Phase field model for cell spreading dynamics

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Abstract
We suggest a 3D phase field model to describe 3D cell spreading on a flat substrate. The model is a simplified version of a minimal model that was developed in Winkler (Commun Phys 2:82, 2019). Our model couples the order parameter $u$ with 3D polarization (orientation) vector field $P$ of the actin network. We derive a closed integro-differential equation governing the 3D cell spreading dynamics on a flat substrate, which includes the normal velocity of the membrane, curvature, volume relaxation rate, a function determined by the molecular effects of the subcell level, and the adhesion effect. This equation is easily solved numerically. The results are in agreement with the early fast phase observed experimentally in Dobereiner (Phys Rev Lett 93:108105, 2004). Also we find agreement with the universal power law (Cuvelier in Curr Biol 17:694-699, 2007) which suggest that cell adhesion or contact area versus time behave as $\sim t^{1/2}$ in the early stage of cell spreading dynamics, and slow down at the next stages.

Keywords Cell motility \cdot Phase filed method \cdot Sharp interface method

Mathematics Subject Classification 00A71 General theory of mathematical modeling

1 Introduction

Understanding the phenomenon of cell spreading has numerous potential applications, which include designing biomaterials for optimal control of cell behavior (Gong et al. 2018), insight into cell morphology (Folkman and Moscona 1978), and developing efficient methods for gene transfection in biomaterials (Yang et al. 2019).
In the last two decades, several models have been developed that describe cell spreading on a flat substrate. Those models take into account the elastic (Li et al. 2015; Xiong et al. 2010) or visco-elastic properties of the cell and/or the substrate (Gong et al. 2018; Nisenholz et al. 2014). In addition, those models describe the dynamics of some subcellular components such as cortical cytoskeleton, cell nuclear, actin filaments, and microtubules (Fang and Lai 2016; Vernerey and Farsad 2014). Also, they consider the mechanical interactions between cell adhesion molecules like cross-membrane protein, molecular clutches, and the extracellular property of the substrate. There exist other models that describe cell spreading on non-flat substrate such as V or Y-shaped micro-patterned substrates (McEvoy et al. 2017). All of the previous models were compared with and validated by experimental measurements.

Typically, the implementation of computational models needs hard numerical simulations based on finite elements methods (Vernerey and Farsad 2014; Odenthal et al. 2013) or minimizing some free energy functionals (Fang and Lai 2016); some models include stochastic effects (McEvoy et al. 2017). Relatively speaking, the phase field approach (Shao et al. 2010; Ziebert and Aranson 2016), applied for modeling cell motility, is simple. Within that approach, the cell boundary is not defined explicitly, but it is a diffuse interface. Starting with phase field equations, one can rigorously derive a sharp interface limit equation for the interface alone. In the one-dimensional case, that was done in Berlyand et al. (2016). In the present paper, we apply the phase field approach and derive a sharp interface limit equation for the interface in the three-dimensional case.

Based on experimental data and measurements, some universality properties of cell spreading have been discovered. Usually early spreading is isotropic. Cell spreading may experience three sequential phases, basal (cell touches the substrate), fast continuous spreading (generation of lamellipodial sheet), and periodic local contractile spreading (Dobereiner et al. 2004). These phases obey a power-law area growth with distinct exponents when we plot cell adhesion area (contact area) versus time. Later the authors in Cuvelier et al. (2007) succeed to explain these power-law relationships with a relatively simple physical model. They consider energy balance and assume that actin cortex is a viscous liquid (McGrath 2007).

A minimal computational phase field model of 3D cell crawling on general substrate topography was developed in Winkler et al. (2019). In the present paper we consider a simplified version of that model. We choose the substrate to be a flat surface, \( z = 0 \), in order to model the dynamics of cell spreading on the plane. Unlike the models mentioned above, our model is simple. We describe the cell spreading dynamics by a single scalar non-local partial differential equation of the cell interface (16), which could be solved easily with Wolfram Mathematica program. Our model is in qualitative agreement with observations at the early fast phase, and the universal power law at the earlier stages of cell spreading.

The structure of the paper is as follows. In Sect. 2 we present the minimal 3D phase field model. In Sect. 3 we introduce the proper length and time scales of the spreading dynamics. We perform asymptotic analysis and find the fields at the leading order, and then we use the solvability condition to derive a closed evolutionary nonlocal equation that describes the cell interface dynamics (16). We solve this equation numerically via
the function “\texttt{NDSolve}” of Wolfram Mathematica. We reveal the agreement with the universal power law. Finally, in Sect. 4 we present the conclusions.

2 Formulation of the problem

In order to describe the dynamics of cell located in region $z > 0$ and spreading on the flat substrate $z = 0$, see Fig. 1, we extend the problem into the whole space, postulating the reflection symmetry or antisymmetry of our fields under the transformation $z \rightarrow -z$.

Let us consider the following simplified version of the model that was formulated in Winkler et al. (2019):

\begin{align*}
    u_t &= D_u \nabla^2 u - (1 - u)(\delta - u) u - \alpha \nabla u \cdot \mathbf{P} - k \nabla \Psi_u \cdot \nabla u, \\
    \delta &= \frac{1}{2} + \mu \delta V - \sigma |\mathbf{P}|^2, \quad \delta V(t) = \int u d^3r - v_0, \\
    \mathbf{P}_t &= D_p \nabla^2 \mathbf{P} - \tau^{-1} \mathbf{P} - \beta \Psi_p(z) \left[ (1 - \nu) \dot{\mathbf{P}} \nabla u + \nu \nabla u \right], \\
    u(r = 0) &= 1, \quad u(r \rightarrow \infty) = 0,
\end{align*}

Fig. 1 A schematic description of cell spreading dynamics in spherical coordinate system and the boundary conditions of model (1). The cell is only the shape in the upper region $z \geq 0$ while model (1) is formally formulated in the whole space with reflection symmetry assumption with respect to the substrate plane $z = 0$, (4). The thickness of the cell wall (i.e., the width of the transition zone, where $u(r, t)$ is changed from nearly 1 to nearly 0) is $O(1)$, and the cell size is large. Therefore the ratio $\epsilon$ of the thickness of the cell wall to the size of the cell is small. In addition we emphasize the regions where the fields $\nabla \Psi_u \cdot \nabla u$ and $\Psi_p \nabla u$ give their main contribution and are exponentially small otherwise. These are the regions where protrusions are developed.
\[ P(r = 0) = P(r \to \infty) = 0; \]  

(1e)

see Fig. 1; here \( u \) is the order parameter that is close to 1 inside the cell and 0 outside, and \( P \) is the three-dimensional polarization vector field representing the actin orientations. In (1c), \( \hat{P} = \hat{I} - \hat{n}\hat{n} \) is the projection operator onto the local tangential plane, where \( \hat{n} = \nabla \Psi_p / |\nabla \Psi_p| \) (in our case \( \hat{n} = \pm \hat{z} \)). Therefore,

\[ \hat{P} \nabla u = \nabla u - \hat{z}\hat{z} \nabla u = u_x \hat{x} + u_y \hat{y}. \]

The parameter \( 0 \leq \nu \leq 1 \) models the contribution of actin polarization from the tangential limit \( \nu = 0 \), and the isotropic limit \( \nu = 1 \).

The constant parameters of the problem are: \( D_u \) is the stiffness of diffuse interface, \( D_p \) is the diffusion coefficient for \( P \), \( \alpha \) is the coefficient characterizing advection of \( u \) by \( P \), \( \beta \) determines the creation of \( P \) at the interface, \( \tau^{-1} \) is the inverse time of the degradation of \( P \) inside the cell, \( v_0 \) is twice the overall initial volume of the cell due to the reflection symmetry, \( \mu \) is the stiffness of the volume constraint, and \( \sigma \) is the contractility of actin filament bundles. All the parameters listed above are positive.

In addition, we make the basic assumption that the ratio \( \epsilon \) of the thickness of the cell wall (i.e., the width of the transition zone, where \( u \) is changed from nearly 1 to nearly 0) to the characteristic size of the cell is small, \( \epsilon \ll 1 \), see Fig. 1.

Motivated by Winkler et al. (2019), we define the static fields as

\[ \Psi_u(z) = e^{-\epsilon z^2/D_u}, \quad \Psi_p(z) = e^{-\epsilon z^2/l_p}, \quad l_p = \tau D_p, \]  

(2)

see Fig. 2. We choose \( l_p > D_u \) to allow more substantial actin inside the cell. The appearance of \( \epsilon \) in the exponents of (2) allows to avoid boundary layer problem complications both in time and space. The expression \( k \nabla \Psi_u \cdot \nabla u \) in (1a) models the adhesion effect of the substrate; \( k \) is adhesion strength parameter. Notice that \( \nabla \Psi_u \cdot \nabla u = O(1) \) only in region nearby the substrate and also at the cell boundary or membrane i.e., where protrusion holds. Also the appearance of \( \Psi_p \nabla u \) in (1c) allows high actin concentration nearby the flat substrate \( z = 0 \) and at the membrane edge where protrusions are developed during cell spreading, and low actin concentration otherwise, see Fig. 1.

This scenario is in agreement with experimental studies, see Barnhart et al. (2011); Li et al. (2015), and the review paper Mattila and Lappalainen (2008). Notice that we drop the myosin effect in our model (1) since it has been shown by direct simulations of the phase field equations that it does not have a significant effect, see Reeves et al. (2018).

Below we carry out the following modification of the model. Though the cell is located only in the region \( z \geq 0 \), to simplify the analysis, we formally extend the problem to the whole space postulating the “soft” reflection boundary conditions at the substrate plane \( z = 0 \). That modification does not affect the most important part of the boundary where the protrusion takes place.

We apply the spherical coordinate system, see Fig. 1, hence \( u = u(r, \theta, \varphi, t), \quad P(r, \theta, \varphi, t) = p\hat{r} + q\hat{\theta} + w\hat{\varphi}. \) We define the iso-surface of the interface as
Fig. 2 Plot of the density functions $\Psi_u, p$ in (2). Notice that $\Psi_u, p = O(1)$ nearby the substrate $z = 0$ (red region) while attenuate far away (blue region). The width of the layer where $\Psi_p = O(1)$ is $O(\sqrt{D_p})$. Therefore it is larger than the width of the layer where $\Psi_u = O(1)$ that is $O(\sqrt{D_u})$.

$$u(r = \rho(\theta, \varphi, t)) = 1/2.$$  

As a result of our definition of the spherical coordinate, we have

\begin{align}
(r, \theta, \varphi), & \ 0 < r < \infty, \ -\frac{\pi}{2} < \theta < \frac{\pi}{2}, \ 0 < \varphi < 2\pi, \\
x & = r \cos \theta \cos \varphi, \ y = r \cos \theta \sin \varphi, \ z = r \sin \theta, \\
\nabla & = \hat{r} \partial_r + \hat{\theta} \frac{\partial}{\partial \theta} + \hat{\varphi} \frac{\partial}{\partial \varphi}, \\
\nabla^2 & = \partial_r^2 + \frac{2}{r} \partial_r + \frac{1}{r^2} \left( \frac{1}{\sin^2 \theta} \partial_\theta^2 - \tan \theta \partial_\varphi + \frac{\partial_\varphi^2}{\cos^2 \theta} \right), \\
\nabla^2 P & = \hat{r} \nabla^2 p + \hat{\theta} \nabla^2 q + \hat{\varphi} \nabla^2 w + O \left( \frac{1}{r^2} \right).
\end{align}

One can calculate,

\[
\begin{bmatrix}
(1 - v) \hat{P} + v \hat{I}
\end{bmatrix} \nabla u = u_x \hat{x} + u_y \hat{y} + nu_z \hat{z} = \nabla u + (v - 1)u_z \hat{z}
\]

\[
= \begin{bmatrix}
(1 + (v - 1) \sin^2 \theta)u_r + (v - 1) \frac{\sin 2\theta}{2r} u_\theta \\
(1 + (v - 1) \cos^2 \theta) \frac{u_\theta}{r} + (v - 1) \frac{\sin 2\theta}{2} u_r
\end{bmatrix} \hat{r} + \frac{u_\varphi}{r \cos \theta} \hat{\varphi}.
\]

Notice that due to the appearance of $\Psi_{u, p}(z)$, the system (1a)-(1e) does not have any rotationally spherical symmetric solutions. Therefore, we have to look for general shape solutions.
The reflection symmetry assumption relative to the substrate plane \( z = 0 \), yields the conditions,

\[
\begin{align*}
    u(-\theta) &= u(\theta), & \rho(-\theta) &= \rho(\theta), \\
    p(-\theta) &= p(\theta), & w(-\theta) &= w(\theta), & q(-\theta) &= -q(\theta).
\end{align*}
\]

\( 4 \text{a} \)

\( 4 \text{b} \)

3 Dynamics of general shape interface

In order to balance the front dynamics with curvature we impose the following scaling that describes slow dynamics of a large-size cell (Abu Hamed and Nepomnyashchy 2020),

\[
\tilde{t} = \epsilon^2 t, \quad \rho(\theta, \varphi, t) = \epsilon^{-1} R(\theta, \varphi, t), \quad \epsilon \ll 1.
\]

\( 5 \)

The transition zone variable is defined as

\[
\xi = r - \rho(\theta, \varphi, t) = O(1).
\]

\( 6 \)

Also we define,

\[
\begin{align*}
    R(\theta, \varphi, t) &= \tilde{R}(\theta, \varphi, \tilde{t}), \quad u(r, \theta, \varphi, t) = \tilde{u}(\xi, \theta, \varphi, \tilde{t}), \\
    P(r, \theta, \varphi, t) &= \tilde{P}(\xi, \theta, \varphi, \tilde{t}).
\end{align*}
\]

\( 7 \text{a} \)

\( 7 \text{b} \)

The chain rule yields

\[
\partial_t = -\epsilon \tilde{R} \partial_{\xi} + \epsilon^2 \partial_{\tilde{t}}, \quad \partial_r = \partial_{\xi}.
\]

\( 8 \)

later on we drop the tildes. It holds that

\[
\begin{align*}
    \frac{1}{r} &= \frac{\epsilon}{R} - \frac{\epsilon^2 \xi}{R^2} + ..., \\
    \Psi_P(z) &= e^{-(\epsilon \xi)^2/l_p} = e^{-\epsilon^2 r^2 \sin^2 \theta/l_p} \\
    &= e^{-\epsilon^2 (\xi + \epsilon^{-1} R)^2 \sin^2 \theta/l_p} \sim e^{-R^2 \sin^2 \theta/l_p}, \\
    \nabla \Psi_u &\sim -\frac{\epsilon R}{D_u} e^{-R^2 \sin^2 \theta/D_u} \left( 2 \sin^2 \theta \hat{r} + \sin 2 \theta \hat{\theta} \right).
\end{align*}
\]

\( 9 \text{a} \)

\( 9 \text{b} \)

\( 9 \text{c} \)

In addition one can calculate,

\[
\begin{align*}
    \partial_\theta &= -\epsilon^{-1} R \partial_\xi + \partial_\theta, & \partial_\varphi &= -\epsilon^{-1} R \partial_\xi + \partial_\varphi, \\
    \partial_\theta^2 &= \epsilon^2 R^2 \partial_\xi^2 - \epsilon^{-1} (R \partial_\theta \partial_\xi + 2 R \partial_\xi \partial_\xi) + \partial_\theta^2, \\
    \partial_\varphi^2 &= \epsilon^2 R^2 \partial_\xi^2 - \epsilon^{-1} (R \partial_\varphi \partial_\xi + 2 R \partial_\xi \partial_\varphi) + \partial_\varphi^2, \\
    \frac{\partial_\theta}{r} &= -\frac{R \partial_\xi}{R} + O(\epsilon), & \frac{\partial_\theta}{r^2} &= -\frac{R \partial_\xi}{R^2} + O(\epsilon^2), \\
    \frac{\partial_\varphi}{r} &= -\frac{R \partial_\xi}{R} + O(\epsilon), & \frac{\partial_\varphi}{r^2} &= -\frac{R \partial_\xi}{R^2} + O(\epsilon^2),
\end{align*}
\]

\( 10 \text{a} \)

\( 10 \text{b} \)

\( 10 \text{c} \)

\( 10 \text{d} \)

\( 10 \text{e} \)
\[\nabla^2 u = \left(1 + \frac{R_\theta^2}{R^2} + \frac{R_\varphi^2}{R^2 \cos^2 \theta}\right) u_{\zeta\zeta} + \epsilon \left[ \frac{2}{R^2} \left( \frac{R_\theta}{R^2} \tan \theta - \frac{R_\theta R_\varphi}{R^2} - \frac{R_\varphi^2}{R^2 \cos^2 \theta} \right) \right. \\
- \frac{2}{R^2} \left( \frac{R_\theta^2}{R^2} + \frac{R_\varphi^2}{\cos^2 \theta} \right) u_{\zeta\zeta} \left] + O(\epsilon^2). \right. \]

We can approximate the nonlocality in (1b) as follows,

\[\int u \, d^3r \sim \frac{\epsilon^{-3}}{3} \int_0^{2\pi} d\varphi \int_{-\pi/2}^{\pi/2} R^3(\theta, \varphi, t) \cos \theta d\theta. \]

Consider the following scaling of the model parameters

\[\alpha = \epsilon A, \quad \frac{4\pi \mu}{3} \epsilon^{-3} = \epsilon M, \quad \sigma = \epsilon S, \quad \nu_0 = \epsilon^{-3} V_0, \quad k = O(1). \]

Let us introduce the expansions

\[u = u_0 + \epsilon u_1 + ..., \quad p = p_0 + \epsilon p_1 + ... \]

We define the auxiliary function,

\[\Lambda(\theta, \varphi, t) = \left(1 + \frac{R_\theta^2}{R^2} + \frac{R_\varphi^2}{R^2 \cos^2 \theta}\right)^{-1/2}, \]

and the function,

\[\Phi(\tau, D_u, D_p, \zeta) = \frac{1}{8} \sqrt{\frac{\tau}{2D_u D_p}} \int_{-\infty}^{\infty} e^{-|s|/\sqrt{\tau D_p}} \cosh^{-2} \left(\frac{s - \zeta}{\sqrt{8D_u}}\right) ds, \]

that are basic for our next analysis.

We substitute the length, time (5), and the parameters scaling (12) into system (1). We write the system (1) in the transition zone variable (6,fieldspsz) via the expansions and the chain rules (8)–(11). We substitute the asymptotic expansions (13) and finally we collect terms of the same order.

Consequently we obtain at the leading order the following system,

\[D_u \Lambda^{-2} u_{0\zeta\zeta} = (1 - u_0)\left(\frac{1}{2} - u_0\right)u_0. \]
\[
\begin{align*}
D_p \Lambda^{-2} p_{0\xi \zeta} - \tau^{-1} p_0 &= 
\beta e^{-R^2 \sin^2 \theta / l_p} \left[ 1 + (v - 1) \sin^2 \theta - (v - 1) \frac{\sin 2\theta R_{\theta}}{2} \right] u_{0\zeta}, \\
D_p \Lambda^{-2} q_{0\xi \zeta} - \tau^{-1} q_0 &= 
-\beta e^{-R^2 \sin^2 \theta / l_p} \left[ (1 + (v - 1) \cos^2 \theta) \frac{R_{\theta}}{R} - (v - 1) \frac{\sin 2\theta}{2} \right] u_{0\zeta}, \\
D_p \Lambda^{-2} w_{0\xi \zeta} - \tau^{-1} w_0 &= -\beta e^{-R^2 \sin^2 \theta / l_p} \frac{R_{\varphi}}{R \cos \theta} u_{0\zeta}.
\end{align*}
\]

Following the Ginzburg-Landau theory and Fourier transform method the solution of this system is given by,

\[
\begin{align*}
&u_0(\zeta) = \frac{1}{2} \left[ 1 - \text{tanh} \left( \frac{\Lambda \zeta}{\sqrt{8D_u}} \right) \right] , \\
p_0(\zeta) = \beta \lambda_p \Lambda \Phi(\Lambda \zeta), \\
\lambda_p = e^{-R^2 \sin^2 \theta / l_p} \left[ 1 + (v - 1) \sin^2 \theta - (v - 1) \frac{\sin 2\theta R_{\theta}}{2} \right], \\
q_0(\zeta) = -\beta \lambda_q \Lambda \Phi(\Lambda \zeta), \\
\lambda_q = e^{-R^2 \sin^2 \theta / l_p} \left[ (1 + (v - 1) \cos^2 \theta) \frac{R_{\theta}}{R} - (v - 1) \frac{\sin 2\theta}{2} \right], \\
w_0(\zeta) = -\beta \lambda_w \Lambda \Phi(\Lambda \zeta), \\
\lambda_w = e^{-R^2 \sin^2 \theta / l_p} \frac{R_{\varphi}}{R \cos \theta}.
\end{align*}
\]

Notice that these results satisfy the symmetry conditions (4), if \( R(-\theta) = R(\theta) \).

The equation for the correction term \( u_1 \) at the order \( O(\epsilon) \) have the form,

\[
\begin{align*}
L[u_1] = \text{RHS}, \\
L = D_u \Lambda^{-2} \partial_\zeta^2 - \left( \frac{1}{2} - 3u_0 + 3u_0^2 \right) \hat{1}, \\
\text{RHS} = -R_1 u_{0\zeta} - D_u \left( \frac{2}{R} + \frac{R_{\theta}}{R^2} \tan \theta - \frac{R_{\theta\theta}}{R^2} - \frac{R_{\varphi \varphi}}{R^2 \cos^2 \theta} \right) u_{0\zeta} \\
- \frac{2}{R^2} \left( R_{\theta} u_{0\zeta \theta} + \frac{R_{\varphi}}{\cos^2 \theta} u_{0\zeta \varphi} \right) - \frac{2 \zeta}{R^3} \left( R_{\theta}^2 + \frac{R_{\varphi}^2}{\cos^2 \theta} \right) u_{0\zeta} \\
+ A \left( p_0 - \frac{R_{\theta}}{R} q_0 - \frac{R_{\varphi}}{R \cos \theta} w_0 \right) u_{0\zeta} \\
- \frac{k}{D_u} R \cdot e^{-R^2 \sin^2 \theta / D_u} \left( 2 \sin^2 \theta - \sin(2\theta) \frac{R_{\theta}}{R} \right) u_{0\zeta} \\
+ (1 - u_0) u_0 \left\{ \tilde{V}(t) - S(p_0^2 + q_0^2 + w_0^2) \right\}.
\end{align*}
\]

where the volume variation have the form,

\[
\tilde{V}(t) = M \left[ \frac{1}{4\pi} \int_0^{2\pi} d\varphi \int_{-\pi/2}^{\pi/2} R^3(\theta, \varphi, t) \cos \theta d\theta - \frac{3}{4\pi} V_0 \right].
\]
We apply the solvability condition, which is the orthogonality of the right-hand side (RHS) of Eq. (15) to the solution \( u_0 \xi \) of the homogenous equation \( L[u] = 0 \) of (15) i.e.,

\[
\int_{-\infty}^{\infty} \text{RHS}(\xi) \cdot u_0(\xi) d\xi = 0.
\]

We therefore obtain a closed equation governing the interface dynamics \( R(\theta, \varphi, t) \),

\[
a \Lambda R_t = -2a D_u \mathcal{H} - \tilde{V} + \Omega - N,
\]

where

\[
\mathcal{H} = \frac{1}{2} \nabla \cdot \hat{n} = \frac{1}{2} \nabla \cdot \left( \frac{\nabla (r - R)}{|\nabla (r - R)|} \right)
\]

is the mean local curvature of the surface \( r = R(\theta, \varphi, t) \), see Appendix A, and

\[
\Omega(\theta, \varphi, t) = 6\beta A \Omega_1 \Lambda^2 \left( \lambda_p + \frac{R_\theta}{R} \lambda_q + \frac{R_\varphi}{R \cos \theta} \lambda_w \right) + 6\beta^2 S \Omega_2 \Lambda^2 \left( \lambda_p^2 + \lambda_q^2 + \lambda_w^2 \right),
\]

\[
\Omega_1(\tau, D_u, D_p) = \int_{-\infty}^{\infty} \Phi(\xi) \bar{u}_0^2(\xi) d\xi,
\]

\[
\Omega_2(\tau, D_u, D_p) = \int_{-\infty}^{\infty} \Phi^2(\xi)(\bar{u}_0(\xi) - 1) \bar{u}_0(\xi) \bar{u}_0(\xi) d\xi > 0,
\]

where

\[
\bar{u}_0(\xi) = \frac{1}{2} \left[ 1 - \tanh \left( \frac{\xi}{\sqrt{8 D_u}} \right) \right].
\]

Notice that \( \Omega \) implement the actin polarization since it contains both terms linear and quadratic in \( \beta \). It depend on all the parameters except the adhesion, therefore it includes all the significant non-equilibrium effects related to the cytoskeleton dynamics, (Reeves et al. 2018).

The adhesion effect is implemented by

\[
N = \frac{ak}{D_u} \Lambda R \cdot e^{-R^2 \sin^2 \theta / D_u} \left( 2 \sin^2 \theta - \sin(2\theta) \frac{R_\theta}{R} \right)
\]

For more details and explanations about arguments for the derivation of the governing Eq. (16) see Abu Hamed and Nepomnyashchy (2016, 2020, 2021).

Equation (16) comes in conjunction with the Neumann boundary conditions

\[
R_\theta(\theta = 0) = R_\theta(\theta = \pi/2) = 0,
\]

and some initial interface \( R(t = 0) \).
In order to model cell spreading, we may consider the axi-symmetric case $R_{\phi} = 0$, since according to experimental observation, the onset of cell spreading is isotropic (Dobereiner et al. 2004). As for the initial interface shape, we take the truncated sphere with radius $R_0$ and center $(0, 0, \eta)$, see Fig. 3a.

$$R(t = 0) = \eta \sin \theta + \sqrt{R_0^2 - \eta^2 \cos^2 \theta}, \quad 0 \leq \eta \leq 1.$$  \hspace{1cm} (19)

Then the initial normalized volume in this case is given by

$$V_0 = \int_0^{\pi/2} R(t = 0)^3 \cos \theta d\theta,$$

which is twice the volume of the truncated sphere.

In Fig. 3(a)–(f) we present the sequence of plots that show the results of the numerical simulation of the interface $R(\theta, \phi, t)$ according to Eq. (16) and boundary condition (18). We use the function ’NDSolve’ of Wolfram Mathematica. We plot $R(\theta, \phi, t)$ only in the upper region $0 \leq \theta \leq \pi/2$, the plot in the lower region is only a mirror reflection of the upper surface due to our symmetry assumption (4). Following experimental scenarios where the spherical-like cell almost touch the substrate we may take the parameters of our initial interface as $\eta = 0.95$, and $R_0 = 1$, see Fig. 3a. This simulation as we see describes cell spreading. We begin from almost full sphere and end up with pancake-like shape which is the steady state solution of the system (16), (18), and (19). In Fig. 3g we display the cell hight $R(\pi/2, t)$ which decreases from almost 2–1.21, while in Fig. 3h we display the cell contact area (radius) $R(0, t)$ which increases to 2.

In addition Fig. 3g, h display the fast spreading phenomena at the beginning of cell spreading in agreement with the continuous spreading fast phase that was observed experimentally in Dobereiner et al. (2004). Also, in Fig 3i, j we consider the Log-Log plot of the cell radius versus time, for the cases $\nu = 0.5$ (equally weighted), and $\nu = 0$ (purely tangential actin generation), respectively. Also we plot the piecewise function that connect two function of the form $b_1 t^{1/2}$, and $b_2 t^{1/4}$, for a proper choice of the parameters $b_{1,2}$, and for the connecting point. We notice the agreement with the universal power law (Cuvelier et al. 2007) that suggest that cell adhesion or contact area versus time behave as $\sim t^{1/2}$ in the early state of cell spreading dynamics, and slow down in the next states. The plot of the slope $\sim t^{1/4}$ in Fig. 3i, j is only to emphasize the slowing down of the next phase.

In Fig. 4 we perform similar analysis where we choose $D_u = 0.5$, and $D_p = 0.02$ while the other parameters remain as those of Fig. 3. Notice that in this case we have $\tau D_p < D_u$, unlike the previous case of Fig. 3.

Let us consider now the influence of the variation of biologically significant parameters. In Fig. 5, we present the results of the simulation of Eqs. (16) and (18) with different values of $\nu$. When the polarization is purely in the tangential direction $\nu = 0$, we observe that the cell hight decreases much faster than in the equally weighted case $\nu = 0.5$, Fig. 5a. For the cell radius, we observe that in the case $\nu = 0.5$ its increase is faster than in the the case $\nu = 0$, Fig. 5b. The reason is due to the expression in (1c).
When $\nu = 0$ we have only one contribution, $\hat{P} \nabla u$ is directed tangentially, while for $\nu = 0.5$ we have two equally weighted contribution $\hat{P} \nabla u$, and $\nabla u$ in the tangential direction, thus the radius is faster in the later case.

We also consider the cell behavior by the adhesion parameter variation Fig. 6. When $k = 15$, the height decreases faster than in the case of weaker adhesion $k = 5$, Fig. 6a, while the cell radius for the case $k = 5$ increases faster than in the case of the stronger adhesion case $k = 15$, Fig. 6b.

4 Conclusions

We utilize a simplified version of minimal 3D phase field model that was developed in Winkler et al. (2019), in order to model cell spreading dynamics on a flat substrate. The model (1) couples the order parameter $u$ with 3D polarization (orientation) vector field $P$ of the actin network. The model is formulated in the whole space but with appropriate symmetry conditions with respect to transformation $z \rightarrow -z$, (4).

After we introduce the proper time and length scale and perform asymptotic expansion, we solve equations for the fields at the leading order. As a result of the solvability condition we derive a closed integro-differential Eq. (16) governing the 3D cell spreading dynamics, which includes the normal velocity $\omega_n = \Lambda R_t$ of the membrane, curvature $H$, volume relaxation rate $\tilde{V}$, a function $\Omega(t)$ determined by the molecular effects of the subcell level, and the adhesion effect $N$.

Excluding the adhesion effect this result is similar to the 2D case which describes the onset of 2D cell dynamics on flat substrate (Abu Hamed and Nepomnyashchy 2020) and 3D case that describe the onset of 3D cell motility immersed in 3D extracellular matrices (Abu Hamed and Nepomnyashchy 2021).

The equation governing the interface or membrane dynamics during spreading may be presented in the form:

$$\omega_n = -2D u H - \tilde{V} + \Omega - N,$$

after we put the proper scaling transformation, $t \rightarrow a^2 t$ and $R(t) \rightarrow a R(t)$ in (16). This equation is easily solved numerically via the function NDSolve of Wolfram Mathematica. The simulation presents cell spreading with significant height decreasing and radius increasing of the initial truncated spheres, see Figs. 3 and 4.

These results are in agreement with the early fast phase that was observed experimentally in Dobereiner et al. (2004). Surprisingly, the results are in qualitative agreement with universal power law which suggest that adhesion or contact area versus time behave as $\sim t^{1/2}$ in the early state of cell spreading dynamics, and then it slows down. The appearance of the slope $\sim t^{1/4}$ in Figs. 3i, j and 4k is only to emphasize the slowing down of the later phase. This is a surprising result since in our phase field model we did not assume any viscosity property of the cell membrane as it is assumed in Cuvelier et al. (2007).

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Appendix A

Here we give an explicit expression for the mean curvature of a surface given in spherical coordinate description \( r = R(\theta, \varphi, t) \), see Fig. 1. Following the definition

Fig. 3  a–f  Time sequence of the simulation of Eq. (16) in the axisymmetric case with initial upwards shifted sphere (19) with radius \( R_0 = 1 \) and center \((0, 0, 0.95)\). We employ the following values of parameters: \( \beta = 5, A = 1, \tau = 10, D_u = 1, D_p = 0.2, M = 8, S = 2, \nu = 0.5, k = 15 \). g is the plot of the pancake-like cell height \( R(\pi/2, t) \), h is the plot of the pancake-like cell radius \( R(0, t) \), both within the time interval \( 0 \leq t \leq 0.1 \). Notice that the stationary pancake-like cell has height 1.21 and radii 2. i and j are the Log-Log plot of the cell radius \( R(0, t) \) versus time \( t \) (blue), for \( \nu = 0.5 \), and \( \nu = 0 \), respectively. Also we plot the piecewise function that connects two functions of the form \( b_1 t^{1/2} \), and \( b_2 t^{1/4} \), for a proper choice of the parameters \( b_1, b_2 \), and for the connecting point (orange). Notice the qualitative agreement with the universal power law in the initial fast phase and next the slower phase. The appearance of the slope \( \sim t^{1/4} \) in (i)-(j), is shown only to emphasize the slowing down of the later phase.
Fig. 4  Time sequence of the simulation of Eq. (16) in the axisymmetric case. We employ following values of parameters: \( D_u = 0.2, D_p = 0.02 \), the other parameters and the initial sphere are as in Fig 3. i is the plot of the pancake-like cell height \( R(\pi/2, t) \), j is the plot of the pancake-like cell radius \( R(0, t) \), both within the time interval \( 0 \leq t \leq 0.1 \). Notice that the stationary pancake-like cell has height 1.3 and radii 2.74. Notice also that here we have \( \tau D_p < D_u \), unlike the previous case of Fig. 3. k Log-Log plot as that of Fig. 3

(17),(3), one can calculate,

\[
\nabla \cdot \mathbf{\hat{n}} = \Lambda \left\{ \frac{2}{R} - \frac{R_{\theta\theta}}{R^2} + \frac{R_{\theta} \tan \theta}{R^2} - \frac{R_{\varphi\varphi}}{R^2 \cos^2 \theta} \right\} \\
+ \Lambda^3 \left\{ \frac{1}{R^3} \left( \frac{R_{\varphi}^2}{\cos^2 \theta} \right) + \frac{R_{\theta}^2 R_{\theta\theta}}{R^4} + \frac{2 R_{\theta} R_{\varphi} R_{\theta\varphi}}{R^4 \cos^2 \theta} \\
+ \frac{R_{\varphi}^2}{R^4 \cos^4 \theta} \left( \frac{1}{2} R_{\theta} \sin 2\theta + R_{\varphi\varphi} \right) \right\} \\
\]  

(A1)
Fig. 5 Plots of the cell height (a), and radius (b) for the two values, $v = 0.5$ (blue), and $v = 0$ (orange). The cell height (a) for the purely tangential polarization $v = 0$ evolves faster than that for the less tangential $v = 0.5$. For the cell radius (b) the situation is opposite. We use the same values of the other parameters as in Fig. 3. We add zoom in figures to clarify the behaviour at $t = 0$.

Fig. 6 Plots of the cell height (a), and radius (b) for the two values of the adhesion parameter, $k = 15$ (blue), and $k = 5$ (orange). The cell height for $k = 15$ evolves faster than that of $k = 5$. For the cell radius (b) the situation is opposite. We use the same values of the other parameters as in Fig. 3. We add zoom in figures to clarify the behaviour at $t = 0$. Notice that they are very close at the beginning.

References

Abu Hamed M, Nepomnyashchy AA (2016) Dynamics of curved fronts in systems with power-law memory. Phys D 328–329:1–8

Abu Hamed M, Nepomnyashchy AA (2020) A simple model of keratocyte membrane dynamics: the case of motionless living cell. Phys D 408:1–18

Abu Hamed M, Nepomnyashchy AA (2021) Three-dimensional phase field model for actin-based cell membrane dynamics. Math Model Nat Phenom 16:1–15

Barnhart EL, Lee K-C, Keren K, Mogilner A, Theriot JA (2011) An adhesion-dependent switch between mechanisms that determine motile cell shape. PLoS Biol 9(5):1–46

Berlyand L, Potomkin M, Rybalko V (2016) Phase-field model of cell motility: traveling waves and sharp interface limit. C R Acad Sci Paris Ser I 354:986–992

Cuvelier D, Thery M, Chu YS, Dufour S, Thiery JP, Bornens M, Nassoy P, Mahadevan L (2007) The universal dynamics of cell spreading. Curr Biol 17:694–699

Dobereiner HG, Dubin-Thaler B, Giannone G, Xenias HS, Sheetz MP (2004) Dynamic phase transitions in cell spreading. Phys Rev Lett 93:1–4

Fang Y, Lai KWC (2016) Modeling the mechanics of cells in the cell-spreading process driven by traction forces. Phys Rev E 93:1–15

Folkman J, Moscona A (1978) Role of cell shape in growth control. Nature 273:345–349
Gong Z, Szczesny SE, Caliarie SR, Chaudhuri O, Cao X, Lin Y, Mauck RL, Janmey PA, Burdick JA, Shenoy VB (2018) Matching material and cellular timescales maximizes cell spreading on viscoelastic substrates. PNAS 115(12):E2686–E2695
Li Y, Lovett D, Zhang Q, Neelam S, Kuchibhotla RA, Zhu R, Gundersen GG, Lele TP, Dickinson RB (2015) Moving cell boundaries drive nuclear shaping during cell spreading. Biophys J 109:670–686
Mattila PK, Lappalainen P (2008) Filopodia: molecular architecture and cellular functions. Nat Rev Mol Cell Biol 9:446–454
McEvoy E, Deshpande VS, McGarry P (2017) Free energy analysis of cell spreading. J Mech Behav Biomed Mater 74:283–295
McGrath JL (2007) Dispatch: cell spreading: the power to simplify. Curr Biol 17:R358
Nisenholz N, Rajendran K, Dang Q, Chen H, Kemkemer R, Krishnan R, Zemel A (2014) Active mechanics and dynamics of cell spreading on elastic substrates. Soft Matter 10:1–12
Odenthal T, Smeets B, Liedekerke PV, Tijskens E, Oosterwyck HV, Ramon H (2013) Analysis of initial cell spreading using mechanistic contact formulations for a deformable cell model. PLOS Comput Biol 9:e1003267
Reeves C, Winkler B, Ziebert F, Aranson IS (2018) Rotating lamellipodium waves in polarizing cells. Commun Phys 1:1–11. https://doi.org/10.1038/s42005-018-0075-7
Shao D, Rappel WJ, Levine H (2010) Computational model for cell morphodynamics. Phys Rev Lett 105:1–4
Vernerey FJ, Farsad M (2014) A mathematical model of the coupled mechanisms of cell adhesion, contraction and spreading. J Math Biol 68(4):989–1022
Winkler B, Aranson IS, Ziebert F (2019) Confinement and substrate topography control cell migration in a 3d computational model. Commun Phys 2:1–11
Xiong Y, Rangamani P, Fardin MA, Lipshtat A, Thaler BD, Rossier O, Sheetz MP, Iyengar R (2010) Mechanisms controlling cell size and shape during isotropic cell spreading. Biophys J 98:2136–2146
Yang Y, Wang X, Hu X, Kawazoe N, Yang Y, Chen G (2019) Influence of cell morphology on mesenchymal stem cell transfection. ACS Appl Mater Interfaces 11:1932–1941
Ziebert F, Aranson IS, (2016) Computational approaches to substrate-based cell motility. npj Computat Mater 6:1-16

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