Pearling instability of membrane tubes driven by curved proteins and actin polymerization

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Abstract

Membrane deformation inside living cells is crucial for the proper shaping of various intracellular organelles and is necessary during the fission/fusion processes that allow membrane recycling and transport (e.g. endocytosis). Proteins that induce membrane curvature play a key role in such processes, mostly by adsorbing to the membrane and forming a scaffold that deforms the membrane according to the curvature of the proteins. In this paper we explore the possibility of membrane tube destabilization through a pearling mechanism enabled by the combined effects of the adsorbed curved proteins and the actin polymerization that they recruit. The pearling instability can serve as the initiation for fission of the tube into vesicles. We find that adsorbed curved proteins are more likely to stabilize the tubes, while the actin polymerization can provide the additional constrictive force needed for the robust instability. We discuss the relevance of the theoretical results to in vivo and in vitro experiments.

1. Introduction

Intracellular membrane is continuously broken up into small vesicles needed for the transport and recycling of the cell organelles [13, 43] or during endocytosis [14]. By adsorbing to the membrane and bending it, proteins that curve the membrane play an important role during these processes [3, 37]. These proteins are also crucial during endocytosis (e.g. clathrin [39] and Bin-Amphiphysin-Rvs (BAR)-domain proteins [26]) and help during the later stages of fission and transport [12] throughout the cell [10].

In addition, the recruitment of actin is implicated as a key component allowing for the completion of vesicle fission [27] and the endocytosis process [3, 42], especially in the clathrin-independent pathway [8, 18, 20, 25, 35]. The mechanism enabling curved proteins to coordinate and drive the membrane vesiculation process is currently a subject of intense experimental and theoretical studies [22, 23]. Recent in vitro experiments have investigated the ability of curved proteins to induce the formation of the membrane tubes, and it was found that the fission of the tubes into vesicles requires additional components such as actin polymerization [33–35], membrane demixing [2, 36, 41] or dynamin-driven constriction [28]. Similar long membrane tubules were observed also in vivo in the case of the Golgi transport tubules, where the connection between tubulation and COPI-mediated vesiculation was established, although the details of this process are not yet clear [13]. It is therefore still an open problem to understand the physical routes by which curved proteins achieve vesicle formation, rather than form a scaffold that stabilizes membrane tubes [17].

The destabilization of a membrane tube due to adsorbed curved proteins is possible by a finite-wavevector (Turing) instability that leads to non-uniform distribution of the curved proteins, as was explored theoretically in [40], and seen in vitro [31] and in cellular organelles such as Golgi apparatus [38]. In this mechanism large density undulations in the distribution of the adsorbed proteins lead to regions where the membrane is constricted and is rich in protein (condensed rings). While this process can play an important role, we wish to explore whether the tube destabilization is also feasible in the regime of uniform protein coverage. In this regime we investigate the pearling instability mechanism [5, 9, 45]. Note that a previous study of pearling induced by curved...
membrane inclusions [11] treated grafted curved molecules, while here we treat the case where the curved molecules are dynamically adsorbed from the surrounding medium. Finally, in parallel to our work, a recent study [46] simulated the membrane shapes during tubulation and pearling for a model that resembles ours, and was motivated by the fine structural details of the endocytosis process. Our study is aimed at the more general physics of this process.

We explore two possible routes by which curved proteins (such as Fer-CIP4 homology-BAR (F-Bar)-like shape, for example) can lead to the pearling of a membrane tube: (i) a pre-formed, bare membrane tube is rapidly coated by the curved proteins; or (ii) a membrane tube is formed through the adsorption of the proteins, and is then squeezed by the rapid polymerization of an actin coat. Note that for pearling to occur the factors that affect the membrane tube have to act faster than the rate at which the water can flow out of the tube. We find that only coating by curved proteins (i) is not robust, with most cases leading to increased tube stability, while the addition of actin polymerization around the tube (ii) can provide an extra squeezing force to drive a robust pearling instability. The pearling transition can serve to initiate membrane tube fission and vesicle formation.

2. Tubes with adsorbed curved proteins

We begin with the equilibrium state of a membrane tube with adsorbed curved proteins. At equilibrium, there is no net flux of proteins adsorbing and desorbing onto the lipid membrane. The equilibrium condition can be written as (see supplementary information, equations (S1-S3)):

\[ k_\text{ad} (1 - \phi) \rho v = k_\text{de} \phi, \tag{1} \]

where \( \rho = N_0/V \) is the density of the proteins in the surrounding solution (infinite reservoir), \( \phi \) is the occupied area fraction, \( v \) is the volume of a single protein and \( k_\text{ad} \) and \( k_\text{de} \) denote the adsorption and desorption rates, respectively, such that: \( 0 < \phi < 1 \) and \( 0 < \rho v < 1 \). We additionally assume that the rates of adsorption and desorption depend on the protein and tube radius in the following manner [32]

\[ k_\text{ad} = A_\text{f} \exp \left[ -\frac{\kappa_p a \beta}{2} \left( \frac{1}{R_\text{t}} - \frac{1}{R_\text{p}} \right)^2 \right] k_\text{de}, \tag{2} \]

where \( \beta = 1/k_\text{B} T \) and \( \kappa_p \) represents the bending rigidity of the adsorbing protein molecules, \( R_\text{t} \) their intrinsic radius of curvature (several tens of nanometers for BAR, COPI and other intracellular traffic-associated proteins [44, 47]), \( R_\text{p} \) the radius of the lipid tube (in general not a constant), and \( a \) the area of an individual adsorbed protein. The affinity \( A_\text{f} \) is a numerical factor describing the preference of the proteins to adsorb to the membrane. Adsorption will be more probable \( (k_\text{ad} > k_\text{de}) \) when the protein and tube radii match, whereas in the case of a large mismatch, desorption represents the dominating process. Combining equations (1) and (2), we get the occupied area fraction of proteins on the tube (similar to [11]):

\[ \phi = \left\{ \frac{1}{A_\text{f} \rho v} \exp \left[ \frac{\kappa_p a \beta}{2} \left( \frac{1}{R_\text{t}} - \frac{1}{R_\text{p}} \right)^2 \right] \right\}, \tag{3} \]

Let us illustrate this result in the case of a uniform lipid tube of fixed radius \( R_\text{t} \). If the curvature of the protein molecules is large, \( R_\text{p} \ll \sqrt{a/\kappa_p} \) (figure 1(a)), the occupied area fraction of adhered proteins increases

![Figure 1. Total free energy per unit length as a function of tube radius in the case of more (a, \( R_\text{p} = 0.013 \mu m \)) or less (b, \( R_\text{p} = 0.1 \mu m \)) curved protein molecules, at vanishing \( \sigma \). Dotted and dashed lines represent the membrane and protein contributions to the total free energy respectively, and the dash–dotted gray line shows the dependence of occupied area fraction (\( \phi \)) on the tube radius (\( \kappa_p R_\text{t}^2 = \kappa_a R_\text{t} \)). As the protein concentration \( c_\phi \) is increased, the total free energy increases with respect to the bare lipid tube and the membrane and protein contributions are shown by the dotted and dashed lines, respectively.](image-url)
steeply as \( R_t \) approaches \( R_p \) from below, and peaks at \( R_t \approx R_p \). The occupation fraction then decreases rapidly as the tube radius is further increased and the curvature mismatch increases (equation (2)). In the limit of \( R_t \to \infty \) the occupation fraction reaches a finite value, which approaches zero for \( R_p \to 0 \) (equation (3)). The curve \( \phi(R_t) \) is asymmetric which becomes more pronounced for less bent proteins \( (R_p \gg \sqrt{a/3\kappa_p}, \text{figure 1(b)}) \). In this case \( \phi \) again increases sharply as \( R_t \) approaches \( R_p \) from below, but it saturates much before \( R_t \approx R_p \) and remains roughly constant as \( R_t \to \infty \), approaching \( \phi_{\infty} = [(A_F \rho \nu)^{-1} + 1]^{-1} \) for \( R_p \to \infty \) (\( \phi_{\infty} \to 1 \), for the strong affinity case which is of interest here, \( A_F \rho \nu \gg 1 \)). In this limit of \( R_p \to \infty \) the weakly curved proteins do not discriminate greatly between differently curved lipid tubes.

A cylindrical lipid tube that is coated uniformly by the adsorbed proteins has a different equilibrium radius compared to the bare membrane. The new tube radius is found by minimizing the total free energy of the system (per unit length), which is now comprised of the bending energy of the tube, the bending energy of the proteins and the terms associated with the volume/area or pressure/surface tension conservation [41]

\[
f = \frac{\kappa}{R_t^2} + \kappa_p \left( \frac{1}{R_t} - \frac{1}{R_p} \right)^2 \phi + 2 \sigma - p R_t \right) \pi R_t,
\]

and where \( \phi \) is given by the equation (3), \( \kappa \) is the bending modulus of the membrane, \( \sigma \) is the effective membrane tension and \( p \) is the pressure difference across the membrane.

Figure 1 shows the free energy per unit length in the case of \( \sigma = p = 0 \) for two limiting cases. (i) For weakly curved proteins, the free energy has two minima and the global one is found at:

\[
R_t \approx R_p \left( \kappa_p \phi + \kappa \right) / \kappa_p \phi.
\]

This is easily seen from equation (4) in the limit of large \( R_p \), where \( \phi \approx 1 \) (figure 1(b), and case (ii) dash–dot line in figure 2). (b) For highly curved proteins, there are now two local minima and the global minimum can shift to very large values \( R_t \gg R_p \). In this limit (figures 1(a) and 2) the adsorbed proteins act mainly as an additional membrane tension, and \( R_t \approx R_p \sqrt{(\kappa_p \phi + \kappa)} / \kappa_p \phi \), where \( \phi \ll 1 \) (equation (4)). The global minimum at large tube radius is eventually influenced by the finite membrane tension. Note that the local minima in both cases exist only at sufficiently high \( A_F \rho \nu \).

These results can be further generalized by adding a positive surface tension, which non-uniformly raises the free energy curve thus making it possible for the minima to change their characters (from local to global and vice versa) and can cause not only double but also triple energy degeneration. By varying the surface tension any given tube radius can be achieved. We additionally note that in biological systems proteins interact directly among themselves and it has been shown that such interactions (especially in the limit of dense coating) can effect the morphology of the membrane [4]. A detailed analysis of this additional effect is outside of the scope of this paper and direct protein–protein interactions are thus neglected here.

3. Pearlring of pre-formed membrane tubes

Let us now consider a bare cylindrical membrane tube (equilibrated at \( \rho = 0 \) and \( \sigma > 0 \)) with an equilibrium radius \( R_t = \sqrt{\kappa / 2 \sigma} \). Curved proteins are then introduced into the surrounding medium and the tube is quickly coated. If the coating process is slow, so that the solution inside the tube has time to flow and adjust the tube volume, the adsorbed proteins drive the tube to change its radius uniformly, approaching the equilibrium tube radius calculated in the previous...
The more strongly curved protein coating of the tube and a relatively large mismatch between the protein curvature and the coordinate along the cylindrical axis, respectively. Since the volume of the pearled shape is kept fixed (equal to the volume of the initial tube), the following relation holds: \( R_m = \sqrt{R_1^2 - \epsilon^2}/2 \). The free energy in the limit of small amplitude perturbations \( (R_m \gg \epsilon) \) can now be calculated (see supplementary information, equation (S6)). Since we find that the free energy does not depend greatly on the wave vector except for very large \( q \), we additionally concentrate on the limit \( q \to 0 \).

We compare the normalized free energies of the coated pearled tube and the coated uniform tube (at the initial radius \( R_1 \), at \( q \to 0 \). We find that the equilibrium shape depends strongly on the protein curvature (figure 3(a), solid line). The regime where the cylindrical shape has a higher energy than the pearled shape \( (\Delta f > 0) \) is the regime of spontaneous pearling.

In figure 3(b) we plot the critical tension needed to achieve pearling \( \sigma_{\text{trans}} \) (e.g. for the energy difference between pearled and uniform tube to vanish) as a function of the wavevector \( q \), and for different values of the protein curvature radius. We find that weakly curved proteins (large \( R_p \)) act to stabilize the tube, raising the value of \( \sigma_{\text{trans}} \). The more strongly curved proteins can lower \( \sigma_{\text{trans}} \) and even drive it to negative values, thereby ensuring spontaneous pearling (figure 3(b)).

We now evaluate the critical surface tension at \( q \to 0 \) (figures 3(c) and (d)). \( \sigma_c \equiv \sigma_{\text{trans}}(q = 0) \), and then compare it to the equilibrium surface tension \( \sigma_0 \) that is used to create and stabilize the initial membrane tube (prior to the introduction of the proteins). We find that, depending on the mismatch between the initial tube radius and the protein curvature, \( \sigma_c \) can be either bigger or smaller than \( \sigma_0 \). We first focus on figure 3(c) \( (R_p = 0.1 \mu m) \), where we see that with increasing \( R_p \), the critical surface tension \( \sigma_c \) increases \( (\sigma_c > \sigma_0) \), then drops sharply to low (even negative) values \( (\sigma_c < \sigma_0) \), and then monotonically increases as the protein curvature decreases. The initial rise in \( \sigma_c \) at low \( R_p \) is due to a low coverage by the proteins, which have a large mismatch between \( R_p \) and \( R_1 \) (figure 1(b)). The region where the critical tension is lowered is a consequence of the large increase in the protein coating of the tube and a relatively large mismatch between \( R_p \) and \( R_1 \) favouring the shape change, which allows to recruit more proteins from the solution onto the undulated tube. Finally, for larger \( R_p \) the occupation area fraction approaches a constant value and the critical surface tension gradually increases. In this limit \( (R_p \to \infty) \) the protein coat simply acts to stiffen the tube by increasing the effective bending moment.
modulus (equations (3) and (4)), and thereby stabilizing the tube against pearling.

At very low tube radii the critical surface tension exhibits additional spikes (figure 3(d)), due to the additional sharp drop in the occupation area fraction (figure 1(a)), when \( R_p \rightarrow 0 \). The bulk protein density or affinity do not have a strong qualitative effect on our results, except in the limit of very small density of the proteins in the solution or very low affinity.

Note that given enough time the condition of conserved volume does not apply anymore and the system will relax towards the lowest energy state, which is (at any given \( R_p \)) a cylindrical tube with a readjusted radius (figure 2). The timescale for the volume readjustment by water displacement flow depends on the overall change in volume (see supplementary information, equation S9), being faster for shorter tubes and for smaller changes in the tube radius. In the case of long Golgi tubules \( R_t = 1 \mu m, L = 10 \mu m \) the flow rate, due to the pressure exerted on the fluid by the membrane, is relatively small and it would take seconds for the tube to relax towards a radius that is smaller by 10% \( (R_t = 0.9 \mu m) \), and tens of seconds to empty the whole volume (assuming fluid viscosity of \( \eta \approx 5 \text{ mPa}\cdot\text{s} \), and bending modulus of \( \kappa \approx 3 \times 10^{-19} \)). For narrower tubes, observed during endocytosis [21], this time-scale can grow even further, although for short tubes it will be significantly shorter. Since the typical times of protein binding are of order seconds [40], we believe that the limit of conserved volume represents a good approximation for certain biological processes. As we show in figure 2, the equilibrium radius of the protein-coated tube is (in the majority of the domain) close to \( R_p \), which means that the biggest jumps in radius compared to the initial radius happen at low \( R_p \), where the tube has regimes spontaneous pearling. Since the tube can not change its radius fast when the jump in radius is large, the cylindrical membrane will most likely satisfy the conditions for pearling instability upon being coated with the proteins. However, we find that the conditions for spontaneous pearling are met only in limited ‘instability windows’ of \( R_p \) (figures 3(c) and (d)), which makes this mechanism non-robust, as most values of \( R_p \) end up stabilizing the membrane tube. This is particularly so inside the cell where membrane tubes of different radii coexist and would require a large number of specific proteins for each to pearl.

4. Pearling of protein-coated membrane tubes due to actin polymerization

We now address the effect of actin polymerization on the pearling instability. For simplicity we consider that the same curved proteins treated above can recruit the nucleation of actin polymerization, even though in reality these functions are linked by a variety of proteins that act together. The actin filaments that polymerize against the membrane tube can create an inwards squeeze on the tube, thereby acting as an additional effective membrane tension that can drive the pearling instability (figure 3(a)). When actin polymerizes against the membrane, the treadmilling motion of the filament against the surrounding viscous network produces an effective friction force that converts the polymerization into a pushing force acting normal to the membrane (on average) [30]. Alternatively, an expanding coat of cross-linked actin gel builds up internal stress, proportional to the curvature of the membrane surface [29]: assuming that the actin gel is relaxed when forming on the membrane tube, it builds up the following internal tension when pushed to the edge of the actin coat:

\[
\sigma_a \propto E w^2 / 2 R_p, \tag{5}
\]

where \( w \) is the actin coat thickness (determined by the polymerization and depolymerization rates) and \( E \) is the Young’s modulus of the cross-linked actin gel. We therefore expect that the actin-induced tension will increase with the tube curvature, until it reaches a maximal value given by the stall force of actin polymerization (≈1 nN per filament [16]). Note that if myosin-II is also recruited to the actin coat, an additional squeezing force can arise from myosin-driven contractility [7]. However, depending on the overall rates of polymerization/depolymerization, the actin coat can act as an elastic layer around the membrane tube and thus contribute an additional stabilising force against pearling. Taking this into account we modify the free energy by adding the induced surface tension and the elastic deformation term (see supplementary information, equation (S8)). The additional actin-driven tension \( \sigma_a \) alone leads to a more robust pearling since it is equivalent to an increase of the surface tension by some external force. The effect of actin deformation is, however, the opposite—the cylindrical actin coat prefers to keep its initial shape (figure 4(a)).

Let us now consider a scenario where the protein coating is initiating the formation of the tube in the first place, i.e. at a vanishing initial membrane tension \( (\sigma_0 = 0) \). The tube radius of the initial cylinder depends now very strongly on the curvature of the proteins, having usually a radius of the same order, \( R_t \sim R_p \) (figure 2). Depending on the rate of polymerization/depolymerization we can distinguish between two limiting cases; (i) the actin coat is rather static and behaves as a stiff layer, with a dominant shear deformation term in the free energy (supplementary information, equation (S8)), or (ii) the coat can relax any internal shear tensions due to the shape undulations. In the latter case, we assume that the actin network still induces an additional squeezing force (effective surface tension \( \sigma_a \)). If we calculate the critical membrane tension needed to induce the pearling instability \( \sigma_c \), we find that a stiff actin coat strongly discourages pearling and stabilizes the initial cylindrical structure (figure 4(b)). However, if the actin can
relax during the pearling shape transformation the additional surface tension $\sigma_a$ enables the pearling process (figure 4(c)). For each value of $\sigma_a$ (either fixed or $R_p$-dependent, as in equation (5)) there is a value of $R_p$ above which the tube is spontaneously pearled due to the actin-induced tension ($\sigma_a < 0$ in figures 4(c) and (e)). In figure 4(d) (constant $\sigma_a$ for every $R_p$) we plot the necessary $\sigma_a$ versus the critical value $R_{p,c}$ above which the tube is destabilized, and we find that $\sigma_a \propto 1/R_{p,c}^2$; as expected, thinner tubes are harder to destabilize. Figure 4(f) shows similar behavior if we take into account that $\sigma_a$ depends on the Young’s modulus, coat thickness and $R_p$ as given by equation (5). In this case we get: $E \propto 1/R_{p,c}^2$.

The critical values of the actin–induced tension shown in figure 4 are calculated using realistic values for the membrane and protein bending moduli. From the stall force of actin we expect a maximal force of $\sim 10^4 \text{nN} \mu\text{m}^{-2}$ (using a maximal density of one actin filament per 100 nm$^2$), which is much larger than the value estimated in figure 4(d) for the smallest protein radius: $\sigma_a/R_p \sim 10^3 (k_B T \mu\text{m}^2)/0.01 \mu\text{m} \approx 50 \text{nN} \mu\text{m}^{-2}$. We therefore conclude that actin polymerization in a dense gel can supply enough squeezing force to drive pearling of even the thinnest tubes. Although we have presented here two limiting cases, the findings apply also to systems where the actin coat is only partially elastic.

5. Conclusion

We have shown here that curved membrane proteins can both drive the formation of membrane tubes and...
destabilize them to undergo a pearling transition. Curved membrane proteins, such as BAR and F-BAR proteins, can induce membrane curvature and have been suggested to facilitate membrane invagination and scission during endocytosis [21]. COP1 proteins are believed to similarly enable the transition between the long tubules (several microns) to vesicles in the Golgi apparatus [15]. Curved proteins are recruited to the membrane by adsorption from the cytoplasm, and contribute to the shaping of the membrane bud and tubule. Following this adsorption the same curved proteins are required for the recruitment of actin-nucleating components [15], and eventually also the specialized scission machinery of dynamin [19]. The pearling transition which we have studied here can be the first stage towards destabilization of the tube, membrane fission and vesicle formation. However, we find that in general a uniform coat of curved membrane proteins is more likely to stabilize the tube, similar to recent observations [33]. The actin coat that polymerizes around the tube, recruited by the adsorbed curved proteins, induces a squeezing force and this induced surface tension can drive the pearling transition. We find that such a transition is encouraged only in the limit of a relaxed actin gel where there is little (or no) shear deformation elastic restoring force. The latter applies to cases where the rates of polymerization and depolymerization are fast, thus creating a very dynamic coat. These results may help shed light on experimental observations both in vitro and in vivo, where curved membrane proteins, and actin polymerization, have been found to play key roles during membrane deformation, fission and transport [33, 35]. Previously the pearling instability was shown to occur in cellular membranes only in pathological cases [6, 24], and we propose here that it may provide a mechanism used by normal cells for membrane remodeling.

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