Dynamics of a cell motility model near the sharp interface limit

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Abstract

Phase-field models have recently had great success in describing the dynamic morphologies and motility of eukaryotic cells. In this work we investigate the minimal phase-field model introduced in [6]. Rigorous analysis of its sharp interface limit dynamics was completed in [15, 16], where it was observed that persistent cell motion was not stable. In this work we numerically study the pre-limiting phase-field model near the sharp interface limit, to better understand this lack of persistent motion. We find that immobile, persistent, and rotating states are all exhibited in this minimal model, and investigate the loss of persistent motion in the sharp interface limit. In addition we study cell speed as a function of biophysical parameters.

Keywords: phase-field, keratocyte motion, traveling wave, rotating cell

1. Introduction

Eukaryotic cell motility underlies numerous biological processes including the immune response and cancer metastasis. Cell motion is initiated and
maintained by an evolving cytoskeleton comprised of actin and myosin proteins capable of driving a wide range of motility modes. In recent years a variety of modeling techniques have been highly successful in replicating, explaining, and predicting cell morphologies observed in experimental settings, see, e.g., [1, 3, 7, 8, 17, 19, 20, 22, 24]. In this work we focus on the bridge between two modeling paradigms: free boundary problems and phase-field models. Free boundary problems track the cell boundary via a curve (2D) or surface (3D) whose evolution is governed a geometric evolution equation, often dictated by boundary data of a differential equation solved on the interior. Phase-field models, on the other hand, use an evolving order parameter whose finite width transition layer between phases tracks the cell boundary. Phase-field models avoid difficulties of explicitly discretizing and tracking the moving interface, making them ideal for numerical simulation.

We are motivated by the 2D phase-field model for keratocyte fragments (e.g., lacking a nucleus) studied in [6]. It is a minimal version of a more general model introduced by Ziebert, et al. in [30]. The original model in [30] has been extended to include spatial adhesion dynamics [29], non-homogeneous substrate effects [14, 23], and interacting dynamics of multiple cells [12]. These extended models exhibit a wide variety of dynamical modes and can be used to understand the complex morphologies of dynamics cells. On the other hand, the minimal model of [6] allows for rigorous mathematical analyses of the model. For example, in 1D, necessary conditions for the existence and stability of persistent motion was proved [6].

However, we note that a numerical exploration of the simplified phase-field model remains unexplored in 2D. Thus, our primary goal of this work is to numerically study the minimal 2D phase-field model introduced in [6] over a range of parameters. We find that this simplified version is still capable of exhibiting stationary and persistent motions, in qualitative agreement with more sophisticated models, but also permits rotating modes which were unexpected in this setting.

The minimal model admits a non-trivial sharp interface limit: an asymptotic reduction of the phase-field model in the limit that the width of the diffuse interface (representing the cell boundary) tends to zero, transforming the model into a free boundary problem. Rigorous analysis of the sharp interface limit was completed in both 1D [6] and in 2D [15, 16], where sufficient conditions for existence of traveling wave solutions were proved. These analyses were thus able to provide insight into the minimal biophysical mechanisms that are necessary to drive these motility modes, and which modes
require more complex mechanisms.

However, numerical simulations of the 2D sharp interface limit showed that persistent motion was unstable, and more crucially, does not exist when certain symmetry is present. Therefore, a secondary goal of our work is to explore persistent motion in the phase-field equation, and understand the behavior as we approach the sharp interface limit. We find that sufficiently small diffuse interfaces necessarily destabilize persistent motions. This provides evidence for a minimal length and time scale of actin dynamics which allow for persistent motion, and provide insight into the lack of persistent cell motion in the 2D sharp interface limit.

2. Model

2.1. Biological background

Keratocytes are prototypical for the experimental and mathematical study of cell motion. Their characteristic cell length/width is two orders of magnitude larger than the height while motile, hence they are well described by 2D models (for recent advances in 3D models see, e.g., [9, 25, 28]). Keratocytes are additionally able to exhibit persistent motion over many times the cell length with approximately constant cell shape, making them ideal starting points for the study of motion [19, 26].

We recall the following key factors contributing to cell motion, and refer the reader to [17] for a more detailed review. A crawling cell maintains self-propagating motion via internal forces generated by actin polymerization. Actin monomers bind together to form filaments which create a dense network at the leading edge of the cell, known as the lamellipod. The cell’s leading edge protrudes via growth of actin laments at the cell membrane and degradation of the filaments towards the interior of the cell, a process known as actin treadmilling. Intercellular adhesion complexes form ligand bonds to the substrate in order to transform this propulsion force into traction forces. Myosin motors interact with actin filaments to generate contractile forces. Acto-myosin interactions contract of the rear part of the cell, pulling the rear of the cell, and allowing for persistent motion. In idealized mathematical settings, such persistent motion is described by traveling wave solutions.

By varying biophysical parameters (such as actin polymerization strength, substrate adhesion/elasticity properties, or myosin motor strength), cells additionally exhibit a wide range of motility modes beyond persistent motion, such as stick-slip (oscillations in translational velocities) and bipedal (left
and right sides alternating forward motion) motions [4, 5]. Moreover, several recent studies suggest that myosin-driven contraction of the cytoskeleton is sufficient to drive persistent motion of the cell [10, 21], and that random fluctuations are sufficient to spontaneously switch a cell from a symmetric, non-motile state to asymmetric, motile states [2, 9]. As such, there is a deep need to understand the interactions of various biophysical pathways leading to such a variety of behaviors.

Finally, rotating cells were experimentally observed in [13] where cells remain essentially stationary but experience laterally periodic protrusions of the membrane. In this case, these transient protrusions are generated by actin polymerization fronts which are not sufficiently coordinated to generate persistent motion, due to, e.g., short protrusion lifetimes. In experiments, this was caused by the expression of a particular kinase (MLCK) leading to an increase of myosin activity in the cell’s lamellipod ultimately limiting actin activity globally.

2.2. Phase-field model

We study the following 2D phase-field model for cell motility, first introduced in [30] and later modified to this minimal form in [6]:

\[
\begin{align*}
\frac{\partial}{\partial t} \rho &= \Delta \rho - \frac{1}{\varepsilon^2} W'(\rho) - \mathbf{P} \cdot \nabla \rho + \lambda \\
\frac{\partial}{\partial t} \mathbf{P} &= \varepsilon \Delta \mathbf{P} - \frac{1}{\varepsilon} \mathbf{P} - \beta \nabla \rho,
\end{align*}
\]

where \( W(z) = \frac{1}{2} z^2 (1 - z)^2 \) is the standard Allen-Cahn double-well potential and \( \lambda = \lambda(t) \) is a Lagrange multiplier maintaining total enclosed area:

\[
\lambda(t) = \frac{1}{|\Omega|} \int_{\Omega} \frac{1}{\varepsilon^2} W'(\rho) - \mathbf{P} \cdot \nabla \rho \, dx.
\]

The phase-field variable \( \rho = \rho(x, y, t) \) has two phases dictated by the minima of the double well \( W \): \( \rho \approx 1 \) in the interior of the cell and \( \rho \approx 0 \) outside the cell. Competition between the Laplacian regularization and the reaction term \( W'(\rho) \) (forcing \( \rho \) to either 0 or 1), results in an \( O(\varepsilon) \) thick transition layer between the two phases marking the boundary of the cell. In the absence of the vector field \( \mathbf{P} \), (2.1) is the Allen-Cahn equation with volume preservation constraint enforced by \( \lambda \). These terms contribute overall to
mean curvature flow of the boundary whose dynamics drive the boundary to stationary circles.

In the original model in [30], the Lagrange multiplier and double well potential are replaced by

\[
F(\rho) = (1 - \rho)(\delta(\rho) - \sigma|P|^2 - \rho)\rho \tag{2.4}
\]

\[
\delta(\rho) = \frac{1}{2} + \mu \left[ \int_{\Omega} (\rho(x, y, t) - \rho(x, y, 0)) \, dxdy \right], \tag{2.5}
\]

where \(\sigma|P|^2\) represents additional myosin effects and volume preservation is enforced via the penalization in \(\delta(\rho)\). Taking \(\sigma = \mu = 0\) reduces \(F(\rho)\) to our double-well potential. We additionally note that \(\lambda = \lambda(t)\) passively encodes myosin motor effects, by virtue of enhancing contraction of the cell membrane (e.g., when \(\lambda < 0\)). Of course, this is vastly simplified as it is assumed to be constant in space and varying only in time.

Active transport of \(\rho\) occurs along the vector field \(P = P(x, y, t)\) which represents the average local orientation of actin filaments. Physically, advection requires formation of substrate adhesions to generate traction forces. Indeed, in [29] adhesion dynamics are explicitly modeled via a PDE for an auxiliary scalar field \(A = A(x, y, t)\) whose dynamics additionally encode substrate deformations (as a visco-elastic medium), and transport requires adhesion formation so that \(\partial_t \rho \sim AP \cdot \nabla \rho\). For simplicity, we assume that adhesion is formed instantaneously and uniformly.

Dynamics of actin filaments \(P\) are regularized by diffusion and experience global decay due to natural depolymerization. As actin polymerization is localized to the boundary of the cell, the source term for \(P\) is given by \(-\beta \nabla \rho\). Thus, \(\beta\) is a biophysical parameter representing an effective actin polymerization strength.

Competition between advection by \(P\) and curvature motion flow from the Allen-Cahn contribution constitute the main dynamics of interest: one expects that if \(|P|\) is sufficiently small then the cell remains immobile and if \(|P|\) is sufficiently large then the cell has sufficiently many active internal forces to generate motion.

In [23], numerical simulations of the more general phase-field model, including additional non-linear effects from heterogeneous myosin contraction, non-linear dynamics of adhesion complex formation, and substrate viscoelasticity. In that more complex setting, they observe several motility modes including several types of rotating lamellipod solutions.
(left) stationary ($\varepsilon = .02$, $\beta = 80$), (center) rotating ($\varepsilon = .035$, $\beta = 110$), and (right) persistent motion ($\varepsilon = .05$, $\beta = 130$). All simulations here done on the domain $\Omega = [0,5]^2$ with periodic boundary conditions.

2.3. Sharp interface limit

We recall that one reason we study the system (2.1)-(2.2), rather than the more general model in [23], is that the system (2.1)-(2.2) is amenable to rigorous mathematical analysis: it is possible to derive dynamics in the limit $\varepsilon \to 0$ recovering the so-called sharp interface limit. In [6], both the pre-limiting and sharp interface limit dynamics in 1D are rigorously studied. In particular necessary conditions for the existence and stability of traveling wave solutions are established, corresponding to persistently traveling cells. Additionally, they establish the 2D sharp interface limiting equation, recovering a geometric evolution equation for planar curves, $\Gamma(s,t)$ representing the boundary of the cell. They show that the normal velocity $V$ of the curves at each moment solve the equation

$$V = \kappa + \beta \Phi(V) - \frac{1}{|\Gamma(t)|} \int_{\Gamma} \kappa + \beta \Phi(V) ds$$  \hspace{1cm} (2.6)

where $\kappa = \kappa(s,t)$ represents the curvature at location $s$ and time $t$, and $\Phi: \mathbb{R} \to \mathbb{R}$ is a fixed non-linear function whose form is explicit and depends on the double-well potential $W$. The integral term, as before, enforces volume preservation. Analysis and numerical simulation of (2.6) was completed in [15, 16]; we briefly review the relevant results.

Due to the importance of persistently moving cells, the authors considered traveling wave solutions of (2.6). These are solutions of the form

$$\Gamma(s, t) = \Gamma_0(s) + vt,$$

where $v$ is a fixed vector representing the velocity of the cell and $\Gamma_0(s)$ is the unknown cell shape. As expected by physical considerations, we require
sufficiently large $\beta$ in order for traveling wave solutions to exist, as $\beta$ relates to the strength of actin polymerization. Surprisingly, it was also shown that if $\Phi$ was an even function then traveling waves could not exist. This is particularly surprising considering the fact that equal well potentials (including the double-well potential $W$ considered in the current work) would always result in even $\Phi$.

It is thus natural to suspect that the simplified phase-field model (2.1)-(2.2) cannot support persistent motion, perhaps because we have eliminated symmetry breaking effects of myosin motors. However, as we will find below, the minimal phase-field model is capable of exhibiting a wide range of motions for various parameter regimes, thanks to the finite width transition layer allowing for non-trivial dynamics of the vector field $\mathbf{P}$.

3. Numerical simulation of phase-field model near the sharp interface

To understand dynamics near the sharp interface limit, we investigate the long-time dynamics of the phase-field model for various values of $\beta$ and for small values of $\varepsilon$. Simulations of (2.1)-(2.2) were done using an explicit finite difference method on a square with periodic boundary conditions. Time steps were taken sufficiently small to ensure convergence of the simulations: taking smaller time steps did not qualitatively affect any results. Additionally we made sure that the cell volume $V$ satisfied $V \ll |\Omega|$ to ensure that there were no boundary effects caused by the periodic boundary conditions. Again, taking larger domain size did not qualitatively change dynamics.

Initial conditions for the phase-field were a circular cell. We consider both polarized and non-polarized initial conditions for the actin field: for polarized initial conditions we assume that the actin field on the interior of the cell is constant and pointing to the right, with a small random perturbation to ensure robustness of the results. For non-polarized initial conditions we take random initial conditions for the actin field with $|\mathbf{P}| \ll 1$. Moreover, we assume sufficiently long time integration to ignore transient effects. We found that, regardless of initial conditions, the long time behavior was qualitatively the same. Thus, we report only on the results of the polarized initial conditions.

After integrating past a transient time for the cell to reach stable behavior, we record the resultant dynamics. The resultant data is summarized in
Figure 2. We note that taking smaller values of $\varepsilon$ became computationally expensive, due to the singular nature of the evolution of (2.1)-(2.2).

For all solutions which had non-trivial motion, we record the center of mass of the cell in order to track its trajectory. We then calculate the average radius of curvature of this trajectory in order to distinguish between persistently moving cells (straight line trajectory) and rotating cells (circular trajectory). There is an arbitrary distinction between rotating and persistently moving cell, as a persistently moving cell may have a slight turn due to numerical artifact or non-symmetric initial conditions. Thus, to distinguish the two cases we set a threshold radius of curvature to be $10\sqrt{|\Omega|}$: any trajectories with larger radii of curvature are defined to be persistently traveling.

Over the parameter range considered, we observe three modes of motion: **immobile, persistent, and rotating solutions**. Figure 3 presents a snapshot and parameter values giving rise to each type of motion.

**Immobile.** We find that for any fixed $\varepsilon$, there is a critical $\beta_{cr}(\varepsilon) > 0$, so that for any $\beta < \beta_{cr}$ no motion is possible. This agrees qualitatively with the theory developed in the sharp interface limit, as discussed in Section 2.3.

Heuristically, stationary states are expected for sufficiently small $\beta$, since taking $\beta = 0$, the model simplifies to the volume preserving Allen-Cahn
equation (as \( P = 0 \)) which asymptotically relaxes to circular steady states. Then, small values of \( \beta \) constitute a regular perturbation and so stationary states are expected to persist for sufficiently small \( \beta \).

**Rotating states.** Rotating states indicate that the effective actin polymerization strength is not sufficiently strong to overcome surface tension, creating a lateral wave of actin propagation along the cell boundary and resulting in a rotating wave of protrusion in the cell, which results in a rotating solution.

Traveling actin waves leading to such rotating states have been investigated in the more complex version of the phase-field model in [23] and experimentally observed in [13]. Heuristically, if \( \beta \) is very large, then we expect large local deformations caused by the advection of \( P \cdot \nabla \rho \sim -\varepsilon \beta |\nabla \rho|^2 \) (e.g., assuming actin dynamics are fast, \( \partial_t P \sim 0 \) and so \( P \sim -\varepsilon \beta \nabla \rho \)). Then, at the leading edge of protrusion, there is competition between protrusion (caused by the non-linear \( |\nabla \rho|^2 \) term) and retraction enforced by the membrane tension (volume preserving Allen-Cahn dynamics). Indeed, in [23], the formation of such waves was explained via shockwaves from a Burger-like equation, whose non-linear shocks are driven by the quadratic term \( \varepsilon \beta |\nabla \rho|^2 \).

**Persistent motion.** Persistent motion represents a cell traveling with constant shape. Heuristically, the arguments above provide insight into why persistent motion is expected to be robust for intermediate values of \( \beta \): for motion to be persistent and stable, there must be a balance of forces between protrusion and membrane tension (Allen-Cahn). For \( \beta \) too small cells remain stationary and for \( \beta \) too large non-linear effects lead to shock formation and rotations.

Since we use a symmetric double-well potential \( W \), it is perhaps surprising, given the theory developed in the sharp interface limit, that any persistent motion is possible. However, we see that for sufficiently small values of \( \varepsilon \) these persistent motions no longer exist, agreeing qualitatively with the theoretical results of [16]. We thus conclude that stabilization of persistent motion in the sharp interface limit requires additional myosin motor effects [27].

We remark that we did not observe more complicated morphologies such as ameobid or two wave solutions with both actin waves traveling in the same direction, as observed in [23]. This suggests that such dynamics are driven by more complicated biophysical mechanisms, including heterogeneities in the myosin motor density or in the adhesion complex formation.

However, it is surprising that rotating states exist in our simplified model.
Our work thus suggests that even with severely weakened myosin contraction, such motility may be possible in cells.

3.1. Monotone dependence of trajectory curvature in the sharp interface limit

While we have already established that persistent motion does not seem possible for any fixed $\beta$ as $\varepsilon \to 0$, we further analyze the trajectory data of simulation results as $\varepsilon \to 0$.

To that end, for cells classified as rotating we calculate the radius of curvature of the center of mass’s trajectory. Our data reveals that decreasing either $\varepsilon$ or $\beta$ results in a decrease in the radius of the curvature of the trajectory. The data is available in Table 1. This suggests that as $\varepsilon \to 0$, the cell has a stationary center of mass. While certainly this does not preclude the existence of other motile cells with stationary center of mass, we did not observe any such modes in our simulations.

These data in particular provide evidence for why the sharp interface limit (2.6) does not exhibit persistent traveling waves: for small $\varepsilon$ we see that the only stable states which seem to survive are stationary states and rotating states. As $\varepsilon \to 0$, even rotating states have center of mass trajectories with smaller and smaller radii. So, in the limit $\varepsilon \to 0$ one expects that only stationary states to remain stable. Thus, to exhibit stable persistent traveling wave solutions in the sharp interface limit, one must include other biophysical mechanisms into the analysis of the sharp interface limit.

Table 1: Average radius of circular trajectory for rotating solutions. The data show that, for fixed $\beta$, decreasing $\varepsilon$ results in a smaller radius of curvature. That is, rotating cells trace smaller circles. This indicates that for fixed $\beta$, as $\varepsilon \to 0$, the cell becomes stationary.
3.2. Non-monotone dependence of distance traveled on parameters

We investigate the dependence of cell speed on model parameters. To that end, we integrate (2.1)-(2.2) to the end time $t = 5$ and omit the first 75% of data (to disregard transient effects). We then numerically calculate the distance traveled by the center of mass’s trajectory, $p(t)$:

$$d = \sum |p(t_{i+1}) - p(t_i)|.$$  

The data is available in Table 2. We observe that the relationship between distance traveled and parameters is dependent on the motility mode: over parameter ranges where the cell is traveling persistently, if one fixes $\beta$ and increases $\varepsilon$ then the distance travel increases monotonically. This can be heuristically explained that a larger value of $\varepsilon$ provides a wider region where actin polymerization is possible allowing for the generation of more protrusion forces.

However, over parameter ranges where the cell is rotating there is non-monotone dependence on the distance traveled. In that case, the distance traveled is maximized when $\varepsilon = 0.035$, provided $\beta$ is large enough. This suggests that the ratio of the cell volume to the diffuse interface is an optimizable quantity for cell traveling speed. This observation is in qualitative agreement with [18] where it was observed that an optimal density of actin filaments maximizes velocity of the cell (in the current model, we suggest that the transition layer width is a proxy for the amount of actin filaments). Since our numerics suggest that the optimal $\varepsilon$ is constant for large values of $\beta$, we conjecture that this optimal density is effectively independent from the strength of actin polymerization. To our knowledge, this has not been explored experimentally, and thus merits study.

4. Conclusion

Analysis of (2.6), the sharp interface limit of (2.1)-(2.2), was previously completed and sufficient conditions for traveling wave solutions (corresponding to persistently moving cells) were established. Numerical simulations of (2.6) conducted in [16] showed that traveling wave solutions, corresponding to persistently moving cells, were unstable. Moreover, for symmetric potential $W$ (as in (2.1)), we proved that traveling wave solutions could not exist. To
Table 2: Distance traveled for both rotating and traveling states show non-monotone behavior as ε is varied. For fixed ε, as β decreases the distance travels decreases.

|       |       |   |   |   |   |   |
|-------|-------|---|---|---|---|---|
|       | .02   | .025 | .03 | .035 | .04 | .045 | .05 |
| 70    | -     | -    | -   | -    | -   | -   | -   |
| 80    | -     | -    | -   | -    | -   | 3.049 | 4.084 |
| 90    | -     | -    | 2.443 | 4.718 | 6.009 | 6.913 | 7.575 |
| 100   | -     | 8.365 | 9.093 | 9.421 | 9.207 | 9.360 | 9.984 |
| 110   | 9.794 | 10.956 | 11.781 | 12.244 | 12.211 | 11.557 | 11.989 |
| 120   | 11.890 | 13.134 | 14.064 | 14.602 | 14.560 | 13.969 | 13.774 |
| 130   | 13.767 | 15.117 | 16.157 | 16.757 | 16.635 | 15.9103 | 15.417 |
| 140   | 15.513 | 16.985 | 18.157 | 18.793 | 18.529 | 17.614 | 16.961 |
| 150   | 17.1750 | 18.784 | 20.106 | 20.731 | 20.259 | 19.131 | 18.430 |

To better understand the lack of traveling wave solutions in the sharp interface limit, in this work we numerically investigated the pre-limiting phase-field system (2.1)-(2.2).

As this system is a minimal version of the work in [30], etc., there was no evidence that it could support persistently traveling solutions. Our numerics reveal that not only is persistent motion possible, but moreover we could observe rotating states. Similar rotating cells were observed in the more sophisticated model of [23], but it is perhaps surprising to be able to capture them without heterogeneity of myosin motors or adhesion dynamics. We note however that more complex rotating modes, such as two-wave rotating states, were possible in [23], and that the current model only exhibits single wave rotating states. By carefully taking symmetric initial conditions, we were able to observe such two-wave rotating states, but upon perturbation we see that they are unstable in the current model. This suggests that heterogeneity of myosin/adhesion is required to stabilize such complex states.

Finally, our analysis showed that distance traveled (and thus cell velocity) is maximized for a fixed value of ε, over a range of values of β. This suggests that the ratio of cell size to actin filament density plays a more dominant role to cell velocity than actin polymerization strength alone. We conjecture that by reincorporating heterogeneous myosin motor effects we can stabilize persistent motion over a wider range of parameter ranges so as obtain an optimal velocity occurring during persistent motion. In future work we plan to study optimal speed in this more complex setting.
Figure 3: Data from Table 2 shows non-monotone dependence on distance traveled as a function of $\varepsilon$: at $\varepsilon = .035$ we observe (for sufficiently large $\beta$) that distance traveled is maximized. On the other hand, for fixed $\varepsilon$ dependence on $\beta$ is monotone.

Moreover, more rigorous bifurcation analysis between motility modes would be desirable: we anticipate existence of a Hopf bifurcation occurring from immobile to rotating states, and saddle-node bifurcations occurring between immobile and traveling wave states.

All simulations were completed in MATLAB and run on The College of New Jersey’s high performance cluster, ELSA (Electronic Laboratory for Science and Analysis). Codes used to generate data can be provided upon reasonable request to the authors.

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