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Membrane tension feedback on shape and motility of eukaryotic cells

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HIGHLIGHTS

- We investigate how the properties of the cell membrane affect the shape and motility of the cell.
- We find that the most important effect is the feedback of membrane tension on the actin polymerization.
- We observe that the bending rigidity has only minor effects, visible mostly in dynamic reshaping events.
- We investigate how the cell interacts with an obstacle.

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ABSTRACT

In the framework of a phase field model of a single cell crawling on a substrate, we investigate how the properties of the cell membrane affect the shape and motility of the cell. Since the membrane influences the cell dynamics on multiple levels and provides a nontrivial feedback, we consider the following fundamental interactions: (i) the reduction of the actin polymerization rate by membrane tension; (ii) area conservation of the cell's two-dimensional cross-section vs. conservation of the circumference (i.e. membrane inextensibility); and (iii) the contribution from the membrane's bending energy to the shape and integrity of the cell. As in experiments, we investigate two pertinent observables — the cell's velocity and its aspect ratio. We find that the most important effect is the feedback of membrane tension on the actin polymerization. Bending rigidity has only minor effects, visible mostly in dynamic reshaping events, as exemplified by collisions of the cell with an obstacle.

1. Introduction

Motility of cells crawling on substrates attracts substantial interest among biologists, physicists, mathematicians and material scientists alike [1–5]. Cell motility is a fundamental phenomenon that is crucial for a variety of biological processes, from morphogenesis to immune response [6,7]. It is also involved in pathologies like cancer growth and metastasis [6]. Like swimming microorganisms, crawling motile cells are natural and interesting realizations of active, self-propelled systems, displaying self-organized dynamics [8], flows, as well as intriguing collective effects [9]. Moreover, motile cells and living tissues are inspiring novel adaptive materials with intricate properties like active visco-elastic response [10] and self-healing [11]. Cellular materials, responding on the topography, elasticity, and surface chemistry of the substrate they are in contact with, currently inspire microstructured design strategies for cell sorting and guiding [12].

The main processes involved in the motion of eukaryotic cells (such as keratocytes, fibroblasts or neutrophils) are the following: the generation of a propulsive force by actin polymerization against the cell's membrane, the formation of adhesive contact to the substrate to transfer this propulsion force and to move forward, and finally, the action of molecular motors in determining the cell's polarity and to retract the rear of the cell [13]. All these processes have been modeled in some detail, and models for whole moving cells have been recently developed [14–18]. However, there is another important player in the game, that has been neglected (or its consequences not yet thoroughly studied) in most of the modeling approaches: namely, the membrane enclosing the cell. The cell membrane represents a movable interface which constitutes an intricate theoretical and numerical problem. In addition, membrane

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tension leads to a global force feedback, affecting the propulsion by ratcheting the actin filaments. Moreover, membrane bending rigidity may be relevant in some cases, especially for cell collisions with other cells or obstacles.

The first detailed experimental study on the effects of membrane tension on spreading cells (fibroblasts) dates back no longer than in 2000 [19]. There, an inverse relation between spreading/lamellipodium extension and membrane tension was found: lowering the membrane tension by adding detergents (deoxycholic acid) or lipids led to an increased spreading and extension, while an increase in tension by placing cells in a hypotonic medium reduced both effects. The authors concluded that membrane tension may constitute a global coupling involved in determining both the cell's shape and the propulsion dynamics, cf. also the recent reviews [20,21]. The effect of membrane tension was studied also for neutrophils, both during pseudopod formation and for fully developed motion [22], for spreading fibroblasts [23], as well as for moving keratocytes [24]. Some of the observed effects include: (i) increased membrane tension can cause leukocytes to stop moving [22]; (ii) reducing tension can stimulate moving keratocytes to develop several fronts [24]; (iii) softening the cell membrane does not affect the velocity of keratocytes [24,25], it only increases the retrograde flow of actin towards the cell's interior.

Membrane tension has been recently taken into account, for instance, in the one-dimensional model for growth cones [26]. The force balance-based model in [27] includes also an explicit adhesion dynamics between the actin cortex and the membrane. Very recently, tension gradients and flows inside the membrane were addressed [28,29]. However, these models do not take shape changes into account, obviously an important aspect of the membrane's feedback. As a result, they cannot properly describe the onset/cessation of motion. These two important aspects can be easily and inherently modeled within the phase field approach recently developed for motile cells [16,17,30–35], self-propelled active droplets [36–38] and synthetic polymeric capsules [11]. Here we include and study the most pertinent membrane effects—tension and its feedback on polymerization, as well as bending. The study is performed within a simple phase field approach for a moving cell.

2. Phase field model for a crawling cell

The phase field approach to cell motility has been recently reviewed in [39]. Instead of modeling the cell's interface (i.e. the membrane) explicitly, an auxiliary field, the phase field $\rho(x, y; t)$, is introduced. It evaluates to $\rho = 1$ within the cell and to $\rho = 0$ outside the cell, with a smooth transition region in between describing the 'smeared' interface. The simplest implementation of the phase field approach is via a scalar order parameter equation

$$\partial_t \rho = -\frac{\delta F_P}{\delta \rho}, \quad \text{where } F_p = \int \left[f(\rho) + D_\rho (\nabla \rho)^2 \right] dx\, dy. \tag{1}$$

Here $f(\rho) = \frac{\rho^2(1-\rho)^2}{4}$ is a double well potential with minima at $\rho = 0$ and $\rho = 1$ (the two 'phases'). The phase field free energy F_p in addition includes a surface energy term penalizing interfaces. Eq. (1) yields

$$\partial_t \rho = D_\rho \Delta \rho - \rho(1-\rho)(\delta - \rho) =: \lambda, \tag{2}$$

where δ is the 'pressure difference' between the two 'phases'. For $\delta = \frac{1}{2}$ the free energy of both phases is equal, and hence a planar interface connecting states $\rho = 0$ and $\rho = 1$ is stationary. In case δ deviates from this value, the interface moves either forward or backward, i.e. the cell expands or retracts.

We used this simple framework to model a moving cell [17] by coupling the phase field Eq. (2) to the polarization field $\mathbf{p}$, describing the averaged local orientation of the actin filaments inside the cell:

$$\partial_t \rho = D_\rho \Delta \rho - \rho(1-\rho)(\delta - \sigma |\mathbf{p}|^2 - \rho) - \alpha \mathbf{p} \cdot \nabla \rho, \tag{3}$$

$$\partial_t \mathbf{p} = D_p \Delta \mathbf{p} - \beta \nabla \rho - \tau_1^{-1} \mathbf{p} - \tau_2^{-1}(1-\rho^2)\mathbf{p} - \gamma \left[(\nabla \rho) \cdot \mathbf{p} \right] \mathbf{p}. \tag{4}$$

In this description, the α-term models the propulsion of the cell's interface by the ratcheting of actin, and the σ-term accounts for acto-myosin contraction. In Eq. (4), the terms $D_p \Delta \mathbf{p}$ and $-\tau_1^{-1}\mathbf{p}$ describe diffusion of actin and its degradation (depolymerization) in the bulk of the cell, respectively. The term $-\beta \nabla \rho$ describes the creation of actin polarization at the cell membrane (directed normal to the interface) with polymerization rate β. The contribution $-\tau_2^{-1}(1-\rho^2)\mathbf{p}$ assures a vanishing polarization outside of the cell (where $\rho = 0$). Finally, $-\gamma \left[(\nabla \rho) \cdot \mathbf{p} \right] \mathbf{p}$ models the front-rear symmetry breaking induced by motors. For details we refer to [17,39].

Since motile cells are rather thin (typical lamellipodium thicknesses are 200 nm) the model is effectively two-dimensional, i.e. height averaged. In addition, keratocyte cells are known to preserve their contact area with the substrate. To describe this conservation of the cell's contact area, we introduced the following global constraint

$$\delta = \delta_V = \frac{1}{2} + \mu_V \left[V(t) - V_0 \right]. \tag{5}$$

Here μ_V is the stiffness of the constraint and the term in brackets is the difference between the current area (or 2D volume) $V(t) = \int \rho(t)\, dx\, dy$ and the prescribed area V_0. Note that, to avoid confusion, in the following *area* always corresponds to the 2D area of the cell's cross-section (corresponding in a 3D description to the cell's volume), while the membrane refers to the surface, i.e. circumference, of this cross-section (corresponding in a 3D description to the cell's surface area).

The position of the interface – which is identified with the cell membrane – can be defined in the model by the contour at $\rho = \frac{1}{2}$. However, this interface is not an appropriate description for a cell membrane: it has neither membrane tension nor bending energy, but rather an (artificial) wall energy ($\propto \sqrt{D_\rho}$) that is related to the Ginzburg–Landau-type free energy of the phase field, cf. Eq. (2).

Even more important in the context of cell motility is the fact that membrane tension counteracts the polymerization force of the actin filaments: polymerization rate and hence the cell's velocity decrease as a function of the counteracting force, as established theoretically on a single filament level by the Brownian ratchet model [40,41]. Although studies of single/few actin filaments polymerizing against a load are very difficult, this effect could also been established experimentally [42–44]. The membrane tension feedback on actin polymerization possibly not only leads to a change in the overall velocity of the cell, but also to a global feedback on the actin organization and a change in the overall shape of the cell.

3. Membrane tension as a counteracting force to polymerization

We will first focus on the effect of membrane tension on actin polymerization within the whole cell model described in the last section. To this purpose, we remove the – artificial – wall energy of the phase field, and add the restoring force of the membrane counteracting polymerization. For simplicity, we keep the simple volume conservation and ignore at first the effect of tension on the phase field, a limit corresponding to a strongly adhering cell that keeps its contact area constant. The effect of tension on the phase field is added and studied in the next section.