

## Phase-field approach to cell motility in 2-D and 3-D

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**Résumé** — Motility of living cells is widespread in developing and mature organisms and is observed for many cell types. Cell movement *in vivo* is typically characterized by strong confinement and heterogeneous, three-dimensional environments. Here we apply the recently developed phase-field approach to model cell shape waves, their competition on the level of a whole cell, and movement of the cells in 3-D environments. Our model serves as an important benchmark to systematically explore lamellipodium-based motility and its interaction with the heterogeneous environment.

**Mots clés** — cell motility, lamellipodium, phase-field approach

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## 1 Introduction

Tissue and cell motility is an equally important topic for biology, non-equilibrium physics, and applied mathematics. Collective and individual cellular migration can be viewed as examples of self-organized dynamic states. These states transduce the chemical energy delivered by the metabolism into directed self-organized mechanical motion. Many aspects of the enormously complex dynamics of cell and tissue migration can be cast in the framework of relatively simple physics-driven models [1, 2, 3].

Quantitative physics-driven studies of cell motion have in the past focused almost exclusively on cells crawling along flat substrates due to the relative ease in observation, data analysis, and modeling [4]. The biology community [5] often criticized this approach since in living organism cells never function in such an idealized flat world. Furthermore, the cells typically migrate in complex 3-D environments. These environments are strongly inhomogeneous and reorganized by both mechanical forces and chemical action from the cells. For example, leukocytes [6] and metastatic cancer cells [7] migrate along or within blood vessels. To reach a target site, they need to squeeze through epithelial layers, or extracellular matrix (ECM). These examples of such complex heterogeneous substrates involve various topographical and confining features, such as tubular and planar confinement, fibers or fiber bundles, as well as random 3D fiber networks.

Over a number of years, we develop a physics-based modeling framework that describes the cell movement in 2-D and 3-D settings. The model is intentionally kept as simple as possible. Still, it is able to reproduce a plethora of single cell movements and collections of cells in 2-D and 3-D environments. In 2-D, it successfully reproduced a subcritical onset of motion [8], a nontrivial response on modulation of mechanical and adhesive properties of the substrate [9], the onset of collective migration [10], and completion between lamellipodium waves [11]. In 3-D, the elegant use of the phase field approach [12] allows to model motion in arbitrarily shaped and nontrivial environments [13]. In this approach, the phase-field method is used for the cell and for the surroundings it interacts with.

### 1.1 2-D phase-field model

Following the concept of the phase-field method developed in Refs. [8, 14, 15], we use three corresponding physical fields to describe the 2-D cell migration. First, an Allen-Cahn phase-field describes the cell shape with  $\rho(\mathbf{r}, t) = 1$  inside the cell and  $\rho = 0$  outside. The field  $\rho$  is augmented by a (2D) volume conservation to model the cell shape. Second, a vector field  $\mathbf{p}(\mathbf{r}, t)$  describes the actin orientation and

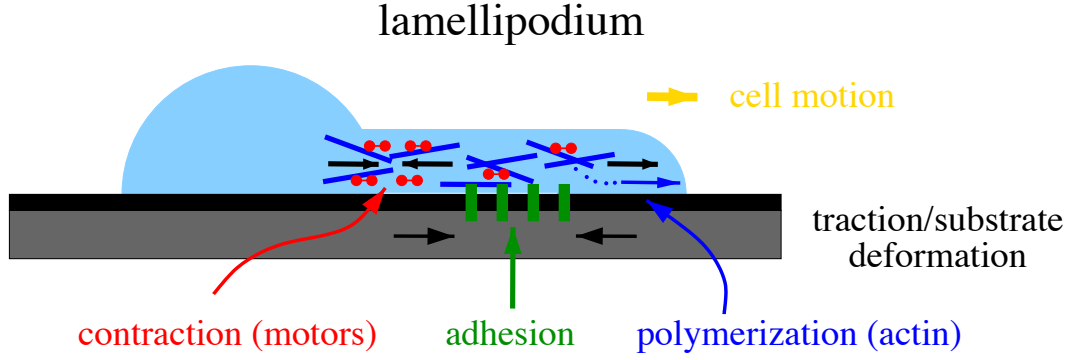


FIGURE 1 – Illustration of the main physical mechanisms governing the substrate-based cellular motion : actin polymerization, substrate adhesion, and contraction by molecular motors.

degree of ordering. Then, the third field describes the density of engaged adhesive bonds  $A(\mathbf{r}, t)$  that is coupled to the deformable (or compliant) substrate, see Fig. 1. The phase field equation takes the form of nonlinear reaction-diffusion equation :

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

with the controlling parameter  $\delta$  given by

$$\delta(\rho) = \frac{1}{2} + \mu \left[ \int \rho dx dy - \pi R_0^2 \right]. \quad (2)$$

Here  $\delta = \frac{1}{2}$  is the stationary point. The second term in Eq. (2) introduces 2-D volume conservation with target volume  $V_0 = \pi R_0^2$  for some fixed initial radius  $R_0$ . The stiffness of the constraint is given by  $\mu$ . The term  $\propto \sigma$  models, on a highly simplified level, actin network contraction by myosin molecular motors with constant rate  $\sigma$ . The last term  $\alpha A(\mathbf{p} \cdot \nabla \rho)$  describes the translation (or ‘advection’) of the cell membrane due to the ratcheting action of actin filament polymerization near the membrane, with the effective velocity  $\alpha$ . Since only filaments that adhere to substrate can transfer the force to the substrate, the advection term is proportional to the adhesion strength  $A$ .

The actin dynamics equation is cast in the form :

$$\partial_t \mathbf{p} = D_\rho \Delta \mathbf{p} - \beta e^{-T_1 c \delta S} \nabla \rho - \tau_1^{-1} \mathbf{p} - \tau_2^{-1} (1 - \rho^2) \mathbf{p} - \gamma (\nabla \rho \cdot \mathbf{p}) \mathbf{p}. \quad (3)$$

The first term models diffusion of actin filaments/elasticity in the ordered state. Actin generation at the membrane (a source) with (polymerization) rate  $\beta$  is modeled by the second term. It also includes the effect of membrane tension feedback on active polymerization as proposed in [15, 11] (in previous approaches this effect was neglected [12]). Thus, the constant  $T_1$  sets the strength of the membrane tension,  $c = -\nabla \cdot \frac{\nabla \rho}{|\nabla \rho|}$  is the local curvature of the cell membrane and  $\delta S = \frac{S(\rho) - S_0}{S_0}$  is (proportional to) the excess surface area. Here  $S(\rho) = \int |\nabla \rho| dx dy$  and  $S_0$  are, respectively, the instantaneous and the reference(or target) surface area. The next two terms in Eq. (3) are sinks and model respectively : (i) the degradation/depolymerization of actin filaments inside the cell with the typical timescale  $\tau_1$ , (ii) suppression of actin outside the cell. The last term in Eq. (3) describes on a phenomenological level the myosin motors’ tendency : (i) to form antiparallel actin bundles reducing the actin polarization, (ii) to breaks the symmetry between the front and rear of the cell [8].

An equation of reaction-diffusion type models the engaged adhesion bonds dynamics :

$$\partial_t A = D_A \Delta A + \rho(a_0 |\mathbf{p}|^2 + a_{nl} A^2) - (d(u) + s A^2) A. \quad (4)$$

Here, correspondingly, the first term is a diffusion. A second term describes the attachment kinetics and has two contributions : (i) a linear contribution due to the presence of actin and (ii) a nonlinear contribution modeling collective effects. The last term  $-(d(u) + s A^2) A$  restricts the number of adhesive bonds

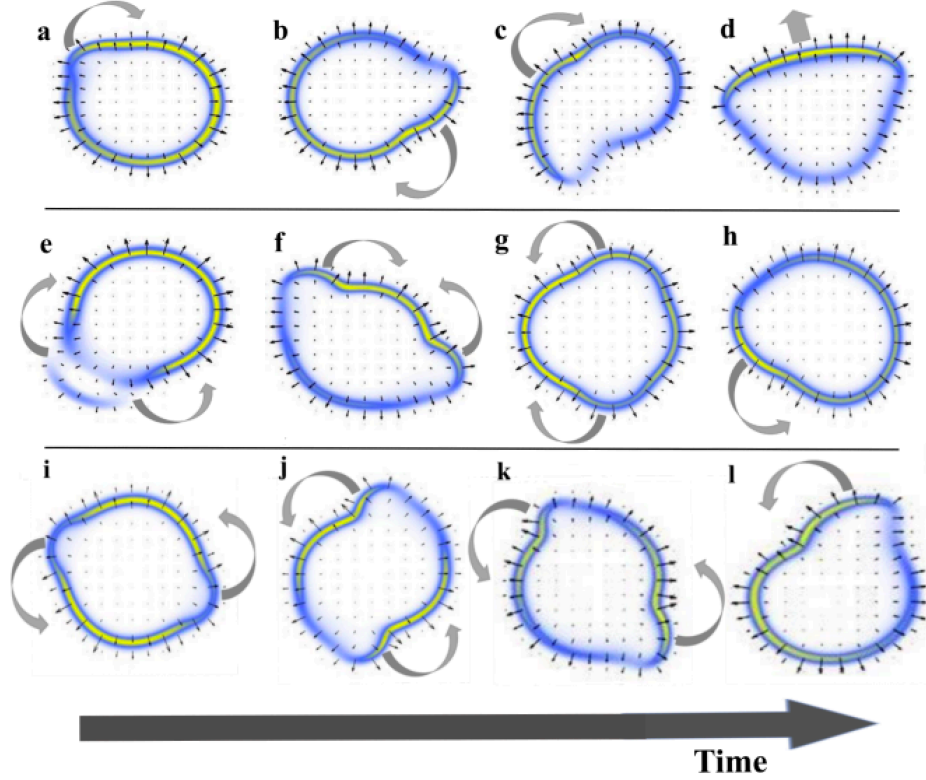


FIGURE 2 – Time evolution of three select rotational states obtained by numerical solution of Eqs. (1)-(6). (a)-(d) shows a cell with one lamellipodium wave rotating clockwise. Finally, the cell polarizes. (e)-(h) shows a cell with two lamellipodium waves rotating in opposite directions. (i)-(l) shows a cell with two lamellipodium waves rotating in the the same (counterclockwise) direction. The magnitude of actin polarization,  $\mathbf{p}(\mathbf{r})$ , is color coded (with blue for small and yellow for large values) and its direction shown as the black arrows. The grey arrows indicate the direction of rotation for the deformation waves or the direction of motion in case of a polarized cell, from [11].

by excluded volume,  $\propto s$ , and substrate-dependent detachment. The corresponding substrate-dependent detachment rate is modeled as follows :

$$d(u) = \frac{d_0}{2} \left[ 1 + \tanh \left( b \left( |\mathbf{u}_{z=H}|^2 - u_c^2 \right) \right) \right] \quad (5)$$

It accounts for the fact that the substrate is soft and can be deformed by the cell via the traction forces it exerts on it by the adhered cell. Equation (5) is based on the assumption that adhesion bonds between cell and substrate will break where the local substrate deformation directly underneath the cell,  $|\mathbf{u}_{z=H}| = |\mathbf{u}(x, y, z = H)|$ , exceeds a critical value  $u_c$ . The substrate itself is modeled as a three-dimensional isotropic homogeneous visco-elastic solid of Kelvin-Voigt-type. Here  $H$  is the effective thickness of the substrate. Substrate visco-elasticity is described by the shear modulus  $G$  and an effective viscosity  $\eta$  modeling energy dissipation due to adhesive bonds rupture. This treatment has been discussed in details in Refs. [11, 14, 16]. It yields the displacement at the top surface of the substrate (in contact with the cell),  $\mathbf{u}_{z=H}$ , due to the traction force distribution exerted by the cell. The traction  $\mathbf{T}$  is of the form

$$\mathbf{T} = -A\rho \left( \mathbf{p} + cT_1 \delta S \hat{n} - \frac{\int A(\mathbf{p} + cT_1 \delta S \hat{n}) \rho \, dx dy}{\int A \rho \, dx dy} \right). \quad (6)$$

The first two terms  $\mathbf{p} + cT_1 \delta S \hat{n}$  are the reaction forces that originate from actin polymerization and membrane tension (due to the preservation of the membrane surface area). The last term is due to friction with the substrate. Since the cell is an isolated self-propelled object, this term ensures that the net force on the substrate is zero.

The above model captured many aspects of cell motility, see for review [12]. Most recently, the model described the onset of rotating lamellipodia waves [11], see Fig. 2, in close agreement with experimental

observations [17, 18]. Thus, this study revealed that the onset and competition of rotating lamellipodia waves can be captured in the framework of a simple physical model incorporating, on a phenomenological level, cell shape dynamics, actin polymerization, substrate deformation, and adhesion. Furthermore, these findings demonstrate that for the emergence of lamellipodia waves one only needs the interplay of protrusion, adhesion, and contraction.

## 1.2 Extension to 3-D

The two-dimensional phase field model of cell motility presented in Ref. [8] can be readily extended to 3-D situation [13]. As before, the cell's interface identified with the membrane is described by the transition region of a dynamic 3D scalar phase field  $\rho(\mathbf{r}, t) \in [0, 1]$  for a closed domain representing the cell. Here  $\rho = 1$  corresponds to the cell's interior,  $\rho = 0$  to the outside. Correspondingly, the  $\rho = 1/2$ -isosurface is identified with the cell membrane. Inside this domain, the 3D vector field  $\mathbf{p}(\mathbf{r}, t)$  describes the mean orientation of actin filaments, compare Eqs. (1), (3). The cellular motility machinery is implemented via its basic physical features as described in Ref. [8].

The main difference with 2-D case is the implementation of the substrate. The substrate/environment is modeled by specifying two additional, static phase fields : (i) a faster phase field  $\Phi(\mathbf{r})$  describing steric exclusion ; (ii) a slower phase field  $\Psi(\mathbf{r})$  restricting the actin generation to regions close to the substrate. The fields  $\Phi(\mathbf{r})$ ,  $\Psi(\mathbf{r})$  have the same shape. However, they have different characteristic decay length. The decay length of  $\Psi(\mathbf{r})$  is chosen to be larger to allow for substantial actin concentration inside the cell. Correspondingly, both steric exclusion interaction and cellular adhesion to the substrate are accounted for. Cellular adhesion to the substrate is modeled on a coarse-grained level [19, 20] by an adhesion strength parameter  $\kappa$ . However, explicit adhesive dynamics can in principle be introduced [9, 14, 21]. Like in 2-D case, the order parameter dynamics is non-conserved, see e.g. the discussion in Ref. [12]. To ensure the cell volume conservation, it needs to be supplemented by volume conservation similar to that of in Eq. (2).

Like in 2-D, the polarization dynamics has three contributions : from actin turnover, a diffusion (or elastic) term, a source term proportional to the parameter  $\beta$  (related to the actin polymerization velocity, of the order of  $0.1 \mu\text{m/s}$ ), and a sink term describing the degradation of actin, e.g. via depolymerization, with time scale  $\tau$  being of the order of the actin turnover time (typically seconds), compared with Eq. (3). On the phenomenological level, actin polymerization is modeled anisotropically with respect to the local tangential plane defined by the substrate.

Using the above 3-D phase-field framework, we observed that the three-dimensional computational model is capable to describe the lamellipodium-driven crawling motion of cells in – in principle – arbitrarily shaped surroundings and for a variety of cell types [13]. In contrast to earlier studies in 3-D [1, 22, 23, 24], our approach does not need to predefine protrusive regions in the cell, as it naturally exhibits bistability between immobile vs. moving states [8]. We explored several well-defined and experimentally studied scenarios of geometrical perturbation during cellular migration : a systematic variation of the substrate's curvature (from cells on thin fibers to the movement inside a capillary or a pore), vertical confinement between two plates, as well as the motion on topographically structured substrates (substrates with ridges). The discovered response in cell behavior is due to purely physical effects (confinement, curvature) and their interplay with the self-organized shape and actomyosin machinery. This study, therefore, is fruitful in helping to differentiate such simpler physical effects from more complex cellular biochemical and regulatory responses.

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