Membrane-mediated interactions and the dynamics of dynamin oligomers on membrane tubes

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Abstract. Dynamin is a protein that plays a key role in the transport and recycling of membrane tubes and vesicles within a living cell. This protein adsorbs from solution to PIP₂-containing membranes, and on these tubes it forms curved oligomers that condense into tight helical domains of uniform radius. The dynamics of this process is treated here in terms of the linear stability of a continuum model, whereby membrane-mediated interactions are shown to drive the spontaneous nucleation of condensed dynamin domains. We furthermore show that the deformation of the membrane outside the dynamin domains induces an energy barrier that can hinder the full coalescence of neighboring growing domains. We compare these calculations to experimental observations on dynamin dynamics in vitro.

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1. Introduction

Lipid membranes are diffusion barriers that separate living cells from their environment and confine organelle contents to ensure their compositional and functional specificity. However, material exchanges between the cell and the outside, or between different organelles within the cell, are powered by the formation of transient membrane carriers in the form of vesicles that bud from their parent membrane. To ensure specificity and avoid backward diffusion of their content, these carriers are separated from the parent membrane by a process called membrane fission. This reaction is executed by dynamin in many of the intracellular traffic routes [1].

So far, dynamin is the only protein whose mechanical role in severing lipid membranes has been clearly shown: it forms 10 nm radius helical collars at the neck of nascent buds [2, 3], and can constrict the membrane further when it hydrolyses GTP [4, 5] through a concerted torsion of the helix [6]. A matter of debate has been to understand how dynamin is specifically recruited to the neck of budding vesicles. It was first proposed that a specific lipid PIP$_2$, whose synthesis is pronounced during the budding of given varieties of carriers, is responsible for dynamin recruitment. Dynamin has a Pleckstrin homology domain that specifically binds the PIP$_2$ lipid [7]. However, this does not explain why dynamin was observed to form the tight collar at the very late stage of budding, whereas PIP$_2$ is present from the beginning of the process [8]. Recent data have suggested the role of high membrane curvature in the neck region, as dynamin in the micromolar range is able to polymerize into tubules of a defined curvature [9]. It is now known that while dynamin dimers readily adsorb to PIP$_2$-containing membranes, they do not polymerize into tight helical domains unless the membrane is highly curved. This curvature control of the process of nucleation of dynamin polymerization essentially comes from a competition between the energy needed to squeeze the tube to
10 nm and the polymerization energy of dynamin. If the polymerization energy overcomes the squeezing energy, then polymerization is thermodynamically favored and nucleation can occur.

Strikingly, once the right range of curvature is reached, the onset of dynamin polymerization is very quick and suggests sharp instability. The previous study \([9]\) dealt with the issue of finding the threshold conditions for the nucleation of condensed dynamin domains on the membrane tube, using a static description. The dynamics of the nucleation of dynamin polymerization, in conjunction with tube constriction, have not been treated previously, and constitute the main aim of the present paper. These dynamics are complex due to the many processes that occur simultaneously, leading eventually (under proper conditions) to the nucleation of polymerized dynamin domains on a very constricted membrane tube. These processes include the adsorption of dynamin dimers from solution and their oligomerization into stiffer and longer polymers. During these processes the membrane tube radius is affected by the adsorbed dynamin dimers and oligomers, which in turn are responsive to the membrane tube shape. The dynamic coupling between the dynamin concentration, oligomerization and the membrane shape, makes this a highly challenging physics problem. The unique role played by dynamin inside cells also makes this problem important from a biological point of view.

In this study, we wish to explore several aspects of the dynamin–membrane interactions that were not treated previously. Our main aim is to explore the dynamical routes by which dynamin forms regions of high concentrations on the membrane tube, which serve as precursors for the nucleation of polymerized dynamin domains. The outline of the paper is as follows. (i) We describe the influence of dynamin oligomers on the membrane tube radius, in the non-polymerized phase. We demonstrate that this effect results in a significant change in the tube radius, including a regime where the uniform tube has two different stable radii. (ii) We then perform a linear-stability analysis around the calculated uniform tube state, and find the regimes where the membrane-mediated interactions between the dynamin oligomers are strong enough to drive the spontaneous formation of dynamin aggregations. These aggregations form the nuclei that evolve into the polymerized dynamin domains observed on membrane tubes. (iii) While the energy balance for nucleation was calculated in \([9]\), the edge energy of such domains due to the membrane deformation beyond the end of the condensed dynamin was not calculated in \([9]\), and is given here. This calculation allows us to estimate the minimal size of a growing condensed dynamin domain, and may also explain the barrier that interferes with the coalescence of neighboring domains. These theoretical results are then compared with experimental data and discussed.

2. The model

In this section, we describe the theoretical model used. We start with the linear stability analysis and in the second part give the calculation of the membrane shape and energy between two neighboring domains. Our model is a more elaborate version of the model we used in \([10]\) to calculate the dynamics of FtsZ rings in tubular liposomes (figure 1(a)). Let us list some of the main assumptions used in our model:

- Dynamin dimers adsorb on the lipid membrane in a curvature-independent manner, and therefore do not interact with the membrane shape.
Figure 1. (a) Schematic description of our model of a cylindrically symmetric membrane tube of uniform equilibrium radius $R_m$. On the membrane there is a population of dynamin dimers (gray circles) that is in equilibrium with the concentration of dimers in the bulk solution, and the dimers on the membrane can polymerize to form oligomers of various lengths (chain of gray circles), dominated by oligomers of length 2 with average concentration $n_o$. The oligomers induce membrane deformations (given by $h(z)$), which in turn give rise to currents and the formation of oligomers, which tend to aggregate in membrane constrictions (dashed gray circles). (b) An example of a dispersion relation $\omega(q)$ (equation (2.1)) arising from the linear stability analysis, and defining the unstable wavevectors for $q_{c,1} < q < q_{c,2}$ (equation (17)) and the most unstable mode $q_{\text{max}}$ (for the case dominated by convection and the fast equilibrium of dimers).

- Adsorbed dimers oligomerize to form stiff dynamin oligomers, in a curvature-dependent manner. The stiff oligomers are affected by the membrane shape and affect it in return.
- The stiff oligomers can diffuse and flow within the membrane, while their orientation is assumed to be fixed along the circumferential direction that minimizes their bending energy.
- Interactions between the oligomers are only mediated by the membrane and the chemical equilibrium with the dimers. The direct polymerization of oligomers into solid-like polymerized domains is not treated here. We assume that regions of high oligomer concentrations are the precursors for the nucleation of such polymerized domains.
- We assume cylindrical symmetry of the membrane and the dynamin concentration field.
The membrane lipid composition is rather uniform and only weakly affected by the adsorption of dynamin.

These assumptions are elaborated in the model below.

The energy of a membrane tube, with bending modulus $\kappa$, is given by the standard Helfrich form

$$E_m = \int \left( \frac{1}{2} \kappa H^2 + \sigma \right) \, dA,$$

where $H$ is the mean curvature of the membrane, $\sigma$ is the effective membrane tension and $dA$ is the surface area. Let $r(z)$ be the radius of the membrane tube; then the mean curvature is

$$H = \frac{r(z) r''(z) - r'(z)^2 - 1}{r(z)(1 + r'(z)^2)^{3/2}} = h''(z) - \frac{1}{R_m} + \frac{h(z)}{R_m^2} + O(h^2),$$

where $h(z)$ is a small deviation: $r(z) = R_m + h(z)$, from the equilibrium (initial) radius $R_m$ of the membrane, and

$$dA = \sqrt{g} \, dz \, d\theta,$$

$$g = r(z)^2 \left( 1 + r'(z)^2 \right).$$

For a free membrane tube the equilibrium radius is simply given by $R_{\text{free}} = \sqrt{\kappa/2\sigma}$.

The dynamin proteins that adsorb on the membrane are found in two states: a dimer and polymerized oligomers of various lengths. Dynamin oligomers all have the same spontaneous curvature of $1/R_p$, where $R_p = 10$ nm. As dimers have no obvious structural features that could be sensitive to the curvature of the membrane [12], we assume that the dimer is very flexible and there is therefore no significant contribution due to its presence to the overall curvature energy (equation (1)). The process of the adsorption of dimers from the solution, together with the formation of oligomers, determines the overall concentration of adsorbed dynamin, which depends on the concentration of dimers in the solution (no oligomers in the solution), the composition of the membrane (mainly PIP$_2$ concentration), etc. It was found empirically [9] that the adsorption of dynamin dimers on the membrane tube is not strongly dependent on the radius, as measured by the fluorescence intensity. Another study [12] also found that the dynamin adsorption is very weakly dependent on the tube radius, unlike the situation in other curved proteins, where adsorption is strongly radius dependent [13].

Oligomers, on the other hand, even short ones, are much more stiff than the dimer, and therefore when adsorbed to the membrane have a significant elastic bending energy as they conform to the local shape of the membrane [14]. In our treatment below we do not describe the length distribution of the oligomers, but simply treat the oligomers of length 2 as the dominant length in the population, of oligomers$^4$, with a polymerization energy of $\epsilon_o \sim 4k_B T$ per oligomer [9], and described by a bending modulus $\kappa_o$. We will assume that the dynamin oligomers are free to rotate in the membrane so that they can orient along the azimuthal direction, which minimizes their bending energy, as long as their radius of curvature is smaller than that of the membrane tube, i.e. $R_m > R_p$. We therefore treat their interaction only with the circumferential radius of curvature of the tube in equation (5) (figure 1(a)). We leave the treatment of orientational effects to a future study, which will also include taking into account the anisotropic curvature of the oligomers [15].

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$^4$ Assuming an exponential distribution typical of the thermodynamic equilibrium of polymerizing filaments.
The energy of the dynamin dimers and oligomers on the membrane is given by

\[
\mathcal{E} = \int \left( \frac{1}{2} N_o n_o \kappa_o \left( \frac{1}{r(z)} - \frac{1}{R_p} \right)^2 - ((\epsilon_d - \mu) + \epsilon_o) N_o n_o - (\epsilon_d - \mu) n_d \right. \\
+ k_B T \left( n_o \ln \left( \frac{n_o}{n_s} \right) + n_d \ln \left( \frac{n_d}{n_s} \right) \right) \\
+ n_s \left( 1 - N_o n_o - n_d \right) \ln \left( 1 - \frac{N_o n_o}{n_s} - \frac{n_d}{n_s} \right) \right) \, dA,
\]

(5)

where \( n_o \) is the local concentration of the oligomers containing \( N_o \) dimers, \( n_d \) is the concentration of the dimers, \( n_s \) is the saturation concentration of the dynamin units on the membrane, \( \epsilon_d \) is the membrane binding energy per dynamin dimer, and \( \mu \) is the chemical potential of the dimers in the solution. The first term in the energy describes the mismatch between the intrinsic curvature of the oligomers and the membrane, while the last terms give the entropy of the dimers and oligomers \cite{16}. Note that we are interested in the early stages when the oligomers are still in a non-polymerized phase, so that they remain mobile with some diffusion coefficient \( D_o = \Lambda k_B T \), where \( \Lambda \) is the mobility. We are also emphasizing that we consider only membrane-mediated interactions between the oligomers, and do not include the direct polymerization of oligomers into polymerized dynamin domains, which eventually takes place after the oligomers condense.

We next find the equilibrium conditions for the uniform tube by solving for the concentrations of dimers and oligomers, as a function of the tube radius. We minimize the free energy of the dynamin \( \mathcal{E} \) with respect to \( n_d \) and \( n_o \), and for the dimers we find a simple expression,

\[
\frac{\delta \mathcal{E}}{\delta n_d} = 0 \Rightarrow n_{d, eq}(z)/n_s = \frac{1 - N_o n_o(z)/n_s}{1 + \exp (\mu - \epsilon_d)/k_B T},
\]

(6)

while the equilibrium oligomer density is given by the solution of the following implicit equation:

\[
\frac{\delta \mathcal{E}}{\delta n_o} = 0 \Rightarrow \\
\log(n_{o, eq}(z)/n_s) - N_o \log(1 - (n_{d, eq} + N_o n_{o, eq}(z))/n_s) \\
= -1 + \frac{\epsilon_o}{k_B T} + \frac{N_o}{2 k_B T} \left( 2 (\epsilon_d + k_B T - \mu) - \kappa_o (R_p - r(z))^2 \right).
\]

(7)

For the value \( N_o = 2 \), there is an analytic solution for this equation that we have used in our calculations below. In the limit of \( n_o/n_s \ll 1 \) we can derive an analytic expression for the equilibrium solution \( n_o(z) \) for any length \( N_o \) (see appendix A).

To proceed further we will work in two opposing limits: (I) fast equilibration of the dimers, so that during the evolution of the tube shape the local concentration of dimers is always at the chemical equilibrium value \( n_{d, eq} \) given by equation (6), while the concentration of oligomers will be allowed to vary dynamically both due to chemical reactions and convection. This essentially assumes that the adsorption/desorption process of dimers from the solution is fast compared to the nucleation process. (II) Slow equilibration of the dimer, so that we take the concentration of the dimers to be constant at the initial equilibrium value of the uniform state.
The true dynamics of the dimers is in between these two limiting cases, which, however, simplify the analysis. Note that the equilibrium value of $R_m$ depends on the concentration of oligomers $n_{o,eq}$ (see below), which means that these two parameters have to be solved self-consistently.

The general equation of motion for the membrane radius $r(z)$ is given by

$$\frac{\partial r(z)}{\partial t} = - \int \mathcal{O}(z - z') \left( \frac{1}{\sqrt{g}} \frac{\delta F}{\delta r(z')} + A_o n_{o}(z') \right) dA,$$

(8)

where $F = E_m + E$ is the total free energy of the membrane with the freely diffusing dynamin oligomers $[17, 18]$. The possibility of the oligomers inducing an active force (due to the consumption of GTP) is represented by the factor $A_o$. In the present work, there is no need for such a term.

The equation of motion for the oligomer density $n_{o}(z)$ is given by $[18]

$$\frac{1}{\sqrt{g}} \frac{\partial}{\partial t} \left( \sqrt{g} n_{o} \right) = \frac{1}{\tau} \left( n_{o,eq} - n_{o} \right) + \Lambda \frac{1}{\sqrt{g}} \frac{\partial}{\partial z} \left( \sqrt{g} n_{o} \frac{\partial}{\partial z} \left( \frac{1}{\sqrt{g}} \frac{\delta F}{\delta n_{o}} \right) \right),$$

(9)

where we have used the covariant derivatives $[18]$, and introduced the time scale $\tau$ for the chemical reactions that drive the oligomers towards their local equilibrium concentration. Note that the hydrodynamic flows in the plane of the membrane are ignored here, which is a reasonable approximation for the linear stability analysis of small fluctuations. Furthermore, the lipid composition is not strongly affected by the adsorption of dynamin: a dynamin dimer covers 20–30 lipids, binding two specific lipids PIP$_2$, so it binds less than 10% of the lipids, even in the close-packed/polymerized domain. We are using 12.5% of PIP$_2$ in these experiments, so the concentration of PIP$_2$ should not change significantly below the adsorbed dynamin. The rest of the lipids is phosphatidylcholine only and should not interact with dynamin. Thus we do not expect the polymerization of dynamin to induce a significant flow of lipids due to concentration gradients.

For case (I), we will treat below the two limiting cases for the dynamics of the oligomers: either dominated purely by convection (second term of equation (9)) or by the chemical reactions (the first term of equation (9)). For case (II), there are no chemical reactions between the dimers and the oligomers during the instability, so only the convection of the oligomers is possible.

2.1. Linear stability analysis

We now calculate the stability of the membrane and adsorbed oligomers, due to a small perturbation to the uniform stable state. This analysis is relevant to the physical dynamics of dynamin aggregation on tubes, since in the experiments it seems very likely that such a state is achieved for a certain period of time, prior to the formation of condensed dynamin domains, for the following reason: the proteins and giant unilamellar vesicles (GUVs) are mixed together in a chamber at least 10 min prior to pulling the tube and it takes about 5 min to pull the tube and reach the desired nucleation radius. In this case, it is more than likely that the membrane-bound dynamin is at equilibrium, since dynamin reaches a constant fluorescence on the membrane in a few tens of seconds (see movie 1 of [9]).

The linear perturbations are:

$$r(z) = R_m + \delta h(z, t),$$

(10)
\begin{align}
n_o(z) &= n_0 + \delta n(z, t), \\
n_d(z) &= n_{d,0} + \delta m(z, t),
\end{align}

where \(R_m, n_0\) and \(n_{d,0}\) are the uniform initial steady-state membrane radius and equilibrium oligomer and dimer concentrations, respectively (from equations (6) and (7)), and \(h(z, t), n(z, t)\) and \(m(z, t)\) are small deviations from these uniform values (figure 1(a)).

It is easier to derive the equations of motion for the small perturbations by first expanding the free energy \(F\) up to quadratic order in \(\delta h, \delta n\). Using this form, we derived explicit expressions for the functions appearing in the linear stability analysis below.

Expanding equations (8) and (9) up to first order in \(\delta\), we obtain the following equations:

\[
\frac{\partial h}{\partial t} = -\int O(z - z')(U + \delta L(h, n) + O(\delta^2)) \, dA, \\
\delta \left( \frac{\partial h}{\partial t} + \frac{\partial n}{\partial t} \right) = \delta N(h, n) + O(\delta^2),
\]

where the functions \(N(h, n)\) and \(L(h, n)\) are given in appendix B.

The forces acting on the uniform tube are described by \(U\) (given in appendix B), and the condition for a stationary solution is \(U = 0\). This condition, together with equations (6) and (7), determines the steady-state uniform tube radius \(R_m\) and the dimer and oligomer densities.

To analyze the linear equations (13) and (14) we Fourier transform and write them in matrix form:

\[
\begin{pmatrix}
h_q \\
n_q
\end{pmatrix} = \begin{pmatrix}
h_q \\
n_q
\end{pmatrix},
\]

where the matrix \(M\) is defined as follows:

\[
M = \begin{pmatrix}
O_q M_{hh} & O_q M_{hn} \\
M_{nh} - n_0 O_q M_{hh} / R_m - \frac{1}{\tau} \frac{\partial n_0}{\partial t} & M_{nn} - n_0 O_q M_{hn} / R_m - \frac{1}{\tau} \frac{\partial n_0}{\partial t} + \Delta_{nm} M_{nm}
\end{pmatrix}.
\]

The different elements are given in appendix B, and \(O_q\) is the Fourier transform of the Oseen interaction kernel \(O(z - z')\).

For fast dimer kinetics the local equilibrium concentration of oligomers depends on the local concentration of dimers \((n_{d,\text{eq}}, \text{equation (7)})\), which in turn depends on the deviation from equilibrium of the oligomer density \(\delta n(z, t)\) that we are introducing (equation (12)). For this case we take the limit of \(\tau \to \infty\), neglecting these terms in \(M\). The case of slow dimer kinetics is simpler, since the local concentration of dimers is constant, fixed at the initial uniform value. In that case, we neglect the terms \(M_{nh}, M_{nn}, \Delta_{nm} M_{nm}\) in the matrix \(M\).

To find the stability of the system we look at one of the eigenvalues of \(M\) (the other one is always negative) \(\omega = \text{Tr}(M) + \sqrt{\text{Tr}(M)^2 - 4 \text{Det}(M)}\). The magnitude of this eigenvalue is proportional to the Oseen factor \(O_q\), and we therefore calculated this factor for the case of cylindrical membrane undulations (see appendix C). This eigenvalue becomes unstable in a regime of wavevectors \(q_{c,1} < q < q_{c,2}\) (figure 1(b)), where \(q_{c,1}\) can vanish. To find \(q_{c,1}\) we need to solve the equation \(\text{Det}(M) = 0\) (note that this equation is not dependent on the Oseen kernel). This equation reduces to a quadratic equation for \(q_{c,1}^2\), of the form \(a q_{c,1}^4 + b q_{c,1}^2 + c = 0\) (for both
types of dynamics), and the solution is

\[ q_c = \sqrt{\frac{b^2 - 4ac - b}{2a}}. \]  

(17)

We find the critical membrane tension \( \sigma \) above (or below) which \( q_c \) is real and the system becomes unstable, and recall that \( R_{m1}, n_0 \) are functions of \( \sigma \). Numerically we find that the instability first appears when \( b < 0 \), so the condition for instability is given by \( b^2 - 4ac = 0 \), corresponding to the condition: \( q_{c,1} = q_{c,2} \).

3. Results

3.1. Uniform tube radius

We begin by describing the uniform solutions for the tube radius as a function of the tension and bulk dynamin concentration (proportional to \( \exp(-\mu) \)). All the calculations shown below were performed using the following values: \( R_p = 0.01 \mu m, \epsilon_d = 1k_B T, \epsilon_o = 4k_B T, \kappa = 16k_B T, \kappa_o = 20k_B T, n_s = 10^4 \mu m^{-2}, \Lambda = 10^4 s gr^{-1}, \eta = 10^{-4} gr s^{-1} \mu m, \tau = 10^{-3} s. \) Note that this choice of units is useful when dealing with systems of membrane vesicles and tethers.

As shown in figure 2(a), the radius decreases with increasing tension, and for vanishing values of the dynamin concentration, the radius is very close to that of a bare membrane tube \( R_{free} \) (green line). When a small amount of dynamin is introduced, at low tensions (large radius), the adsorbed dimers induce an effective membrane pressure that acts to inflate the tube radius compared to that of the dynamin-free tether (compare the green and yellow lines for \( R > 0.021 \mu m \) in figure 2(a)). At larger membrane tensions, i.e. for smaller tube radii, the added dynamin induces a decrease in tube radius below the value for the bare membrane tether, due to the constricting force induced by the dynamin oligomers (compare the green and yellow lines for \( R < 0.021 \mu m \) in figure 2(a)).

At higher dynamin concentrations (purple and blue lines in figure 2(a)), corresponding to smaller values of \( \mu \), there is a bifurcation leading to two stable uniform solutions, and one uniformly unstable branch between them (the segment between the red circles in figure 2(b)). Let us now describe in more detail the bistability regime of the tube radius, shown in figure 2(b) (for \( \mu = 2k_B T \)): as the tension increases the radius decreases smoothly, until the pink circle is reached, where a metastable solution with a smaller tube radius appears, indicated by the dashed vertical line and the red circle (\( \sigma_{bin} \)). The lower branches of stable radii have a higher free energy, and are therefore metastable, until the tension reaches the value indicated by \( \sigma_{bin} \). This is the binodal point, where the free energies of both branches match (figure 2(c)).

At even higher tensions, the radius continues to shrink smoothly along the upper (now metastable) branch, until the red circle (figure 2(b), \( \sigma_{spin} \)), where the upper stable branch ends. This is the spinodal point, where the system jumps to the lower radius (vertical dashed line and lower pink circle), without any energy barrier. At even higher tensions the tube radius continues to shrink smoothly. In the presence of large fluctuations (thermal or other noise), the tube can jump from the upper branch to the lower.

The physical mechanism driving this bifurcation is the following positive feedback: an increase in the oligomer concentration leads to an increase in the constriction force, leading to a shrinking radius. The oligomer concentration then increases in a highly non-linear manner as the radius decreases (equations (6) and (7)), eventually leading to a run-away (catastrophic...
Figure 2. (a) Calculation of the uniform membrane tube radius $R_m$ as a function of the membrane tension $\sigma$ for different bulk dynamin concentrations: $\mu = 0, 2$ and $3k_B T$ (blue, purple and yellow, respectively), and using $\kappa = 16k_B T$, $\kappa_o = 20k_B T$. The green line is the radius of the free membrane tether $R_{\text{free}}$. (b) Bistability, instability and transition of the tube radius (for $\mu = 2k_B T$): the pink and red circles correspond to the limits of the region of bistability (between $\sigma_{\text{bis}}$ and $\sigma_{\text{spin}}$); the dark and light blue circles give the limits of the dynamically unstable regime for cases I and II of the dimer dynamics, respectively. The green circles correspond to the binodal point, at tension $\sigma_{\text{bin}}$. (c) Dependence of the free energy for the uniform tube on the tension, for $\mu = 2k_B T$. The intersection point corresponds to the binodal tension $\sigma_{\text{b}}$. The spinodal tension is indicated by $\sigma_{\text{s}}$. (d) Plot of the dependence of different radii indicated by the colored circles in (b) on the chemical potential $\mu$; each line corresponds to the color of the circle shown in (b). (e) Plot of the equilibrium oligomer concentration $n_0$ (equation (7)) as a function of the membrane tension $\sigma$ (the color scheme as in (a)). (f) The dependence of $R_m$ on the chemical potential $\mu$ for $\sigma = 0.1 \text{ gr s}^{-2}$. The horizontal dashed line gives the radius of the dynamin-free tether $R_{\text{free}}$.

behavior. The nonlinear increase of the oligomer concentration with increasing tension is shown in figure 2(e), and corresponds to the nonlinear dependence of the equilibrium radius on the tension shown in figure 2(a), i.e. the oligomer concentration and tube radius are strongly coupled. Note that we do not describe here further polymerization of the oligomers into
condensed domains, which naturally occurs where the oligomer density is high. However, as long as the polymerization into solid-like dynamin domains has not started, our analysis is valid and is not limited to the regime of small dimer and oligomer concentrations.

Within the bistable region we find that the system can reside in two stable solutions: one with a large radius and a small concentration of oligomerized dynamin, and the second with a small radius (much closer to $R_p$) and a large concentration of dynamin oligomers. The free energy of the two branches shifts as the tension increases, such that for low tensions the upper branch has the lower energy, and at higher tensions the balance shifts in favor of the lower branch.

At higher values of the membrane-bound dynamin concentration (low $\mu$ and high $\epsilon_d$), the tension $\sigma_{bis}$ decreases, until it vanishes. This indicates the possibility for the spontaneous tubulation of flat membranes due to the oligomerization of the dynamin. Indeed experiments show that a high concentration of dynamin can tubulate a flat membrane.

In figure 2(d), we plot the dependence of the different points described by the colored circles in part (a), as a function of the dynamin concentration in the solution (represented by $\mu$). The blue lines in this figure mark the region of dynamic instability described below.

In figure 2(f), we plot the dependence of the tube radius on the dynamin concentration in the bulk, at a fixed tension. We find the same trend shown in (a): the tube shrinks for increasing dimer concentration (decreasing $\mu$), but then increases slightly due to the added entropic pressure.

### 3.2. Dynamic instability

We next describe the dynamic stability of the uniform tube. We find that the regime of dynamic instability closely follows the regime of uniformly unstable tubes described above (blue points in figure 2(b)).

In figures 3(a) and (b), we plot the dispersion relations for case (I), for pure convection or chemical reactions, respectively. While the values of $\omega(q)$ are different, the region of unstable wavevectors is identical for both cases. In appendix D, we show this identity. In figure 3(c), we plot the dependence of the unstable wavevectors on the tube radius. The vertical lines correspond to the radii used to calculate the dispersions in figures 3(a) and (b). In figure 3(d), we plot for comparison the region of unstable wavevectors for case (II) of constant dimer concentration.

We find that the limits of the dynamic instability regime, as a function of the tube radius, are defined by the points where $q_{c,1} = q_{c,2}$, which is the criterion for dynamic instability. We plot the regime of dynamic instability in figure 2(d), in comparison to the bistability regime. We find that for case (II) the dynamic instability exists only in the inaccessible regime of unstable uniform tubes, whereas for case (I) the dynamic instability regime almost perfectly overlaps with the regime of bistability (but always extends over a larger region of radii). This is not surprising, since the driving mechanism for both phenomena is the same, i.e. the positive feedback between shrinking tube radius and increasing oligomer density.

### 4. Calculating the membrane edge-energy of a condensed dynamin domain

While in the previous study [9] the bending energy of the membrane due to a condensed dynamin domain was considered, the energy at the edge of such a domain was not calculated.
Figure 3. Analysis of the linear stability of the membrane tube. Plot of the dispersion relation $\omega(q)$ for case (I), and pure oligomer convection (a) or chemical reactions (b), for tube radii: $R_m = 20, 19.96$ and $19.85$ nm (blue, purple and yellow, respectively). (c) Unstable wavevectors for case (I), where the blue line gives $q_{c,2}$ and the purple gives $q_{c,1}$. The vertical lines indicate the radii used to generate the dispersions in (a, b). The inset gives a magnification of the relevant region. (d) Unstable wavevectors for cases (I) and (II), given by the solid and dashed lines, respectively.

Without the consideration of this edge energy the calculated nucleation threshold could not deal with nucleated domains of finite size, which are of course observed in practice. We calculate this edge energy here, and therefore provide a nucleation threshold that depends both on the tube radius and the length of the nucleated domain.

The edge energy is the bending energy of the free membrane, which extends beyond the edge of the polymerized dynamin domain. It connects the dynamin domain of radius $R_p = 10$ nm smoothly with the rest of the membrane tube that has radius $R_m > R_p$, as shown in figure 4(a). We assume that the membrane outside the dynamin domains is relatively free of oligomers, since they will quickly get incorporated into the growing polymerized domains. We therefore use the energy of a dynamin-free membrane as given in equation (1) to derive the equation for the steady-state membrane shape, which is simply equation (8) but using only the membrane energy $E_m$, and solving for the stationary solution.

We end up with a nonlinear differential equation for the stationary membrane shape,

$$\frac{\delta E_m}{\delta r(z)} = 0,$$

(18)
Figure 4. (a) Calculation of the free membrane shape beyond the edge of a polymerized dynamin domain (located at $z = 0$), for different values of the ratio $\alpha$. The inset shows a three-dimensional rendering of the free membrane profile (purple) beyond the edge of the dynamin domain (cyan), using $\alpha^{-1} = 0.4$. (b, c) Calculated edge energy $E_{\text{edge}}$ and minimal domain length $L_{\text{nuc}}$ for a single dynamin domain, as a function of $\alpha$. From the bottom to the top we used $\varepsilon_{\text{pol}} = 18$, 13.5 and 9 pN, respectively. The vertical dashed lines mark the value of $\alpha$ at which the nucleation length diverges, for each case.

which can be written as

$$r^{\text{iii}}(z) = F(r^{\text{iii}}(z), r^{\text{ii}}(z), r'(z), r(z)), \quad (19)$$

but is too elaborate to give in detail.
The boundary conditions of the membrane at the tube ends are of fixed radius and flat, i.e. the first derivative is zero:

\[ r(0) = R_p, \quad \frac{dr}{d\theta}(0) = 0, \]
\[ r(\infty) = R_m, \quad \frac{dr}{d\theta}(\infty) = 0. \quad (20) \]

Using a boundary-values problem solver (vbp in Matlab), we numerically solve this equation and get the membrane shape. In figure 4(a), we plot the membrane shape at the edge of the dynamin domains, for different values of \( \alpha = R_m/R_p \). We find that the membrane has an overshoot and some undulations, with an amplitude and length scale that increases as the ratio \( \alpha \) increases.

To get the energy cost of this membrane deformation, we integrate the free energy \( E_m \) over the calculated membrane shape, and subtract the energy of a uniform membrane cylinder of the same length with the equilibrium radius. In figure 4(b) we plot the edge energy cost of a dynamin domain (which has two edges), \( E_{\text{edge}} \), as a function of \( \alpha \), and find that it increases as expected with the radius mismatch between the dynamin domain and the membrane tube. This edge energy allows us to calculate the minimal domain length (\( L_{\text{nuc}} \)) that can stably nucleate along the tube, by equating the energy cost of such a nucleus (\( E_{\text{bend}} \)) with the energy gain due to dynamin polymerization (\( E_{\text{pol}} \)) [9]

\[ \varepsilon_{\text{pol}} L_{\text{nuc}} = E_{\text{edge}} + \varepsilon_{\text{bend}} L_{\text{nuc}}, \quad (21) \]

where the membrane bending energy cost per unit length inside the condensed dynamin domain is \( \varepsilon_{\text{bend}} = \pi (\alpha - 1)^2 \kappa / R_p \). The value of \( \varepsilon_{\text{pol}} \) depends on the dynamin concentration, and is estimated to be \( \sim 18 \) pN for 12 µM and \( \sim 4 \) pN for 0.44 µM [9]. Using equation (21), we plot in figure 4(c) the minimal length of nucleating dynamin domains for various values of \( \varepsilon_{\text{pol}} \) and membrane tube radii (denoted by \( \alpha \)). The length of the nucleus diverges at the critical radius calculated in [9]. The divergence in the nucleation length means that the polymerization of dynamin cannot overcome the edge energy of the deforming membrane tube at the two ends of the polymerized domain. In this regime there is no energy advantage for the polymerization of dynamin in any domain of finite length.

We next calculate the membrane shape between two polymerized dynamin domains, as a function of the separation between them, \( L \), as shown in figure 5(a). We see that when the two domains are further than \( \sim 20R_m \), the membrane shape relaxes around each of the two edges, and they therefore do not influence each other and the edge. In figure 5(b), we plot the energy cost of the membrane deformation between the two domains (relative to the energy of a free membrane tube with the same length), so that at large separations it simply gives the edge energy of a single domain, shown in figure 4(b).

As the two domains approach closer to each other, the membrane shape deformations induced by the two domain edges interfere. Correspondingly, we find that the overall energy cost increases up to a maximal value reached at separations of \( \sim 2–4R_m \) (figure 5(b)). As the ratio \( \alpha \) increases, so does the size of the energy barrier. We can compare the value of this energy barrier to the energy gain per unit length of polymerized dynamin at the domain edge. The energy gain per unit length of added dynamin ring at the domain edge is given by (equation (21)): \( \varepsilon_{\text{pol}} - \varepsilon_{\text{bend}} \).

We find that even for large \( \alpha \) the barrier due to the membrane shape gives a maximal energy per unit length of order 1–2pN, which is smaller than the gain due to dynamin polymerization (estimated to be 4–18pN, depending on the dynamin concentration). It is therefore unlikely that the energy barrier due to the membrane shape can completely prevent domains from coalescing, but it may slow down the process significantly.
5. Discussion and comparison to the experiments

5.1. Dynamin domain nucleation

We start by summarizing the main results from our model regarding the dynamical routes for the nucleation of polymerized dynamin domains. The main premise of our model is that the process of dynamin polymerization into solid-like domains can start when the local oligomer concentration is high, i.e. that the driving force for the nucleation of dynamin polymerization is the dynamic condensation of the dynamin oligomers into regions of high density.
We may first ask: are dynamin domains appearing through large thermal fluctuations that allow the formation of an initial nucleus, or do they appear through a dynamic instability? In other words, is this a threshold phenomena of nucleation over an energy barrier or does the system become linearly unstable towards small perturbations? The answer that arises from our model is both, since we find that the region of linear instability resides in the same region where the uniform tube is bistable and susceptible to abrupt changes in the radius due to thermal fluctuations (figure 2).

We find that the tube can become uniformly unstable (figure 2), where thermal fluctuations in the tube radius can lead to a run-away process of an increase in oligomer concentration and tube shrinkage (either close to or at the spinodal point). As the radius shrinks through this transition, the system also passes the regime of dynamic instability that breaks the uniform state and local oligomer condensation is initiated. The threshold phenomenon is entangled with a finite wavevector dynamic instability.

Let us now compare our analysis regarding the stability and nucleation of polymerized dynamin to the observations using in-vitro experiments. A typical experimental setup and the results of two experiments at low dynamin concentrations (440 nM) are shown in figure 6. Figure 6(A) shows the experimental setup, where membrane tubes are extracted from GUVs aspirated into a micropipette using a bead maintained with optical tweezers. Membrane tension and thus tube radius can be fixed by tuning the aspiration into the pipette, and the membrane tube force can be measured by tracking the bead displacement in the optical trap, which acts as a spring. Dynamin was diluted directly in the observation chamber, and the membrane tension was kept low during the extraction of the tubes. The membrane tension was then increased gradually until nucleation of dynamin seeds was observed. From then onwards, we kept the aspiration (imposed membrane tension) constant. In figures 6(B) and (C), we see kymographs of two independent experiments, showing the fluorescence intensity of labeled dynamin along the green axis of figure 6(A).

The average density and radius values are given with the standard error. Since the domains are well separated during the nucleation (spaces between domains ≫ pixel size), our error in the density measurement is quite low. The radius for each experiment is measured by the following procedure: the aspiration pressure is increased by small steps, while measuring the force F and tension σ in the membrane tube. Then \( F^2 \) versus tension is plotted, and we verify the linearity of the relation. We then calculate the radii at each step using \( R = F/4\pi\sigma \). Note that we use the free-tether relation to relate the force and tension to the radius, not taking into account the effects of the adsorbed dynamin. This approximation is good for low concentrations of adsorbed dynamin, which is the regime in which the experiments shown in figure 7 were performed. In figure 2(a), we see that the free-tether radius \( R_{\text{free}} \) is a good approximation to the true radius \( R_m \), during the tube extraction period when the tension \( \sigma \) is still low and before the initiation of the bistable region, which corresponds to the initiation of dynamin polymerization (see figure 7).

The nucleation of polymerized dynamin domains is observed to have a nucleation threshold [9] (figure 7): as the tension in the extracted membrane tether is increased, there is a critical value at which nucleation of dynamin condensed domains first appears [1]. The exact value of this critical tension (i.e. the critical radius) is difficult to obtain experimentally, and the values have a large scatter. Nevertheless, we find that these observations seem to be in qualitative agreement with the largest radius of the calculated bistability region (corresponding to the tension \( \sigma_{\text{bis}} \), figure 2(b)), as shown in figure 7. This observation means that according to our model, as soon as the system enters the bistable regions large fluctuations drive the sudden
Figure 6. (A) Schematic illustration of the experimental setup. In (B, C) two kymographs are shown, which are extracted by plotting the fluorescence along the membrane tube (indicated by the green line in (A)), as a function of time. The tension in the tube increases with time. The tube radius is \( \sim 20-20.7 \text{ nm} \) and \( \sim 24-30 \text{ nm} \) in (B) and (C), respectively.

jump in the tube radius from the upper stable branch to the lower branch. During this process the tube becomes dynamically unstable and localized nucleation is initiated (figure 2(b)).

At large dynamin concentrations the observed critical radius at the nucleation transition seems to grow rapidly. This corresponds in our model to the vanishing of \( \sigma_{\text{bis}} \) for large dynamin concentrations (see figure 2), and indicates that in this regime the dynamin can pull-out and nucleate a tether tube from a flat membrane. Note that the analysis of the nucleation threshold given in [9] results in very similar threshold values for the nucleation of dynamin polymerization. This is not surprising since the essential physics of dynamin interactions opposed by the membrane elasticity are the ingredients of both treatments. Our dynamical model allows us to go beyond the static treatment of [9]. For example, we can use our model to make
Figure 7. Dependence of the nucleation of dynamin polymerization on the tube radius and dynamin concentration in the bulk solution: pink (blue) squares correspond to experiments [9] where nucleation was (was not) observed. The solid lines give the transition points we calculated as in figure 2(c). The vertical dashed line indicates the concentration at which the maximal radius of the tube in the bistable regime diverges. The value of $\mu$ in our model was used to fit the calculations to the data.

The prediction that in the absence of large fluctuations one should be able to reduce the tube radius to a lower threshold value that corresponds to the binodal or even the spinodal lines (green and red lines in figure 7, respectively). These thresholds are weakly dependent on the dynamin concentration.

Additionally, at low dynamin concentrations, as shown in figure 6, it is often observed that the domains nucleate at roughly equal spacing, with an average density of $0.36 \pm 0.14$ domain per $\mu$m (for a tube of average tension $1.3 \times 10^{-4} \pm 6.6 \times 10^{-5}$ N m$^{-1}$, and average radius $21 \pm 4$ nm). Such a spatial correlation would suggest a process of dynamic instability, whereby the spacing between the domains corresponds to the most unstable wavelength. The typical calculated critical wavevectors that we get are shown in figures 3(c) and (d) in this regime, and correspond to wavelengths that are about two to five times smaller than the observed separation between nucleation sites. Note, however, that these wavevectors are calculated with respect to tube radii in a regime where the radius could be in the process of changing globally, as explained above, making the analysis more complex. Nevertheless, we find that domains may be nucleated with separations that are many times the tube radius, due to the long-range membrane-mediated interactions.

From these comparisons, we have indications that the nucleation of dynamin polymerization is a threshold phenomenon, but sometimes displays spatial ordering that hints at a long-wavelength instability. Our model does give these two properties for the
dynamic route towards destabilizing the uniform membrane tube and initiating regions of high dynamin concentration and small tube radius, which we view as precursors to dynamin polymerization.

Finally, our predicted sizes of the nucleated polymerized dynamin nucleus, which can further grow, is in the range of 20–100 nm (figure 4). These values are in agreement with the observations (figure 6) that showed that the domains start from a single pixel that represents ~160 nm in length.

Note that in our dynamic instability model we consider only membrane-mediated interactions between the dynamin oligomers, so their eventual polymerization into a condensed domain is not treated. Our model therefore treats the initiation of dynamin aggregations, where the concentrated dynamin oligomers can then undergo direct interactions and form a polymerized domain.

5.2. Interactions between dynamin domains

After nucleation, dynamin domains are observed to grow at their two ends through the incorporation of dynamin dimers (figure 6). The growth seems to proceed at roughly constant velocity, until they approach their neighboring domains. The excess water and free membrane that are squeezed from the two growing domains get kinetically trapped between the domains and slow their growth. Such trapped ‘bubbles’ and an abrupt slowing down of the domain growth are indeed observed. Nevertheless, over long time periods the excess water and membrane flow through the narrow dynamin-constricted tubes, and the domains appear to anneal into a seemingly continuous coat.

There are, however, clear indications that very small gaps between neighboring domains persist for very long times [9], as seen by the black strips between the domains in the kymographs of figure 6. On average, these stripes are of the order of 190 ± 75 nm. Our calculations of the equilibrium membrane shape trapped between two dynamin domains (figure 5(b)) indeed show an energy barrier at length scales of the order ∼40–140 nm. It is not clear, however, whether the calculated energy barrier due to the deformed trapped membrane is strong enough to prevent dynamin polymerization and the eventual merging between two neighboring dynamin domains.

6. Conclusions

We have presented a study of the dynamical coupling between the processes of dynamin adsorption, oligomerization and condensation on a membrane tube, and the changes induced to the tube radius and shape. We demonstrate that membrane-mediated interactions can result in global and long-range dynamic instabilities, which are entangled in this system with a global bistability of the system. This study highlights several aspects of the interactions between a membrane and adsorbed curved proteins, applied to the case of the dynamin protein. Future experiments may probe these results quantitatively, while detailed dynamical simulations will allow us to probe more precisely the nucleation process of dynamin polymerization.

Importantly, the dynamic instability found in this study may explain the sharp apparition of dynamin to the neck of clathrin-coated pits in vivo [19]. More generally, our study shows that even if protein/membrane interaction is weakly thermodynamically favored, the resulting dynamics can have profound effects on the membrane shape and protein distribution, because of large thermal fluctuations of the membrane.

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Appendix A. Equilibrium oligomer density for an arbitrary length $N_o$

In the limit of $n_o/n_s \ll 1$ we can derive an analytic expression for the equilibrium solution $n_o(z)$ for any value of $N_o$. First taking the exponent and then expanding to the lowest order in $n_o/n_s$, we obtain the following expression:

$$
\frac{n_o}{n_s} = \frac{(1 - n_d/n_s)^{N_o} e^{g(R_m)}}{1 + (1 - n_d/n_s)^{N_o} e^{g(R_m)}}
$$ (A.1)

where $g(R_m)$ is simply the rhs of equation (7).

Appendix B. Details of the linear stability analysis

We give here some of the mathematical details of the linear stability analysis.

The expression for the uniform force $U$ acting on the membrane (equation (13)) is given by

$$
U = f_{\kappa,o} - \frac{\kappa}{2R_m^3} + \frac{\Sigma}{R_m},
$$ (B.1)

where

$$
f_{\kappa,o} = -\frac{n_0 N_o \kappa_o (R_p - R_m)}{n_s R_p R_m^3}
$$ (B.2)

$$
\Sigma = \sigma_d + \sigma + \sigma_{\kappa_o}
$$ (B.3)

$$
\sigma_d = k_B T \left( n_0 (N_o - 1) + n_s \log \left[ 1 - \frac{n_{d,0} + n_0 + n_0 N_o}{n_s} \right] \right) + n_0 f_{1,n} + n_{d,0} f_{1,m}
$$ (B.4)

$$
\sigma_{\kappa_o} = \frac{n_0 N_o (R_p - R_m)^2 \kappa_o}{2n_s R_p^2 R_m^3}
$$ (B.5)

$$
f_{1,n} = -\epsilon_o + k_B T (1 - N_o) + (\mu - \epsilon_d) N_o
$$

$$
+ k_B T \left( \log \left( \frac{n_0}{n_s} \right) - N_o \log \left[ 1 - \frac{n_{d,0} + n_0 + n_0 N_o}{n_s} \right] \right),
$$ (B.6)

$$
f_{1,m} = -\epsilon_d + \mu + k_B T \left( \log \left( \frac{n_{d,0}}{n_s} \right) - \log \left[ 1 - \frac{n_{d,0} + n_0 + n_0 N_o}{n_s} \right] \right).
$$ (B.7)

The uniform forces given here include terms due to effective membrane tension, curvature bending terms due to the membrane and oligomers, entropic pressure terms due to the gas of freely diffusing dimers and oligomers. To find the uniform steady-state radius of the membrane tube around which we perform the linear-stability analysis, $R_m$, we solve self-consistently for $n_0$ (equation (7)) and $n_{d,0}$ (equation (6)), together with the equation $U = 0$ (equation (B.1)). These equations can now be written in a much simpler form: $n_0$ is the solution of: $f_{1,n} - f_{\kappa,o,n} = 0$, where $f_{\kappa,o,n} = -2n_0 R_p f_{\kappa,o,h}/(R_m(R_p - R_m))$, while $n_{d,0}$ is the solution of $f_{1,m} = 0$. 

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The functions given in equation (13) can now also be written explicitly

\[
L(h, n) = \frac{1}{R_m} \left[ \left( 2(f_{k_o, h} + f_{k_o, hh} R_m) + \frac{\kappa}{R_m^2} \right) h + (f_{1, n} + f_{k_o, nn} R_m) n \\
+ f_{1, m} m + \left( \frac{\kappa}{2 R_m} - R_m \Sigma \right) h'' + \kappa R_m h'''ight],
\]

(B.8)

\[
N(h, n) = \frac{n_0^2}{R_m} \left[ (f_{1, n} + f_{k_o, nn} R_m) h'' + R_m (2 f_{nn} n'' + f_{nn} m'') \right],
\]

(B.9)

where

\[
f_{k_o, hn} = \frac{N_o (R_m - R_p) k_o}{n_s R_p R_m^3},
\]

(B.10)

\[
f_{nn} = \frac{k_B T (n_{d, 0} - n_0 (N_o - n_s))}{2 n_0 (n_{d, 0} + n_0 N_o - n_s)},
\]

(B.11)

\[
f_{nm} = -\frac{k_B T N_o}{n_{d, 0} + n_0 N_o - n_s}.
\]

(B.12)

Note that the equation of motion for the dimers, i.e. \( \dot{m} \), reduces to a simple relation whereby \( m \) is determined by the local oligomer and tube radius, i.e. by \( h, n \), since we assume either fast equilibrium of the dimers (case I) or a constant concentration (case II). For case I, we obtain that

\[
m(z, t) = -\frac{R_m f_{nm}}{2 f_{nm} n} n(z, t) = \Delta_{nm} n(z, t),
\]

(B.13)

where \( f_{nm} = k_B T (n_0 N_o - n_s) / (2 n_{d, 0} (n_{d, 0} + n_0 N_o - n_s)) \) and \( \Delta_{nm} = -N_o / (1 + \exp((\mu - \epsilon_d) / k_B T)) \). For case II, \( \Delta_{nm} = 0 \).

The elements of the linear stability matrix (equation (16)) are given by

\[
M_{hh} = -\kappa q^4 + f_{k_o, h} R_m q^2 - \frac{2 f_{k_o, h} R_m^2 + 2 f_{k_o, hh} R_m^4 + \kappa}{R_m^4},
\]

(B.14)

\[
M_{nn} = -f_{k_o, hn},
\]

(B.15)

\[
M_{nh} = -n_0 N f_{k_o, hn} q^2,
\]

(B.16)

\[
M_{nn} = -2 f_{nn} n_0 \Lambda q^2,
\]

(B.17)

\[
M_{nm} = -f_{nm} n_0 \Lambda q^2.
\]

(B.18)

**Appendix C. Oseen kernel for a cylindrically symmetric membrane tube**

To find the Oseen kernel we follow the same method used to calculate this kernel for confined membranes [20, 21]. We first need to solve the Stokes equations that are applicable for small Reynolds numbers

\[
\eta \nabla^2 \vec{v} + \vec{\nabla} p = 0,
\]

(C.1)

\[
\vec{\nabla} \cdot \vec{v} = 0.
\]

(C.2)
Since we assume cylindrical symmetry, the derivative with respect to the angular direction as well as the velocity in the angular direction vanishes. Since the equations are linear, we guess a solution of the following form:

\[
\vec{v} = v(r) e^{iqz},
\]

\[
p = p(r) e^{iqz},
\]

with \( v(r) = (v_r(r), 0, v_z(r)) \). Solving equation (C.2) for \( v_z(r) \), we obtain

\[
v_z(r) = \frac{1}{qr} \left( v_r(r) + rv'_r(r) \right)
\]

and solving the longitudinal part of equation (C.1) for \( p(r) \) we obtain

\[
p(r) = \frac{q^2 rv_z(r) - v'_r(r) - rv''_r(r)}{qr}.
\]

Substituting equation (C.5) into equation (C.6) and both of them into the radial part of equation (C.1), we obtain an ODE equation for \( v_r(r) \). Solving this equation we find that

\[
v_r(r) = Aqr K_0(qr) + BK_1(qr) + Cqr I_0(qr) + DK_0(qr),
\]

where \( K_\alpha \) and \( I_\alpha \) are the modified Bessel functions (also known as the hyperbolic Bessel functions) of the first and second kind.

Since the membrane is separating between two velocity fields \( \vec{v}_{in}, \vec{v}_{out} \) inside and outside the membrane, we have the following boundary conditions on the membrane: (1) the velocity along the radial direction must be continuous \( v_{r,\text{in}} = v_{r,\text{out}} \). For the second boundary condition, we can choose either of these two cases: (2a) assuming no slip boundary condition [21] on the membrane and assuming that the membrane is incompressible imply that there is no change in \( v_z \) on the membrane \( \partial v_{z,\text{in}}/\partial z = \partial v_{z,\text{out}}/\partial z = 0 \). (2b) Another possibility is that the membrane can be compressed but it cannot hold shear stresses [20]: \( \partial v_{z,\text{in}}/\partial r = \partial v_{z,\text{out}}/\partial r = 0 \).

Other boundary conditions are that the velocity at \( r = 0 \) and \( r \) goes to infinity. At infinity we take the velocity to vanish, which implies \( C_{\text{out}}, D_{\text{out}} = 0 \). At \( r = 0 \) the velocity along the radial direction must be zero for an incompressible fluid. In addition the incompressibility equation requires that \( \partial v_{z,\text{in}}/\partial z = 0 \) at the origin. These two conditions are satisfied only if \( A_{\text{in}} = B_{\text{in}} = 0 \).

To find the Oseen kernel \( \mathcal{O}_q \), we solve the equation

\[
v_{r,\text{in}}(R) = v_{r,\text{out}}(R) \equiv v_r.
\]

\[
v_{z,\text{in}}(R) = v_{z,\text{out}}(R),
\]

\[
\sigma_{rr,\text{in}} - \sigma_{rr,\text{in}} = f v_r / \mathcal{O}_q
\]

and obtain the final answer by using the boundary condition (2a)

\[
\mathcal{O}_q = -\frac{R(\rho I_0(\rho)^2 - 2I_1(\rho)I_0(\rho) - \rho I_1(\rho)^2)(\rho K_0(\rho)^2 + 2K_1(\rho)K_0(\rho) - \rho K_1(\rho)^2)}{2\eta(2I_0(\rho) + \rho I_1(\rho))K_0(\rho) - 2\rho \eta I_0(\rho)K_1(\rho)}
\]

and using the boundary condition (2b)

\[
\mathcal{O}_q = \frac{R(\rho I_0(\rho)^2 - 2I_1(\rho)I_0(\rho) - \rho I_1(\rho)^2)K_1(\rho)^2}{\eta \rho I_0(\rho)K_0(\rho) - \eta(2I_0(\rho) + \rho I_1(\rho))K_1(\rho)},
\]

where \( \rho = q R_m \). These results are shown in figure C.1.
Figure C.1. (a) Plot of the calculated Oseen tensor $O_q$ for the no slip boundary condition case (equation (C.11)) (blue), for the no shear stresses case (equation (C.12)) (purple) and for a flat membrane (yellow). (b, c) The calculated velocity field of the fluid surrounding the membrane (arrows), both inside ($r < 1$) and outside the tube ($r > 1$). Panel (b) is for the no slip boundary condition case and panel (c) is for the no shear stresses case. The blue shades correspond to the magnitude of the velocity. The red horizontal line indicates the average membrane position, whereas the blue line illustrates the membrane undulations that follow the calculated flow field.
Appendix D. Identity of the unstable wavevectors for the two types of oligomer dynamics

The region of unstable wavevectors is defined by the roots of the determinant of the matrix $M$ (equation (16)). For the two cases of the oligomer dynamics this gives the following two equations:

$$M_{hh}(M_{nn} + \Delta_{nn}M_{nm}) - M_{hn}M_{nh} = 0,$$

$$-M_{hh} \frac{1}{\tau} \left( 1 - \frac{\partial n_0}{\partial n_0} \right) + M_{hn} \frac{1}{\tau} \frac{\partial n_0}{\partial h} = 0.$$  

We can show that these two equations lead to the same roots, i.e. that

$$\frac{M_{nn} + \Delta_{nn}M_{nm}}{M_{nh}} = 1 - \frac{\partial n_0}{\partial n_0} \frac{\partial n_0}{\partial h}.$$  

We start by rewriting the lhs of equation (D.3) as

$$\frac{M_{nn} + \Delta_{nn}M_{nm}}{M_{nh}} = \frac{\partial^2 F}{\partial n^2} + \frac{\partial^2 F}{\partial n \partial m} \frac{\partial n_{d,eq}}{\partial n} + \frac{\partial^2 F}{\partial h \partial n},$$

where $F$ is the free energy per unit area (the integrand of $\mathcal{F}$).

Next we rewrite the terms appearing on the rhs of equation (D.3)

$$\frac{\partial n_0}{\partial n} = \frac{\partial n_{o,eq}}{n_{d,eq}} \frac{\partial n_{d,eq}}{\partial n},$$

$$\frac{\partial n_0}{\partial h} = -\frac{\partial^2 F}{\partial h \partial n} / \frac{\partial^2 F}{\partial n^2},$$

where the last equality is derived from the following equilibrium condition:

$$0 = \frac{\delta F}{\delta n} = \frac{\delta F}{\delta n} \bigg|_{eq} + \frac{\partial}{\partial n_{d}} \frac{\delta F}{\delta n_{d}} + \frac{\partial}{\partial n} \frac{\delta F}{\delta n} + \frac{\partial}{\partial R} \frac{\delta F}{\delta n} + O(\delta^2).$$

In equilibrium, we have that $\frac{\delta F}{\delta n_{d}} \bigg|_{eq} = 0$. Dividing by $\delta R$, and noting that $\partial n_{d}/\partial R = 0$, we finally obtain equation (D.6). Similarly, we use the following expansion,

$$0 = \frac{\delta F}{\delta n_{d}} = \frac{\delta F}{\delta n_{d}} \bigg|_{eq} + \frac{\partial}{\partial n_{d}} \frac{\delta F}{\delta n_{d}} + \frac{\partial}{\partial n} \frac{\delta F}{\delta n_{d}} + \frac{\partial}{\partial R} \frac{\delta F}{\delta n_{d}} + O(\delta^2)$$

and again, we note that $\frac{\delta F}{\delta n_{d}} \bigg|_{eq} = 0$ and $\frac{\partial}{\partial R} \frac{\delta F}{\delta n_{d}} = 0$, so that finally we obtain that

$$\frac{\partial n_{o,eq}}{\partial n_{d}} \bigg|_{n_{d,eq}} = -\frac{\partial^2 F}{\partial n_{d}^2} / \frac{\partial^2 F}{\partial n_{d} \partial n}.$$  

Combining equations (D.5), (D.6) and (D.9), we can rewrite the rhs of equation (D.3), and find that it is identical with equation (D.4).
References

[1] Praefcke G and McMahon H 2004 The dynamin superfamily: universal membrane tubulation and fission molecules? Nat. Rev. Mol. Cell. Biol. 5 133–47
[2] Koenig J H and Ikeda K 1989 Disappearance and reformation of synaptic vesicle membrane upon transmitter release observed under reversible blockage of membrane retrieval J. Neurosci. 9 3844–60
[3] Takei K, McPherson P S, Schmid S L and De Camilli P 1995 Tubular membrane invaginations coated by dynamin rings are induced by GTP-gamma S in nerve terminals Nature 374 186–90
[4] Sweitzer S M and Hinshaw J E 1998 Dynamin undergoes a GTP-dependent conformational change causing vesiculation Cell 93 1021–9
[5] Danino D, Moon K H and Hinshaw J E 2004 Rapid constriction of lipid bilayers by the mechanochemical enzyme dynamin J. Struct. Biol. 147 259–67
[6] Roux A, Uyhazi K, Frost A and De Camilli P 2006 GTP-dependent twisting of dynamin implicates constriction and tension in membrane fission Nature 441 528–31
[7] Salim K et al 1996 Distinct specificity in the recognition of phosphoinositides by the pleckstrin homology domains of dynamin and Bruton’s tyrosine kinase EMBO J. 15 6241–50
[8] Perrais D and Merrifield C J 2005 Dynamics of endocytic vesicle creation Dev. Cell 9 581–92
[9] Roux A, Koster G, Lenz M, Sorre B, Manneville J B, Nassoy P and Bassereau P 2010 Membrane curvature controls dynamin polymerization Proc. Natl Acad. Sci. USA 107 4141–6
[10] Shlomovitz R and Gov N S 2009 Membrane-mediated interactions drive the condensation and coalescence of FtsZ rings Phys. Biol. 6 046017
[11] Helfrich W 1973 Z. Naturforsch. C 28 693–703
[12] Ramachandran R and Schmid S 2008 Real-time detection reveals that effectors couple dynamin’s GTP-dependent conformational changes to the membrane EMBO J. 27 27–37
[13] Ambrogi E, Sorre B, Bassereau P, Goud B, Manneville J-B and Antonny B 2010 ArfGAP1 generates an Arf1 gradient on continuous lipid membranes displaying flat and curved regions EMBO J. 29 292–303
[14] Hinshaw J E and Schmid S L 1995 Dynamin self-assembles into rings suggesting a mechanism for coated vesicle budding Nature 374 190–2
[15] Iglic A, Hägerstrand H, Veranic P, Plemenitas A and Kralj-Iglic V 2006 Curvature-induced accumulation of anisotropic membrane components and raft formation in cylindrical membrane protrusions J. Theor. Biol. 240 368–73
[16] de Gennes P G 1979 Scaling Concepts in Polymer Physics (Ithaca, NY: Cornell University Press)
[17] Ramaswamy S, Toner J and Prost J 2000 Phys. Rev. Lett. 84 3494
[18] Weicheng C and Lubensky T C 1994 Phys. Rev. Lett. 73 1186–9
[19] Merrifield C J, Feldman M E, Wan L and Almers W 2002 Nat. Cell Biol. 4 691–8
[20] Gov N, Zilman A G and Safran S 2004 Phys. Rev. E 70 011104
[21] Seifert U 1994 Phys. Rev. E 49 3124