Analysis of a Kinetic Model for Cell Movement in Network Tissues

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Abstract

Mesenchymal motion describes the movement of cells in biological tissues formed by fiber networks, for example during the migration of tumor cells through collagen networks. We investigate the mesenchymal motion model proposed by T. Hillen in [2] in higher dimensions. We formulate the problem as an evolution equation in a Banach space of measure-valued functions and use methods from semigroup theory to show the global existence of classical solutions. We investigate steady states of the model and show that patterns of network type exist as steady states. For the case of constant fiber distribution, we find an explicit solution and we prove the convergence to the parabolic limit.

1. Introduction

In [2], the author introduced a mathematical model for cell movement in fibrous tissues. As observed for mesenchymal tumor cells in works by Friedl and collaborators [1], cells move in a field of symmetric fibers (e.g. collagen) and change their velocities according to the local orientation of the fibers. At the same time the cells also remodel the fibers, primarily through expression of matrix-degrading enzymes (proteases) that cut selected fibers.

Complete alignments of cells and fibers (corresponding to Dirac measures) can occur as steady states of the model, hence a measure-valued formulation becomes necessary.

2. The Model

Let $V = [s_1, s_2] \times \mathbb{S}^{n-1}$, where $0 \le s_1 \le s_2 < \infty$ is the range of possible cell speeds. The cells are described by a measure on V while the fiber network is described by a symmetric measure on $\mathbb{S}^{n-1}$.

Moving cells in the field of fibers turn away from their old direction at rate $\mu > 0$, they turn into a new direction with a probability that corresponds to the fiber distribution q. The new speed of the cells is chosen from the interval $[s_1, s_2]$. The cells degrade (at rate $\kappa > 0$) those fibers that they meet at an approximately right angle while they leave fibers that are parallel to their own orientation unchanged (see Figure 1).

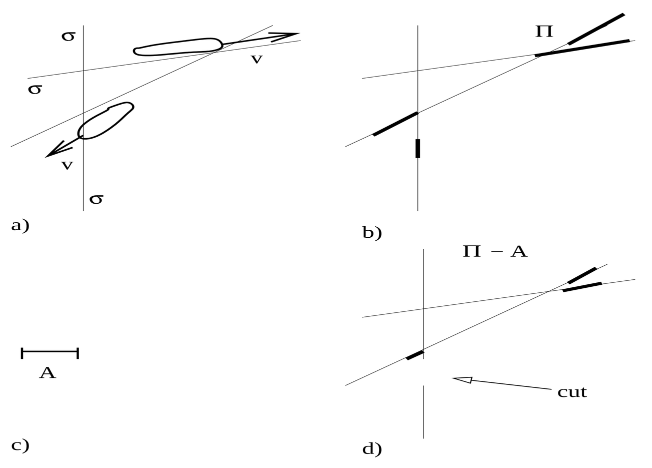

Figure 1: *Schematic representation of fiber remodeling. From [2].*

Let $\mathcal{B}(V)$ and $\mathcal{B}(\mathbb{S}^{n-1})$ denote the Banach spaces of regular signed real-valued (finite) Borel measures on V, respectively on $\mathbb{S}^{n-1}$ with the total variation norms and positive cones $\mathcal{B}(V)^+$ and $\mathcal{B}(\mathbb{S}^{n-1})^+$. Let

$$\mathbb{X}_1 = L^1(\mathbb{R}^n, \mathcal{B}(V)),\ \mathbb{X}_2 = L^\infty(\mathbb{R}^n, \mathcal{B}(\mathbb{S}^{n-1})),\ \mathbb{X} = \mathbb{X}_1 \times \mathbb{X}_2,$$

and write

$$||p||_\infty = \operatorname*{ess\,sup}_{x \in \mathbb{R}^n} ||p(x)||_{\mathcal{B}(V)}$$

for those $p \in \mathbb{X}_1$ for which the essential supremum is finite. We define

- The spatial *mass* density of a velocity distribution,

$$\bar{\ }: \mathcal{B}(V) \to \mathbb{R}, \qquad \bar{p} = p(V).$$

- The *lifting* of a measure on $\mathbb{S}^{n-1}$ to a measure on V,

$$\tilde{\ }: \mathcal{B}(\mathbb{S}^{n-1}) \to \mathcal{B}(V), \qquad \tilde{q} = m \otimes q$$

  where m is a probability measure on $[s_1, s_2]$.
- The *mean projection operator*

$$\Lambda : \mathbb{X}_1 \to L^1(\mathbb{R}^n, L^\infty(\mathbb{S}^{n-1})), \Lambda(p)(\theta) = \int_V \left| \theta \cdot \frac{v}{||v||} \right| \mathrm{d}p(v).$$

- The *relative alignment operator*

$$B : \mathbb{X} \to L^1(\mathbb{R}^n, \mathbb{R}), \qquad B(p,q) = \int_{\mathbb{S}^{n-1}} \Lambda(p)(\theta)\, \mathrm{d}q(\theta).$$

  Notice that B is bilinear and if $||p||_\infty < \infty$, then

$$||B(p,q)||_{L^\infty(\mathbb{R}^n,\mathbb{R})} \le ||\bar{p}||_{L^\infty(\mathbb{R}^n,\mathbb{R})} ||q||_{\mathbb{X}_2}.$$

Let $\mu > 0$ denote the turning rate and $\kappa > 0$ the rate of fiber degradation. Then we consider

$$\begin{aligned} \frac{\partial p}{\partial t} + v \cdot \nabla p &= -\mu p + \mu \bar{p}\, \tilde{q}, \\ \frac{\partial q}{\partial t} &= \kappa(\Lambda(p) - B(p,q))q, \\ p(x,0) = p_0(x), &\quad q(x,0) = q_0(x). \end{aligned} \tag{1}$$

3. Existence Results

Let

$$D(\mathcal{A}) = \{(p,q) \in \mathbb{X} \,:\, \nabla p \in \mathbb{X}_1^n\},$$
$$\mathcal{A}\begin{pmatrix} p \\ q \end{pmatrix} = \begin{pmatrix} -v \cdot \nabla & 0 \\ 0 & 0 \end{pmatrix}\begin{pmatrix} p \\ q \end{pmatrix},\ \mathcal{D} = \{u \in \mathbb{X} \,:\, ||u||_\infty < \infty\}$$

and consider the abstract Cauchy problem

$$u' = \mathcal{A}u + F(u), \quad u(0) = u_0, \tag{2}$$

where F is given by the right hand side of (1).

Theorem 1 *The problem* (2) *has a unique global positive mild solution for every $u_0 \in \mathcal{D} \cap \mathbb{X}^+$.*

Proof. By a standard fixed point technique, and *a priori* estimates on $||u||_{\mathbb{X}}$. □

4. Fixed Fiber Distribution

Assume that cells do not remodel the fiber network and that $q(x)$ is a given (time-independent) distribution. Then (1) can be solved using the method of characteristics. For given $v \in V$, the characteristic equation is $\frac{d}{dt}x(t) = v$, hence the characteristic through $x_0 \in \mathbb{R}^n$ is given by $x(t) = x_0 + vt$. We can solve (1) by considering

$$\frac{d}{dt}p(x(t),t) + \mu p(x(t),t) = \mu \tilde{q}(x(t))\bar{p}(x(t),t), \tag{3}$$

using the fact that $\tilde{q}(x(t),V) = 1$. The solution $p(x,t)$ of (3) can then be written entirely in terms of the initial condition

$$p(x,t) = e^{-\mu t}p_0(x - t\,\mathrm{d}v) + (1 - e^{-\mu t})p_0(x - Vt, V)\tilde{q}, \tag{4}$$

where

$$p_0(x - At, A) = \int_A p_0(x - t\,\mathrm{d}v, \mathrm{d}v).$$

Hence the solution is a convex combination of the initial condition p_0 and the current amount of cells $\bar{p}$ redistributed with respect to the "controlling" distribution $\tilde{q}$.

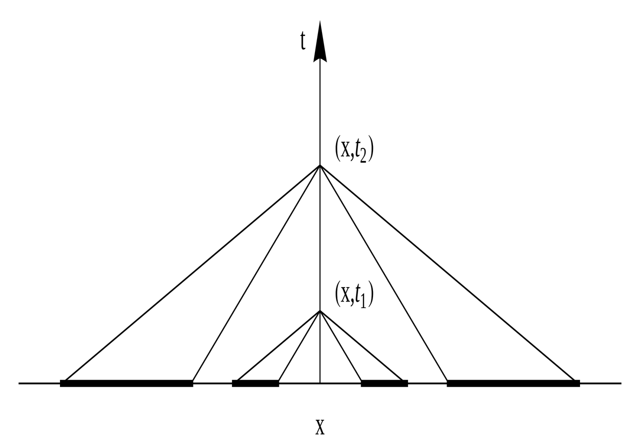

Figure 2: *The domain of dependence of the point x at different times (the generalized Huygens principle).*

5. Parabolic Limit Problem

In [2], the author formally derive a diffusion limit equation from equation (1) under suitable scaling of space and time. Let $\hat{x}$ and $\hat{v}$ denote reference length, and speed, respectively, with the dimensionless quantity

$$\varepsilon = \frac{\hat{v}}{\mu \hat{x}}$$

being small. We obtain, the reduced parabolically scaled equation

$$\begin{aligned} \varepsilon^2 \frac{\partial p_\varepsilon}{\partial t} + \varepsilon v \cdot \nabla p_\varepsilon &= \mu(\tilde{q}\bar{p}_\varepsilon - p_\varepsilon), \\ p_\varepsilon(x,0) &= p_0(x) \in \mathcal{D} \cap \mathbb{X}_1^+. \end{aligned} \tag{P$_\varepsilon$}$$

Simultaneously, we consider the limit problem

$$\begin{aligned} \frac{\partial \varrho}{\partial t} &= \nabla \cdot (D[q]\nabla \varrho), \\ \varrho(x,0) = p_0(x,V) &= \bar{p}_0(x) \in L^{1,+},\ ||\varrho(\,\cdot\,,0)||_\infty < \infty(\mathbb{R}^n, \mathbb{R}), \end{aligned} \tag{P$_0$}$$

where the diffusion tensor is given by

$$D[q] = \frac{1}{\mu}\int_V v \otimes v\, \mathrm{d}\tilde{q}(v).$$

Theorem 2 *Assume that q is time-independent and fix $T > 0$. Let $(p_\varepsilon)_{\varepsilon \ge 0}$ be the family of solutions to problem* (P$_\varepsilon$) *and ϱ the weak solution to problem* (P$_0$)*. Then, after possibly extracting a subsequence we have the convergence*

$$p_\varepsilon \rightharpoonup \varrho\tilde{q}$$

in the weak topology on the space $L^\infty([0,T], \mathbb{X}_1)$.*

Proof. We use (4) to represent the solution p_ε. This family is uniformly bounded in $L^\infty([0,T], \mathbb{X}_1)$, hence a weak* limit p_* exists, it can be shown that $p_*(x,t) = \varrho(x,t)\tilde{q}$. We show that the residua converge,

$$r_\varepsilon(x,t) = \frac{p_\varepsilon - \bar{p}_\varepsilon\tilde{q}}{\varepsilon} \rightharpoonup r_* = -\frac{1}{\mu}v \cdot \nabla(\varrho\tilde{q}) \quad (\text{weak}^*).$$

We evaluate equation (P$_\varepsilon$) at V and obtain the conservation law (using the symmetry of q)

$$\frac{\partial \bar{p}_\varepsilon}{\partial t} + \nabla \cdot \left(\int_V v\, \mathrm{d}r_\varepsilon \right) = 0. \tag{5}$$

Letting $\varepsilon \to 0$, we obtain

$$\frac{\partial \varrho}{\partial t} = -\nabla \cdot \int_V v\, \mathrm{d}r_*(v),$$

this gives the desired result, using the representation for r_*. □.

6. Steady States

Numerical simulations by Kevin Painter [4], shown in Figure 3 result in interesting network patterns that form from random initial data. These simulations suggest that networks of aligned tissue can surround areas of uniform tissue.

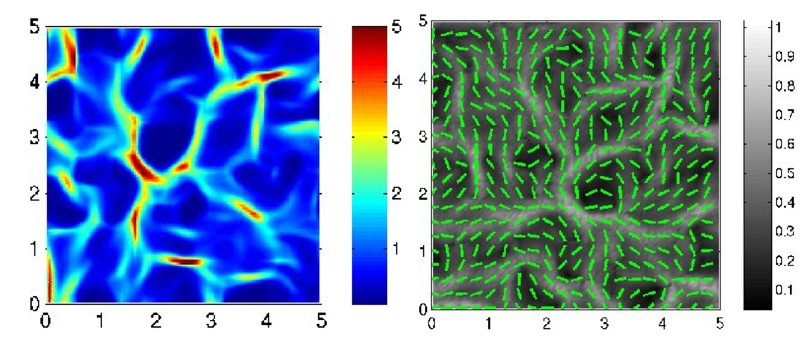

Figure 3: *Typical simulation of network formation for model* (1)*. Left: cell density $\bar{p}(x,t)$ (red = high, blue = low). Right: the underlying network. Courtesy of Kevin Painter [4].*

We define *weak* and *pointwise* steady states by testing the steady state of (1) with suitable test functions. As a result we obtain symmetry properties at intersections of multiple directions. For a given vector $\gamma \in \mathbb{S}^1$ define

$$\delta_{|\gamma|} = \frac{1}{2}(\delta_{-\gamma} + \delta_\gamma).$$

We can show for planar triple intersections

Theorem 3 *Assume (p,q) is a pointwise steady state of* (1) *and at x it satisfies*

$$q(x) = \frac{1}{3}(\delta_{|\gamma_1|} + \delta_{|\gamma_N|} + \delta_{|\gamma_3|}) \quad \textit{and} \quad p(x) = \tilde{q}(x).$$

for $\gamma_1, \gamma_2, \gamma_3 \in \mathbb{S}^1$. Then $|\gamma_1\gamma_2| = |\gamma_2\gamma_3| = |\gamma_3\gamma_1|$.

7. Acknowledgments

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