Processivity and collectivity of biomolecular motors extracting membrane nanotubes
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Membranes are fluid-lipid interfaces of remarkable biological functionality. They mediate transport processes at the cellular level, exhibiting soft mechanical properties and highly adaptive geometries. Vesicles, for instance, hold a spherical shape under most equilibrium conditions. But in the presence of spatiotemporal stimuli, membrane tubes can emerge over lengths of several micrometers with diameters in the nanometer scale [1,2]. This is the case of sensorial protrusions, tether networks, and sensorial tentacles. Here we focus on the extraction of a single tube from a vesicle. Via a force balance coupled to binding kinetics, we analytically determine the phase diagram of tube formation as function of the motor processivity, the surface viscosity of the membrane $\eta_m$, and the density of motors on the vesicle $\rho$. Three tubulation mechanisms are identified: (i) tip pulling, due to the accumulation of motors at the leading edge of the membrane, (ii) viscous drag, emergent from the translation of motors along the tube, and (iii) hybrid extraction, such that tip pulling and viscous drag are equally important. For experimental values of $\eta_m$ and $\rho$, we find that the growth of biomonotubes tends to be driven by viscous forces, whereas artificial membranes are dominated by tip pulling.

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cylindrical membrane of radius $r \ll \ell_0$ is given by [24]

$$\zeta = \frac{4\pi \eta_m'}{\ln (r/\lambda) + \frac{1}{2}}. \tag{1}$$

In the context of this Rapid Communication, we take $r = \sqrt{\kappa_c/(2\sigma)}$ and identify the length $\lambda$ with the tail of the molecular motor. The resulting stem force,

$$F_b = N_b \frac{4\pi \eta_m' (v_0 - \dot{L})}{\ln (r/\lambda) + \frac{1}{2}}, \tag{2}$$

is to be compared with its counterpart $f_b$ at the tip.

**Tip force.** Towards the hemispherical cap of the tube, the membrane exhibits a curvature change around which $n_b$ bound motors have their velocities reduced to $L$. Such a drop depends on the force-velocity properties of the molecular motors. In its simplest form, the force $f_1$ due to a single motor is given by $f_1 = f_0(1 - u/v_0)$, where $f_0$ denotes the stall force and $v$ the motor velocity under load [27]. On the basis of this individual contribution, we write the force $f_b \equiv n_b f_1(L)$ on the tip of the tube as

$$f_b = n_b f_0 \left(1 - \frac{\dot{L}}{v_0}\right). \tag{3}$$

**Multimotor force versus membrane force.** The multimotor drive $F_b = F_b + f_b$ is opposed by the membrane force $F_m$. But how does $F_m$ depend on the mechanical and geometrical properties of the vesiculotubular structure? We assume $F_m = F_c + F_k$, such that $F_c = 2\pi \sqrt{2\sigma \kappa_c}$ is the barrier for tube formation [1,2] and $F_k$ the stretching force. The latter arises from the energy $\mathcal{E}_k \equiv \kappa_k (A - A_0)^2/(2A_0)$, where $A_0$ and $A$ are the areas of the unstretched and stretched membranes, respectively [1]. For tube extraction from a spherical vesicle, $A_0 = 4\pi r^2$, $A - A_0 \approx 2\pi r L$, and $\mathcal{E}_k \approx \frac{1}{2} \kappa_k \pi (r/R)^2 L^2$. Thus, $F_k = \partial \mathcal{E}_k / \partial L = \kappa_k \pi (r/R)^2 L$, leading to

$$F_m = 2\pi \sqrt{2\sigma \kappa_c} + \kappa_k \pi (r/R)^2 L. \tag{4}$$

Balancing $F_b$ and $F_m$, one readily finds

$$\frac{v_0 - \dot{L}}{v_0} = \frac{2\pi \sqrt{2\sigma \kappa_c} + \kappa_k \pi (r/R)^2 L}{N_b \xi v_0 + n_b f_0}. \tag{5}$$

Equation (5) governs the evolution of the tube length $L$ and the current $J_b \equiv (v_0 - L)N_b/L$ of bound motors towards the tip [12]. Both are coupled to the binding kinetics.

**Binding kinetics.** The membrane tube hosts a total of $N = 2\pi r L_0$ motors, of which $N_b = N_b + n_b$ bound and $N_u = N - N_b$ unbound to the substrate. We model the binding kinetics over the stem and tip regions by

$$\frac{dN_b}{dt} = I - k_u N_b - J_b, \tag{6}$$

$$\frac{dn_b}{dt} = J_b - k_u n_b, \tag{7}$$

where $I$ denotes the influx of motors to the filament. This flux involves geometric constraints and excluded volume effects on binding. We assume $I = k_b N_0 \phi_b(1 - \phi_b)$, where $N_0$ is the number of attachable motors and $\phi_b$ the occupation of the filament. Letting $N_b' \equiv n_b$ denote the number of tracks accessible to a motor (see Fig. 3 and Ref. [13]), we estimate the number of stepping sites as $N_b' \frac{L}{\ell}$ and $\phi_b \approx (N_b + n_b)/(N_b' \frac{L}{\ell})$. Analogous arguments hold for $N_u$. Considering that unbound motors tend to be uniformly distributed on the membrane, only those on the lower surface of the tube can bind to a track. The corresponding fraction of attachable motors is $\phi_a$.
so that \( N'_b = \phi_0 N'_m \). As shown in Fig. 3, \( \phi_0 \approx (2\ell)/(2\pi r) \) since a cross section of the tube hosts two unbound motors that neighbor the filament. In terms of such estimates, \( I = k_b \zeta V_0 (2\pi r P - N_b - n_b)(1 - N_b/N_m) \).

**Dimensionless equations.** Introducing \( \tau \equiv t k_a \) and \( X \equiv L/\ell \), Eqs. (5)–(7) can be written in dimensionless form as

\[
\frac{dX}{d\tau} = P \left( 1 - \frac{E + SX}{N_b D + n_b} \right),
\]

\[
\frac{dN_b}{d\tau} = B \phi_0 (M X - N_b - n_b) \left( 1 - \frac{N_b + n_b}{N'_b X} \right) - N_b - \frac{P N_b}{X} \left( \frac{E + SX}{N_b D + n_b} \right),
\]

\[
\frac{d\phi_0}{d\tau} = \frac{P N_b}{X} \left( \frac{E + SX}{N_b D + n_b} \right) - n_b,
\]

where \( P \equiv \rho_0/(\ell k_a) \), \( E \equiv 2\pi \sqrt{2\sigma \kappa_c / f_0} \), \( S \equiv \kappa_A \pi (r/R)^2 \ell / f_0 \), \( D \equiv \zeta V_0 / f_0 \), \( B \equiv k_b / k_a \), and \( M \equiv 2\pi r P \). These dimensionless parameters comprise one indicator of collectivity (number \( M \) of motors in a tube element of radius \( r \) and length \( \ell \)), two kinetic ratios (representing binding \( B \) and processivity \( P \)), and three force ratios (extraction barrier \( E \), viscous drag \( D \), and membrane stretching \( S \)). In them, the dimensionless current \( j_b \equiv j_b / k_a \) is given by \( j_b = P(N_b/X)(E + SX)/(N_b D + n_b) \).

**Collectivity and processivity.** Focus on motor collectivity and processivity suggests the study of Eqs. (8)–(10) as a function of \( M \) and \( P \). The former is experimentally controllable via the density \( \rho \) of motors on the vesicle. The latter involves stepping and unbinding properties, in such a way that \( P = 1 \) for an ideal nonprocessive motor and \( P \gg 1 \) for processive motors. Of particular interest is the question of how \( M \) and \( P \) are reflected in the driving force of tube extraction. To address this issue, we consider the ratio \( F_3 / f_3 = D N_b / n_b \), where \( D = 4\pi \eta_m v_0 f_0^{-1} / [\ln(r/\lambda) + 1] \).

Depending on the surface viscosity \( \eta'_m \) of the membrane, three tubulation mechanisms can emerge: (i) tip pulling, where \( f_3 > F_3 \), (ii) viscous drag, for which \( F_3 > f_3 \), and (iii) hybrid extraction, such that \( F_3 = f_3 \). Since hybrid extraction is a key limiting case, we shall determine its steady state solution \((\overline{X}, \overline{N}_b, \overline{n}_b)\) and its locus on the \( \eta'_m \) vs \( \rho \) plane.

**Steady state and phase diagram.** Setting \( d\overline{X}/d\tau = d\overline{N}_b/d\tau = d\overline{n}_b/d\tau = 0 \) in Eqs. (8)–(10) and invoking the condition \( \overline{F}_3 = \overline{f}_3 \), one analytically finds

\[
\overline{X} = \frac{P}{D}, \quad \overline{N}_b = \frac{E + PS}{2D}, \quad \overline{n}_b = \frac{E}{2} + \frac{PS}{2D}.
\]

This leads to a current \( \overline{j}_b = \overline{n}_b \sim P/D \) that linearly increases with processivity and monotonically decreases with the membrane viscosity. The corresponding density of motors, though, has a more involved dependence on \( P \) and \( D \). It follows from Eq. (9) evaluated at (11),

\[
\overline{M} \equiv \frac{\frac{1}{\overline{\phi}_0} + 1 - \overline{\phi}_0 N'_b / \overline{\phi}_0}{1 - \overline{\phi}_0},
\]

with \( \overline{\phi}_0 \equiv (\overline{N}_b + \overline{n}_b) / (\overline{N'}_b \overline{X}) \). Here, the tube length \( \overline{X} \) and the number of stepping tracks \( \overline{N}_b \) limit the population of bound motors \( \overline{N}_b + \overline{n}_b \), so that Eq. (12) is physically relevant only if \( \overline{\phi}_0 < 1 \). This constraint is violated at membrane viscosities (e.g., \( \eta'_m \lesssim 10^{-9} \) Pa m s) for which \( \overline{F}_3 = \overline{f}_3 \) requires an excessive number of bound motors. Discarding \( \overline{\phi}_0 \geq 1 \) from the graphical representation of Eq. (12), we plot in Fig. 4 the hybrid extraction density as function of the membrane viscosity, for motors at low \( P = 2 \) and at high \( P = 100 \) processivities.

**Discussion.** What are the biophysical implications of Fig. 4? On the one hand, we note that the experiments of Refs. [9–15] remarkably fall into the viscosity range \( \eta'_m \approx 10^{-10} \sim 10^{-9} \) Pa m s. This is within the dominance of the tip force, because of the artificiality of PC membranes rather than the processivity of the motors. In contrast, biological membranes are more viscous (\( \eta'_m \approx 10^{-9} \) Pa m s) for which \( \overline{F}_3 = \overline{f}_3 \) and hence susceptible to the drag exerted by stem motors. For instance, tubulation in a neuron (\( \eta'_m \approx 10^{-8} \) Pa m s [20,21]) by kinesins (\( P \approx 100 \) at, say, \( \rho = 500 \mu \text{m}^{-2} \)) falls into the stem regime. But as the processivity is decreased from \( P = 100 \) to \( P = 2 \), the hybrid extraction line is shifted to higher densities so that \( \rho \gtrsim 10^3 \) \( \mu \text{m}^{-2} \). Physically, this degree of motor collectivity seems indeed required to compensate large membrane viscosities.

**Summary and outlook.** On the basis of forces (2)–(4) and binding kinetics (6) and (7), we sketched the phase diagram of membrane tubulation by molecular motors. Our results of Fig. 4 indicate that artificial (PC) membranes inexorably fall into the tip regime, whereas biological membranes can be dragged by stem motors. Such a contrast suggests that the surface viscosity \( \eta'_m \) likely affects the spatial distribution of...
bound motors. In particular, since the current $J_b \sim 1/\eta_m'$, we expect that the accumulation of processive motors at the tip of nanotubes becomes less pronounced for increasing $\eta_m'$. Fluorescence imaging experiments could tackle this issue, along the lines of Ref. [9].

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