Chapter 1
Chemotaxis and haptotaxis on cellular level

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Abstract Chemotaxis and haptotaxis have been a main theme in the macroscopic study of bacterial and cellular motility. In this work we use a successful model that describes cellular motility and investigate the influence these processes have on the shape and motility of fast migrating cells. We note that, despite the biological and modelling differences of chemotaxis and haptotaxis, the cells exhibit many similarities in their migration. In particular, after an initial adjustment phase, the cells obtain a stable shape, similar in both cases, and move with constant velocity.

1.1 Introduction

In the biology of many diseases and, in particular, in the growth and metastasis of cancer, the processes of chemotaxis and haptotaxis play a fundamental role, see e.g. [11].

Chemotaxis is the directed motion of biological organisms (cells in particular) as response to an extracellular chemical signal. Due to their size, cells
Fig. 1.1 (a) NIH3T3 cell during migration. The lamellipodium is located in the light-coloured front of the cell; (License: Cell Image Library, CIL:26542). (b) The inside of the lamellipodium as reconstructed by realistic experimental data.

Chemotaxis can identify spatial gradients of the chemical ingredient along their membrane and adjust their migration accordingly. Haptotaxis, on the other hand, can be described as the directed cell motion as response to a gradient of extracellular adhesion sites or substrate-bound chemo-attractant/repellents. The cells attach on the adhesion sites by use of specialized transmembrane proteins like the integrins.

Mathematically, chemotaxis and haptotaxis are often studied in the spirit of Keller-Segel systems [10, 12, 4]. In such approach, the involved quantities are represented by their densities. This has created a gap between the mathematical investigations—at least from a macroscopic point of view—and the experimental biological/medical sciences where most of the knowledge/understanding refers to single cells and their properties. The current work is an effort to shed some light in this research direction.

In more detail, we consider very motile cells, like fibroblast, keratocyte, or even cancer cells, that migrate over adhesive substrates. These cells develop thin protrusions, called lamellipodia, see Fig. 1.1 and [13]. The lamellipodium can be found at the leading edge of the cells, and is comprised of a network of actin-filaments, which are highly dynamic linear bio-polymers [14]. Intra- or extracellular reasons might lead to polarizations of the lamellipodium and to cell motion that resembles to “crawling” [15, 3].

For the modelling of the lamellipodium and the ensuing cell motility, we follow the approach proposed in [9] and later extended in [6], and consider the Filament Based Lamellipodium Model (FBLM); a two-dimensional continuum model that describes the dynamics of the actin meshwork and results to the motility of the cell. The FBLM distinguishes between two different families of filaments and takes into account the interactions between them and the Extracellular Matrix (ECM). Numerically, we use a problem specific Finite Element Method (FEM) that we have previously developed and that allows for efficient investigation of the FBLM, see [7].

The main aim of this paper is to investigate, the influence chemotaxis and haptotaxis have on the shape and the motion of migrating cell, when this is modelled and simulated by the FBLM and the corresponding FEM. In more detail: in section 1.2 we present the main components of the FBLM and of the FEM. In Sections 1.3 and 1.4 we elucidate on the way that chemo-
Chemotaxis and haptotaxis are incorporated in our study. In Section 1.5 we present comparative results between the two motility scenarios.

1.2 The model and the method

This section is devoted in the brief presentation of the FBLM and the corresponding FEM.

**Model.** The main assumption behind the model is that the lamellipodium is a two dimensional structure comprised of actin filaments organized in two locally parallel families, see [9, 6] for details.

The filaments of each family (denoted as $\mathbf{F}^\pm$) are labelled by an index $\alpha \in [0, 2\pi)$, they have, at time $t$, length $L^\pm(\alpha, t)$, and can be parametrized with respect to their arclength as $\{\mathbf{F}^\pm(\alpha, s, t) : -L^\pm(\alpha, t) \leq s \leq 0\} \subset \mathbb{R}^2$, where the membrane of the cell corresponds to $s = 0$. The two families define identical membranes

$$\{\mathbf{F}^+(\alpha, 0, t) : 0 \leq \alpha < 2\pi\} = \{\mathbf{F}^-(\alpha, 0, t) : 0 \leq \alpha < 2\pi\} , \quad (1.1)$$

which, along with the *inextensibility* assumption

$$[\partial_s \mathbf{F}^\pm(\alpha, s, t)] = 1 \quad \forall (\alpha, s, t) , \quad (1.2)$$

constitute additional constraints for the unknowns $\mathbf{F}^\pm$. The FBLM reads for the family $\mathbf{F} = \mathbf{F}^+$ as (and similarly for $\mathbf{F} = \mathbf{F}^-$):

$$0 = \mu^A \eta D_t \mathbf{F} - \partial_s (\eta \lambda \text{inext} \partial_s \mathbf{F}) + \partial_s (p(\rho) \partial_\alpha \mathbf{F}^\perp) - \partial_\alpha (p(\rho) \partial_s \mathbf{F}^\perp)$$

$$+ \mu^B \partial_s^2 \left(\eta \partial^2_s \mathbf{F}\right) \pm \partial_s \left(\eta \mu^T (\phi - \phi_0) \partial_s \mathbf{F}^\perp\right) + \eta \mu^S \left(D_t \mathbf{F} - D_t^- \mathbf{F}^-\right) , \quad (1.3)$$

with $\mathbf{F}^\perp = (F_1, F_2)^\perp = (-F_2, F_1)$. The function $\eta(\alpha, s, t)$ represents the number density of filaments of the family $\mathbf{F}$ with length at least $-s$ at time $t$ with respect to $\alpha$.

The first term in the (1.3) is responsible for the interaction of the intra- and the extracellular environment, and in particular for the momentum transfer between the cell and the ECM. It is the prominent term of (1.3) and, in this sense, the model (1.3) is *advection dominated*. The polymerization speed of the filaments is given by $v(\alpha, t) \geq 0$, and the *material derivative*

$$D_t \mathbf{F} := \partial_t \mathbf{F} - v \partial_s \mathbf{F} , \quad (1.4)$$

describes the velocity of the actin material relative to the substrate.
The inextensibility term follows from the constraint (1.2) with a Lagrange multiplier $\lambda_{\text{inext}}(\alpha, s, t)$. The pressure term models the electrostatic repulsion between filaments of the same family. The filament bending is modeled according to Kirchhoff’s bending theory. The last two terms in (1.3) model the interaction between the two families caused by elastic cross-link junctions. They resist against twisting away from the equilibrium angle $\phi_0$ of the cross-linking molecule, and against the stretching between filaments of the two families.

The system (1.3) is subject to boundary conditions; at $s = 0$ they describe the tethering forces of the filaments at the membrane, and at $s = -L$ the contraction effect of the actin-myosin interaction with the interior region of the cell.

**Numerical method.** For the numerical treatment of the FBLM, we have developed a problem specific FEM. We present here its main characteristics and refer to [7] for details.

The maximal filament length varies around the lamellipodium, hence, the computational domain

$$B(t) = \{(\alpha, s) : 0 \leq \alpha < 2\pi, -L(\alpha, t) \leq s < 0\}$$

is non-rectangular. The orthogonality of the domain is recovered using the coordinate transformation $(\alpha, s, t) \rightarrow (\alpha, L(\alpha, t)s, t)$. This gives rise to the orthogonal domain $B_0 := [0, 2\pi] \times [-1, 0] \ni (\alpha, s)$.

We discretize $B_0$ as $B_0 = \bigcup_{i=1}^{N_\alpha} \bigcup_{j=1}^{N_s} C_{i,j}$, with $C_{i,j} = [\alpha_i, \alpha_{i+1}) \times [s_j, s_{j+1})$ where $\alpha_i = (i - 1)\Delta\alpha$, $\Delta\alpha = \frac{2\pi}{N_\alpha}$, and $s_j = -1 + (j - 1)\Delta s$, $\Delta s = \frac{1}{N_s - 1}$. The conforming Finite Element space we consider is

$$\mathcal{V} := \left\{ F \in C_\alpha \left([0, 2\pi]; C^1_\alpha([-1, 0])\right)^2 \text{ such that } F \big|_{C_{i,j}} (\cdot, s) \in \mathbb{P}^i_{\alpha}, \quad F \big|_{C_{i,j}} (\alpha, \cdot) \in \mathbb{P}^j_s \text{ for } i = 1, \ldots, N_\alpha; j = 1, \ldots, N_s - 1 \right\}, \quad (1.5)$$

and includes the, per direction and per cell $C_{i,j}$, shape functions

$$H^{i,j}_{k}\left(\alpha, s\right) = \begin{cases} L^{i,j}_{1}\left(\alpha\right)G^{i,j}_{k}\left(s\right), & \text{for } k = 1, \ldots, 4 \\ L^{i,j}_{2}\left(\alpha\right)G^{i,j}_{k-4}\left(s\right), & \text{for } k = 5, \ldots, 8 \end{cases}, \quad (1.6)$$

where, for $(\alpha, s) \in C_{i,j}$ holds

$$H^{i,j}_{k}\left(\alpha, s\right) = \begin{cases} \alpha_{i+1} - \alpha, & \text{for } \alpha = 1, \ldots, 4 \\ 1 - L^{i,j}_{1}\left(\alpha\right), & \text{for } \alpha = 5, \ldots, 8 \end{cases}$$

$$G^{i,j}_{1}\left(s\right) = 1 - \frac{3(s-s_j)^2}{\Delta s^2} + \frac{2(s-s_j)^3}{\Delta s^3}$$

$$G^{i,j}_{2}\left(s\right) = s - s_j - \frac{2(s-s_j)^2}{\Delta s} + \frac{(s-s_j)^3}{\Delta s^2}$$

$$G^{i,j}_{3}\left(s\right) = 1 - G^{i,j}_{1}\left(s\right)$$

$$G^{i,j}_{4}\left(s\right) = -G^{i,j}_{2}\left(s_j + s_{j+1} - s\right)$$

and where $H^{i,j}_{k}\left(\alpha, s\right) = 0$ for $(\alpha, s) \notin C_{i,j}$.
Accordingly, the weak formulation of (1.3) (neglecting the boundary conditions) reads as:

\[
0 = \int_{B_0} \eta \left( \mu^B \partial_\alpha^2 \mathbf{F} \cdot \partial_\alpha^2 \mathbf{G} + L^4 \mu^A \tilde{D}_t \mathbf{F} \cdot \mathbf{G} + L^2 \lambda_{\text{inext}} \partial_\alpha \mathbf{F} \cdot \partial_\alpha \mathbf{G} \right) d(\alpha, s) \\
+ \int_{B_0} \eta \left( L^4 \mu^S \left( \tilde{D}_t \mathbf{F} - \tilde{D}_t \mathbf{F}^\top \right) \cdot \mathbf{G} + L^2 \mu^T (\phi - \phi_0) \partial_\alpha \mathbf{F}^\perp \cdot \partial_\alpha \mathbf{G} \right) d(\alpha, s) \\
- \int_{B_0} p(\rho) \left( L^3 \partial_\alpha \mathbf{F}^\perp \cdot \partial_\alpha \mathbf{G} - \frac{1}{L} \partial_\alpha \mathbf{F}^\perp \cdot \partial_\alpha (L^4 \mathbf{G}) \right) d(\alpha, s),
\]

(1.8)

for \( \mathbf{F}, \mathbf{G} \in H^1_\alpha \left( (0, 2\pi); H^2_s (-1,0) \right) \) and the modified material derivative \( \tilde{D}_t = \partial_t - \left( \frac{\nu}{L} + \frac{\nu \partial \mathbf{L}}{L} \right) \partial_s \) and in-extensibility constraint \( |\partial_\alpha \mathbf{F}(\alpha, s, t)| = L(\alpha, t) \).

### 1.3 Cellular level chemotaxis driven cell migration

We prescribe the sensing of the extracellular chemical signal, directly on the membrane of the cell, using the function

\[
S = S_0 + S_1 \left( x \cos(\phi_{ca}) + y \sin(\phi_{ca}) \right),
\]

where \((x, y)\) traverses the membrane, \(\phi_{ca}\) denotes the relative direction of the chemical signal with respect to the cell, and \(S_0\) and \(S_1\) the strength of the signal. We introduce a cut-off value \(c\) on the relative signal intensity \(S\) to account for the sensitivity of the cell to the low chemical ingredient densities. The higher the value of \(c\) the smaller is the part of the cell that “senses” the chemical ingredient. Accordingly, the polymerization rate \(v_{\text{ref}}\) is adjusted between a minimum and a maximum value \(v_{\text{min}}\) and \(v_{\text{max}}\).

Furthermore, the polymerization rate is adjusted by the signed local curvature \(\kappa\) of the membrane as

\[
v = \frac{2v_{\text{ref}}}{1 + e^{v_{\text{ref}}}}
\]

(1.9)
where $\kappa_{\text{ref}}$ is the reference membrane curvature related to the local intensity of the chemical signal. In its turn, the polymerization rate $v$ influences the length of the lamellipodium as follows:

$$L = -\frac{\kappa_{\text{cap,eff}}}{\kappa_{\text{sev}}} + \sqrt{\frac{\kappa_{\text{cap,eff}}^2}{\kappa_{\text{sev}}^2} + \frac{2v}{\kappa_{\text{sev}}} \log \frac{\eta(s = 0)}{\eta_{\text{min}}}},$$

cf. with Table 1.1 and [7] for a biological justification of $\eta_{\text{min}}$.

**Experiment 1.3.1. [Less sensitive cells]:** The cell moves over a uniform substrate with $\mu^A = 0.4101$. The sensitivity cut-off value is set to $c = 0.33$. The rest of the parameters are given in Table 1.1. For this, and for the rest experiments in this paper, the resolution of the mesh is set to $s_{\text{nodes}} = 7$ and $\alpha_{\text{nodes}} = 36$. The initial conformation of the cell is assumed to be circular with a uniform-sized lamellipodium. This experiment is visualized in Fig. 1.2, where we see the creation of a “tail” on the retracting side of the cell. After an initial transition phase, the cell continues its migration with a constant shape, see also Fig. 1.8.

**Experiment 1.3.2. [More sensitive cells]:** With similar parameters as in Experiment 1.3.1, and for a sensitivity cut-off set at $c = 0.5$ instead of $c = 0.33$, we obtain the results exhibited in Fig. 1.3. Due to the higher value of $c$, a smaller part of the membrane senses the chemical, and the cell exhibits a longer tail than in the $c = 0.33$ case. The cell is robust and after an initial adjustment phase it attains a stable moving shape.

Further experiments on the effect of chemotaxis on the motility and shape of the cells, using the FBLM-FEM, can be found in [6].

### 1.4 Cellular level haptotaxis driven cell migration

Here we study the influence that haptotaxis has in the motility of the cells, in the absence of a chemotaxis influence. We take haptotaxis into account by the density of the ECM fibres and the coefficient $\mu^A$ in (1.3). Variations
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\[ t = 0.0015 \]
\[ t = 3.0015 \]
\[ t = 9.0015 \]

Fig. 1.4 Continuous non-linear adhesion haptotaxis Experiment 1.4.1. The cell resides initially over a non-uniform ECM with density described by the background colour and colour-bar. The higher adhesion in the right side of the domain and the internal myosin pulling force lead to a larger cell which migrates to the right. The smoothness of the ECM and the small gradients simulate healthy extracellular tissue.

\[ (a) \ t = 0.0015 \]
\[ (b) \ t = 3.0015 \]
\[ (c) \ t = 12.0015 \]

Fig. 1.5 Haptotaxis Experiment 1.4.2. As in the Experiment 1.4.1, the cell migrates towards the higher adhesion environment. The higher gradients of the (smooth) ECM simulate tissue under repair. The higher cell speed (factor 2 when compared to Fig. 1.4) is responsible for the resulting cell shape.

\[ (a) \ t = 0.0015 \]
\[ (b) \ t = 3.0015 \]
\[ (c) \ t = 9.0015 \]

Fig. 1.6 Haptotaxis Experiment 1.4.3, representation of a damaged tissue. Compared with Fig. 1.4 the cell attains a different shape due to the discontinuity of the ECM density.

in the density of the ECM are introduced by a spatial non-uniform adhesion coefficient \( \mu^A \).

The polymerization rate \( \nu \) is considered constant, but is locally adjusted by the curvature of the membrane as in (1.9). There is no influence on \( \nu \) by the density or any other characteristic of the ECM.

Biologically, the condition of the ECM is a strong indication of health. For cancer in particular, the interaction of the cancer cells with the ECM
is of fundamental importance for the invasion and the metastasis steps of the disease. For that reason we investigate three particular cases: a “normal tissue” where the ECM is smooth and exhibits small gradients, a “tissue repair” experiment where the ECM is smooth and exhibits larger gradients, and a “damaged tissue” experiment where the ECM exhibits discontinuities. Moreover, we consider an experiment where the ECM is “pulled” below the cell and accordingly the cell is dragged along with it.

**Experiment 1.4.1. [Normal tissue]:** We consider an ECM that varies spatially in a non-linear but smooth manner as follows:

\[
\mu^A(x, y) = 0.4101 \times \begin{cases} 
0.1, & x < 0 \\
0.2 \frac{x}{1 + e^{-0.1x}}, & x \geq 0
\end{cases}
\]

We visualize the results in Fig. 1.4 and note the smooth transition of the cell in the direction of the higher gradient. As a result of the higher adhesion, the cell at first elongates and creates an effective pulling force towards the one side of the cell. We also see that after an initial growing phase the cell maintains a robust moving cell shape.

**Experiment 1.4.2. [Tissue repair]:** During the remodelling process, the ECM exhibits continuous gradients. We model this effect by the adhesion function

\[
\mu^A(x, y) = 0.4101 \times \begin{cases} 
0.1, & x < 0 \\
0.1 + x/30, & x \geq 0
\end{cases}
\]

We visualize the result in the Fig. 1.5, where we see that the higher gradient that the ECM presents, when compared to the Experiment 1.4.1, causes the cell to grow larger and to create an effective pulling force towards the higher adhesion part of the domain. As a result of the internal myosin pulling force, the protruding front is followed by a retracting “tail” that ceases to exist after the cell has crawled on the non-constant ECM part of the domain.

**Experiment 1.4.3. [Damaged tissue]:** Of particular medical and biological importance are cases where the ECM exhibits abrupt variations in its consistency, characteristic examples are possible wounds, or the degradation of the matrix by the cancer cells. By introducing a discontinuity in the ECM, we partially replicate these cases:

\[
\mu^A(x, y) = 0.4101 \times \begin{cases} 
0.1, & x < 0 \\
0.8 \frac{x}{1 + e^{-0.1x}}, & x \geq 0
\end{cases}
\]

We visualize the results in Fig. 1.6, where we see that despite the discontinuity, the cell adheres and crawls once again to the more stiff part of the ECM. When compared with the previous Experiment 1.4.1, we see that the
Fig. 1.7 Haptotaxis Experiment 1.4.4. Here, the ECM is dragged to the right. The cell remains attached on the higher-density ECM, slides over the lower-adhesion substrate, and deforms.

“tail” the cell develops, is sharper despite the small gradient of the ECM. The smaller values of the ECM density are also depicted in the final size of the cell, that is small in this case.

Experiment 1.4.4. [Sliding ECM]: The cell resides initially over a non-uniform and discontinuous ECM as in Experiment 1.4.3. We shift the stiffer part of the ECM to the right with a constant velocity and the cell remains attached to it, while the rear side slides over the less-adhesive substrate. The results are visualized in Fig. 1.7.

1.5 Comparison of chemotaxis and haptotaxis on cellular level

We have seen so far that, due to biological particularities and modelling considerations, the chemotaxis and haptotaxis cell migration can be considerably distinct. On the one hand, in chemotaxis, the width of the lamellipodium is influenced by the extracellular chemical signal and the polymerization rate. The lamellipodium grows wider when the chemical signal is stronger. As a result the total friction and the effective pulling force is stronger towards this direction. On the other hand, in haptotaxis, variations of the ECM lead to larger cell sizes (but not lamellipodium widths) in the parts of the cell that reside over higher ECM densities. As the friction is stronger in these parts of the cell, the corresponding resistance to the contractile myosin force is also stronger.

Despite these qualitative differences between chemotaxis and haptotaxis, we exhibit with two generic experiments that the resulting cell shapes and cell are more similar than not.

Experiment 1.5.1. For the first comparison case, visualized in Fig. 1.9, we consider the chemotaxis Experiment 1.3.2 and the haptotaxis Experiment 1.4.1. We notice that the transitional conformations that the cells acquire
Fig. 1.8 Time evolution of the area the cell occupies. After an initial adjustment phase, a stable moving shape is attained. (a) Chemotaxis Experiment 1.3.2. (b) Haptotaxis Experiment 1.4.2.

Fig. 1.9 Comparison of the chemotaxis Experiment 1.3.2 shown in (a), with the haptotaxis Experiment 1.4.1 shown in (b). The overlay of the outer and inner boundaries of the simulated cells, exhibits that the cells in the two cases are qualitatively similar, despite the significant biological and modelling differences between them.

Fig. 1.10 Comparison of the chemotaxis Experiment 1.3.1 shown in (a), with the haptotaxis Experiment 1.4.2 shown in (b). The overlay graph shown in (c) exhibits that the areas that the cells occupy are qualitatively similar. It moreover shows that the the “inner cells” are similar also in size.

before their final stable state, are qualitatively similar in the shape of the membrane (external boundary), but differ in size.

The size of the lamellipodium, we see in the chemotaxis case that it is not uniform where as in the haptotaxis case seems to be the equally wide in the protruding and the retracting part of the cell.

In the “inner boundary” of the lamellipodium, which has more of a modelling rather than a biological interpretation, we notice similarities both in shape and size. The shape and size of this inner area, determine the contractile myosin forces (see [6] for modelling details) and we can safely deduce that it is similar in the two cases. Any differences hence in the size and shape of the (full) cell are due to external influences.
**Experiment 1.5.2.** The second comparison case is visualized in Fig. 1.10 and refers to the more dynamic chemotaxis Experiment 1.3.2 and haptotaxis Experiment 1.4.2. Once again the transition shapes of the two cases are qualitatively similar despite stark differences in their biological as well as modelling properties.

In more detail, we notice further similarities between the different experimental settings. In particular, the chemotaxis experiments in Figs. 1.9 and 1.10 exhibit an inner-over-outer area ratio of approximately 0.3, where as in the haptotaxis experiments, the area ratio is approximately 0.45. The exact values depend on the particular parameter set that we use, but they are robust within the biological accepted values, see Table 1.1.

### 1.6 Discussion

We have compared the influence that chemotaxis and haptotaxis have in the lamellipodium driven cell migration. We have used the detailed FBLM to model the influences these biological processes have in the shape and the motility of the cell. For the numerical simulations we have employed a problem specific FEM that we have previously developed.

We have seen that chemotaxis and haptotaxis have significantly different qualitative results on the polymerization rate of the filaments, the friction forces with the substrate, the size of the cell, the width of the lamellipodium, and on the shape of the motile cell.

Although not exhaustive in terms of numerical experimentation, our investigations clearly indicate that the shapes of the migrating cells are more similar than not, between the two cases. This provides with a first indication that, an abstraction and simplification of the cell motility, could possibly merge these two effects under the same paradigm. In effect, this would facilitate the overall effort of simulating the motility of the cells and bring the corresponding research one step closer to deriving a macroscopic model from the particular dynamical properties of single cell dynamics.

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