathbf{v}'_*) \rightarrow \mathbf{v}) d\mathbf{v} = 1, \quad \text{and} \quad \int_V \psi_m((\mathbf{v}', \mathbf{n}') \rightarrow \mathbf{v}) d\mathbf{v} = 1, \quad (14)$$

which lead to

$$\begin{aligned} J_c &= \int_V \int_V \eta_c(\mathbf{v}', \mathbf{v}'_*) \psi_c((\mathbf{v}', \mathbf{v}'_*) \rightarrow \mathbf{v}) p(\mathbf{v}') p(\mathbf{v}'_*) d\mathbf{v}' d\mathbf{v}'_* \\ &\quad - p(\mathbf{v}) \int_V \eta_c(\mathbf{v}, \mathbf{v}'_*) p(\mathbf{v}'_*) d\mathbf{v}'_*, \end{aligned} \quad (15)$$

and

$$\begin{aligned} J_m &= \int_V \int_{S_+^{n-1}} \eta_m(\mathbf{v}', \mathbf{n}') \psi_m((\mathbf{v}', \mathbf{n}') \rightarrow \mathbf{v}) p(\mathbf{v}') q(\mathbf{n}') d\mathbf{v}' d\mathbf{n}' \\ &\quad - p(\mathbf{v}) \int_{S_+^{n-1}} \eta_c(\mathbf{v}, \mathbf{n}') q(\mathbf{n}') d\mathbf{n}'. \end{aligned} \quad (16)$$

Keeping in mind the biological application we are dealing with, we use the following hypothesis which also enable us to explicitly compute the momentum dissipation terms  $\mathbf{j}_c$  and  $\mathbf{j}_m$ :

- The encounter rate  $\eta_c$  does not depend on the particular incoming velocities;
- The encounter rate  $\eta_m$  does not depend neither on the particular incoming velocity nor on the fiber orientation;
- The transition probability density  $\psi_c$  does not depend on the particular incoming velocities, but only on the outgoing velocity modulus;
- After the interaction with a fiber oriented along a direction  $\mathbf{n}$  the cell tends to align with it (e.g.  $\hat{\mathbf{v}} = \pm \mathbf{n}$ ), independently from the particular incoming velocity.

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.

Moreover, whereas an after fiber-interaction cell tends to align with the encountered fiber, a cell which interacted with another cell can choose any direction of motion at random. These assumptions allow to take as transition probability densities the functions

$$\psi_c((\mathbf{v}', \mathbf{v}'_*) \rightarrow \mathbf{v}) \equiv \psi_c(\mathbf{v}) = \frac{1}{S^{n-1}} \bar{\psi}_c(v), \quad (17)$$

where  $S^{n-1} = \int_{S^{n-1}} d\hat{\mathbf{v}} = 2(n-1)\pi$ , and

$$\psi_m((\mathbf{v}', \mathbf{n}') \rightarrow \mathbf{v}) \equiv \psi_m(\mathbf{n}'; \mathbf{v}) = \psi_m(v) \frac{1}{2} [\delta(\mathbf{n}' - \hat{\mathbf{v}}) + \delta(\mathbf{n}' + \hat{\mathbf{v}})], \quad (18)$$

where the  $\delta$  are Dirac's deltas. The functions  $\bar{\psi}_c(v)$  and  $\psi_m(v)$  have to satisfy

$$\int_{\mathbb{R}_+} \bar{\psi}_c(v) v^{n-1} dv = 1 \quad \text{and} \quad \int_{\mathbb{R}_+} \psi_m(v) v^{n-1} dv = 1. \quad (19)$$

It allows to simplify considerably the cell-cell interaction term as

$$\begin{aligned} J_c &= \eta_c \psi_c(\mathbf{v}) \int_V \int_V p(\mathbf{v}') p(\mathbf{v}'_*) d\mathbf{v}' d\mathbf{v}'_* - \eta_c p(\mathbf{v}) \int_V p(\mathbf{v}'_*) d\mathbf{v}'_* \\ &= \eta_c \rho [\rho \psi_c(\mathbf{v}) - p(\mathbf{v})]. \end{aligned} \quad (20)$$

It is trivial to check that

$$\int_V J_c d\mathbf{v} = \eta_c \rho \int_V [\rho \psi_c(\mathbf{v}) - p(\mathbf{v})] d\mathbf{v} = 0. \quad (21)$$

In order to compute the higher moments of  $J_c$ , it is useful to observe that as  $\psi_c$  depends only on the velocity modulus

$$\int_V \psi_c(\mathbf{v}) \mathbf{v} d\mathbf{v} = \frac{1}{S^{n-1}} \int_{\mathbb{R}_+} \bar{\psi}_c(v) v^n dv \int_{S^{n-1}} \hat{\mathbf{v}} d\hat{\mathbf{v}} = \mathbf{0}. \quad (22)$$

It is also useful for the sequel to introduce the variance

$$\sigma_c = \frac{1}{n} \int_{\mathbb{R}_+} \bar{\psi}_c(v) v^{n+1} dv, \quad (23)$$

and the tensor

$$\int_V \psi_c(\mathbf{v}) \mathbf{v} \otimes \mathbf{v} d\mathbf{v} = \sigma_c \mathbb{I}, \quad (24)$$

whose diagonal expression is obtained by symmetry arguments related to the expression (17) of the function  $\psi_c$ .

One can finally explicitly compute the momentum dissipation due to cell-cell interaction

$$\begin{aligned} \mathbf{j}_c &= \int_V J_c \mathbf{v} d\mathbf{v} = \eta_c \rho \int_V [\rho \psi_c(\mathbf{v}) \mathbf{v} - p(\mathbf{v}) \mathbf{v}] d\mathbf{v} \\ &= -\eta_c \rho^2 \mathbf{U}. \end{aligned} \quad (25)$$

We will proceed in a similar way for the interaction with the extra-cellular matrix. First the independency from the incoming velocity allows to reduce Eq.(16) to

$$J_m = \eta_m \left[ \rho \int_{S_+^{n-1}} \psi_m(\mathbf{n}'; \mathbf{v}) q(\mathbf{n}') d\mathbf{n}' - Qp(\mathbf{v}) \right]. \quad (26)$$

Then using the expression of the transition probability density given by (18), the calculus is split in

$$J_m = \begin{cases} \frac{\eta_m}{2} \rho \psi_m(v) q(\hat{\mathbf{v}}) - \eta_m Qp(\mathbf{v}) & \text{if } \hat{\mathbf{v}} \in S_+^{n-1}, \\ \frac{\eta_m}{2} \rho \psi_m(v) q(-\hat{\mathbf{v}}) - \eta_m Qp(\mathbf{v}) & \text{if } \hat{\mathbf{v}} \in S_-^{n-1}. \end{cases} \quad (27)$$

Using  $q^e$  as extended in (5) over  $S^{n-1}$  leads to

$$J_m = \eta_m \left[ \frac{1}{2} \rho \psi_m(v) q^e(\hat{\mathbf{v}}) - Qp(\mathbf{v}) \right]. \quad (28)$$

It is trivial to check that

$$\int_V J_m d\mathbf{v} = \eta_m \left[ \frac{1}{2} \rho \int_{\mathbb{R}_+} \psi_m(v) v^{n-1} dv \int_{S^{n-1}} q^e(\hat{\mathbf{v}}) d\hat{\mathbf{v}} - Q\rho \right] = 0, \quad (29)$$

corresponding to mass conservation, and as for the cell-cell interaction, we introduce the variance

$$\sigma_m = \frac{1}{n} \int_{\mathbb{R}_+} \psi_m(v) v^{n+1} dv. \quad (30)$$

On the other hand, thanks to the symmetry property of the function  $q^e$ , one finally obtains the momentum dissipation due to the cell-ECM interaction

$$\begin{aligned} \mathbf{j}_m &= \int_V J_m \mathbf{v} d\mathbf{v} \\ &= \eta_m \left[ \frac{1}{2} \rho \int_{\mathbb{R}_+} \psi_m(v) v^n dv \int_{S^{n-1}} q^e(\hat{\mathbf{v}}) \hat{\mathbf{v}} d\hat{\mathbf{v}} - Q\rho \mathbf{U} \right] \\ &= -\eta_m Q\rho \mathbf{U}. \end{aligned} \quad (31)$$

Expressions (25) and (31) allow to write the momentum balance equation (13) as

$$\frac{\partial}{\partial t} (\rho \mathbf{U}) + \nabla_{\mathbf{x}} \cdot (\rho \mathbf{U} \otimes \mathbf{U}) = -\nabla_{\mathbf{x}} \cdot \mathbb{P} + \rho \mathbf{f}(c) - (\eta_m Q + \eta_c \rho) \rho \mathbf{U}, \quad (32)$$

where the momentum dissipation terms can be identified as the drag forces due to the cell interaction with the ECM and the other cells.

Of course, the system of equations (11) and (32) 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 for Mesenchymal Motion in a Stationary Tissue.** In order to close the system of conservation equations, we consider the interaction terms

$$J_c + J_m = \eta_c \rho [\rho \psi_c(\mathbf{v}) - p(\mathbf{v})] + \eta_m \left[ \frac{1}{2} \rho \psi_m(v) q^e(\hat{\mathbf{v}}) - Q p(\mathbf{v}) \right]. \quad (33)$$

This term vanishes when

$$p(\mathbf{v}) \equiv p_\infty(\mathbf{v}) = \frac{\rho}{\eta_c \rho + \eta_m Q} \left[ \frac{\eta_m}{2} \psi_m(v) q^e(\hat{\mathbf{v}}) + \eta_c \rho \psi_c(\mathbf{v}) \right], \quad (34)$$

which we define as the equilibrium distribution for the transport equation.

So we plan now to evaluate the conservation equations for small perturbations around the equilibrium distribution above. Since, as it can be easily checked, the drift velocity corresponding to  $p_\infty$  vanishes, this implies that the velocity field pertains to the perturbation.

Evaluating the pressure tensor for this equilibrium distribution one obtains

$$\mathbb{P} = \frac{\rho}{\eta_c \rho + \eta_m Q} \left[ \frac{\eta_m}{2} \int_V \psi_m(v) q^e(\hat{\mathbf{v}}) \mathbf{v} \otimes \mathbf{v} d\mathbf{v} + \eta_c \rho \int_V \psi_c(\mathbf{v}) \mathbf{v} \otimes \mathbf{v} d\mathbf{v} \right], \quad (35)$$

which, recalling the tensor computed in (24) and the definition (7) of the tensor  $\mathbb{D}$ , can be written as

$$\mathbb{P} = \frac{\rho}{\eta_c \rho + \eta_m Q} (\eta_m Q \sigma_m \mathbb{D} + \eta_c \rho \sigma_c \mathbb{I}). \quad (36)$$

If we assume that after any interaction (with cell or fiber) the intensity of the velocity of a cell does not depend on the type of encounter, that leads to  $\sigma_m = \sigma_c \equiv \sigma$  and

$$\mathbb{P} = \sigma \rho \mathbb{I} + \frac{\eta_m \sigma \rho Q}{\eta_c \rho + \eta_m Q} (\mathbb{D} - \mathbb{I}). \quad (37)$$

Coherently with the assumption of small perturbations with respect to the equilibrium distribution, neglecting inertia, one can write Eq.(32) as

$$\rho \mathbf{U} = \frac{-\nabla_{\mathbf{x}} \cdot \mathbb{P} + \rho \mathbf{f}(c)}{\eta_c \rho + \eta_m Q}. \quad (38)$$

Then substituting in the mass conservation equation gives

$$\frac{\partial \rho}{\partial t} = \nabla_{\mathbf{x}} \cdot \left[ \frac{\nabla_{\mathbf{x}} \cdot \mathbb{P} - \rho \mathbf{f}(c)}{\eta_c \rho + \eta_m Q} \right], \quad (39)$$

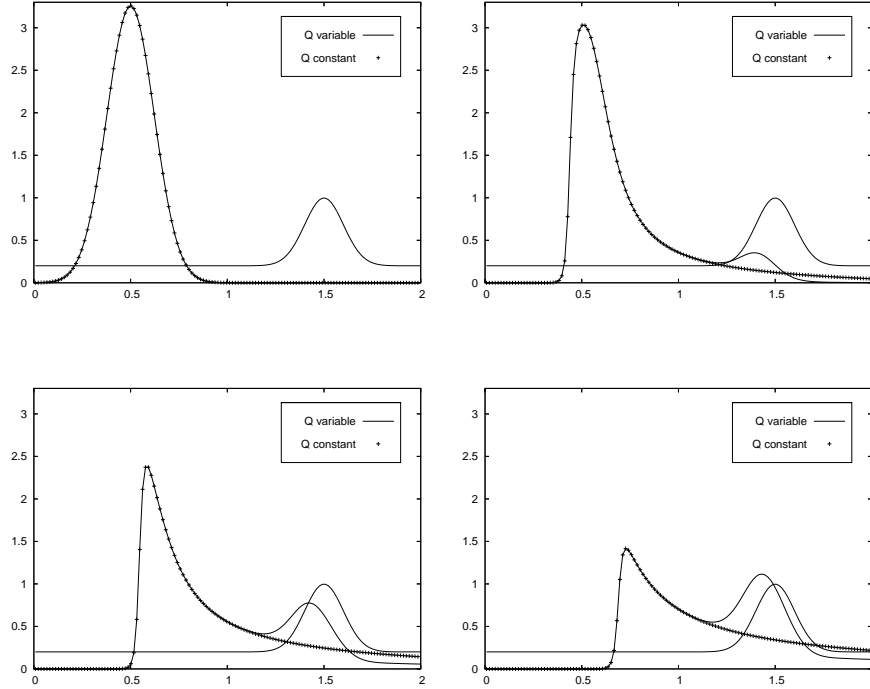
in which recalling the form of the pressure tensor given in (37), and taking  $\mathbf{f}(c) = \lambda \nabla_{\mathbf{x}} c$ , leads finally to the evolution equation for the cell density

$$\begin{aligned} \frac{\partial \rho}{\partial t} + \nabla_{\mathbf{x}} \cdot \left( \frac{\lambda \rho \nabla_{\mathbf{x}} c}{\eta_c \rho + \eta_m Q} \right) &= \nabla_{\mathbf{x}} \cdot \left[ \frac{1}{\eta_c \rho + \eta_m Q} \nabla_{\mathbf{x}} (\sigma \rho) \right] \\ &+ \nabla_{\mathbf{x}} \cdot \left[ \frac{1}{\eta_c \rho + \eta_m Q} \nabla_{\mathbf{x}} \cdot \left( \frac{\eta_m \sigma Q \rho}{\eta_c \rho + \eta_m Q} (\mathbb{D} - \mathbb{I}) \right) \right]. \end{aligned} \quad (40)$$

The first term on the right hand side gives rise to an isotropic diffusion term, while the second one takes into account possible anisotropies due to the presence of the fibrous network. As a validation of this equation, it is worth mentioning that Eq.(40) is also obtained as the diffusion limit of the transport equation (9) using the method developed in [6].

**6. Numerical simulations.** We propose in this section the numerical solving of the equation (40). A symmetric splitting operator scheme of order two has been used. 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 [1], [2]) 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 [8].

As a first step in the validation of the model, the one-dimensional configuration is considered. It does not allow to take into account any anisotropy of the fibrous network. Actually the tensor  $\mathbb{D}$  reduces in this case to the identity, which cancels the last term in Eq.(40). Thus, 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 chemoattractive force  $\mathbf{f}(c)$ . The two curves show the evolution of the same initial gaussian-like distribution of cells attracted by a chemoattractant located outside at the right of the domain. The dot-style curve corresponds to a constant density  $Q$  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 normality.



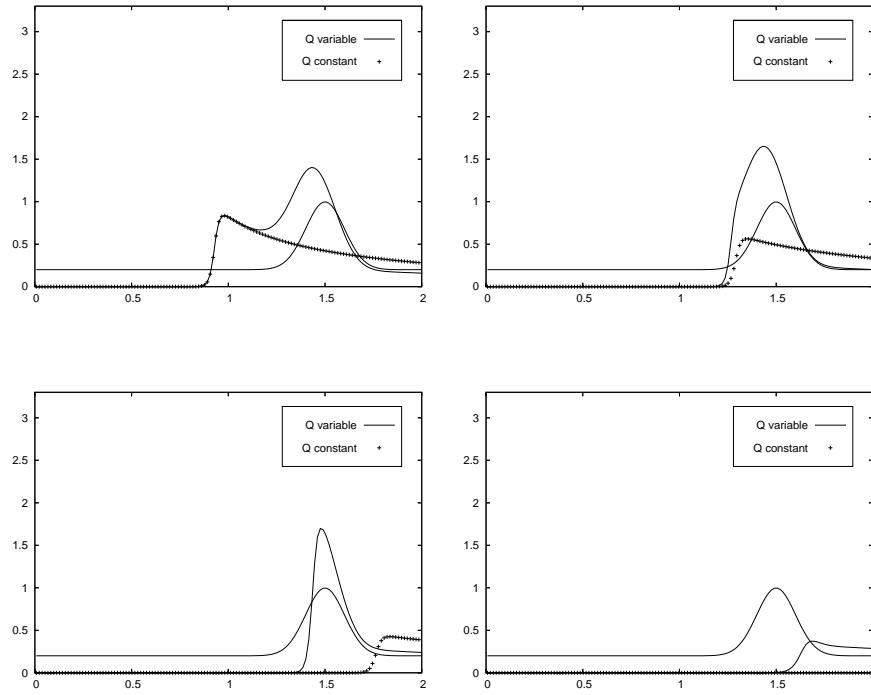


FIGURE 1. Motion slowed down by the inhomogeneities of an isotropic fibrous network (to be read from left to right while going down)

Before the model may be validated from an experimental point of view, the numerical simulations have to be extended to the two-dimensional configuration so that possible anisotropies of the ECM may also be taken into account. That is one of the main goals 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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