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An extended Filament Based Lamellipodium Model produces various moving cell shapes in the presence of chemotactic signals

Angelika Manhart^{a,*}, Dietmar Oelz^b, Christian Schmeiser^a, Nikolaos Sfakianakis^c

^a Faculty of Mathematics, University of Vienna, Oskar-Morgenstern Platz 1, 1090 Vienna, Austria

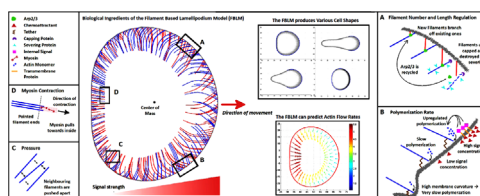
^b Courant Institute of Mathematical Sciences, New York University, 251 Mercer Street, New York, NY 10012-1185, United States

^c Johannes Gutenberg University, Staudingerweg 9, 55099 Mainz, Germany

HIGHLIGHTS

- Highly flexible Filament Based Lamellipodium Model.
- Modeling of filament dynamics, accessory proteins and polymerization rate effects.
- Describes chemotaxis and turning processes.
- Produces various cell shapes depending on the signal transduction process.

GRAPHICAL ABSTRACT



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ABSTRACT

The Filament Based Lamellipodium Model (FBLM) is a two-phase two-dimensional continuum model, describing the dynamics of two interacting families of locally parallel actin filaments (Oelz and Schmeiser, 2010b). It contains accounts of the filaments' bending stiffness, of adhesion to the substrate, and of cross-links connecting the two families.

An extension of the model is presented with contributions from nucleation of filaments by branching, from capping, from contraction by actin–myosin interaction, and from a pressure-like repulsion between parallel filaments due to Coulomb interaction. The effect of a chemoattractant is described by a simple signal transduction model influencing the polymerization speed. Simulations with the extended model show its potential for describing various moving cell shapes, depending on the signal transduction procedure, and for predicting transients between non-moving and moving states as well as changes of direction.

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1. Introduction

In contact to flat adhesive substrates, many cell types tend to develop thin protrusions, called lamellipodia (Small et al., 2002). These are very dynamic structures, supported by a network of filaments of polymerized actin, which is continuously remodeled by polymerization and depolymerization as well as by the building and breaking of cross-links and adhesive bonds to the substrate.

* Corresponding author. Tel.: +43 1427750716.

E-mail addresses: angelika.manhart@univie.ac.at (A. Manhart), dietmar@cims.nyu.edu (D. Oelz), christian.schmeiser@univie.ac.at (C. Schmeiser), sfakiana@uni-mainz.de (N. Sfakianakis).

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Polarization of cells due to internal instabilities (Svitkina et al., 1997; Yam et al., 2007) or to external signals (Postlethwaite and Keski-Oja, 1987; Gerisch and Keller, 1981; Iijima et al., 2002; Zigmond and Hirsch, 1973) might lead to crawling movement along the substrate. This or similar types of motility can be observed in various cell types in natural environments, such as fibroblasts, tumor cells, leukocytes, keratocytes, and others.

The dynamics of the filament network is a complicated process, and effects to be taken into account, additional to what has been mentioned above, include the nucleation of new filaments by branching off existing filaments, deactivation of filaments by capping, and contraction by actin–myosin interaction (Lauffenburger and Horwitz, 1996, references therein, and more references below).

Various attempts have dealt with the formulation of mechanical and, consequentially, mathematical models for the involved sub-processes as well as for the whole integrated system (Mogilner, 2009 and references therein). On the level of individual actin filaments, polymerization, depolymerization, branching, and capping are typically modeled as stochastic processes, where the regulation of polymerization as the key process pushing the lamellipodium outward has received the biggest attention (Mogilner and Oster, 1996; Peskin et al., 1993). Models based on individual filaments have provided possible explanations for various phenomena, such as the motility of pathogens in host cells (Mueller et al., 2014). For the description of the morphology dynamics of whole lamellipodia these models are too complex, however. Therefore, continuum models for the mechanics of the filament network have been used, where the choice of model is typically guided by the expected rheological properties, such as viscoelasticity or active contraction due to actin–myosin interaction (Rubinstein et al., 2005; Mogilner et al., 2001; Alt and Dembo, 1999; Gracheva and Hans, 2004).

This work is a continuation of previous efforts (Oelz and Schmeiser, 2010b) to systematically derive a continuum model from filament based descriptions by an averaging process similar to homogenization of materials with microstructure. This allows to include detailed knowledge or assumptions on all subprocesses. We discuss the modeling assumptions of the *Filament Based Lamellipodium Model* (FBLM), starting with those aspects, which are taken from Oelz and Schmeiser (2010b) without changes.

Geometry: As common in homogenization, the averaging process is facilitated by idealizing assumptions on the microstructure. For lamellipodia, the two main assumptions are a restriction to a two-dimensional model motivated by the observed small aspect ratios (100–200 nm thickness, tens of microns lateral extension, Small et al., 2002) and the idealization to a network consisting of two families of locally parallel filaments crossing each other transversally. The latter assumption is supported by experimental evidence for steadily moving cells (Winkler et al., 2012). It has to be conceded, however, that it is questionable in certain conditions such as retracting lamellipodia (Koestler et al., 2008).

It is assumed that the whole cell is surrounded by the lamellipodium, whose width might vary along the cell periphery. Mathematically speaking, the lamellipodium has the topology of a ring lying between two curves, the outer one representing the *leading edge* and the inner one an artificially drawn boundary between the lamellipodium and the rest of the cell, roughly defined by a minimum actin density. More precisely, two non-identical inner boundaries for the two filament families are allowed.

Actin filaments are polar with so-called *barbed* and *pointed ends*. All barbed ends are assumed to meet the leading edge (Small et al., 1978).

Filament mechanics: Filaments are assumed to resist bending. More precisely, they are modeled as quasi-stationary Euler–Bernoulli beams. They are assumed to be inextensible (Gittes et al., 1993).

Cross-links: The mechanical stability of the network largely relies on the existence of cross-links between the two families. Candidates for cross-linkers are proteins such as filamin (Nakamura et al., 2007), but also the Arp2/3 complex providing the connection between filaments at branch points (Mullins et al., 1998). It is assumed that cross-linking is dynamic with the building and breaking of cross-links as stochastic processes. While attached, cross-links are assumed as elastic, providing resistance against relative translational as well as rotational movement (away from an equilibrium angle) of the two filament families (Schwaiger et al., 2004). Characteristic life times of cross-links are assumed to be small compared to the dynamics induced by actin polymerization. The corresponding limiting process, which has been carried out in Oelz and Schmeiser (2010b), leads to a friction model for the interaction between the filament families.

Adhesion to the substrate: Transmembrane protein complexes with integrins as their most important constituent provide adhesive connections between the cytoskeleton and the substrate (Li et al., 2003; Pierini et al., 2000). Similar to cross-links it is assumed that these adhesions are transient with relatively small recycling times, such that the averaged effect is friction between the actin network and the substrate. The short life time of adhesions is another questionable assumption, only satisfied for fast moving cells, where so-called *focal adhesions*, i.e. large and very stable adhesion complexes, do not occur.

The FBLM of Oelz and Schmeiser (2010b) is still rather far from a complete description of all relevant processes. Some of these gaps are filled by the extensions below. Most importantly, the total number of filaments is kept fixed and their length distribution is prescribed in Oelz and Schmeiser (2010b). Here, filaments will be added by branching and removed by capping and subsequent decomposition. The length distribution will be determined by a quasi-equilibrium between polymerization and severing. In Oelz and Schmeiser (2010b) cell size is regulated by a model for the effect of membrane tension. Here, this will be replaced by a contractive force in the cell center due to actin–myosin interaction. In certain applications it might be appropriate to combine these two effects. A further extension is a little speculative from a modeling point of view, but stabilizes the FBLM: We introduce a repulsive effect between parallel filaments of the same family, motivated by Coulomb interaction caused by the significant charges distributed along filaments. Finally, instead of a given fixed polymerization speed as in Oelz and Schmeiser (2010b), a model will be formulated involving both the effect of a chemo-tactic signal and of local leading edge bending. More details about these extensions are given in the following paragraphs.

Polymerization and degradation: A desired polymerization speed is determined between a minimal and a maximal value, depending on the local concentration of an activator like PIP₃, determined by a simple signal transduction model for a given chemoattractant distribution along the leading edge. The desired polymerization speed is modified by the pushing force depending on the curvature of the leading edge (see Fig. 1B).

Several degradation processes of filaments are known. Aided by proteins of the ADF/cofilin family and other severing proteins like gelsolin (Chaponnier et al., 1986), they can depolymerize at the pointed ends (Carlier et al., 1997), or bigger pieces of actin can be removed. We assume a severing process (see Fig. 1A), a mathematical description of which will lead to formulas for the filament length distribution, replacing the ad hoc approximations used in Oelz and Schmeiser (2010b).

Branching and capping: In a lamellipodium, new filaments need to be created in order to maintain a polarized state. New filaments are nucleated by branching off existing filaments of the other family at or near to the leading edge (*dentritic nucleation model* Mullins et al., 1998; Svitkina and Borisy, 1999). To form a branch the presence of the Actin-Related Protein-2/3 Complex (Arp2/3) at the membrane is necessary. Arp2/3 needs to be activated by nucleation promoting factors. Activated Arp2/3 is incorporated in the branches and later (e.g. upon filament degradation) reenters the cytoplasm, from which it is again recruited to the membrane (Machesky and Insall, 1998). Finally filaments can be capped at their branched ends by capping proteins (Weeds and Maciver, 1993), which blocks further polymerization (see Fig. 1A). The addition and removal of filaments had not been taken into account in Oelz and Schmeiser (2010b).

Confinement: As a consequence of polymerization and adhesion, cells would spread indefinitely according to the model components described so far. In Oelz and Schmeiser (2010b) cell confinement has been modeled as a consequence of membrane tension. However, there is some experimental evidence (Svitkina

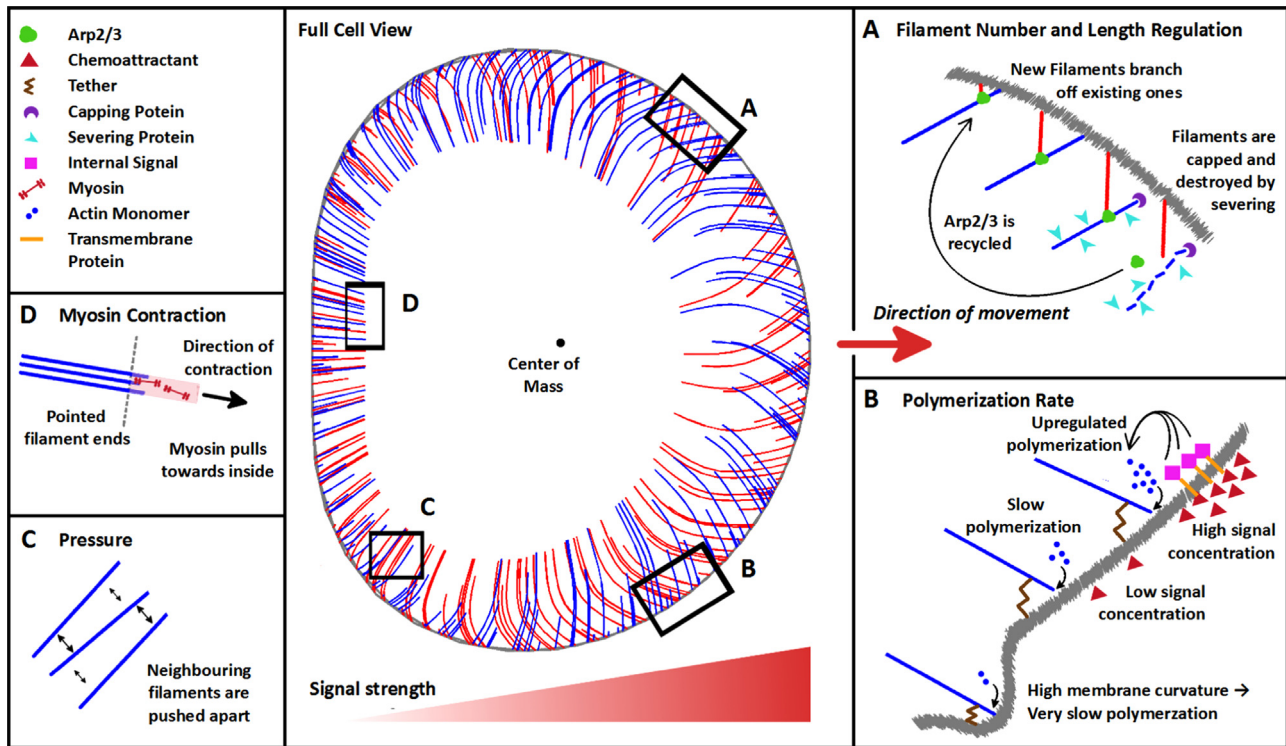


Fig. 1. New ingredients to the FBLM.

et al., 1997) that confinement is mostly due to contractive effects caused by actin–myosin interaction in the rear of the lamellipodium. Myosin has the ability to utilize energy to move towards the barbed ends of actin and because of its bipolar structure this leads to contraction of antiparallel actin filaments. This mechanism plays an important role in cell movement, because it allows the cell to pull its rear parts (Tojkander et al., 2012; Mitchison and Cramer, 1996; Jay et al., 1995; Chen, 1981).

We assume that the artificial inner boundary of the simulated lamellipodium is chosen such that the actin–myosin interaction takes place in the interior region not covered by the lamellipodium model. The lamellipodial actin network is assumed to be connected to an interior network of acto-myosin bundles providing a contractive effect (see Fig. 1D).

Coulomb interaction: So far the model assumed no direct interaction between filaments of the same family. Upon trying to understand the bundling of F-actin, it was discovered that F-actin, similar to DNA, behaves like a polyelectrolyte (Tang et al., 1997, 1996; Tang and Janmey, 1996). This means that F-actin is negatively charged (about $4e/nm$) at physiological conditions, hence there exists a repulsive force between the filaments. On the other hand, it has been shown that certain positively charged polycations, like divalent metal ions and basic polypeptides (Tang and Janmey, 1996), which act as counterions and neutralize the negative charges along the filament, promote filament bundling.

As a modeling assumption, we introduce a repulsive effect between filaments of the same family (see Fig. 1C). The consequential inhibition of bundle formation in the lamellipodium is desired, since this is not our modeling goal at present (although it will be in future work). An additional motivation is the fact that a lack of coupling between filaments of the same family may lead to numerical instabilities, which can be avoided by the diffusive effect caused by repulsion.

The rest of this work is structured as follows. In the following Section 2 the model of Oelz and Schmeiser (2010b) will be recalled. The new aspects will be introduced in Section 3, and

the complete new model will be summarized in Section 4. Finally in Section 5 we will demonstrate the effect of the new terms and the potential of the full new model numerically. The power and flexibility of the model will become especially evident in simulations of the polarization process induced by a chemotactic signal, of steady movement, and of a turning process. Movies of these simulations including visualizations of the stochastic filament dynamics are contained in the Supplementary Material. Examples of moving cell shapes, influenced by the response to the chemotactic signal, are shown.

2. The Filament Based Lamellipodium Model

Detailed derivations of the FBLM presented in this section can be found in Oelz and Schmeiser (2010b) and Oelz et al. (2008), first simulation results in Oelz and Schmeiser (2012), and analytical results for the rotationally symmetric case in Oelz and Schmeiser (2010a).

In the following, the superscripts $+$ and $-$ refer to the two filament families, also called clockwise and, respectively, anti-clockwise. These superscripts will however be omitted, whenever we concentrate on one filament family. Quantities related to the other family will then be indicated by the superscript $*$.

A semi-Lagrangian description of each family is used, where one coordinate α is a filament index varying on a torus (represented by $\alpha \in [0, 2\pi)$) because of the ring topology, and the other coordinate is the negative arc-length s along a filament measured from the leading edge, i.e. $s \in [-L, 0]$ with the maximal (simulated) filament length L . Because of the inextensibility of filaments, s can also be seen as a material coordinate. However, this is only true for fixed time since, by polymerization at the leading edge with speed $v(\alpha, t) \geq 0$ and the consequential inward flow of actin relative to the leading edge, a Lagrangian coordinate would be $\sigma = s + \int_0^t v(\alpha, \tau) d\tau$. For this reason the material derivative (i.e. the

time derivative at fixed (α, σ)

$$D_t = \partial_t - v \partial_s$$

will be used below.

The main unknown in the model is $F(\alpha, s, t) \in \mathbb{R}^2$ which, for fixed α and t , represents a parametrization of the filament with index α at time t . By the inextensibility assumption

$$|\partial_s F(\alpha, s, t)| \equiv 1 \quad \text{for } (\alpha, s) \in B := [0, 2\pi] \times [-L, 0], \quad t \geq 0, \quad (1)$$

it is an arc-length parametrization. More precisely, F represents the deformation of all filaments in an infinitesimal α -interval, where the length distribution of the filaments is determined by the given function $\eta(\alpha, s, t)$, whose value (between 0 and 1) is the fraction of filaments with length at least $|s|$. The assumption that all barbed ends meet the leading edge implies that $\eta(\alpha, 0, t) = 1$ and that η is monotonically increasing as a function of s . Note that $\eta(\alpha, s, t) d(\alpha, s)$ can be interpreted as the total filament length in the infinitesimal coordinate volume $d(\alpha, s)$. In the FBLM formulated below (6), η is a factor in all filament related force terms. For example, a large value of η increases the effective bending stiffness of computational filaments, with the interpretation that loads are distributed over a larger number of filaments. The modeling of the dynamics of $\eta(\alpha, s, t)$ is one of the contributions of this work. In Section 3, Eq. (12) for η will be derived, taking into account the polymerization speed v , branching and filament degradation.

At time t , the lamellipodium is represented by the set $\mathcal{L}(t) = \mathcal{L}^+(t) \cup \mathcal{L}^-(t)$ with $\mathcal{L}^\pm(t) = \{F^\pm(\alpha, s, t) : (\alpha, s) \in B\}$. Note that $\mathcal{L}^+(t)$ and $\mathcal{L}^-(t)$ do not have to be identical. We request, however, that they share the leading edge, which can be motivated by the assumption of tethering of barbed ends to the membrane (“acto-clampin model” Dickinson, 2008; Dickinson and Purich, 2002):

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

The artificial inner boundaries ($s = -L$) might be different.

For the interaction between the two families, the points where filaments cross each other have to be described. This is done on the basis of two assumptions: First, there are no crossings of filaments of the same family, i.e. the map $F^\pm(\cdot, \cdot, t) : B \rightarrow \mathcal{L}^\pm(t)$ is invertible. In particular, we assume that

$$\det(\partial_\alpha F^\pm, \partial_s F^\pm) > 0 \quad (3)$$

holds, corresponding to a clockwise parametrization by α . Second, for each pair of filaments from different families there is at most one crossing, which is transversal. We need representations of the set $\mathcal{L}^+(t) \cap \mathcal{L}^-(t)$ in the coordinate domains. First we identify all pairs of crossing filaments:

$$\begin{aligned} \mathcal{C}(t) := & \{(\alpha^+, \alpha^-) \in [0, 2\pi]^2 : \exists s^\pm(\alpha^+, \alpha^-, t) : \\ & F^+(\alpha^+, s^+(\alpha^+, \alpha^-, t), t) = F^-(\alpha^-, s^-(\alpha^+, \alpha^-, t), t)\}. \end{aligned}$$

Then we define the parameter domains for both families such that $F^\pm(B_C^\pm(t), t) = \mathcal{L}^\pm(t) \cap \mathcal{L}^\mp(t)$:

$$B_C^\pm(t) := \{(\alpha^\pm, s^\pm(\alpha^+, \alpha^-, t)) : (\alpha^+, \alpha^-) \in \mathcal{C}(t)\} \subseteq B.$$

Note that, by our assumptions, the transformations

$$(\alpha^+, \alpha^-) \mapsto (\alpha^\pm, s^\pm(\alpha^+, \alpha^-, t)) \quad (4)$$

from $\mathcal{C}(t)$ to $B_C^\pm(t)$ are invertible and can be combined to transformations $\psi^\pm : B_C^\mp(t) \rightarrow B_C^\pm(t)$ with the property

$$F^\mp = F^\pm \circ \psi^\pm \quad \text{on } B_C^\mp(t) \quad (\text{for fixed } t). \quad (5)$$

The positions and deformations of the filaments are computed on the basis of a quasi-stationary force balance obtained by minimizing a potential energy functional, which contains contributions from the bending of filaments, the stretching and twisting of cross-links, the stretching of substrate adhesions, and the membrane tension. This is coupled to age-structured population models

for the distributions of cross-links and adhesions, assuming the building and breaking of these connections as stochastic processes. The resulting model involves continuous delay terms, since, for the computation of the stretching forces, past deformations of the filaments are needed. With the model in this form, numerical simulations would be very expensive, partially also because it mixes different length scales. Whereas the effects of interest occur on the (μm) scale of the width of the lamellipodium, the stretching of cross-links and adhesions occurs on molecular (nm) scales. This implies that motion on the lamellipodium scale of the two filament families relative to each other and relative to the substrate is only possible, if the turnover of cross-links and adhesions is fast compared to other mechanisms (e.g. polymerization and depolymerization).

The corresponding limit has been carried out formally (Oelz and Schmeiser, 2010b) and rigorously for a simplified model problem (Milišić and Oelz, 2011). It leads to a friction model. The original idea seems to be more than 50 years old and has been formulated first for the derivation of models for rubber friction (Schallamach, 1963). Recently it has been used for the modeling of the plastic reorganization of tissues due to cell–cell adhesion dynamics (Preziosi and Vitale, 2011).

The assumption of fast turnover of substrate adhesions is reasonable for fast moving cells such as fish keratocytes, but certainly not satisfied for focal adhesions, i.e. large stable and long lived adhesion complexes as found, e.g., in fibroblasts. The limiting procedure removes not only the delay terms, but also the coupling to the population models, which can be solved explicitly in the limit.

The variational procedure involves the formulation of a Lagrangian functional where, besides the potential energy, also an account of the constraints (1) and (2) is included. Variation of this functional and, subsequently, the limit of fast cross-link and adhesion turnover described above lead to a weak formulation of the problem for F :

$$\begin{aligned} 0 = & \int_0^{2\pi} \left[\mu^M (C - C_0)_+ \frac{\partial_\alpha F}{|\partial_\alpha F|} \cdot \partial_\alpha(\delta F) \mp \lambda_{\text{tether}} \nu \cdot \delta F \right]_{s=0} d\alpha \\ & + \int_B \left[\mu^B \partial_s^2 F \cdot \partial_s^2(\delta F) + \mu^A D_t F \cdot \delta F + \lambda_{\text{inext}} \partial_s F \cdot \partial_s(\delta F) \right] \eta d(\alpha, s) \\ & + \int_{\mathcal{C}(t)} \left[\mu^S (D_t F - D_t^* F^*) \cdot \delta F \right. \\ & \left. \mp \mu^T (\varphi - \varphi_0) \partial_s F^\pm \cdot \partial_s(\delta F) \right] \eta \eta^* d(\alpha, \alpha^*), \quad (6) \end{aligned}$$

for all variations δF , where the first line contains contributions from the leading edge, and the convention $(F_1, F_2)^\pm = (-F_2, F_1)$ is used. The first term corresponds to the tension of the membrane with the total length of the leading edge,

$$C := \int_0^{2\pi} |\partial_\alpha F^+(\alpha, 0, t)| d\alpha = \int_0^{2\pi} |\partial_\alpha F^-(\alpha, 0, t)| d\alpha,$$

its prescribed equilibrium value C_0 , and an elasticity coefficient μ^M . It is the variation of an energy describing the leading edge just as an elastic rubber band stretched around the barbed ends of the actin filaments (see Oelz and Schmeiser, 2010b). The Lagrange multiplier for the constraint (2) is a function defined along the leading edge denoted by λ_{tether} , and ν is the unit outward normal along the leading edge. The second line of (6) deals with forces within individual filaments: resistance against bending with bending modulus μ^B , friction with the substrate caused by adhesions with a friction coefficient μ^A , and a tangential force due to the inextensibility constraint (1) with Lagrange multiplier λ_{inext} . The third and fourth lines of (6) describe the effects of cross-links between the two families with a friction term caused by resistance against stretching of cross-links with friction coefficient μ^S and a turning force term caused by resistance of twisting cross-links

away from the equilibrium angle φ_0 . The angle between the filaments is determined by

$$\cos \varphi(\alpha, \alpha^*, t) = \partial_s F(\alpha, s(\alpha, \alpha^*, t), t) \cdot \partial_s F^*(\alpha^*, s^*(\alpha, \alpha^*, t), t),$$

and μ^T is the corresponding stiffness parameter. The above-mentioned limit of fast adhesion and cross-link turnover provides explicit formulas for the coefficients μ^A , μ^S , and μ^T in terms of mechanical and chemical properties of adhesion and cross-link molecules.

A strong formulation of the Euler–Lagrange equations requires to transform the domain of the last integral in (6) to B . For this purpose, we use the maps from $\mathcal{C}(t)$ to $B_C(t)$ described in (4) and introduce the modified friction coefficient and stiffness parameter

$$\widehat{\mu^S} = \begin{cases} \mu^S \left| \frac{\partial \alpha^*}{\partial s} \right| & \text{in } B_C(t), \\ 0 & \text{else,} \end{cases} \quad \widehat{\mu^T} = \begin{cases} \mu^T \left| \frac{\partial \alpha^*}{\partial s} \right| & \text{in } B_C(t), \\ 0 & \text{else.} \end{cases} \quad (7)$$

The expression $\frac{\partial \alpha^*}{\partial s}$ refers to the inverse of the map given in (4). The strong formulation is then given by

$$0 = \mu^B \partial_s^2 (\eta \partial_s^2 F) + \mu^A \eta D_t F - \partial_s (\eta \lambda_{\text{inext}} \partial_s F) + \widehat{\mu^S} \eta \eta^* \Delta V \pm \partial_s (\widehat{\mu^T} \eta \eta^* (\varphi - \varphi_0) \partial_s F^\perp),$$

where the computation of the relative velocity $\Delta V = D_t F - D_t^* F \circ \psi^*$ and of the angle between the families, $\cos \varphi = \partial_s F \cdot (\partial_s F^* \circ \psi^*)$, requires the transformation ψ^* between the coordinate domains.

The corresponding boundary conditions are

$$\begin{aligned} & -\mu^B \partial_s (\eta \partial_s^2 F) + \eta \lambda_{\text{inext}} \partial_s F \mp \widehat{\mu^T} \eta \eta^* (\varphi - \varphi_0) \partial_s F^\perp \\ & = \begin{cases} 0 & \text{for } s = -L, \\ \pm \lambda_{\text{tether}} \nu + \mu^M (C - C_0) + \partial_\alpha \left(\frac{\partial_\alpha F}{|\partial_\alpha F|} \right) & \text{for } s = 0, \end{cases} \\ & \eta \partial_s^2 F = 0 \quad \text{for } s = -L, 0. \end{aligned}$$

3. Modifications and extensions

3.1. Length distribution and filament number regulation

In the model of Oelz and Schmeiser (2010b), the filament number was conserved and the length distribution of filaments was prescribed with a fixed maximum length. In this section the model will be extended to include the effects of capping, branching, and severing on the filament number and length distribution. The results partially depend on the polymerization speed, the choice of which will be discussed below.

The changes in filament numbers by branching and capping require a different interpretation of the length distribution $\eta(\alpha, s, t)$. For fixed s , $\eta(\alpha, s, t)$ will be considered as the number density of filaments of length at least $-s$ in terms of α . Instead of the uniform distribution $\eta(\alpha, 0, t) d\alpha = d\alpha$ of barbed ends, values of $\eta(\alpha, 0, t)$ different from one are allowed. The density of barbed ends per leading edge length is then given by

$$\bar{\rho}(\alpha, t) = \frac{\eta(\alpha, 0, t)}{|\partial_\alpha F(\alpha, 0, t)|}$$

For the other family, the barbed end density $\bar{\rho}^*(\alpha^*, t)$ is defined analogously. With $s=0$, the map between the coordinate domains (see (5)) reduces to a map $\alpha^*(\alpha, t)$, and in the following $\bar{\rho}^*$ means $\bar{\rho}^*(\alpha^*(\alpha, t), t)$. In the rest of this subsection we shall deal with fixed values of α . The dependence on α will therefore be suppressed for ease of reading.

We start with the evolution of the number of barbed ends and assume that it depends on the barbed end densities per unit

length:

$$\partial_t \eta(0, t) = f(\bar{\rho}, \bar{\rho}^*) |\partial_\alpha F(0, t)| \quad (8)$$

where $f(\bar{\rho}, \bar{\rho}^*)$ is the change of barbed end number per unit length and time, modeling the effects of branching and capping at the barbed ends. Capped filaments become inactive and are assumed to be depolymerized very fast, such that they can be eliminated from the system immediately.

It is instructive to rewrite (8) in terms of the length $x = \int |\partial_\alpha F| d\alpha$ along the leading edge, instead of the Lagrangian variable α . With the lateral flow velocity $v_l = \int \partial_t |\partial_\alpha F| d\alpha$ (implicitly given as part of the filament dynamics), it can be written as

$$\partial_t \bar{\rho} + \partial_x (v_l \bar{\rho}) = f. \quad (9)$$

Branching is assumed to be limited by the availability of activated Arp2/3 complex at the leading edge with density $a(t)$ (number/leading edge unit length). Its equilibrium value in the absence of branching is denoted by a_0 , the branching rate at equilibrium Arp2/3 density by κ_{br} , and the capping rate by κ_{cap} . This leads to the model

$$f = \kappa_{\text{br}} \frac{a}{a_0} \bar{\rho}^* - \kappa_{\text{cap}} \bar{\rho}.$$

With the rate c_{rec} of recruitment and activation of Arp2/3 from the cytoplasm, the evolution of Arp2/3 at the leading edge is governed by

$$\frac{da}{dt} = c_{\text{rec}} \left(1 - \frac{a}{a_0} \right) - \kappa_{\text{br}} \frac{a}{a_0} (\bar{\rho} + \bar{\rho}^*),$$

The second term reflects the fact that activated Arp2/3 is incorporated into branches of both families. We assume that the Arp2/3 dynamics is fast compared to branching and capping and use the quasi-steady (Michaelis–Menten) approximation

$$a = \frac{a_0 c_{\text{rec}}}{c_{\text{rec}} + \kappa_{\text{br}} (\bar{\rho} + \bar{\rho}^*)}, \quad f(\bar{\rho}, \bar{\rho}^*) = \frac{\kappa_{\text{br}} c_{\text{rec}} \bar{\rho}^*}{c_{\text{rec}} + \kappa_{\text{br}} (\bar{\rho} + \bar{\rho}^*)} - \kappa_{\text{cap}} \bar{\rho}.$$

The model (9) has already been used in Grimm et al. (2003) with a prescribed lateral flow velocity and with $f = \beta \bar{\rho}^* / (\bar{\rho} + \bar{\rho}^*) - \gamma \bar{\rho}$. A significant difference between our model and Grimm et al. (2003) is in the branching rate: For $\bar{\rho} = 0$ and small values of $\bar{\rho}^*$, the branching rate of Grimm et al. (2003) is constant, i.e., not limited by the number of barbed ends of the other family, while in our model it is approximately $\kappa_{\text{br}} \bar{\rho}^*$.

An indication of the qualitative behavior of the model can be obtained from considering a situation, where the barbed end densities do not vary along the leading edge and are governed by the ODE system

$$\dot{\bar{\rho}} = f(\bar{\rho}, \bar{\rho}^*), \quad \dot{\bar{\rho}^*} = f(\bar{\rho}^*, \bar{\rho}). \quad (10)$$

It is easily seen that for $\kappa_{\text{br}} < \kappa_{\text{cap}}$, i.e. capping exceeds branching, the densities converge to 0, otherwise the non-trivial steady state

$$\bar{\rho} = \bar{\rho}^* = \frac{c_{\text{rec}}}{2} \left(\frac{1}{\kappa_{\text{cap}}} - \frac{1}{\kappa_{\text{br}}} \right) =: \bar{\rho}_{\text{ref}}, \quad (11)$$

is stable. In separate work (Manhart and Schmeiser, 2015) we prove that this qualitative behavior carries over to the corresponding transport-reaction system with prescribed lateral flow velocities.

The length distribution $\eta(s, t)$ of filaments is influenced by branching and capping through the model (8) for $\eta(0, t)$, but also directly by capping, which removes whole filaments by our above assumptions. We make the modeling decision that newly branched filaments are capped preferentially. This means that if branching exceeds capping, i.e., $f(\bar{\rho}, \bar{\rho}^*) \geq 0$, we interpret f as an effective net rate of production of new branches without further capping, whereas in the opposite case no new filaments are

nucleated and $-f$ is an effective rate of capping, affecting already existing filaments with a probability independent of their length.

Degradation of filaments is also assumed to be facilitated by the action of severing proteins such as gelsolin (Chaponnier et al., 1986) or ADF/cofilin (Roland et al., 2008), cutting filaments at random positions. Similar to the capping process, we assume that rear parts of filaments, which have been cut off, are completely decomposed immediately.

Instead of using η as unknown, it is more intuitive to write the model in terms of the density $u(s, t) = \partial_s \eta(s, t)$ of filaments with respect to their length $-s$. Following Edelstein-Keshet and Ermentrout (1998), Ermentrout and Edelstein-Keshet (1998), and Roland et al. (2008) for the severing part, we use the model

$$D_t u = \kappa_{\text{sev}} \int_{-\infty}^0 [H(s-s')u' - H(s'-s)u] ds' - \kappa_{\text{cap,eff}} u$$

$$= \kappa_{\text{sev}} \left(\int_{-\infty}^s u' ds' + su \right) - \kappa_{\text{cap,eff}} u,$$

where u' abbreviates $u(s', t)$. Cutting of a filament of length $-s$ at the new length $-s'$ occurs with the rate $\kappa_{\text{sev}} H(s'-s)$ leading to a total severing rate $-\kappa_{\text{sev}} s$ proportional to the length. This is the simplest possible model. More elaborate severing rates, e.g., with an account of aging of actin filament subunits (Roland et al., 2008), could be included easily.

The effective capping rate is given, according to the discussion above, by

$$\kappa_{\text{cap,eff}} = \frac{(-f(\bar{\rho}, \bar{\rho}^*))_+}{\bar{\rho}}.$$

It remains to rewrite the model in terms of $\eta(s, t) = \int_{-\infty}^s u(\sigma, t) d\sigma$:

$$D_t \eta = \kappa_{\text{sev}} s \eta - \kappa_{\text{cap,eff}} \eta.$$

For a constant polymerization speed v this equation can be solved explicitly by the method of characteristics:

$$\eta(s, t) = \eta(0, t+s/v) \exp\left(-\frac{\kappa_{\text{sev}} s^2}{2v} - \int_{t+s/v}^t \kappa_{\text{cap,eff}}(\tau) d\tau\right), \quad (12)$$

where $\eta(0, t)$ is given as the solution of (8). Assuming that the changes of the polymerization velocity are slow compared to the filament dynamics, this formula is a valid approximation also for time dependent velocities $v(t)$.

Finally, the maximum simulation length L of filaments is defined by a cut-off at small actin densities, i.e. a value η_{min} for η . With the rough approximations of replacing $\eta(0, t+s/v)$ by $\eta(0, t)$ and $\kappa_{\text{cap,eff}}(\tau)$ by $\kappa_{\text{cap,eff}}(t)$, L can be computed explicitly:

$$L(t) := -\frac{\kappa_{\text{cap,eff}}(t)}{\kappa_{\text{sev}}} + \sqrt{\frac{\kappa_{\text{cap,eff}}(t)^2}{\kappa_{\text{sev}}^2} + \frac{2v(t)}{\kappa_{\text{sev}}} \log\left(\frac{\eta(0, t)}{\eta_{\text{min}}}\right)}, \quad (13)$$

resulting in the time dependent coordinate domain

$$B(t) = \{(\alpha, s) : 0 \leq \alpha < 2\pi, -L(\alpha, t) \leq s \leq 0\}. \quad (14)$$

Most notably, faster polymerization leads to wider lamellipodia.

3.2. Myosin contraction

Supported by the fact that actin–myosin interaction is concentrated at the rear of the lamellipodium, we assume that in the outer lamellipodium region covered by the FBLM this effect is negligible. Therefore we model the action of myosin only as forces pulling the (artificial) pointed ends of lamellipodial actin filaments along the inner boundary of the simulation domain. Neglecting the effect of other forces (such as substrate adhesion) in the interior region, the pulling forces are assumed to add up to zero by the action–reaction principle.

The question of an appropriate direction for the pulling forces arises. We consider two scenarios: one where the contractile bundles pull the filaments tangentially, and one where they pull towards a central point, chosen as the center of actin mass (without having particularly strong arguments for this choice). Although one can argue for tangential pulling, which does not perturb the directional order of filaments in the lamellipodium, this choice has two disadvantages: If filaments get too tangential to the inner boundary of the lamellipodium, tangential pulling fails to control the size of the cell. Secondly, tangential pulling is a slightly unstable process, since it might reinforce any small deflections of the pointed ends. For those reasons and in order to allow more flexibility of the model, we include a mixture of both choices.

We again use the notation of dropping the superscript \pm for the family under discussion and using $*$ for the other one. The magnitude of the tangential force acting on the filament with index α is denoted by $f_{\text{tan}}(\alpha)$ and that of the centripetal force by $f_{\text{in}}(\alpha)$. We define $V(\alpha)$ as the normalized vector pointing from the center of mass

$$C_M := \int_B \eta F d(s, \alpha) \left(\int_B \eta d(s, \alpha) \right)^{-1}$$

to the end $F(\alpha, -L(\alpha))$ of filament α . The forces can be included in the boundary conditions as

$$-\mu^B \partial_s (\eta \partial_s^2 F) + \eta \lambda_{\text{inext}} \partial_s F \mp \eta \eta^* \mu^T (\phi - \phi_0) \partial_s F \pm$$

$$= \eta (f_{\text{tan}} \partial_s F + f_{\text{in}} V), \quad s = -L.$$

We postulate a scalar positive quantity A , which measures the size of the contraction effect and which is chosen as $A := \mu^{\text{IP}} (A_c - A_0)_+$ with the area A_c encircled by the lamellipodium and its equilibrium value A_0 .

The forces $f_{\text{tan}}(\alpha)$ and $f_{\text{in}}(\alpha)$ are determined by the conditions that

1. the total force should be close to the current contractility A ,
2. it should be split between the tangential and centripetal contributions according to a weight $\gamma \in [0, 1]$, and
3. the sum of all forces has to be zero.

Mathematically this is realized by minimizing

$$\int_0^{2\pi} \eta(s = -L) \left[\frac{(f_{\text{tan}} - \gamma A)^2}{\gamma} + \frac{(f_{\text{in}} - (1 - \gamma) A)^2}{1 - \gamma} \right] d\alpha$$

with the constraint

$$\int_0^{2\pi} \eta(s = -L) [f_{\text{tan}} \partial_s F(s = -L) + f_{\text{in}} V] d\alpha = 0, \quad (15)$$

giving

$$f_{\text{tan}}(\alpha) = \gamma A [1 - \mu \cdot \partial_s F(\alpha, -L(\alpha))], \quad f_{\text{in}}(\alpha) = (1 - \gamma) A [1 - \mu \cdot V(\alpha)], \quad (16)$$

with

$$\mu = \left(\int_0^{2\pi} \eta [\gamma \partial_s F \otimes \partial_s F + (1 - \gamma) V \otimes V] d\alpha \right)^{-1} \int_0^{2\pi} \eta [\gamma \partial_s F + (1 - \gamma) V] d\alpha.$$

In Section 5 it will be shown that myosin pulling can effectively control cell size, and that the contraction force allows to produce moving cells. For these reasons we neglect the contribution of membrane tension.

3.3. Filament repulsion

We consider a repulsive effect between parallel filaments caused by Coulomb interaction. The presence of mobile charge

carriers in the cytoplasm leads to Debye screening with a typical Debye length in the range of a few nm, such that only local Coulomb interaction can be assumed, leading to a pressure-like repulsion effect. The electrostatic energy

$$U_{\text{pressure}} = \int_{\mathcal{L}} \rho \Phi \, dA$$

is added to the potential energy, where $\mathcal{L}(t)$ is the area covered by the filament family under discussion at time t (again dropping the superscript \pm), $\rho \, dA$ is the filament length in the infinitesimal area element dA , with

$$\rho = \frac{\eta}{\det(\partial_\alpha F, \partial_s F)} \quad (17)$$

(where (3) has been used) and Φ is the electrostatic potential (see Ramic, 2011 for a derivation from a microscopic model based on individual filaments). A quasineutral approximation (justified by the relative smallness of the Debye length) and an equilibrium assumption for the mobile charge carriers result in a model for the electrostatic potential of the form $\Phi = \Phi(\rho)$. As example, the Boltzmann–Poisson model for the mobile carrier density leads to $\Phi = \mu^P \log(\rho)$, $\mu^P > 0$.

For the purpose of computing its variation, the electrostatic energy is written in terms of the quasi-Lagrangian coordinates,

$$U_{\text{pressure}}[F] = \int_{B(t)} \Phi(\rho) \eta \, d(\alpha, s),$$

with the variation in the direction δF ,

$$\delta U_{\text{pressure}}[F] \delta F = - \int_B p(\rho) [\det(\partial_\alpha F, \partial_s(\delta F)) + \det(\partial_\alpha(\delta F), \partial_s F)] \, d(\alpha, s).$$

The considerations below will show that for stability reasons the pressure $p(\rho) = \Phi'(\rho)\rho^2$ has to be a nondecreasing function of the density ρ , which holds for the Boltzmann–Poisson model $p(\rho) = \mu^P \rho$. Although we expect the pressure only to act in the direction orthogonal to the filaments, this consideration has not entered the discussion so far. However, the action of the pressure along filaments is eliminated by the (incompressibility) constraint (1).

Model problem: It is instructive to look at a one-dimensional model problem, where points with Lagrangian label $\alpha \in \mathbb{R}$ move along a line with positions $x(\alpha, t) \in \mathbb{R}$ (assumed a strictly increasing function of α). The density of points is then given by $\rho = 1/\partial_\alpha x$. The electrostatic energy takes the form $U_{\text{pressure}}[x] = \int \Phi(1/\partial_\alpha x) \, d\alpha$. Its (L^2 -)gradient is given by $\partial_\alpha p(\rho)$. If only the Coulomb interaction and friction (i.e. adhesions) are taken into account, the dynamics is governed by the gradient flow

$$\partial_t x = -\partial_\alpha p(\rho).$$

With the continuity equation (in Eulerian coordinates) $\partial_t \rho + \partial_x(\rho \partial_t x) = 0$, this can be rewritten in Eulerian coordinates as

$$\partial_t \rho = \partial_x^2 p(\rho) = \partial_x(p'(\rho) \partial_x \rho).$$

This is a nonlinear diffusion equation, where nonnegativity of the diffusivity $p'(\rho)$ is necessary for stability.

For the lamellipodium model, we may hope that the pressure term, by causing diffusion in the α -direction, avoids intersections within a family and thereby stabilizes the system by ensuring that the modeling assumptions are not destroyed by the dynamics. This stabilizing effect is sometimes useful for numerical simulations as demonstrated in Section 5.

3.4. Polymerization rate

Polymerization rates and, consequentially, polymerization speeds $v(\alpha, t)$ are subject to different regulatory mechanisms. We consider reaction to chemotactic signals, where the cell senses

concentration gradients of a chemoattractant and translates them to varying polymerization rates. This leads to cell polarization and directed movement. The chemoattractant binds to receptors on the cell membrane that can trigger signaling pathways producing intracellular gradients along the membrane reflecting the distribution of occupied receptors. For example, higher concentrations of PIP₃ have been observed towards chemotactic signals at the leading edge of *Dictyostelium discoideum* and of neutrophils (King and Insall, 2009). This in turn is expected to induce a local upregulation of actin polymerization (Iijima et al., 2002; Weiner et al., 1999).

We consider constant planar chemoattractant gradients with the chemoattractant concentration $S(x, y) = S_0 + S_1(x \cos(\varphi_{ca}) + y \sin(\varphi_{ca}))$, where S_1 determines the strength of the gradient and φ_{ca} its direction. We model a chemotactic response independent of the strength of the chemoattractant gradient. A normalized internal quantity defined along the leading edge is given by

$$d_{ca}(\alpha, t) = \frac{S(F(\alpha, 0, t)) - \min_{\beta \in [0, 2\pi]} S(F(\beta, 0, t))}{\max_{\beta \in [0, 2\pi]} S(F(\beta, 0, t)) - \min_{\beta \in [0, 2\pi]} S(F(\beta, 0, t))}$$

Typically, PIP₃ is only observed at a part of the leading edge, possibly as consequence of a thresholding phenomenon of the signaling pathway. To account for this, we choose a threshold $c \in [0, 1]$ and define

$$I(\alpha, t) = \begin{cases} \frac{d_{ca}(\alpha, t) - c}{1 - c} & \text{for } d_{ca}(\alpha, t) > c, \\ 0 & \text{else,} \end{cases} \quad (18)$$

which can be interpreted as a normalized PIP₃ concentration. The desired polymerization speed is chosen between prescribed minimal and maximal values:

$$v_{\text{opt}}(\alpha, t) = v_{\text{min}} + I(\alpha, t)(v_{\text{max}} - v_{\text{min}}).$$

Finally, the polymerization speed is reduced by the force required to bend the leading edge outwards. On the other hand, due to filament tethering, we expect some acceleration of polymerization at leading edge segments which are curved inwards. These effects are described by an ad hoc model for the polymerization speed v , depending on the signed local curvature $\kappa(\alpha)$ (positive for convex leading edge regions):

$$v = \frac{2v_{\text{opt}}}{1 + \exp(\kappa/\kappa_{\text{ref}})}$$

4. Full new model

The functions and variables used are the same as in the original model described in Section 2. To account for the different width of the lamellipodium for different filament indices α , we replace B by

$$B(t) := \{(\alpha, s) \mid \alpha \in [0, 2\pi], s \in [-L(\alpha, t), 0]\}$$

where $L(\alpha, t)$ is given by (13), as already introduced in (14).

The full weak formulation reads

$$\begin{aligned} 0 = & \int_{B(t)} \left(\underbrace{\mu^B \partial_s^2 F \cdot \partial_s^2 \delta F}_{\text{bending}} + \underbrace{\mu^A D_t F \cdot \delta F}_{\text{adhesion}} + \underbrace{\lambda_{\text{inext}} \partial_s F \cdot \partial_s \delta F}_{\text{in-extensibility}} \right) \eta \, d(\alpha, s) \\ & - \int_{B(t)} \underbrace{p(\rho) [\det(\partial_\alpha F, \partial_s \delta F) + \det(\partial_\alpha \delta F, \partial_s F)]}_{\text{pressure}} \, d(\alpha, s) \\ & + \int_{C(t)} \left(\underbrace{\mu^S (D_t F - D_t^* F^*) \cdot \delta F}_{\text{cross link stretching}} \mp \underbrace{\mu^T (\phi - \phi_0) \partial_s F^\perp \cdot \partial_s \delta F}_{\text{cross link twisting}} \right) \eta \eta^* \, d(\alpha, \alpha^*) \end{aligned}$$

$$+ \underbrace{\int_{(0,2\pi]} (f_{\tan} \partial_s F + f_{\text{in}} V) \cdot \delta F \eta|_{s=-L} d\alpha}_{\text{myosin contraction}} \mp \underbrace{\int_{(0,2\pi]} \lambda_{\text{tether}} \nu \cdot \delta F|_{s=0} d\alpha}_{\text{tethering}}$$

The filament dependent magnitude of the inner pulling force f_{tan} and f_{in} is given by (16) and ρ is defined by (17). The filament densities $\eta(\alpha, s, t)$ are determined by (8) and (12).

For the strong form, i.e. the Euler Lagrange Equations, the modified stiffness parameters are defined analogously as in (7):

$$0 = \mu^B \partial_s^2 (\eta \partial_s^2 F) - \partial_s (\eta \lambda_{\text{inext}} \partial_s F) + \mu^A \eta D_t F + \partial_s (p(\rho) \partial_\alpha F^\perp) - \partial_\alpha (p(\rho) \partial_s F^\perp) \pm \partial_s (\eta \eta^* \widehat{\mu}^T (\phi - \phi_0) \partial_s F^\perp) + \eta \eta^* \widehat{\mu}^S (D_t F - D_t^* F^*), \quad (19)$$

where in the equation for F^+ , the derivatives of F^- are evaluated at $(\alpha^-(\alpha, s, t), s^-(\alpha, s, t))$ and vice versa. The corresponding boundary

conditions are

$$-\mu^B \partial_s (\eta \partial_s^2 F) - p(\rho) \partial_\alpha F^\perp + \eta \lambda_{\text{inext}} \partial_s F \mp \eta \eta^* \widehat{\mu}^T (\phi - \phi_0) \partial_s F^\perp = \begin{cases} \eta (f_{\tan}(\alpha) \partial_s F + f_{\text{in}}(\alpha) V(\alpha)) & \text{for } s = -L, \\ \pm \lambda_{\text{tether}} \nu & \text{for } s = 0, \end{cases}$$

$$\eta \partial_s^2 F = 0 \quad \text{for } s = -L, 0. \quad (20)$$

5. Numerical approach, simulation results, and discussion

In this section we sketch the numerical method for the solution of (19), (20), described in more detail in Manhart et al. (2015). Simulations of model problems will demonstrate the effect of the new ingredients to the model introduced in this work. Finally, the

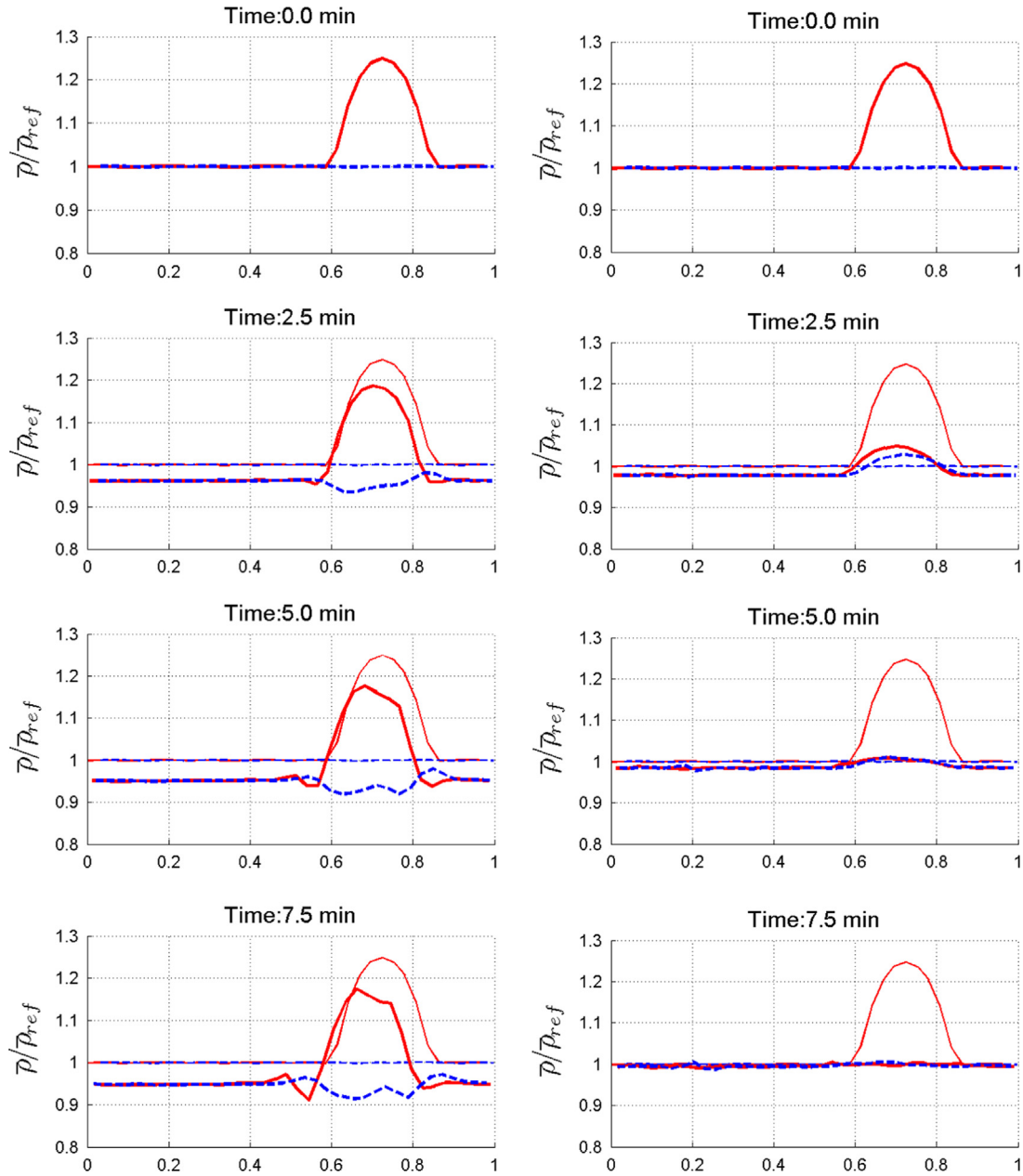


Fig. 2. Barbed end density perturbation with and without branching/capping: the density of left-moving filaments (red) is perturbed initially, that of right-moving filaments (dashed, blue) not. Thick lines represent the current state, thin lines represent the state at time $t=0$. The left column shows the evolution in the absence of branching and capping, i.e. $\kappa_{\text{br}} = \kappa_{\text{cap}} = 0$. In the right column branching and capping are active with parameters as shown in Table 1, except $\mu^P = 0$. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

full model is used to simulate the reaction of a cell to a chemotactic signal.

5.1. Numerical method

The numerical approximation of (19), (20) is a formidable task. Filament families as described here are a new type of continuum, where both analytical and numerical approaches are still in early states of development (see Oelz and Schmeiser, 2010a, 2012 for first results). The new numerical method used here will be described only briefly, since it is the subject of parallel work (Manhart et al., 2015), which we refer to for details.

Instead of dealing with the time-dependent domains $B^\pm(t)$, the equations for both families are transformed to the rectangular and time-independent computational domain $[0, 2\pi] \times [-1, 0]$ by rescaling the variable s . A rectangular grid with uniform step-lengths is used. The grid lines in the s -direction can be interpreted as computational filaments, each discretized by the same number of grid points, independent of its (time dependent) length.

The strong anisotropy in (19) is reflected in the choice of the finite element space for the spatial discretization. A tensor product space is used, where on each grid cell each component of F is represented by a fourth order polynomial, linear in α and cubic in s . These interpolate positions and first s -derivatives at the nodes. In other words, each computational filament is approximated by a cubic spline with linear interpolation in between. The finite element space is conforming for the weak formulation of (19), being continuous in α and C^1 in s and, thus, a subspace of $H_\alpha^1((0, 2\pi), H_s^2(-1, 0))$.

An implicit–explicit time discretization is used, based on a linearization. The evaluation of the interaction terms between the two filament families requires approximations of the mappings ψ^\pm , derived from (4), in order to represent filaments of one family on the grid of the other. The inextensibility constraint has been implemented by an Augmented Lagrangian approach.

5.2. Effects of new model ingredients

Filament number regulation: Branching and capping regulate the number of barbed ends. This is of particular importance when the polymerization rate varies along the leading edge. For an

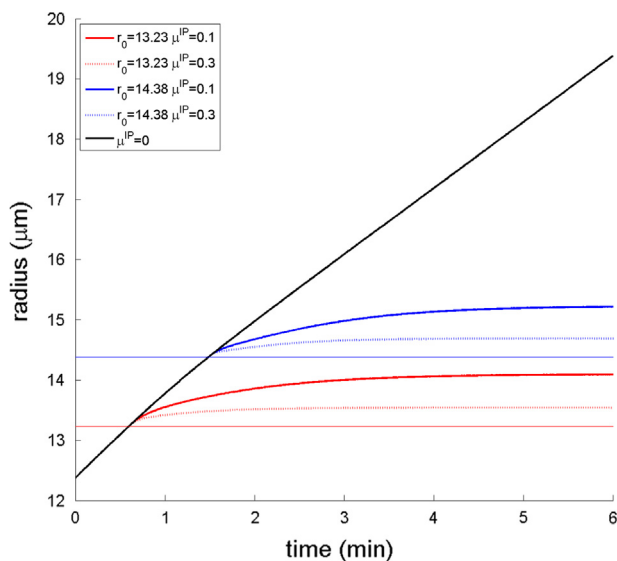


Fig. 3. Effect of the actin–myosin interaction: comparison of the evolution of the radius of a circular cell for different values of r_0 and μ^P . The horizontal lines mark the values of r_0 . All parameters as in Table 1 except the polymerization speed $v_{\text{opt}} = 0.5 \mu\text{m min}^{-1}$.

explanation the *lateral flow* phenomenon is needed, i.e. the movement of barbed ends along the leading edge, caused by polymerization and the inclination of filaments. In our model, the (+)-family filaments typically move to the left (relative to the protrusion direction), and the (–)-family filaments to the right. Since bigger polymerization speeds increase the lateral flow, this would lead to filament depletion in regions with higher polymerization activity without the regulatory effect of branching and

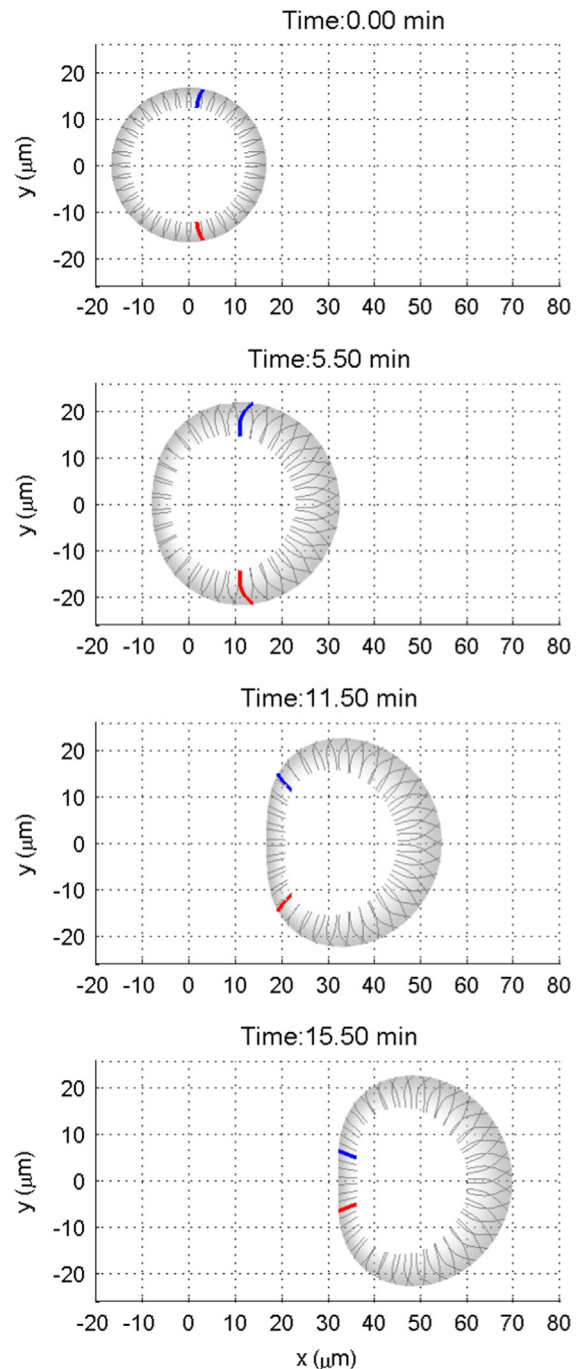


Fig. 4. Polarization and movement in the presence of a chemical gradient: a time series is shown, where the shading represents filament number, thin dashed lines show filament shape, and the thick filaments show the movement of a left moving (red) and right moving (blue) filament with time. Parameter values as in Table 1 with the internal signal threshold $c=0$. For a movie of the simulation including a visualization of the stochastic filament dynamics see the Supplementary Material. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

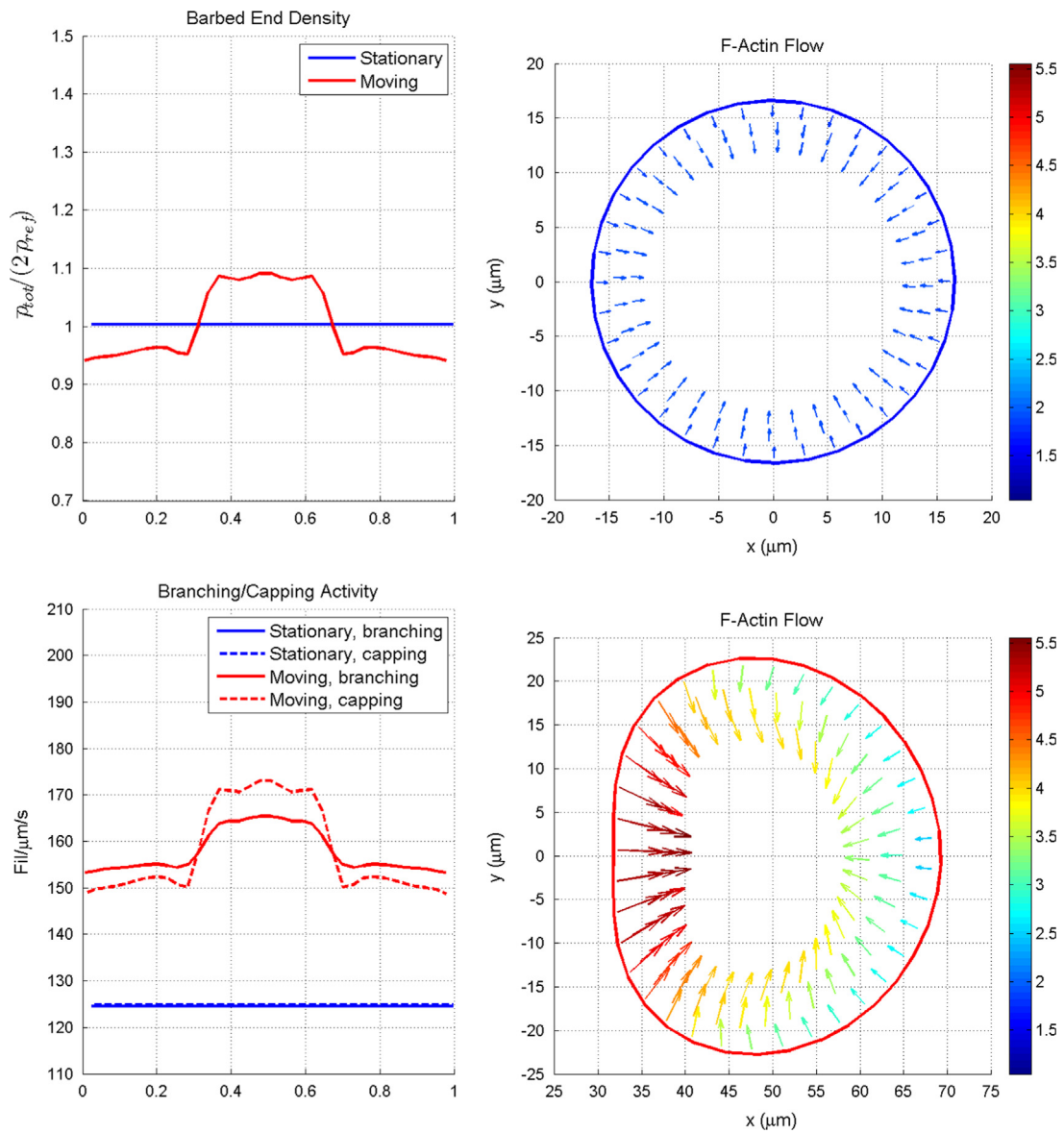


Fig. 5. Nonmoving vs. moving steady state: left side pictures show data along the leading edge. On the horizontal axes, 0 and 1 correspond to the cell front and 0.5 to the cell rear. The upper left picture shows the barbed end density for the stationary steady state (blue) and the moving steady state (red). The lower left picture shows the branching (solid) and capping (dashed) rates. The two pictures on the right show the F-actin flow field, i.e. the velocity of polymerized actin relative to the substrate. Top: Stationary steady state. Bottom: Moving steady state. Arrow length and color (values of the colorbars in $\mu\text{m}/\text{min}$) represent speed. Parameters as in Table 1.

capping. This typically reduces cell motility (see the paragraph on chemotaxis below and Fig. 6).

To observe the regulation more directly, we started with a radially symmetric cell, where the barbed end density along the leading edge is constant and equal to the equilibrium value (11). Then the density of barbed ends of the (+)-family is perturbed locally. In the subsequent simulation a constant polymerization speed is used. Fig. 2 shows the evolution of the barbed end densities $\bar{\rho}^\pm$ for both families. If there is no branching and capping, the perturbation in η^+ is simply moved to the left by lateral flow without any changes (data not shown). The situation for $\bar{\rho}^+$ is somewhat more complicated, because the geometry changes brought about by the higher number of filaments affects the number of filaments per length. Both $\bar{\rho}^+$ and $\bar{\rho}^-$ decrease initially because the membrane is locally pushed outward, making the cell slightly larger. The lateral flow is also visible here by the shift of the maximum filament number of $\bar{\rho}^+$.

For the case where branching and capping are active, one can see how initially the number of (-)-family filaments increases

because of branching. Additionally $\bar{\rho}^\pm$ drops everywhere, again because the cell becomes slightly larger. However the dynamics eventually force the number of filaments to return to its equilibrium value everywhere.

Actin-myosin interaction: Constraint (15) ensures that the myosin pulling on the inside of the lamellipodium is an internal force. We define $A_0 = r_0^2 \pi$. Fig. 3 shows the evolution of the inner radius of a rotational symmetric cell in time for different values of r_0 and μ^{IP} . It can be observed that smaller equilibrium areas and a stronger myosin force (i.e. larger μ^{IP}) leads to smaller cell sizes. This shows that the actin-myosin interaction helps to control the cell size. In the section on chemotaxis below it will be shown that a moving cell can pull its rear due to this effect.

Pressure: The pressure term is a force acting only within one family. To demonstrate its effect one can therefore look at a simplified model for one family only with: constant η , i.e. all filaments of the same length, no polymerization or bending, and only the tangential component of the myosin force ($\gamma=1$). If additionally assuming that the cell is rotationally symmetric, it is

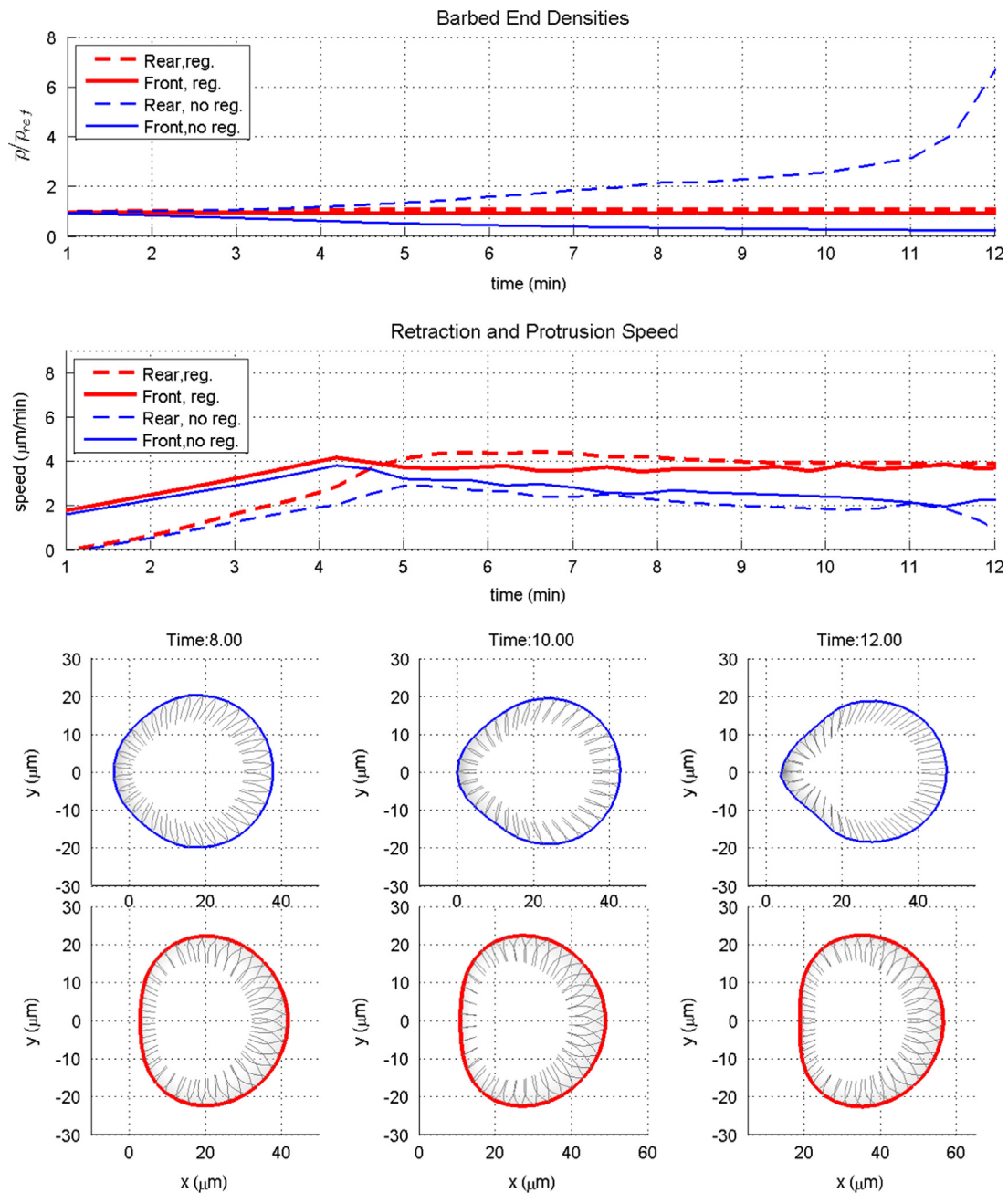


Fig. 6. Movement with and without filament number regulation. First row: Retraction speed at the rear (dashed) and protrusion speed (solid) at the front of the cell. Red lines (thick) show a cell, which can regulate filament number, blue (thin) lines a cell which cannot. Second row: Same as above, but showing the barbed end densities at the rear (dashed) and the front (solid) for the regulated (thick) and the unregulated (thin) case. Third and fourth rows of pictures: Cell shapes at different times. Shading represents actin density, thin gray lines the filament shape. Third row (blue, thin leading edge): Cell without regulation. Fourth row (red, thick leading edge): Cell with regulation. Parameters as in Table 1, except in the unregulated case $\kappa_{br} = \kappa_{cap} = 0$. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

possible to calculate explicitly a stationary solution. Starting with rotationally symmetric perturbations we numerically observed convergence to the analytical steady state. This has been supported by a linearized stability analysis (Leingang, 2015). The simplified system as well as the simulation results can be found in the Supplemental Material.

5.3. Chemotaxis

Finally we want to demonstrate the potential of the full new model, in particular its ability to simulate directed cell movement in the presence of a chemotactic signal, direction changes, and

various cell shapes under different assumptions on the internal signaling network. We point out that cell polarization and directed movement induced by a chemotactic signal as considered here has to be distinguished from the spontaneous polarization observed in certain cell types such as fish keratocytes. It seems to be agreed upon that this effect requires actin–myosin interaction in the lamellipodium as a symmetry breaking mechanism (Kozlov and Mogilner, 2007; Verkhovsky et al., 1999), which the FBLM in its present form is not able to describe.

We want to point out that we are aiming at a proof of principle and that serious comparisons with and fitting to experimental observations are the subject of ongoing work. In particular,

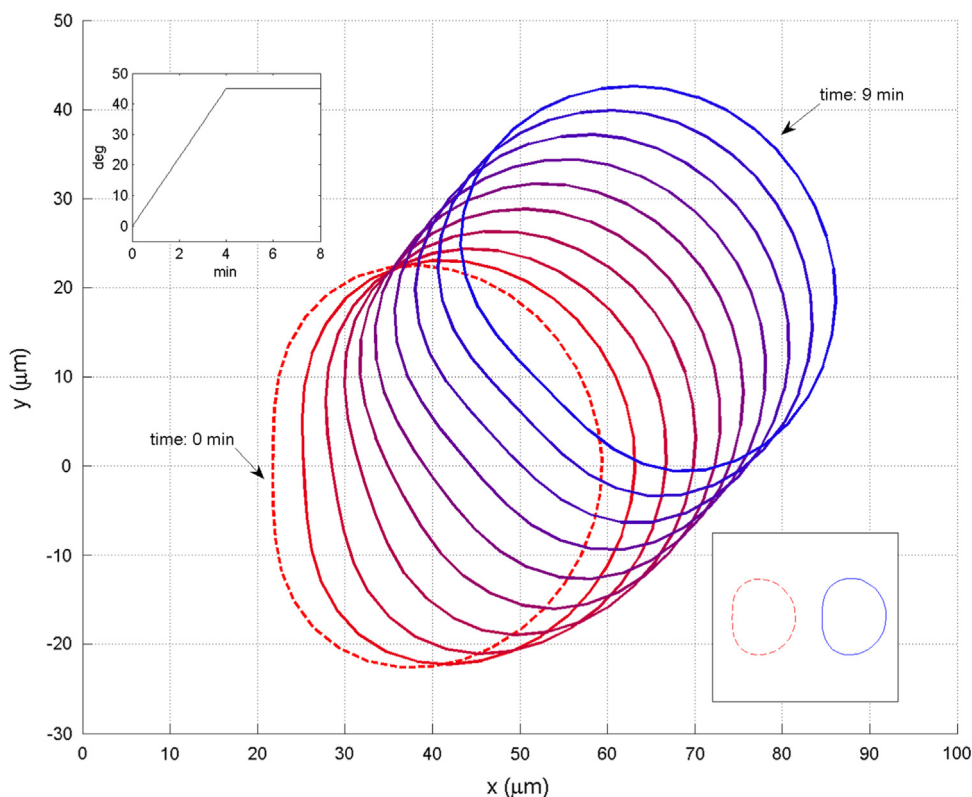


Fig. 7. A turning cell. The picture shows the cell shapes of a turning cell over 9 min. Top left inset: The direction of the chemoattractant gradient as a function of time. Bottom right inset: The initial state (red, dashed) and the turned final state (blue, solid) are compared. Parameter values as in Table 1. For a movie of the simulation including a visualization of the stochastic filament dynamics see the Supplementary Material. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

although our parameter values (discussed below) and results are in realistic ranges, we do not claim the simulated cell shapes to be close to experiments for any particular cell type.

Starting to move: The following experiment mimics chemotaxis, i.e. a situation where the cell, in reaction to a chemical stimulus (chemoattractant) increases its polymerization rate (Iijima et al., 2002; Weiner et al., 1999). For the effect of the chemotactic signal on the polymerization speed we use the model introduced in Section 3. A time evolution starting with a rotationally symmetric cell put in a chemical gradient oriented to the right is shown in Fig. 4. The first visible effect is that the lamellipodium on the right grows wider. The reason is that the increased polymerization rate also increases the maximum filament length as modeled in (13). Next the cell starts moving, because filaments grow faster on the right. Additionally, the wider lamellipodium at the cell front exerts more friction than the thinner one at the cell rear. Eventually the cell shape remains constant and the cell moves steadily towards the right with a speed of about $3.9 \mu\text{m}/\text{min}$, which is in the biologically observed range (Svitkina et al., 1997; Iijima et al., 2002). In Fig. 5 the two (numerical) steady states, the stationary cell and the moving cell, are shown together with some data. For the stationary cell the number of barbed ends is constant along the leading edge, whereas in the moving cell more filaments can be found at the back. To maintain this distribution the cell has to balance branching, capping and movement of filaments. For the stationary cell this simply means having branching and capping rates equal everywhere. For the moving cell, branching dominates at the front, whereas capping exceeds branching in the back. Additionally, the F-actin flow, i.e. the velocity of polymerized actin relative to the substrate is depicted in Fig. 5. For the stationary cell, the flow is rather slow and uniform. For the moving cell one can observe small retrograde flow at the cell front and faster flow in

the movement direction at the back, where retraction takes place. The flow speeds and distributions found are similar to those observed in Grimm et al. (2003).

Why filament number regulation? Fig. 6 demonstrates the importance of filament number regulation by branching and capping. The upper picture shows how for a cell with filament number regulation the filament densities at the rear and at the front remain close to each other and quite steady over time, whilst in the unregulated case they move away from each other. This is because in a cell where regulation is absent, filaments are transported to the back by lateral flow, which leads to an accumulation of filaments at the cell rear, whereas the pulling front is depleted of filaments. The middle picture shows how this affects protrusion speed: In the regulated case rear retraction and front protrusion speeds approach the same value, as is necessary for constant movement, whilst in the unregulated case rear retraction is slower and protrusion velocities decrease with time. In the time series below, one can see that this also affects cell shape: In the unregulated case filaments accumulate in the back, leading to a more prolonged shape.

A turning cell: One can ask the question if the steady state shape of a moving cell is affected by the initial conditions. A reasonable scenario for investigating this question, is a situation where the chemoattractant gradient is gradually turned by 45° . Fig. 7 shows the corresponding evolution. The final shape is very close to the original shape turned by 45° .

Various moving shapes: The shape of the moving cell strongly depends on the transduction of the chemotactic signal. In Fig. 8A–C three scenarios are depicted, where only a certain fraction of the leading edge senses the stimulus. The more “local” the effect of the stimulus is, the longer the cell gets, because a smaller fraction of filaments pull the cell forward. The differences

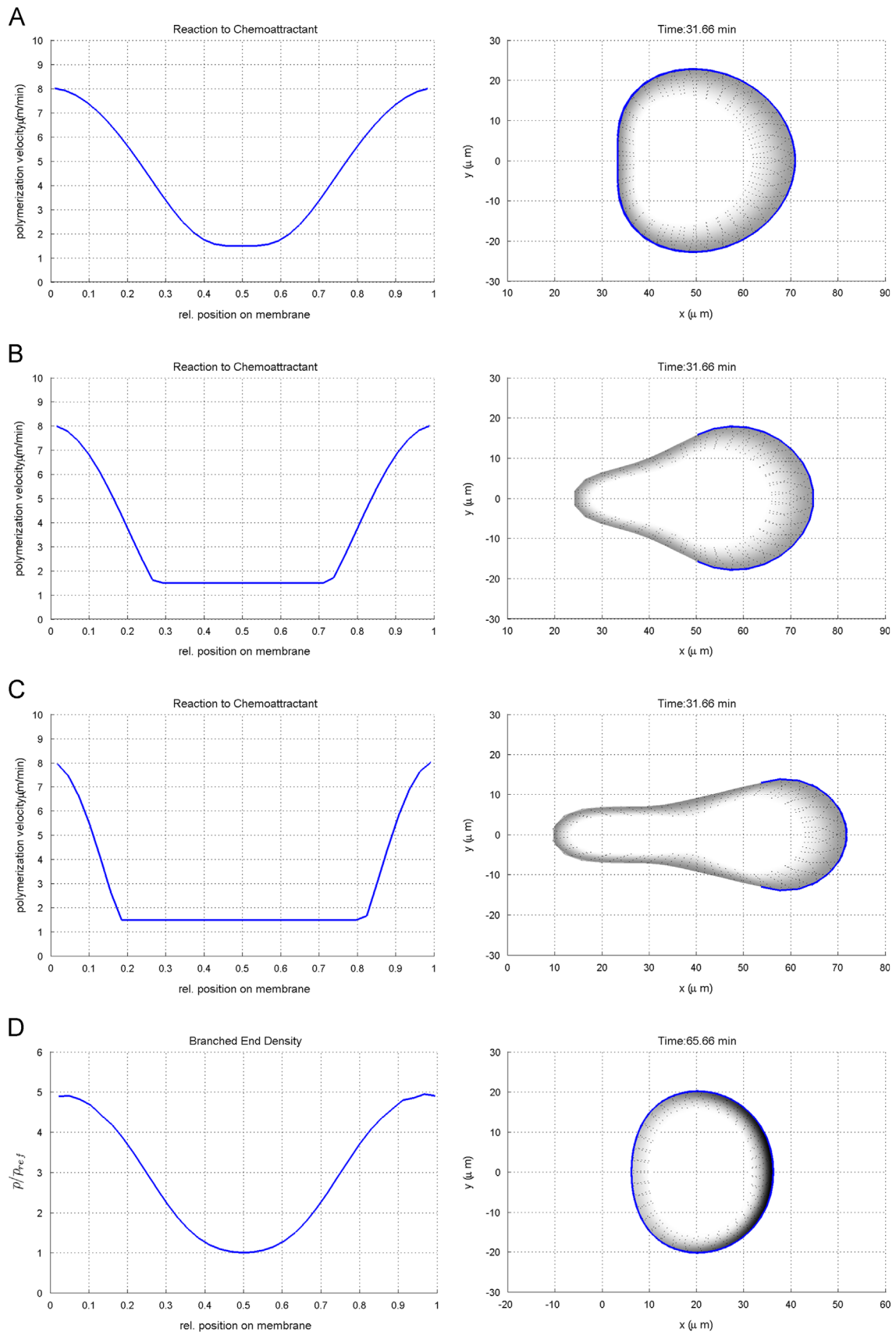


Fig. 8. Different shapes of moving cells: Left pictures, A–C: Polymerization velocity along the leading edge (0 and 1 representing the cell front and 0.5 the cell rear). Left picture, D: Barbed end density along the leading edge. Right pictures: Final shapes. Shading represents actin density, thin lines in the cells (black, dotted) the filament shapes and lines at the leading edge (thick, blue) indicate the regions affected by the stimulus. A–C: The polymerization rate is affected, A: $c=0$, B: $c=0.5$, C: $c=0.7$. D: The branching rate is affected, $c=0$. Parameter values as in Table 1. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

Table 1
Parameter values.

Var.	Meaning	Value	Comment
μ^B	Bending elasticity	0.07 pN μm^2	Gittes et al. (1993)
μ^A	Macroscopic friction caused by adhesions	0.14 pN min μm^{-2}	Measurements in Li et al. (2003), Oberhauser et al. (2002), estimation and calculations in Oelz et al. (2008), Oelz and Schmeiser (2010a), Oelz and Schmeiser (2010b)
κ_{br}	Branching rate	10 min ⁻¹	Order of magnitude from Grimm et al. (2003)
κ_{cap}	Capping rate	5 min ⁻¹	Order of magnitude from Grimm et al. (2003)
c_{rec}	Arp2/3 recruitment	900 μm^{-1} min ⁻¹	Chosen to fit $2\bar{\rho}_{\text{ref}} = 90 \mu\text{m}^{-1}$ Koestler et al. (2008)
κ_{sev}	Severing rate	0.38 min ⁻¹ μm^{-1}	Chosen to give lamellipodium widths as described in Small et al. (2002)
μ^{IP}	Actin–myosin interaction strength	0.1 pN μm^{-2}	
A_0	Equilibrium inner area	450 μm^2	Order of magnitude as in Verkhovsky et al. (1999); Small et al. (1978)
v_{min}	Minimal polymerization speed	1.5 μm min ⁻¹	In biological range
v_{max}	Maximal polymerization speed	8 μm min ⁻¹	In biological range
μ^P	Pressure constant	0.05 pN μm	
μ^S	Cross-link stretching constant	7.1×10^{-3} pN min μm^{-1}	
μ^T	Cross-link twisting constant	7.1×10^{-3} μm	
κ_{ref}	Reference leading edge curvature for polymerization speed reduction	(5 μm) ⁻¹	

have been created in the model by variation of the threshold parameter c in (18). The fourth shape in Fig. 8D shows results of an alternative mechanism, where not the polymerization speed but the branching rate is upregulated by the signal. The upregulating mechanism is as in Fig. 8A with a maximally threefold increase of the branching rate leading to a much denser actin network at the front.

Parameters values: The parameter values used for the simulation are the ones summarized in Table 1 unless stated differently. Where available, values available in the literature have been used (e.g. for μ^B, μ^A, A_0, v^\pm). Values for the branching and capping parameters $\kappa_{\text{br}}, \kappa_{\text{cap}}, c_{\text{rec}}$ have been chosen in order to give an equilibrium value of the total density of pushing filaments of $2\bar{\rho}_{\text{ref}} = 90$ filaments per μm leading edge (compare to (11)), which has been observed in real cells (Koestler et al., 2008). κ_{sev} has been chosen in order to give a lamellipodial width in the relevant range of several μm (Small et al., 2002). Other parameters however ($\mu^S, \mu^T, \mu^P, \mu^{IP}, \kappa_{\text{ref}}$) result from averaging processes in the derivation of the model (see Oelz and Schmeiser, 2010b). In principle they can be derived from molecular properties, but they depend in a complicated way on quantities, where not much experimental data is available, such as mechanical properties of cross-linker molecules, their binding and unbinding rates, and their densities. These parameters can be used in a fitting process. Values within reasonable ranges have been chosen here.

5.4. Discussion

The lamellipodium is a complex system, whose dynamics is governed by a host of chemical and mechanical processes driven by a large number of different proteins. The FBLM provides a modeling framework where, on the one hand, most of the relevant processes can be accounted for and, on the other hand, numerical simulations of the resulting models remain feasible. This is achieved by two-dimensional modeling on the molecular level, based on the assumptions of two dominant filament directions, and a subsequent upscaling, leading to a continuum description.

The version of the model presented here accounts for bending, cross-linking, substrate adhesion, repulsion, polymerization, severing, branching, and capping of filaments as well as membrane tension and contractive effects. Enriched by a simple description of chemotactic signaling, it is able to predict cell polarization and directed movement. From the simulation results, data can be extracted, which are also available from light

microscopy or electron tomograms, such as actin density and predominant filament directions.

Further model development is needed and is the subject of future work. Most importantly, it has to be demonstrated that a full parametrization by comparison to experimental data is possible. In the present state, biologically reasonable parameter values are used and give quantitatively reasonable results, but to achieve a good fit for a particular experiment is still to be done. Various extensions of the model are conceivable. Examples are the effects of hydrostatic pressure induced by contraction on the behavior of the membrane, or actin–myosin interaction within the simulated lamellipodium region. An important part of the future development is the coupling of the FBLM with models for other cell compartments, such as contractive actin–myosin bundles, filopodia, the nucleus, and microtubuli.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jtbi.2015.06.044>.

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