Role of particle local curvature in cellular wrapping

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Cellular uptake through membranes plays an important role in adsorbing nutrients and fighting infection and can be used for nanomedicine developments. Endocytosis is one of the pathways of cellular uptake which associate with elastic deformation of the membrane wrapping around the foreign particle. The deformability of the membrane is strongly regulated by the presence of a cortical cytoskeleton placed underneath the membrane. It is shown that shape and orientation of the particles influence on their internalization. Here, we study the role of particle local curvature in cellular uptake by investigating the wrapping of an elastic membrane around a long cylindrical object with an elliptical cross-section. The membrane itself is adhered to a substrate mimicking the cytoskeleton. Membrane wrapping proceeds differently whether the initial contact occurs at the target’s highly curved part (vertical) or along its long side (horizontal). We obtain a wrapping phase diagram as a function of the membrane-cytoskeleton and the membrane-target adhesion energy, which includes three distinct regimes (unwrapped, partially wrapped and fully wrapped), separated by two phase transitions. We also provide analytical expressions for the boundaries between the different regimes which confirm that the transitions strongly depend on the orientation and aspect ratio of the nanowire.

1. Introduction

Internalization of particles is an essential cellular process by which cells adsorb nutrients and fight infections [1]. The interaction of nanoparticles with lipid membranes also provides a broad range of potential applications in biomedical fields such as chemotherapy, bioimaging, biosensing and drug and gene delivery [2–7]. Receptor-mediated endocytosis and phagocytosis are two prominent pathways of cellular uptake [1]. These complex cellular processes involve energy consumption and cytoskeleton rearrangement [8,9]. However, the mechanics and dynamics of internalization can be studied by simplified theoretical and computational approaches to provide a quantitative physical model of endocytosis [10–16]. In most of these approaches, the wrapping process is considered as the minimization of the total system energy, including the elastic energy of the membrane and adhesion energy to the target [17–19] or a substrate [20–22]. Therefore, for the sake of simplicity, the vast majority of previous papers have studied spherical [17,23–26] or cylindrical particles [19–21,27].

In realistic situations, cells often take up targets of different shapes [28–33]. For example, cells are capable of interacting with rod-like bacteria or dumb-bell-shaped dividing cells. As a result, the subject matter of recent studies turned to the role of particle shape and orientation in the wrapping process [11,34–45], but the results remain contentious. Some of these studies found that the uptake of rod-like particles, with a high aspect ratio, is less likely than that of spherical particles with similar size [40,46], but the opposite behaviour has also been reported from both experiment and simulations [11,37].
In the case of ellipsoidal particles, Bahrami [44] computationally studied the wrapping of these particles by a vesicle and found that the internalization of these particles depends on their orientation and is more restrictive than spherical ones. The experimental studies of Champion and Mitragotri also showed that phagocytosis of ellipsoidal discs depends on their orientation with respect to the membrane [35]. Engulfment was easiest when particles contacted the cell through their highly curved tip, and wrapping was generally incomplete when initial contact occurred through the particle’s long side. These kind of experiments indicated that besides the shape of particles their orientation needs to be studied, as well. Dasgupta et al. [41,42] explained that high-aspect-ratio particles with round tip tend to enter the cell from their long side, while particles with small aspect ratio and a flat tip enter from the tip. A molecular dynamics (MD) simulation with spherocylindrical particles, showed that when these particles initially have an upright docking position on the membrane, they rotate and first adhere to the membrane from the long side. Then they stand up again and complete the engulfment when their long axis is perpendicular to the membrane [47].

One of the essential parts of a cell’s structure is an actin network underneath the membrane named cytoskeleton [48]. The crucial role of the cytoskeleton in the wrapping process should be considered from two aspects. First, it controls the shape of the cell and restricts the deformation of membrane anchored to it, and second, it can generate active forces to push the membrane protrusions around the target. The present model focuses on the first aspect, and considers an inert cytoskeleton on which the membrane adheres. As such, it is also appropriate to study the wrapping of particles by supported membranes adhered on a substrate [49]. We consider the effect of cytoskeleton as a fixed substrate under the membrane [20] and study the impact of the particle’s curvature on the wrapping process. For this, we simulate the cellular wrapping of a long particle (nanowire) with elliptical cross-section (figure 1). Because of the translational symmetry along the target axis, this case can be considered as a two-dimensional problem. In one case the nanowire initially contacts the membrane through its highly curved part (vertical orientation), and in another case from its long side (horizontal configuration).

In §2, we present the details of the coarse-grained MD model used for simulations. In §3, we summarize the simulation results of horizontal and vertical configurations in two phase diagrams, including three distinct regimes (unwrapped, partially and fully wrapped) accompanied by two phase transitions. These results show that horizontal and vertical orientations have distinct phase diagrams, which differ from that of a symmetric circular object. The differences in the phase diagrams are explained by the theoretical calculations of transitions between the three regimes. While wrapping is triggered more easily for ellipses with horizontal orientation, the fully wrapped configuration is more favourable for the vertical one. These results are in qualitative agreement with previous works that studied the role of particle shape and orientation as a competition between the elasticity of a free membrane and adhesion to an external particle [17,41,42,44]. Here, we show that substrate adhesion affects the degree of wrapping in an orientation-dependent manner. We find that substrate adhesion enhances the effect of particle orientation on the partial and full wrapping transition: it hinders the partial wrapping transition more in the vertical than in the horizontal orientation, while the reverse is true, although the effect is weaker, for the full wrapping transition. In §4, we analyse the numerical and analytical results and discuss how they can help the understanding of a biological mechanism like phagocytosis. Some details of the calculations and more detailed simulation results appear in the appendix and electronic supplementary material.

**2. Model and methods**

The simulations presented in this work are based on a highly coarse-grained description of the membrane [20], which is appropriate for simulating large-scale membranes under finite tension. In addition, because the model is obtained from the discretization of the Helfrich energy [50], the results can be easily compared with theoretical calculations.

The cellular membrane (in blue in figure 1) is initially adhered to a flat cytoskeleton cortex surface (in green). Owing to adhesion to an external object (in pink), an infinitely long cylinder (a nanowire) with elliptical cross-section, the membrane deforms and wraps around the target. The ellipse which is centred at the origin is characterized as

\[ \frac{x^2}{a^2} + \frac{y^2}{b^2} = 1 \tag{2.1} \]

where 2a and 2b are the length of axes in the x- and y-direction, respectively. In our simulations, the target’s dimensions are fixed to 70σ and 140σ (where σ is the simulations unit length scale; see equation (2.7)), therefore, the axial ratio for the horizontal orientation is \(D = a/b = 2\) and for vertical one \(D = 1/2\).

The adhesion energy difference (per unit length) with respect to the initial state can be written as

\[ \frac{\Delta E_{ad}}{L} = -\omega \int_{0}^{\pi} t(r) \, d\alpha + \omega_{t} (l_{t,H} + l_{t,K}) \tag{2.2} \]

where \(\omega\) and \(\omega_{t}\) denote the target-membrane and the cytoskeleton-membrane adhesion energy per unit area, respectively. The membrane wrapping around the target is characterized by the wrapping angle \(\alpha = \alpha_{K} + \alpha_{L}\), where \(\alpha_{K}\) and \(\alpha_{L}\) are the wrapping angle at the right and left side of

![Figure 1.](https://royalsocietypublishing.org/doi/10.1098/rsif.2020.0462)
the nanowire, respectively. \( l_{a,R} \) and \( l_{b,R} \) indicate the left and right membrane contour length detached from the cytoskeleton (the contour length between the points \( i \) and \( e \) in figure 1a). One should note that in principle the wrapping angle can be asymmetric and therefore \( l_{a,L} \) can be different from \( l_{b,R} \).

The elastic energy of the deformed membrane can be described by the Helfrich energy [50] as
\[
E_H = \frac{1}{2} \kappa \int_A (2H)^2 \, dA + \Sigma_{s} \int_{A_s} \kappa_0 \, dA_s, \tag{2.3}
\]
where \( \kappa \) and \( \Sigma \) denote the bending rigidity and the surface tension of the membrane, respectively, and \( H \) is the mean curvature of the membrane. Long particles are invariant along their long axis which means a single tangent vector, \( \hat{t}(s) \), defined at each point of the membrane, \( s \), suffices for full characterization of its shape. Therefore, the total deformation energy per unit length of the target can be written as
\[
E_{H} = \frac{1}{2} \kappa \int_{s} \partial_s \hat{t}(s)^2 \, ds + \Sigma \int_{s} \delta s, \tag{2.4}
\]
where \( \partial_s \hat{t}(s) \) indicates differentiation with respect to the arclength \( s \), and \( L \) is the length of the cylinder. Consequently, this one-dimensional integral can be discretized as a chain of beads which are connected to each other by a harmonic spring potential,
\[
E_{\text{spring}} = \frac{1}{2} \sum_{i=1}^{N-1} \left[ |\hat{t}(i) - d_0|^2 \right], \tag{2.5}
\]
where \( d(i) \) is the actual bond length, \( d_0 \) is the equilibrium bond length and \( \Lambda \) is the spring's stiffness. The bending energy of the membrane is expressed as the following potential energy between each three connected beads (figure 1b):
\[
E_B = \sum_{i=1}^{N-2} \left[ 1 - \cos(\theta(i, i+1)) \right], \tag{2.6}
\]
where \( \theta(i, i+1) \) represents the angle between the neighbouring springs. Furthermore, adding a lateral force at the edges of the membrane reproduces the effect of the membrane tension. In this paper, the membrane is constructed by 1000 monomers, is allowed to move only in \( x\)-\( y \) plane, and the excluded volume interactions between the membrane beads are implemented using the Weeks–Chandler–Andersen potential
\[
V_{\text{WCA}}(\tau_{ij}) = \begin{cases} 
4 \varepsilon \left( \left( \frac{\tau_{ij}}{\sigma} \right)^{12} - \left( \frac{\tau_{ij}}{\sigma} \right)^{6} + \frac{1}{4} \right), & \tau_{ij} \leq \sigma, \\
0, & \tau_{ij} > \sigma,
\end{cases} \tag{2.7}
\]
where \( \tau_{ij} = 2^{1/6} \sigma \), \( \sigma \) is the distance between the \( i \)th and \( j \)th beads, and \( \varepsilon \) and \( \sigma \) are the unit energy and length scale of the simulation, respectively. In our simulations, the spring’s equilibrium bond length, \( d_0 \), and the diameter of the membrane’s monomers are considered by the same length equal to \( \sigma \).

The cytoskeleton is implemented by 2600 immobile beads laid underneath the membrane. The elliptical cross-section of the nanowire is also made of 678 fixed monomers positioned on the top of the membrane. The distance between the monomers forming the cytoskeleton and those forming the ellipse is taken to be 0.5\( \sigma \) to simplify the sliding of the membrane over the cytoskeleton.

Both the membrane–cytoskeleton and the membrane-target interactions are modelled with the following potential [51,52]:
\[
V(\tau_{ij}) = \begin{cases} 
4 \lambda_s \left[ \left( \frac{\tau_{ij}}{\sigma} \right)^{12} - \left( \frac{\tau_{ij}}{\sigma} \right)^{6} \right], & \tau_{ij} \leq \sigma, \\
-\lambda_s \cos^2 \left( \frac{\pi}{4} \left( \tau_{ij} - \sigma \right) \right), & \sigma \leq \tau_{ij} \leq \sigma + \zeta, \\
0, & \tau_{ij} \geq \sigma + \zeta,
\end{cases} \tag{2.8}
\]
where \( \lambda_s \) in the unit of the energy, denotes the strength of the ligand–receptor interactions (\( k = 1 \) corresponds to the membrane-target, and \( k = 2 \) corresponds to the membrane-cytoskeleton), and \( \zeta = 0.5 \sigma \). This interaction potential smoothly decays to zero for \( r > r_c \), and the attraction tail can be tuned by changing the parameter \( \zeta \) (see [20]). The values of the average adhesion energy per unit area between the membrane and cytoskeleton (\( \omega_c \)) and between the membrane and the nanowire (\( \omega_n \)) can be tuned by varying \( \lambda_1 \) and \( \lambda_2 \).

Our MD simulations were performed at the constant temperature \( k_B T = 1.0 \varepsilon \), with the Langevin thermostat, and using ESPResSo [53]. The time step in the Verlet algorithm and the damping constant in the Langevin thermostat were set \( \delta t = 0.01 \tau_0 \) and \( \Gamma = \tau_0^{-1} \), respectively, in which \( \tau_0 = \sqrt{m \sigma^2 / \varepsilon} \) is the MD time scale and \( m \) is the monomer mass.

3. Results

3.1. Numerical results

To investigate the role of the particle’s local curvature in the wrapping process we study the cases where the ellipse is introduced to the membrane from its narrow part (vertical orientation) or its long side (horizontal configuration).

In summary, our model contains two membrane elastic parameters (bending rigidity \( \kappa \) and surface tension \( \Sigma \)), two adhesion parameters (cortex and target adhesion energy densities \( \omega_c \) and \( \omega_n \)) and one geometrical parameter (axial ratio \( D \)). We fixed the values of \( \Lambda = 5000 \varepsilon / \sigma^2 \), \( \kappa = 20 \varepsilon \) and \( \Sigma = 1.5 \varepsilon / \sigma^2 \), and investigate the wrapping process as a function of the cortex adhesion energy density \( \omega_c = [0.65 - 3.63 \varepsilon / \sigma^2 \) and the target adhesion energy density \( \omega_n = [0.65 - 11.30 \varepsilon / \sigma^2 \). For this, we change the values of \( \lambda_1 \) and \( \lambda_2 \) in the range of \([0.3 - 1.2] \varepsilon \) and \([0.3 - 3.5] \varepsilon \), respectively. Considering \( \sigma = 3 \) nm as the thickness of a lipid membrane, and \( \varepsilon = 1 k_B T \) the mentioned values corresponds to \( \kappa = 20 k_B T \) [54], \( \Sigma = 0.17 (k_B T \text{ nm}^{-2}) \) [55,56], \( \omega_c = [0.072 - 0.4] (k_B T \text{ nm}^{-2}) \) [57–59] and \( \omega_n = [0.072 - 1.26] (k_B T \text{ nm}^{-2}) \) [60–62].

After a sufficient number of MD steps, the system reaches an equilibrium state where the representing parameters of the system fluctuate around their equilibrium values. The equilibrium state of the system can be specified by looking at the time variation of the energies, and the wrapping angles of the target. Figure 2 represents the results of a typical simulation of a vertically oriented ellipse corresponding to \( \omega_c = 2.30 \varepsilon \) and \( \omega_n = 7.28 \varepsilon / \sigma^2 \) (see also electronic supplementary material, figure S1). Figure 2a shows the time course of the total system’s energy (blue), the membrane-target adhesion energy (red) and the membrane-cytoskeleton adhesion energy (green). Figure 2b represents the total (blue), left (red) and right (green) wrapping angles. Figure 2c–e represents the distribution of the total wrapping angle, \( \alpha \), the left side, \( \alpha_l \), and the right side of the nanowire \( \alpha_R \), when the
system is equilibrated. Corresponding to figure 2c–e, these distributions are Gaussian, which is in agreement with thermal fluctuation of energies and wrapping angles in figure 2a,b. A typical snapshot of the membrane conformation around the vertical ellipse is displayed in figure 2f.

The results of the simulations are summarized in figure 3. In figure 3a, the equilibrium wrapping angle, \( \alpha = \alpha_s + \alpha_r \), is represented as a function of the target adhesion density, \( \omega_t \), for different values of the cytoskeleton adhesion density, \( \omega_c \), in the vertical and horizontal configurations. The phase diagrams as a function of \( \omega_t \) and \( \omega_c \) are shown in figure 3b. For small values of \( \omega_t \), the system is in the unwrapped regime (U). Beyond a threshold value, \( \omega_u \), the membrane stably wraps around the target, and the equilibrium wrapping angle increases continuously with the target adhesion, \( \omega_t \). This is the partially wrapped regime (P) and it is nearly symmetric on the left and right sides. Previous works have shown that the transition from unwrapped to partially wrapped regime is continuous in the absence of substrate adhesion [17,42,63]. This is also the case with substrate adhesion (see Analytical results, equation (3.4) below), but the value of the adhesion density at the transition, \( \omega_u \), increases with \( \omega_t \) in an orientation-dependent manner. In the horizontal case, owing to the low curvature contact point with the substrate, the variation of the wrapping angles in the partially wrapped transition shows a fast change. In contrast, the angle in the vertical case with a highly curved contact point changes smoothly. Beyond yet another threshold value, \( \omega_d \), which also increases with \( \omega_c \), an abrupt transition happens and the nanowire is fully wrapped by the membrane, the fully wrapped state (F). In this regime, the left and right angles can be asymmetric. It is worth mentioning that because of the steric interactions between the membrane’s monomers (equation (2.7)), a full wrapping state with \( \alpha = 360^\circ \) cannot be achieved in our simulations.

Figure 3 shows that the wrapping behaviour is strongly influenced by the target’s orientation. The threshold value of the adhesion density for partial wrapping, \( \omega_u \), is smaller in the horizontal case than in the vertical case. This means that in the early stages of cellular wrapping, adhesion is easier for particles with smaller curvatures [42,44]. At the onset of wrapping, the variation of the wrapping angle with the adhesion density, \( \omega_t \), is much sharper in the horizontal orientation than in the vertical one. However, partial wrapping remains confined to half wrapping (\( \alpha \approx 180^\circ \)) for a broad range of \( \omega_t \) in the horizontal case, while it increases smoothly with \( \omega_t \) in the vertical case. In fact, for the same value of \( \omega_t \), the wrapping angle \( \alpha \) is smaller in the vertical case than in the horizontal one if \( \alpha < 180^\circ \), while the opposite is true if \( \alpha > 180^\circ \). As a result, the phase diagram of the vertical orientation includes all the wrapping fractions, while the horizontal one is confined to half wrapping fractions followed by an abrupt jump to full wrapping. However, the phase diagram of the horizontal orientation is wider than the vertical one (pink lines in figure 3b on the right panel). The full wrapping transition is much more abrupt in the horizontal orientation, where the wrapping angle essentially jumps from \( \alpha \approx 180^\circ \) to full wrapping at \( \omega_f \). In the vertical orientation, partial wrapping extends to large values of the
wrapping angle, and the full wrapping transition is less sharp. Varying the substrate adhesion density, $\omega_s$, does not affect this behaviour qualitatively, but merely modifies the values of the adhesion thresholds. Our simulations show that, all parameters being the same, the full wrapping threshold $\omega_0$ is slightly smaller in the vertical case than in the horizontal one (compare the pink and green dashed lines in figure 3b on the right panel).

These results are in qualitative agreement with those found in [44], where Bahrami found that ellipsoidal particles engulfed by vesicles start adhering from their flat side and then change their orientation, so that the internalization is achieved from highly curved tips. He reported the same behaviour for both oblate and prolate ellipsoids. Huang et al. [47] also found the same behaviour in the dynamics of wrapping of spherocylindrical particles. They showed that spherocylindrical particles tend to adhere to the membrane first from the long side. Then, they become vertical again and complete the engulfment with their long axis perpendicular to the membrane.

3.2. Analytical results

In the following sections, we calculate the analytical expression for the two threshold values $\omega_0$ and $\omega_s$. Here, we focus on the partially wrapped regime and assume that the left and right sides are nearly symmetric, so we can write $\alpha_R = \alpha_L = \theta$ and $L_{R,L} = L_u$.

Figure 3. (a) Variation of the wrapping angle as a function of $\omega$ for different values of $\omega_s$ in the case of the horizontal (left) and vertical (right) configuration of the object. (b) Wrapping phase diagrams of the nanowire in the phase space of $\omega_0$ and $\omega_s$. The colour bar shows the extent of the wrapping angle (in degrees). There are three distinct regimes: unwrapped ($U$), partial wrapped ($P$) and full wrapped ($F$). The dotted lines correspond to the transition to a partially wrapped state (equation (3.4)) while the dashed lines represent the theoretical value of $\omega$ in transition to the fully wrapped state (equation (3.15)). The pink lines in panel (b) on the right side represent the threshold values of the horizontal configuration to help a better comparison.

3.2.1. Unwrapped–partial wrapped ($U$–$P$) transition

The transition from the unwrapped regime to the partially wrapped state ($U$–$P$ transition) can be described analytically by expanding the total energy of the system for small wrapping angles $\theta \ll 1$. In general, the total energy of the system can be divided into two main parts: the cap (in contact with the target) and the free part (the part which the membrane is neither in contact with the target, nor with the cytoskeleton). At the $U$–$P$ transition, the wrapping angle is zero, $\theta = 0$. As shown in the appendix (equation (A 8)), the target's local radius of curvature at this point is $r_{\text{eff}} = a^2/b = D_s$. At the $U$–$P$ transition, this radius can be considered as the effective radius of a cylinder and be substituted into the analytical expression obtained in [20] and briefly summarized below. The contributions of the cap and free parts to the energy difference (per unit length of the nanowire) with respect to the reference state, for which the membrane is fully adhered to the cytoskeleton, are

$$\Delta E_{\text{cap}} = \frac{\kappa \theta}{r_{\text{eff}}} + 2 \Sigma \theta r_{\text{eff}} \left( 1 - \frac{\sin \theta}{\theta} \right) + 2(\omega_s - \omega) r_{\text{eff}} \theta, \quad (3.1)$$

and

$$\Delta E_{\text{free}} = 2 \int_0^\delta ds \left[ \frac{\kappa}{2} \psi^2 + \Sigma (1 - \cos \psi) + \omega_s \right], \quad (3.2)$$

where $\psi = d\psi/ds$, and $S$ represents the total contour length of the membrane in the free segment. For small $\theta$, the energy
difference of the system per unit length of the target has a general form as
\[ \Delta E = \frac{K}{l_{\text{eff}}} [A_1 \psi + A_2 \theta], \]  
where \( A_1 \) and \( A_2 \) are functions of physical parameters of the system and can be found in explicit form in [20]. The wrapping angle can be found by minimizing equation (3.3) with respect to \( \theta \). We note that when \( A_1 \) becomes zero, the transition from the unwrapped regime to the partially wrapped regime happens. Using this criterion, we find a threshold for the membrane-target adhesion energy density for unwrapped–partially wrapped transition as
\[ \omega_c = \frac{K}{2D^2 \alpha^2} \left[ 1 + \sqrt{D^2 \alpha^2} \right]^2 \frac{4}{9} \left[ 1 + 3 \sqrt{D^2 \alpha^2} \right]^{3/2} - 1. \]  
(3.4)
where \( \omega_c \) is defined as \( \omega_c = (2\omega_c a^2)/\kappa \). This transition is indicated by the green dotted lines separating the unwrapping region from the partial wrapping region in figure 3(b). Equation (3.4) is insensitive to the membrane tension and for \( \omega_c \to 0 \) converts to \( \omega_c = \kappa/2D^2 a^2 \), which is in agreement with those found in [64]. Regardless of a numerical prefactor, arising from three-dimensional simulations, our results confirm those found in [42] for oblate particles. For cylindrical targets, \( D = 1 \), \( \omega_c \) shows the same value as in [63]. Equation (3.4) shows that the threshold values of \( \omega_c \) in the horizontal case are smaller than the vertical one (compare the pink and green dotted lines in figure 3(b) on the right panel). This equation also indicates that the adhesion to the substrate enhances the effect of particle orientation in the partially wrapped transition, and it hinders the partial wrapping transition more in the vertical than in the horizontal orientation.

### 3.2.2. Partial wrapped–full wrapped (P–F) transition

In order to understand the transition from the partial wrapped to the full wrapped state (P–F transition), first we need to derive the force (per unit length) acting on the membrane by calculating energy changes associated with infinitesimal membrane displacements. The generalized force per unit length of the cylinder acting on the membrane, \( \mathcal{F} \), is given by Khorasanizadeh et al. [20] and Hashemi et al. [21]
\[ \mathcal{F}(s) = \left[ \frac{1}{2} \kappa \tilde{\psi}^2 - (\Sigma + \omega_c) \right] \ell(s) + \kappa \psi \ell(s), \]  
(3.5)
where \( \tilde{\psi} = \partial^2 \psi / \partial s^2 \). At the equilibrium, the total force acting on each segment of the membrane should be zero, which means that \( \mathcal{F}(s) \) does not depend on \( s \) and is constant. By decomposing \( \mathcal{F} \) in x- and y-directions, we can write
\[ \frac{\kappa \psi^2}{2} - (\Sigma + \omega_c) = \mathcal{F}_x \cos \psi + \mathcal{F}_y \sin \psi. \]  
(3.6)
Using equations (3.6) and the boundary conditions at point \( c \), \( \psi_c = 0 \) and \( \psi_b = \sqrt{2\omega_c / \kappa} \) [65], the horizontal component of the force can be determined as
\[ \mathcal{F}_y = -\tilde{\Sigma}, \]  
(3.7)
where \( \Sigma \) and \( \mathcal{F}_0 \) are defined as \( \Sigma = (2\Sigma a^2 / \kappa) \), \( \mathcal{F}_0 = (\kappa / 2a^2) \), respectively. The vertical component of the force can also be derived by applying the boundary condition at point \( m, \psi_m \) and \( \psi_m \), in equation (3.6)
\[ \mathcal{F}_y / \mathcal{F}_0 = \frac{1}{\sin \psi_m} \left[ \alpha_c^2 \psi_m^2 - \Sigma (1 - \cos \psi_m) - \omega_c \right], \]  
(3.8)
where \( \psi_m \) can be found as [65]
\[ \psi_m = \left[ C(\theta) - \sqrt{2 \omega_c / \kappa} \right] \]  
\[ = 1 \left[ \Sigma^2 / \kappa \right] + D^2 (\Sigma^2 / \kappa) + \tan^2 \psi \right]^{3/2} - \sqrt{\omega_c}, \]  
(3.9)
where we replaced \( C(\theta) \) from equation (A.8) and \( \omega_c \) is defined as \( \omega_c = (2\omega_c / \kappa) \). Figure 4a represents the behaviour of \( \mathcal{F}_y \) with respect to \( \theta \), corresponding to the different values of \( \omega \) in the simulation. This force is constant for large enough values of \( \theta \) in both vertical and horizontal cases. It means that for large enough values of \( \theta \) both vertical and horizontal components of the force at the free part of the membrane remain constant.

Inspection of the membrane shape in figures 2 and 4c (see also electronic supplementary material, figure S1) shows that when the wrapping angle is large, there is a region of the free membrane segment where the angle \( \psi \) is constant, named \( \psi_{\text{ss}} \), which implies \( \psi |_{\psi_{\text{ss}}} = 0 \) and \( \psi |_{\psi_{\text{ss}}} = 0 \). As the force \( \mathcal{F} \) must be constant through the contour length at the equilibrium, its vertical and horizontal components can be written in terms of \( \psi_0 \) as
\[ \mathcal{F}_y / \mathcal{F}_0 = \left\{ \right\} \]  
(3.10)
and
\[ \mathcal{F}_x / \mathcal{F}_0 = \left\{ \right\} \]  
(3.11)
Therefore, we have \( \mathcal{F}_y / \mathcal{F}_0 = \tan \psi_0 \) and considering equation (3.7), we can write the following equations
\[ \cos \psi_0 = \frac{\Sigma}{\Sigma + \omega_c} \quad \text{and} \quad \tan \psi_0 = \sqrt{\omega_c^2 + 2 \Sigma \omega_c} / \Sigma. \]  
(3.12)
These equations show that increasing the wrapping angle does not change the angle of the force (consequently the angle of the membrane) in the free part (figure 4b). On the other hand, the angle of the membrane at the detachment of the target, \( \psi_m \), is an increasing function of the wrapping angle (equation (A.7)). The P–F transition occurs when \( \psi_0 = \psi_m \). Therefore, by substituting equation (3.11) into equation (A.7), we can determine the transition angle \( \theta_t \) as
\[ \tan \theta_t = -\Sigma^2 / \kappa \]  
(3.12)
The full wrapped regime occurs in \( \alpha = 2\theta_t \). The transition to the fully wrapped state has been argued to be either continuous [63] or discontinuous [17,42]. Equation (3.12) is negative, which predicts an abrupt transition from partially wrapped to fully wrapped state in the range of \( 90^\circ < \theta_t < 180^\circ \), depending on the orientation of the target, \( \Sigma \), and adhesion to the substrate, \( \omega_c \). For \( \omega_c \ll 1 \), the transition angle approaches 180°, while a very large \( \omega_c \) leads to \( \theta_t \to 90^\circ \). The transition angle \( \alpha = 2\theta_t \) is indicated by the dashed lines in figure 3a. Equation (3.12) shows that for the same range of parameters the transition in the horizontal case, \( D = 2 \), is sharper than the vertical orientation, \( D = 1/2 \).
Now, the vertical component of the force can be written as
\[
\mathcal{F}_y = -\Sigma \tan \psi_0 = \frac{1}{\sin \psi_0} [a^2 \psi_m^2 - \Sigma (1 - \cos \psi_0) - \omega_0].
\] (3.13)

Using equation (3.11) and some manipulation we have
\[
2(\Sigma + \omega_0) = a^2 \psi_m^2.
\] (3.14)

By substituting \(\hat{\psi}_0\) from equation (3.9) and using equation (3.12), the membrane-target adhesion energy density for partial-full wrapped transition can be found as
\[
\omega_\ell = \frac{\kappa}{2a} \left[ \sqrt{2(\Sigma + \omega_0)} + \frac{(\Sigma^2 + D^2(\omega_\ell^2 + 2\Sigma \omega_0))^{3/2}}{D(\Sigma + \omega_0)} \right].
\] (3.15)

where \(\Sigma\) and \(\omega_0\) are defined as \(\Sigma = 2a^2/\kappa\), \(\omega_0 = 2\omega_0 a^2/\kappa\), respectively. This equation confirms the cylindrical equation with \(D = 1\) [20]. This transition is shown as a dashed line in figure 3b. Equation (3.15) shows that the threshold values of \(\omega_\ell\) in the vertical case are slightly smaller than the horizontal one (compare the pink and green dashed lines in figure 3b on the right panel). The full wrapped transition, equation (3.15), strongly depends on the membrane tension, which is in agreement with the previous studies [17,42,63]. In the case of a tension-less membrane, \(\Sigma = 0\), equation (3.15) converts to \(\omega_\ell = \kappa/2a(\sqrt{2\omega_0 + D^2})^2\), and for the very weak adhesion between the membrane and the substrate, \(\omega_0 \ll 1\), it changes to \(\omega_\ell \approx \kappa D^4/2a^2\). For the cylindrical targets, \(D = 1\), this equation shows that \(\omega_\ell\) is equal to \(\omega_0\). This is in agreement with the previous studies that found in the tension-less membranes, there is no partial wrapped regime for symmetrical targets [42]. However, for asymmetrical particles, this leads to two different cases. In the case of the vertical configuration, \(\omega_0\) is smaller than \(\omega_\ell\), which means if the membrane can overcome the partial wrapped threshold, the target can be fully engulfed. However, in the horizontal case, always \(\omega_\ell < \omega_0\), which means a partial wrapped regime exists both for finite and for vanishing surface tension.

The energy of the system in the full wrapped regime is degenerate [20], and the left and right angles can fluctuate between \(\theta_1\) and \(2\pi - \theta_1\), which means the engulfment can be asymmetric (see electronic supplementary material, figure S1). The \(P-F\) transition angle, \(a = 2\theta_1\) (equation (3.12)) for the horizontally oriented configuration is \(a \approx \pi\), while for the vertical case it is mostly close to \(2\pi\). As a result, the membrane in horizontal configuration is more likely to be asymmetric than in the vertical one. Moreover, because there is an energy barrier in the highly curved part, if the membrane could pass just one of these parts it will engulf the whole target.

### 4. Discussion and conclusion

In this paper, we used a two-dimensional coarse-grained model of lipid membranes to investigate the impact of local curvature of particles in the wrapping process. This model is constructed by discretization of the Helfrich energy. Using this model we studied the engulfment of a very long cylindrical nanoparticle (a nanowire) with elliptical cross-section. The lipid membrane itself is adhered to a planar substrate mimicking the cortical cytoskeleton. To understand the role of local curvature, we have studied a system with two different orientations of the nanowire: in one case, the object is placed upon the membrane from its long side (horizontal orientation), and in the second case it is introduced to the membrane from its highly curved part (vertical state). While the importance of particle’s shape and orientation in the cellular wrapping has been studied previously [17,41,42,44], the role of an actin-based cortical cytoskeleton underneath the membrane has not. The cytoskeleton cortex can strongly influence the membrane’s ability to deform. In previous studies, the wrapping of the membrane around an external particle was controlled by the elastic energy of the deformed membrane and the membrane-target adhesion...
energy. In the present work we have studied this process as an interplay between the membrane-target, the membrane-cytoskeleton adhesion and the elasticity of the membrane. While the elastic parameters of the membrane are fixed, the competition between the membrane adhesion energy with the target (characterized by the parameter \( \omega \)) and with the cytoskeleton (parameter \( \omega_c \)) defines three distinct regimes of engulfment, separated by two phase transitions (figure 3).

The target remains unengulfed (\( U \)) by the membrane if \( \omega < \omega_u \), given by equation (3.4). Owing to the high curvature at the tip, the values of \( \omega_u \) in the vertical case are larger than in the horizontal configuration (equation (3.4)). This means that in the initial stages of phagocytosis, wrapping of particles with small curvature is easier than the particles with high curvature. For \( \omega > \omega_u \), the target is partially engulfed (\( P \)) and the wrapping angle continuously grow with increasing \( \omega \). In the partial wrapped regime, the vertical case shows a more rapid progression of the wrapping angle with the adhesion energy than the horizontal one. The target is fully engulfed (\( F \)) by the membrane if \( \omega > \omega_f \), given by equation (3.15).

Both threshold target adhesion densities \( \omega_u \) and \( \omega_f \) depend on the shape, and the local curvature of the object, given by the axial ratio \( D \). Both \( \omega_u \) and \( \omega_f \) are increasing functions of the cytoskeleton adhesion density \( \omega_c \) and of the membrane bending rigidity \( \kappa \). Although the full critical adhesion \( \omega_f \) strongly depends on the membrane tension, the partial wrapped threshold is insensitive to membrane tension. The numerical and analytical results show that the substrate adhesion enhances the effect of particle orientation on the partial and full wrapping transition: it hinders the partial wrapping transition more in the vertical than in the horizontal orientation, while the reverse is true, although the effect is weaker, for the full wrapping transition.

It should be noted that the MD simulations have been used to find the equilibrium conformations of the membrane, which corresponds to the minimum energy of the system. Although we considered a two-dimensional case (a very long object), our results regarding the effect of local curvature on the wrapping process can be expanded to the cases in three dimensions such as phagocytosis, endocytosis and viral infection.

It has been shown that phagocytosis occurs in two distinct stages. During the first stage, engulfment is relatively passive and determined by receptor diffusion and adhesion to the target, whereas the second stage is more active [66] and dependent upon actin polymerization and myosin motor proteins [9]. While one can add these forces to the simulation [67,68], the results can be anticipated by the current model. In the vertical case, the membrane can easily proceed to larger wrapping fractions so that the process enters the second active stage, and the active forces coming from the cytoskeleton can continuously grow around the target to assist the wrapping process. On the other hand, in the horizontal case, there is a bottleneck around the highly curved parts that prevents reaching large wrapping fractions; and one can anticipate that entering the second stage is less likely in the horizontal orientation. Besides, in contrast with the vertical case, the actomyosin ring around the horizontal configuration must experience a substantial deformation at the highly curved parts. It also should be mentioned that phagocytosis strongly depends on the diffusion time of the phagocytic receptors. If during a specific time the process cannot be completed, these receptors will diffuse and the particle cannot be internalized [9,69]. Although the present model is a pure equilibrium one without kinetics, one can infer from the dependence of the wrapping angle with the adhesion energy that there exists a high energy barrier associated with the wrapping of the highly curved sides in the horizontal case, while such a barrier is absent for the vertical case. In the latter case, diffusing receptors on the cell membrane can be expected to find ligands on the object easily, while in the former case, there is a bottleneck around the highly curved parts, which makes the process less likely. These results are in agreement with the experimental results of Champion & Mitragotri [35], who observed that the ellipsoidal discs introduced to neutrophils by their tips could be completely engulfed after 3 min. But, even after 110 min, these particles could not enter to cells when they were introduced to neutrophils by their long sides. One possible extension to bring the active forces to this model is to tune the adhesion between the membrane and the target, \( \omega \), as the function of the wrapping angle and over time. This provides an extra force that can help to overcome the \( U-P \) and \( P-F \) thresholds. Such a similar method can also be used for the membrane-cytoskeleton adhesion, \( \omega_c \), to describe the reorganization of the cytoskeleton over the wrapping process.

**Data accessibility.** The data are provided in electronic supplementary material [70].

**Authors’ contributions.** A.K.: conceptualization, data curation, formal analysis, investigation, methodology, software, validation, visualization, writing—original draft, writing—review and editing; P.S.: conceptualization, methodology, supervision, validation, writing—review and editing; F.M.-R.: conceptualization, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, writing—review and editing.

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### Appendix A. Curvature of the ellipse

Here, we derive the equation of the curvature at the membrane-target detachment point. According to figure 1, the Cartesian components \( x \) and \( y \) can be written as

\[
\begin{align*}
x &= r(\theta) \sin \theta \\
y &= -r(\theta) \cos \theta
\end{align*}
\]  
(A 1)

By replacing equation (A1) in equation (2.1) the ellipse is described as

\[
r(\theta) = \frac{ab}{\sqrt{b^2 \sin^2 \theta + a^2 \cos^2 \theta}} \hat{e}_r
\]  
(A 2)

where \( \hat{e}_r \) and \( \hat{e}_\theta \) are the radial and azimuthal unit vectors, written as

\[
\begin{align*}
\hat{e}_r &= i \sin \theta - j \cos \theta \\
\hat{e}_\theta &= i \cos \theta + j \sin \theta
\end{align*}
\]  
(A 3)
By differentiation of $r(\theta)$ with respect to the contour length, $s$, the tangent unit vector of the ellipse can be calculated as

$$\hat{r} = \frac{\partial r}{\partial s} = \frac{a \sec \theta}{\sqrt{D^2 + \tan^2 \theta}} \left[ \frac{(D^2 - 1) \tan \theta}{(D^2 + \tan^2 \theta)} \hat{e}_r + \hat{e}_\theta \right] \frac{\partial \theta}{ds}. \quad (A 4)$$

where $ds$ is written as

$$ds = \left| \frac{dr}{d\theta} \right| d\theta = \frac{a \sec \theta}{\sqrt{D^2 + \tan^2 \theta}} \left[ \frac{(D^2 - 1) \tan^2 \theta}{(D^2 + \tan^2 \theta)^2} + 1 \right]^{1/2} d\theta. \quad (A 5)$$

By replacing $\partial r/\partial s$ from equation (A 5) in equation (A 4) the tangent unit vector of the ellipse can be described as a function of the wrapping angle $\theta$ as

$$\hat{r} = \left( \frac{(D^2 - 1) \tan^2 \theta}{(D^2 + \tan^2 \theta)^2} + 1 \right)^{-1/2} \left( \frac{(D^2 - 1) \tan \theta}{(D^2 + \tan^2 \theta)} \hat{e}_r + \hat{e}_\theta \right). \quad (A 6)$$

Using equation (A 3), one can find the angle of the membrane at the point $m$ where it detaches from the ellipse (see figure 1a),

$$\cos \psi_m = \hat{r} \cdot \hat{e} = \frac{D^2}{\sqrt{D^4 + \tan^2 \theta}}, \quad (A 7)$$

and

$$\tan \psi_m = \tan \theta \frac{D}{\sqrt{D^4 + \tan^2 \theta}}.$$

where $\psi$ is the angle between the tangent vector of the membrane and the $x$-axis. The local curvature of the ellipse as a function of the wrapping angle can be found by differentiation of $\hat{r}(\theta)$ with respect to the contour length

$$C(\theta) = |\hat{r}| = \frac{D}{\sqrt{D^4 + \tan^2 \theta}}^{3/2}. \quad (A 8)$$

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