Model for self-polarization and motility of keratocyte fragments

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Computational modelling of cell motility on substrates is a formidable challenge; regulatory pathways are intertwined and forces that influence cell motion are not fully quantified. Additional challenges arise from the need to describe a moving deformable cell boundary. Here, we present a simple mathematical model coupling cell shape dynamics, treated by the phase-field approach, to a vector field describing the mean orientation (polarization) of the actin filament network. The model successfully reproduces the primary phenomenology of cell motility: discontinuous onset of motion, diversity of cell shapes and shape oscillations. The results are in qualitative agreement with recent experiments on motility of keratocyte cells and cell fragments. The asymmetry of the shapes is captured to a large extent in this simple model, which may prove useful for the interpretation of experiments.

Keywords: cell motility; actin self-assembly; nonlinear physics

1. INTRODUCTION

Crawling motion of eukaryotic cells on substrates is caused by polymerization–depolymerization cycles in the actin filament network. The propulsion forces exerted by the cell on the substrate are determined by a balance of actin polymerization at the leading edge, intermittent adhesion of the cell to the substrate and detachment of the back of the cell; all of these processes are further mediated by a complex protein regulatory system [1–3]. Detailed modelling of cell motion that includes the entire complexity of all regulatory pathways is a formidable challenge; many pathways are intertwined and poorly understood, and forces that give rise to motion are not fully quantified [4]. Moreover, cell motion is a complex dynamic process associated with cell shape deformation and complicated flow geometries. Direct numerical modelling requires the inclusion of movable deformable interfaces or thin-film theories of multi-phase reactive flow, which introduce additional computational challenges [5–11].

The accepted, though simplified, picture of cell motility is the following: actin filament polymerization occurs predominantly at the front of the cell, where Wiskott–Aldrich syndrome proteins nucleate new branches of actin filaments by activating the Arp2/3 complex located close to the cell membrane [12]. Actin polymerization, via adhesion complexes, produces forces on the substrate and, consequently, induces cell movement. At the same time, conventional myosin molecular motors are expressed at the rear of the cell, triggering formation of actin filament bundles. The bundles exert contractile stresses at the rear and are responsible for the overall anisotropy and crescent-like shape of the moving cell. Actin filaments are concurrently disassembled into G-actin monomers in the bulk of the cell. Rapidly diffusing G-actin is then recycled at the cell membrane allowing for polymerization of new actin filaments.

In the proposed model, we use a phase-field approach based on ideas developed for solidification [13], crack propagation [14], fluidization transition in granular media [15,16] and for actin gel-bead motility [17]. In the context of vesicles, this approach is also known as the advected-field approach [18]. Recently, in a similar framework, Shao et al. [19] suggested a model for the cell shape dynamics during motion. The main advantage of this approach is that no explicit tracking of the cell’s boundary is required as the auxiliary phase-field distinguishes the interior of the cell from the exterior. Shao et al. [19] applied this method to the motion of epithelial keratocytes [20], crescent-shape cells that extend a thin lamellipodium at the front and sides. While the model reproduced cell
motion and shapes, it used two scalar fields, cross-linked actin filaments and actin bundles, instead of a vector field describing the orientation and intrinsic anisotropy of actin. The latter one is believed to be important for motility and has been characterized experimentally [20].

In this work, we propose a simple phase-field model describing the cell shape coupled to the orientation (or polarization) of the actin filament network. Two fundamental issues distinguish our work from Shao et al. [19]: first, we include the actin filament polarization in our modelling; this is more realistic and yields additional information, e.g., of the traction on the substrate. Second, we do not need to explicitly use two separate fields (hence separate forces) for the protrusion and the retraction to sustain cell motion as was the case in the study of Shao et al. [19].

Our model reproduces the primary phenomenology of cell motility: we find a discontinuous onset of cell motion, as observed experimentally for cell fragments [21]. To date, this is the first model describing this transition without pre-imposing the shape. We also obtain correct stationary crescent-like shapes of moving cells as well as periodic cell shape oscillations in the course of motion. Finally, the outcome of our modelling can be directly compared with recent experiments on actin network polarization distribution, distribution of traction on the substrate and cell shape [12,20–23].

2. PHASE-FIELD MODEL

Our approach is based on two fields: first, the phase-field variable \( \rho(x, y; t) \) is an auxiliary field separating the interior of the cell from the exterior: \( \rho \) has a value of 1 inside the cell, 0 outside the cell and varies smoothly at the interface. This diffuse interface is interpreted as the location of the cell membrane, see below. Second, the vector field \( \mathbf{p}(x, y; t) \) describes the polar orientation (or polarization) of the actin filaments. It points in the direction of the local mean orientation of filaments and its absolute value is a measure of the degree of ordering. The overall description is depth-averaged, i.e., we do not resolve the actual height of the cell and the model is effectively two-dimensional.

Before proceeding to the derivation of the model, let us discuss in detail the interpretation of the phase-field variable \( \rho \). As we stated above, the phase-field approach became a legitimate mathematical tool and effective numerical alternative to the sharp interface limit for systems undergoing first-order phase transition [13–15]. It was successfully applied to a broad range of phenomena, from solidification to granular fluidization. While it was originally designed as an auxiliary field, in some cases the phase field can be associated with relevant physical variables, such as the number of broken atomic bonds in the case of crack propagation [14] or the ratio of static versus sliding contacts in dense granular flows [15,16]. In the context of vesicles, the membrane is not a boundary between true phases; hence, the advected-field interpretation (the membrane is advected by flows in the two domains) has been developed [17]. It is in this spirit that we interpret the phase-field approach as the advecting of the membrane (given by the diffuse interface) by forces created in the cell’s interior. We should stress that the phase-field variable does not capture any of the structure of the cytoplasm; it is rather the orientation field \( \mathbf{p} \) that resolves this missing piece by describing the average orientation and the degree of orientation of the filaments that polymerize and push against the membrane. Below (see §5), we show that a simplified sharp interface limit of our model indeed yields the correct kinematic condition, i.e., the steady-state velocity of the cell is proportional to the protrusive force diminished by a surface tension contribution owing to the local two-dimensional curvature of the membrane.

We start by writing the evolution equation for the phase-field \( \rho \),

\[
\partial_t \rho = D_\rho \Delta \rho - (1 - \rho)(\delta - \rho)p. \tag{2.1}
\]

The parameter \( D_\rho \) (with units of length squared as time is already rescaled) has two meanings: first, it characterizes the width of the phase-field interface. Second, it can be shown to be the ratio of the surface tension of the cell membrane to the friction with the substrate [19]. As the width of the interface is in consequence, we do not introduce two separate parameters for these two effects. It is known how to generalize this approach [18], a step which is needed to perform a strict sharp-interface limit (where the width goes to zero while the surface tension remains finite), on which we will report elsewhere. In the following, we also neglect the membrane’s bending rigidity, which would correspond to higher order differentials in \( \rho \) [18,19]. While of possible importance in the unresolved \( z \)-direction (where the radius of curvature is 100 nm), the bending rigidity can be estimated to be negligible for typical curvature radii of the order of 10 \( \mu \)m involved in the two-dimensional crawling motion of a cell.

The parameter \( \delta \) is introduced in equation (2.1) to control the motion of the cell boundary and to ensure the approximate (effective two-dimensional) volume or area conservation of the cell (cf. [15,16]). Equation (2.1) has three fixed points resulting from the local nonlinearity \((1 - \rho)(\delta - \rho)p\): \( \rho = 0 \), \( \rho = 1 \) and \( \rho = \delta \). For \( 0 < \delta < 1 \), the two fixed points \( \rho = 0 \) are stable and separated by the unstable fixed point \( \rho = \delta \). Correspondingly, in spatially extended systems for \( \delta = \delta_0 = 1/2 \) the interface between the two ‘phases’ \( \rho = 1 \) and \( \rho = 0 \) is stationary. This is the so-called Maxwell rule. Increasing \( \delta \) above 1/2, on the other hand, leads to an advance of the phase with \( \rho = 0 \) into the one with \( \rho = 1 \), and vice versa for \( \delta < 1/2 \). For the present situation, we assume \( \delta \) to be of the form

\[
\delta = \delta_0 + \mu \left( \int dx \, dy \, \rho(x, y) - V_0 \right) - \sigma |\mathbf{p}|^2. \tag{2.2}
\]

The rational for this special choice in equation (2.2) is the following: the parameter \( \delta_0 \) characterizes the ‘internal’ hydrostatic pressure of the cell. For \( \delta_0 < 1/2 \), the cell tends to expand (positive pressure), and for \( \delta_0 = 1/2 \), the cell shape is quasi-stationary (no pressure). The second term, \( \int dx \, dy \, \rho(x, y) - V_0 \), is an implementation of the constraint of total area conservation: if the...
cell’s total area \( \int dx \, dy \, \rho(x, y) \) exceeds the chosen initial area \( V_0 \), the parameter \( \delta \) increases, leading to overall contraction of the cell or an advance of the phase with \( \rho = 0 \) into the one with \( \rho = 1 \). The parameter \( \mu \) characterizes the stiffness of this constraint, and may depend on membrane surface tension and elasticity. However, the overall behaviour is not very sensitive to variations of \( \mu \). The last term \( \sim |\mathbf{p}|^2 \) in equation (2.2) models a contractile stress due to motor-induced contraction of actin filament bundles with the dimensionless model parameter \( \sigma \) being a ratio of maximum tensile stress to maximum internal pressure. The bundles, comprising either parallel- or anti-parallel-oriented filaments \([24]\), can be described by a nematic tensor \( \mathbf{S}_p \), which is related to the orientation vector \( \mathbf{p} \) according to

\[
\tau \partial t \mathbf{S}_p = - (\mathbf{S}_p - \mathbf{S}_p^T) + \left( p_i p_j - \frac{|\mathbf{p}|^2}{2} \delta_{ij} \right). \tag{2.3}
\]

This equation describes the following behaviour: in the absence of polarization \( (\rho = 0) \), the nematic tensor relaxes towards an equilibrium value \( \mathbf{S}_p = \mathbf{S}_p^0 \) given by filaments that are not in motor contact but still may display a certain amount of nematic ordering. \( \tau \) is the relaxation time for the nematic field and \( \mathbf{S}_p^0 \) is a constant traceless tensor, which for simplicity we set to zero here. If there is finite motor-induced polarization \( \mathbf{p} \), the value of the nematic order parameter \( \mathbf{S}_p \) increases. In the following, we assume that the relaxation time \( \tau \) is small and that the nematic field is enslaved to the polarization \([25]\), i.e. we neglect the time derivative in equation (2.3). The nematic tensor is then of the form

\[
\mathbf{S}_p \sim \left( p_i p_j - \frac{|\mathbf{p}|^2}{2} \delta_{ij} \right). \tag{2.4}
\]

It is known from the theory of ‘active gels’ \([26]\) that the stress tensor due to motor contraction of bundles is given by \( \sigma_{ij} \sim \mathbf{S}_p \). Correspondingly, the tensor’s invariant, \( |\mathbf{p}|^2 \), describes the magnitude of contractile deformations and couples cell dynamics and mechanics.

The full coupled model equations for the phase-field \( \rho \) and the orientation vector \( \mathbf{p} \) read

\[
\partial_t \rho = D_\rho \Delta \rho - (1 - \rho) (\delta - \rho) \rho - \alpha (\nabla \rho) \cdot \mathbf{p} \tag{2.5}
\]

and

\[
\partial_t \mathbf{p} = D_\mathbf{p} \Delta \mathbf{p} - \tau_1^{-1} (1 - \rho) \mathbf{p} - \tau_2^{-1} |\mathbf{p}|^2 \mathbf{p} - \beta (\nabla \rho) - \gamma (\nabla \rho) \cdot \mathbf{p}. \tag{2.6}
\]

The two fields \( \rho, \mathbf{p} \) are dimensionless and \( 0 < \rho, |\mathbf{p}| < 1 \), i.e. the orientation field is normalized by its maximum value. In equation (2.5), \( \alpha \) describes the advection of \( \rho \) along the orientation vector \( \mathbf{p} \) due to polymerization of actin filaments against the membrane. Its relation to the cell’s velocity via a kinematic condition is discussed in §5. Also note that here cell adhesion is tacitly assumed: for the growing filaments to push, they have to transfer momentum to the substrate, see also the discussion of traction forces below.

The orientation field \( \mathbf{p} \) is non-conserved, as it can be created by polymerization: this is described by the \( \beta \)-term in equation (2.6), stating that polarization is created by \( \nabla \rho \). Hence, at the location of the membrane, given in the diffuse interface description by the maximum of \( \nabla \rho \), orientation is created perpendicular to the interface, owing to polymerization of new actin filaments. On the other hand, the \( \tau_1 \)-term in equation (2.6) describes degradation of orientation by diffusion, depolymerization, etc. The \( \tau_2 \)-term dampens the orientation field \( \mathbf{p} \) outside the cell while not changing the behaviour inside where \( \rho = 1 \). Note that the cell does not advect the filaments (and hence \( \mathbf{p} \)) considered here; rather, since the polymerization exerts a force on the membrane, the respective filaments must be connected to the substrate via adhesion sites. Hence, we do not advect the orientation field but rather suppress the variable \( \mathbf{p} \) outside the cell. We verified that this changes neither the shapes nor the dynamics. The term \( D_\rho \Delta \mathbf{p} \) describes diffusion and stiffness of the polar orientation field.

Finally, the \( \gamma \)-term breaks the reflection symmetry of the orientation \( \mathbf{p} \). This can be motivated as being an effect of another (overdamped) field, namely the concentration of myosin motors \( m \). For the latter, we can write the following equation:

\[
\partial_t m = D_m \Delta m - \tau_m^{-1} (m - m_0) + V_m \mathbf{p} \cdot \nabla m - \gamma \nabla \rho \cdot \mathbf{p}. \tag{2.7}
\]

where \( D_m, V_m \) and \( \tau_m \) are the motors’ diffusion, speed along the filaments and relaxation time, respectively, and \( m_0 \) is the steady-state motor concentration. The motors are suppressed near the front of the cell with a rate \( \sim \gamma \nabla \rho \cdot \mathbf{p} \). For small \( \tau_m \), we can neglect the terms \( D_m \Delta m, V_m \mathbf{p} \cdot \nabla m \) and write \( m - m_0 \sim -\tau_m \gamma (\nabla \rho \cdot \mathbf{p}) \).

Hence, the motor density is higher at the rear, and the corresponding term in the equation for \( \mathbf{p} \) effectively decreases polarization as filaments are absorbed into (anti-parallel) bundles at the rear of the cell.

3. RESULTS

We solved equations (2.5) and (2.6) on a periodic two-dimensional square-shaped domain using a numerical, quasi-spectral split-step method. Typically, \( 256 \times 256 \) fast Fourier transformation harmonics were used. The integration domain was chosen large enough to ensure negligible contributions from the boundaries (typically \( 100 \times 100 \) dimensionless units). The initial conditions were generally a circular domain for the phase-field variable, i.e. \( \rho = 1 \) inside a circle of radius \( r_0 \) (hence \( V_0 = \pi r_0^2 \) is the cell’s area) and \( \rho = 0 \) otherwise. The orientation field was set to a constant value \( \mathbf{p} = \text{const} \) inside the circle and pointing in the \( x \)-direction. Depending on the model parameters, the initial conditions either restored a circular symmetric shape and became stationary, or they evolved into stable polarized moving crescent-shape patterns, closely reminiscent of forms observed experimentally for keratocyte fragments \([20,21]\).

Before discussing moving cells, a brief comparison between the obtained static cell shape and nematic droplets is in order: a similar shape (called radial structure) is found for nematic droplets with perpendicular surface anchoring (homeotropic alignment) \([27,28]\). Despite the similarity in overall conformation and alignment
orientation, there are several important differences due to the activity of the cytoskeleton: first, a nematic system is not described by a vector field $p$ like the polar cytoskeletal filaments (the modulus of which describes the amount of ordering [25]), but rather by a director field $^\wedge n$ with no direction specified, $^\wedge n = C_0 ^\wedge n$, and where the extent of ordering is given by the second moment, i.e. the nematic tensor $S_{ij}$. Second, in a nematic droplet the active terms, i.e. the advection term (proportional to $a$) and the motor-related term (proportional to $g$) do not exist. Finally, there is no continuous creation of new ordered filaments at the interface (the $b$-term), but only passive surface anchoring.

Select shapes of moving cells obtained by solving equations (2.5) and (2.6) are shown in figure 1. While the model has a substantial number of parameters, the overall outcome of the numerical modelling is the following: self-sustained moving cells emerge from initial conditions for sufficiently large values of the parameters $a$, $b$ and $c$ (characterizing the polymerization force, the polymerization rate and the motor-induced asymmetry, respectively). In turn, increase of the parameter $\sigma$ accounting for the contribution from tensile stresses generated by actin–myosin bundles results in an increase of the aspect ratio of the cells (figure 1a–c).

Surprisingly, if the parameters $a$ and $c$ are moderate but of similar order, we observed a transition from steady motion to a state displaying motion with periodic oscillations in both the velocity and the shape of the cell. Typical shapes for this oscillating moving state are shown in figure 1d–f. Oscillations of the velocity $V$ and the cell’s aspect ratio and anisotropy are not in phase: there is approximately a quarter-period shift between the maximum velocity and the maximum of the aspect ratio. While no conclusive data are available on shape oscillations of keratocytes in vivo, periodic lamellipodium contractions of crawling fibroblasts [29] were reported as well as periodic motion and dynamics of filopodia on compliant substrates [30]. Usually, a stick-slip mechanism is used to rationalize these findings. However, our simple model shows that the nonlinear coupling between the filament polarization and the cell shape is sufficient to allow for oscillatory states.

To characterize the onset of motion and the minimal propagation velocity, we performed simulations for various parameter ranges. Results are shown in figure 3 as...
perturbed by noise it remains stationary for the parameters shown in that figure. One needs a nonlinear perturbation to trigger motion, e.g. by choosing a region inside the cell and adding a constant p inside that region. This overall behaviour shows that the onset of cellular motion is a subcritical instability, in agreement with experiments on fragments [21]: there fragments had to be perturbed to initiate motion, while unperturbed or slightly perturbed fragments stayed immobile. This subcriticality is caused by the motor-related symmetry-breaking term (proportional to γ), and reflects the fact that a perturbation has to be large enough for the motors to establish a significant asymmetry in their distribution across the cell.

To further characterize the shapes, we have investigated the dependence of the cell’s aspect ratio h – 1 and the asymmetry measures characterizing deviations from reflection symmetry, ζ, η, on the parameters and the cell’s velocity V. The aspect ratio, in particular, has been used experimentally to characterize moving cells and has been related to the cell’s speed. Figure 4 illustrates the dependence of the cell’s aspect ratio h – 1 and the asymmetry measures ζ, η on the cell’s velocity V. The simulation conditions were as shown in figure 3. The aspect ratio and η decrease with decreasing velocity, while the other asymmetry measure ζ increases.

Figure 5 features the cell’s velocity V and the aspect ratio h – 1 as a function of the cell’s overall area V₀.

While there is a monotounous and only slight increase of the velocity with cell size, the variation for the aspect ratio is high and exhibits a surprising nonmonotonous behaviour with a maximum at some ‘optimal area’. Namely, as the parameter σ describing the contractility was kept constant, cells of small area attain a nearly elliptical shape. Increasing the area leads to more asymmetric and extended shapes, as seen in figure 1. For even larger volume the shape becomes extended in the direction of motion, with a comparatively small propulsive front and a large tail shaped as a conical frustum dragged behind.

Thus, the relation between the cell’s velocity and its shape, characterized here both by the aspect ratio and the asymmetry measures, is far more complicated as a function of the parameter γ describing the asymmetry induced by the molecular motor distribution. We started with a stationary moving structure for a large value of γ and then slowly ramped down γ. As one can see from the figure, the cell’s motion stops abruptly below a critical value γc ≈ 0.42, at a minimal velocity of Vmin ≈ 0.62, which of course both depend on the other model parameters. The velocity V, the aspect ratio h – 1 and the asymmetry measures ζ, η (see §4 for a detailed definition) drop to zero for γ < γc. Remarkably, one of the asymmetry measures, ζ, increases approaching the transition point, while the second, η, decreases monotonically.

In figure 3, we showed that a moving cell stops abruptly when the parameter γ is reduced. On the other hand, when a stationary spherical fragment is

Figure 2. Oscillatory cell motion as shown in figure 1d–f. Velocity of the cell, V (black line), deviation from the axial symmetry, h – 1 (red line) and asymmetry parameter ζ (green line) as a function of time (in dimensionless units).

See §4 for a definition of the asymmetry measures. Parameters as in figure 1d–f.

Figure 3. Illustration of the subcritical transition between moving and stationary state. Cell velocity V (black line), aspect ratio h – 1 (red line), and asymmetry measures ζ (green line), η (blue line) are shown as a function of γ. The plot was obtained by decreasing γ: for γ < γc ≈ 0.425 all the quantities vanish and a symmetric stationary solution ensues (indicated by cross symbol). Parameters used are α = 3, β = 1.6, V₀ = 100π, varying γ; the others are as indicated in table 1.

Figure 4. The aspect ratio h – 1 (black line) and the asymmetry measures ζ (red line), η (green line) as a function of the cell’s velocity V for oscillatory motion shown in figure 1d–f.
than recently suggested [19,20]. The influence of the overall volume, in particular, must be accounted for (when experimentally addressing this issue, cells with similar area should be compared).

4. MATERIAL AND METHODS

The velocity, aspect ratio and asymmetry measures of oscillating cells have been shown in figure 2. To extract the velocity, we determined the centre-of-mass position \( x^c \) according to

\[
x^c_i = \int x_\rho(x, y) dx dy, \quad i = 1, 2.
\]

The aspect ratio was determined via the corresponding 2 \( \times \) 2 variance matrix \( I_{ij} \)

\[
I_{ij} = \int (x_i - x^c_i)(x_j - x^c_j)\rho(x, y) dx dy.
\]

Its eigenvalues \( \lambda_{1,2} \) were calculated and their ratio

\[
h = \frac{\lambda_1}{\lambda_2}
\]

is a measure for the aspect ratio of the cell. For a cell moving in \( x \)-direction \((i = 1)\), for the off-diagonal elements follows \( I_{12} = I_{21} = 0 \) and the aspect ratio is simply given by \( h = \sqrt{I_{22}/I_{11}} \). As for an axisymmetric shape the aspect ratio parameter is \( h = 1 \), in the figures we trace \( h - 1 \).

We also characterized the asymmetry of moving cells, namely the deviation from reflection symmetry. For this purpose, we calculated the skewness tensor \( G_{ijk} \)

\[
G_{ijk} = \int (x_i - x^c_i)(x_j - x^c_j)(x_k - x^c_k)\rho(x, y) dx dy.
\]

Obviously, for an ellipse \( G_{ijk} = 0 \). For an asymmetric, e.g. crescent-shape, cell moving in the \( x \)-direction \((i, j, k = 1)\), only four elements of the skewness tensor are non-zero: \( G_{111} \neq 0 \), and \( G_{122} = G_{212} = G_{221} \neq 0 \).

Table 1. Summary of important parameters, typical rescaled values used in numerical solution and typical values for the ‘real’ system. Other parameters: stiffness of volume conservation: \( \mu = 0.1 \); decay of \( p \) outside cell: \( \tau_p^{-1} = 0.4 \).

<table>
<thead>
<tr>
<th>value</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \tau_p^{-1} )</td>
<td>0.1 degradation of ( p ) inside cell (actin depolymerization rate of 10 s(^{-1}))</td>
</tr>
<tr>
<td>( D_p )</td>
<td>0.2 diffusion/elastic coeff. for ( p )</td>
</tr>
<tr>
<td>( D_r )</td>
<td>1 stiffness of diffuse interface( ^a )</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>0.5–3 advection of ( p ) by ( \mathbf{p} )</td>
</tr>
<tr>
<td>( \beta )</td>
<td>1–2 creation of ( \mathbf{p} ) at interface</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>0.4–1 symmetry breaking due to motors, corresponding motor velocity 0.1 ( \mu ) m s(^{-1})</td>
</tr>
<tr>
<td>( V_0 )</td>
<td>0.8–1 symmetry breaking due to motors, corresponding motor velocity 0.1 ( \mu ) m s(^{-1})</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>0–0.7 contractility due to bundles</td>
</tr>
</tbody>
</table>

\( ^a \)See main text, §5.4.

Hence we can define the following relative asymmetry measures

\[
\zeta = \frac{|G_{111}|^{1/3}}{\sqrt{I_{11} + I_{22}}}
\]

and

\[
\eta = \frac{|G_{222}|^{1/3}}{\sqrt{I_{11} + I_{22}}}.
\]

For an ellipse, \( \zeta, \eta = 0 \); for the asymmetric moving cells obtained by our simulations one has \( \zeta, \eta \neq 0 \).

5. DISCUSSION

5.1. Interface dynamics

Our description is depth-averaged and does not explicitly account for the substrate. However, the propulsion of the phase-field \( \rho \) by polymerization obviously implies that filaments are attached to the substrate or to the rest of the actin gel. Hence, equation (2.5) for the phase field can be related to a simple kinematic condition at the interface. Let us consider a constant velocity solution to equation (2.5), namely \( \rho(x, y, t) = \rho_0(x - Vt, y) \), where \( V \) is the velocity. Substituting into equation (2.5), in the local coordinate system, we get for the front position

\[
(-V - \alpha p_n + D_\rho \kappa)\partial_n \rho + \text{higher order terms} = 0,
\]

(5.1)

where \( n \) is the coordinate normal to the front and \( \kappa \) is the local two-dimensional curvature. Thus, to leading order the front dynamics is described by

\[
V + \alpha p_n - D_\rho \kappa = 0.
\]

(5.2)

If we multiply equation (5.2) by a viscous friction coefficient \( \xi \), we rewrite it as a local force balance equation (cf. [19]): \( F_{ln} + F_{pol} + F_{ten} = 0 \), where \( F_{ln} = \xi V \) is a
Here we introduced the common factor $\xi$ as follows: approximate traction field can be determined from the condition that the total force applied to the surface must be zero (cell is a force dipole). In conclusion, the latter can be determined self-consistently from the equation (5.4). It is directed from the leading edge towards the inside of the cell. All parameters as in figure 1a.

Supplementary information

5.2. Traction distribution

The polymerization force $\sim \alpha p$ is balanced by the viscous drag force proportional to the cell's velocity $V$. The resulting traction $T$ on the surface will be the sum of these two forces (neglecting additional elastic bulk forces and other complications). Hence, $T \sim p - \nu V$, where $\nu$ is an effective friction coefficient. Note that the latter can be determined self-consistently from the condition that the total force applied to the surface must be zero (cell is a force dipole). In conclusion, the approximate traction field can be determined from the simulation as follows:

$$ T \sim -\rho \left( p - \frac{\int p \, dx \, dy}{\int \rho \, dx \, dy} \right) \quad (5.3) $$

Here we introduced the common factor $\rho$ to ensure that the traction vanishes outside of the cell. The obtained traction distribution is shown in figure 6b. It is in qualitative agreement with experimental measurements [22].

5.3. Retrograde flow

A so-called retrograde flow of actin filaments from the leading edge towards the rear is observed in the course of motion for most cell types; for keratocytes, this was not experimentally observed until recently [23] due to a rather strong interaction between the actin network and the substrate. It seems like the retrograde flow is not of crucial importance for motility in this case, although this is at present still debated. To approximately reconstruct the retrograde flow $\nu$ inside a moving cell, we apply Darcy’s law known from porous media, assuming that filaments flow through meshes in the actin network. Hence,

$$ \nu = -\nabla |p|^2. \quad (5.4) $$

where $\phi$ is transport coefficient. Here we assumed that the flow is generated by an effective pressure (due to polymerization at the front and depolymerization at the rear) determined by the absolute value of the orientation vector. The image shown in figure 6c is again in qualitative agreement with experimental data [23]: the flow is retrograde and slightly increased at the sides of the cell. The flow is of the order of 10 per cent of the cell’s velocity.

5.4. Estimation of model parameters

Some parameters in our model can be estimated from available experimental values: the maximum actin polymerization velocity ($\alpha \cdot \beta \approx 0.1 \mu m \, s^{-1}$), the actin depolymerization rate ($1/\tau_1 \approx 0.02–0.1 \, s^{-1}$, depending on physiological conditions of the cell) and the diffusion coefficient of actin filaments $D_\alpha \approx 0.1–0.2 \mu m^2 \, s^{-1}$ [4]. As in our model we set $1/\tau_1 = 0.1$, the unit of time is set approximately to 10 s. From the diffusion coefficient of $p$ used, $D_\beta = 0.2$, we obtain the typical length scale of 1 $\mu m$, which is of the order of an actin filament. Correspondingly, the range for the dimensionless values of the parameters $\alpha$, $\beta$ in equations (2.5) and (2.6) is 0.2–2. The stiffness of the interface is given by the ratio of surface tension (typically 1 pN) and friction coefficient (typically several pNs $\mu m^{-2}$) [19] which yields the estimate $D_\beta \approx 1$. The motor-related parameter $\gamma$ was varied from zero to a value $\gamma \approx 0.1 \mu m \, s^{-1}$, which is of the order of a typical motor speed, implying that it takes at least 100 s to establish a broken symmetry across a 10 $\mu m$ cell. A list of the model parameters and typical values used in the simulations are summarized in table 1.
6. CONCLUSIONS
In this work, we proposed and studied a nonlinear dynamical model for cell motility, which is computationally effective and gives insights into the dynamics and shapes of moving cells or cell fragments. The results are in overall qualitative agreement with available experimental data. Our model yields some non-trivial predictions worthy of experimental verification. In particular, our results indicate that there is no unique relation between the cell’s aspect ratio and speed; the mutual dependence is influenced by the total area/volume of the cell, as well as by other model parameters, and it could be even non-monotonous as shown in figure 5. This multiparametric dependence may explain significant scatter of the data on aspect ratio versus speed plots measured experimentally (cf. fig. 4b in [20]).

The proposed model can be extended in many directions. For example, the effects of mechanical stresses (elasticity or viscoelasticity of the actin gel) or intracellular flow (which we discussed here only very briefly in the Darcy limit) could be incorporated into the model as additional fields directly coupled to the polarization and phase field. Another important avenue for the development is a more realistic implementation of the interaction with the substrate. The substrate’s elastic properties (as shown in Chan & Oded [30]) strongly affect the character and dynamics of cell motion, an effect that can be possibly captured in a refined model.

Finally, in addition to insights into the biological problem of cell motility, our results could prove useful for the design of synthetic systems, such as self-propelled polymer functionalized microcapsules [31,32] that are currently investigated for the design of self-healing materials with artificial microvascular networks: their mobile healing agents (e.g. glue-filled microcapsules) are transported along the microvascular network to damaged areas to make repairs [33].

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