Phase-field approach to chemotactic driving of neutrophil morphodynamics

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To simulate the motion of neutrophils and their morphodynamics in response to chemical cues, we construct a model based on the phase-field method utilizing a description with a free-energy functional and associated dynamics which captures the basic features of the phenomenon. We additionally incorporate spatial sensing by introducing an auxiliary field which depicts the polymerization of the region of the cell facing the highest concentration of the chemical attractant.

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I. INTRODUCTION

Cell motion involves microscopic processes responsible for the production of protrusive forces shared by a multitude of biological systems. These include cancer metastasis, embryogenesis, and chemotaxis [1]. The last is the migration of the cell under the effect of chemical cues present in the environment. Neutrophils, being among the first responders of the immune system, chemotax and are able to detect the small chemical gradients in the surroundings induced by specific mediators. These mediators instigate a polymerization mechanism at the leading edge of the cell which, together with an active actin cytoskeleton, makes the immobile cell gain movement in the direction of the gradient, and drives it to the site of infection [2]. This sensing process is realized by reordering or activating lipids or proteins in the plasma membrane and by setting a favorable direction for the cell’s motion. Moreover, the mechanism prevails when the cell is immobile, suggesting its capability for performing spatial sensing [3–6].

Actin, indispensable for inducing the cell’s movement, has complex intertwined and fast-paced dynamics on the time scale of motion. However, simplifying models suggest that it can be reduced to a handful of mechanisms [7]. More precisely, the actin filament is assimilated to a rodlike polymer with a positive end, called the barbed end, which points towards the membrane, and a negative end which points towards the cells interior. Capping and coflin and/or β-thymosin binding of the barbed end dampen the accumulation of profilin-ATP-G actin near the membrane, the complex responsible for the production of the protrusion force.

The intricacy of modeling cell motion, particularly that of neutrophils, lies in the dependence of their dynamics on a moving boundary; the cells exhibit notable changes in their membranes as they move towards the target. This highly nonlinear interdependence in such systems, called a free-boundary problem, requires methods that allow us to locate boundaries with high efficiency. The level set method shows the presence of the boundary, while a first-order sensitivity analysis provides a first-order estimate of the concentration of the chemical attractant.

In this work, we develop a phase-field model for a migrating neutrophil and follow its morphodynamics in response to an external chemical cue in two and three dimensions. Additionally, internal structural changes affecting the cell’s homogeneity are included. For that purpose, we introduce a field \( \phi \) distinguishing between the cell’s interior and its surroundings, and assign a value of 1 and 0 for those regions. A smooth transition between them designates the interface, which is the cell membrane characterized by surface tension. Also, the leading edge of the cell is described by \( \psi = 1 \) and 0 elsewhere. Compositional changes in the environment are reflected by the presence of an attractive cue to which we assign a variable \( c \). Our approach reproduces physical properties related to membrane deformation as well as the cell’s velocity profile when compared to that of a migrating in vitro neutrophil. In constructing the model, simplifications are made, specifically at the molecular level of the cell and in the form of external driving. However, the model still recovers salient features of cell chemotaxis and can be generalized to other single- as well as collective cell motion.

II. THEORY

The molecular level disparities between two phases of a material are reflected at the macroscopic level and are quantified by an average field distinguishing their properties called the order parameter or the phase field \( \phi \), to which a specific value is assigned in each phase. Its functional relation to the free energy describes the equilibrium properties of the system [11,12]. To construct the free-energy functional, we make use of its analyticity. Thus, it can be expanded in powers of \( \phi \), which is the energy in the bulk, and \( \nabla \phi \), the extra energy resulting from the presence of an interface. These together form the heart of the Ginzburg-Landau premise [13]. The symmetry constraints of the system determine the coefficients of this expansion. Additionally, any external field \( H \) that acts on the system by driving transitions between its phases must be included in the functional as well. For a two-phase system the free energy of the bulk is a double-well function with minima located at the values assigned to the field in each phase and chosen to be 1 and 0, which guarantees their coexistence. Expansion in powers of \( \nabla \phi \) are considered to second order which shows the presence of the boundary, while a first-order term vanishes since the system should be invariant under the...
change of coordinates $x \rightarrow -x$. The free-energy functional in its most general form can be written as follows:

$$\mathcal{F} = \int \left[ \frac{\epsilon (\nabla \phi)^2}{2} + f(\phi) + H\phi \right] dV, \quad (1)$$

where $\epsilon$ is proportional to the surface tension, and $f(\phi) = a \phi^2(1 - \phi)^2$, where $a$ has units of energy per volume.

Now the cell and its environment can be considered as two coexisting phases to which we assign fields $\phi = 1$ and $\phi = 0$ respectively. In addition, to reflect the cell interior’s inhomogeneity [14], another field that differentiates disparate regions within its interior is needed. It is denoted by $\psi$; it delineates the cell’s polymerized edge, which is localized near the cell membrane [4]. $\psi$ is 1 at the leading edge and 0 elsewhere. The evolution of both fields defines the cell, its boundary, and its leading edge and is governed by partial differential equations derived from the system’s energy functional, which we modify to include the contribution of $\psi$. Then the free energy of the bulk takes the form $f(\phi, \psi) = f(\phi) + f(\psi) = a \phi^2(1 - \phi)^2 + a \psi^2(1 - \psi)^2$, guaranteeing coexistence; that is, $\phi = 1$ and $\phi = 0$ minimize the corresponding free energy $f(\phi)$, while $\psi = 1$ and $\psi = 0$ minimize $f(\psi)$. Moreover, the field describing the leading edge $\psi$ and that describing the cell $\phi$ are always coupled. They are always sharing part of the interface so that the interfacial penalty $a$ is the same for both fields. $\mathcal{F}$ is now given by modifying Eq. (1):

$$\mathcal{F} = \int \left[ \frac{\epsilon (\nabla \phi)^2}{2} + H\phi + \frac{\epsilon (\nabla \psi)^2}{2} + f(\phi, \psi) \right] dV, \quad (2)$$

where the expansion in powers of the derivatives of $\psi$ is also taken to second order.

A volume conserving cell is followed; the rate of change of $\phi$ is proportional to its conjugate force given by $\frac{d\phi}{dt} = \Gamma \nabla \cdot (\nabla \frac{\partial f}{\partial \phi})$, where $\Gamma$ is the mobility. On the other hand, the polymerized edge disappears when the cell attains the point of highest chemical concentration. Then its dynamics is nonconservative and is given by $\frac{d\psi}{dt} = -\Gamma(\frac{\partial f}{\partial \psi})$, where $\Gamma$ is the mobility of the $\psi$ field.

Now in order to include chemotactic effects in our model we note that the total derivatives of the fields are related to their partial derivatives with respect to space and time via $\frac{d\phi}{dt} = \Gamma \nabla \cdot (\nabla \frac{\partial f}{\partial \phi}) = \frac{\partial \phi}{\partial t} + \nabla \cdot \nabla \phi$, and $\frac{d\psi}{dt} = -\Gamma(\frac{\partial f}{\partial \psi}) = \frac{\partial \psi}{\partial t} + \nabla \cdot \nabla \psi$, where $\nabla$ and $\nabla'$ are the velocities of the $\phi$ and $\psi$ fields, respectively. In the chemotaxis regime the velocity of the cell is assumed to be linearly proportional to the gradient of the chemical concentration $c$ and controlled by the presence of an active actin cytoskeleton represented by $b$; it is given by $\nabla = b \nabla c$. Also, identifying the velocity of $\psi$ to be $\nabla' = b \nabla c$ guarantees the coupling of the leading edge $\psi$ to the rest of the cell $\phi$ and forces $\psi$ to move in synchrony with $\phi$ under the effect of the chemical cue $c$. The proportionality constant appearing in both definitions of the field velocities, $b$, is nonzero and is due to the existence of a functional actin mechanism; it is zero otherwise, when no motion is induced. The validity of this assumption relies on the observation that the dynamics of actin is fast compared to the other mechanisms so that its concentration available in the cell assumes the steady state value once it is triggered. This approach is a simplification of a complex regulation mechanism between the detachment of myosin from the rear of the cell and polymerization of an actin network at its leading edge.

The external field $H$ was added to the functional to impose the conservation of the field $\phi$, such that $\frac{d\phi}{dt} = \nabla \cdot J$, where $J$ is a flux. This forces $H$ to be constrained by $\Gamma \nabla \cdot (\nabla H) = -b \phi \nabla^2 c$; then $J = -\Gamma \nabla [\epsilon \nabla^2 \phi - f_\phi(\phi, \psi)] - b \phi \nabla c$. Using Eq. (2), we get

$$\frac{\partial \phi}{\partial t} = -\Gamma \nabla^2 [\epsilon \nabla^2 \phi - f_\phi(\phi, \psi)] - b \nabla \cdot (\phi \nabla c), \quad \frac{\partial \psi}{\partial t} = \Gamma [\epsilon \nabla^2 \psi - f_\psi(\phi, \psi)] - b(\phi \nabla c) \cdot \nabla \psi, \quad (3)$$

To simulate the presence of a chemical cue, we assume that the concentration $c$ follows the diffusion equation (2) where $a_1$ is the chemical concentration degradation rate, and $D_1$ is the diffusion coefficient of the attractant. $f_\phi$ and $f_\psi$ are the derivatives of $f(\phi, \psi)$ with respect to $\phi$ and $\psi$, respectively.

### III. RESULTS

The system of Eq. (3) is solved in two and three dimensions, as shown in Figs. 1 and 2, respectively. The fields are initialized as follows: $\phi = [1 + \tanh(x - d)]/2$, where $d$ is the cell diameter, and $\psi = \Theta(-\nabla \cdot \nabla \phi)$, where $\Theta$ is the Heaviside step function. This mimics the emergence of the structural changes at the leading edge; this term is 0 everywhere except at the region of the cell facing the highest chemical concentration, which is physically the locus of the plasma membrane.

Figure 1 shows snapshots of the neutrophil crawling to its target position, together with its leading edge. Figure 2 shows it in three dimensions, as depicted by the red deforming
The analysis of the motion on an in vitro neutrophil subject to a chemical stimulus [15] confirmed our results. The video depicting the motion was transformed into a time-lapse video, and the velocity was repeatedly measured at different locations along the line joining the cell’s center of mass and the target position using manual tracking in IMAGEJ. The standard deviation of these measurements allows us to estimate error bars. The video showed an exponentially decaying behavior proportional to $e^{-x/\xi}$. This is consistent with our result that the motion is primarily diffusive. Additionally, this allowed us to retrieve the value of the diffusion length $l_d = \xi = 6.7 \pm 0.5$ in units of cell diameter, as well as the diffusion coefficient $D' = \frac{\xi^2}{2\tau'} = 5.1 \pm 0.7$ in units of cell diameter squared per second, where $\tau'$ denotes the time needed to reach the steady state; this lies close to the value of $D$ calculated above.

In Fig. 3 both the nondimensionalized velocities were plotted as functions of the ratio of distance to half the diffusion length, $X = x/\sqrt{Dt} = \frac{x}{\xi}$. The dots show the velocity of the cell at different positions predicted by our model, while the stars show the actual in vitro velocity of the neutrophil. This again shows agreement between our results and the experimental observations.

The one-dimensional version of our model was implemented, and compared with the Keller and Segel [16] minimal one-dimensional model (M1). The latter expects cells to aggregate at the location of zero chemical gradient, where the cell density shows a sharp boundary peak [17].

Our model follows the evolution of a cell with linear sensitivity to chemical cues. A sharp peak is observed at steady state, mimicking that of M1. Furthermore, M1 exhibits a finite-time blowup in dimension $d \geq 2$, as successfully portrayed by our model Eq. (3) in Figs. 2 and 1. On the other hand, when comparing our results with the level set method developed to model a cell crawling [9], our model reproduces deformations of the cell not observed in that approach. There the cell’s boundary deformations are not comparable to those of the neutrophil. Also, in the other models where the phase-field method is used, the numerical results show a simple flattening of the cell as it crawls towards its target [1,10] and do not reproduce the complex morphological alterations the cell undergoes.

**IV. DISCUSSION**

The model presented here successfully reproduces the motion of a neutrophil induced by the presence of a chemical attractant. The one-dimensional model showed a similar steady state solution as in previous work [16] (M1). However, unlike the latter which exhibits a finite-time blowup in dimension $d \geq 2$, our model remains stable for all dimensions. It depicts the morphological changes that the cell undergoes during motion, as seen experimentally. The experimental imaging of the directional sensing shows a high pixel intensity in the...
region of the cell that faces the highest chemical concentration [18]. Additionally, the cell is classified as motile if clear-cut shape deformations are discernible, even without resorting to time-lapse procedures [16]. The appearance of a tail and a contracted region indicates the posterior part of the cell, while the growing area marks its anterior, which was captured qualitatively in our model. To additionally test for the validity of our model we analyzed a time-lapsed video of the motion of the neutrophil using IMAGEJ, an image-processing software program. The velocity was measured at different locations along the cell’s direction of motion and our simulations were used to obtain the values of the correlation length as well as the diffusion coefficient.

The actin polymerization dominance over the retrograde flow is simplified and is described by a constant which takes nonzero values in that case and zero when the cytoskeleton is not active. A more complex dynamics governs actin polymerization and thus a modification of the model to account for that process would be a useful subject for future work.

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