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 tentacles developed during phagocytosis [3] and intercellular tethers activated by the transmission of viruses [4]. In vitro experiments mimicking such vesicotubular structures have been performed via micropipette aspiration [5], optical tweezers [6], polymerization of biofilaments [7], concentration gradients [8], and molecular motors [9–15]. The latter scenario, in particular, is sketched in Fig. 1.

The force necessary to extract a membrane tube is typically five times larger than the pulling scale $f_0 \approx 5$ pN associated with a single motor protein [9–15]. Overcoming this barrier requires at least two physical conditions: (i) a sufficiently high density of motors on the vesicle and (ii) a sustainable kinetic of motor binding to the substrate. Furthermore, the mechanical work done by each bound motor depends on the population of bound motors experiences a velocity drop in the course of their walk on the substrate, Kinesin, for example, can walk hundreds of steps of length $\ell$ immersed in an fluid of viscosity $\eta_w$. The velocity surplus of length $\ell$ that defines the stem. Moreover, what is the impact of $\eta_m$ on the driving force behind tube formation? Can $\eta_m$ affect the spatial distribution of motors along the tube? And what is the interplay between viscous and (non)processivity effects? The present Rapid Communication addresses these issues via a simple force balance coupled to the binding kinetics of motors.

**Model setup.** As shown in Fig. 1, consider a spherical vesicle of radius $R$ immersed in an fluid of viscosity $\eta_w$. The vesicle is coated with a density $\rho$ of molecular motors, which bind and unbind to the substrate at constant rates $k_b$ and $k_u$, respectively. While bound, each motor takes unidirectional propulsion, 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 protrusions, tether networks, and sensorial tentacles. This is the case of sensorial tentacles developed during phagocytosis [3] and intercellular tethers activated by the transmission of viruses [4].

The force balance consists in decomposing the tube into two parts: stem and tip pulling. Typically, $L \approx 0.15 f_0 [9,14]$, suggesting that the population of bound motors experiences a velocity drop along the axial length $L$. A convenient way to approach this effect consists in decomposing the tube into two parts: stem and tip [12,13], as illustrated in Fig. 2. The tip is formed by $n_b$ bound motors that walk at the same speed $L$ of the tube, pulling the membrane with a force $f_b$. The remaining $N_b$ bound motors have a velocity surplus $v_0 - L$ that defines the stem. Their viscous drag force on the membrane is $F_b$.

**Stem force.** In the course of their walk on the substrate, stem motors impart momentum to the membrane tube. The corresponding force can be expressed as $F_b \equiv N_b f_c$, where $F_c \equiv \xi (v_0 - L)$ denotes the viscous drag of a single motor on the membrane. The coefficient $\xi$ is nontrivial, because it involves the following: (i) the size $\ell$ of the protein domain moving in the membrane and (ii) the local radius of curvature $r$ of the membrane relative to the Saffman-Delbrück length $\ell_m \equiv \eta_m/\eta_w$ (the scale below which $\eta_m$ dominates the viscous dissipation [24]). According to recent experiments [25] and theoretical analyses [24,26], the axial drag coefficient in a
cylindrical membrane of radius $r \ll \ell_b$ is given by [24]
\[
\xi = \frac{4\pi \eta_m'}{\ln (r/\lambda) + \frac{1}{2}}.
\] (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,
\[
F_b = N_b 4\pi \eta_m' (v_0 - \dot{L}) \ln (r/\lambda) + \frac{1}{2},
\] (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 $f_1 = f_0 (1 - v/v_0)$, 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 $f_b = n_b f_1(L)$ on the tip of the tube as
\[
f_b = n_b f_0 \left(1 - \frac{L}{v_0}\right).
\] (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 vesiculobular structure? We assume $F_m = F_c + F_A$, such that $F_c = 2\pi \sqrt{2\sigma \kappa_c}$ is the barrier for tube formation [1,2] and $F_A$ the stretching force. The latter arises from the energy $\Delta E_A = \kappa_c (A - A_0)^2/(2A_0)$, where $A_0$ and $A$ are the areas of the unstretched and stretched membranes, respectively [1]. For tube extraction from a spherical vesicle, $A_0 = 4\pi r^2$, $A - A_0 \approx 2\pi rL$, and $\Delta E_A = \frac{3}{2} \kappa_c \pi (r/R)^2 L^2$.

Thus, $F_A = \Delta E_A / \partial L = \kappa_A (r/R)^2 L$, leading to
\[
F_m = 2\pi \sqrt{2\sigma \kappa_c + \kappa_A (r/R)^2}.
\] (4)
Balancing $F_b$ and $F_m$, one readily finds
\[
\frac{v_0 - \dot{L}}{v_0} = \frac{2\pi \sqrt{2\sigma \kappa_c + \kappa_A (r/R)^2}}{N_b \xi v_0 + n_b f_0}.
\] (5)
Equation (5) governs the evolution of the tube length $L$ and the current$I_b \equiv (v_0 - \dot{L}) N_b / L$ 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 $N_b = N_0 + n_b$ bound and $N_a = N - N_b$ unbound to the substrate. We model the binding kinetics over the stem and tip regions by
\[
\frac{dN_b}{dt} = I - k_a N_b - J_b,
\] (6)
\[
\frac{dn_b}{dt} = J_b - k_a n_b,
\] (7)
where $I$ denotes the influx of motors to the filament. This flux involves geometric constraints and excluded volume effects on binding. We assume $I = k_b N_a (1 - \phi_a)$, where $N_a$ is the number of attachable motors and $\phi_a$ the occupation of the filament. Letting $N_0$ denote the number of tracks accessible to a motor (see Fig. 3 and Ref. [13]), we estimate the number of stepping sites as $N_0 L / \ell$ and $\phi_a \approx (N_b + n_b)/(N_0 L / \ell)$. Analogous arguments hold for $N_a$. 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 $N_b = \phi_b N_d$. As shown in Fig. 3, $\phi_b \simeq (2l)/(2\pi r)$ since a cross section of the tube hosts two unbound motors that neighbor the filament. In terms of such estimates, $I = \langle k_b \rangle (2\pi r)^2 \ell B/N_b - n_b(1 - N_b/n_b) \lambda/\ell$.

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

$$dX \over d\tau = P \left(1 - {E + SX \over N_bD + n_b}\right),$$

$$dN_b \over d\tau = B\phi_b \left(MX - N_b - n_b\right) \left(1 - {N_b + n_b \over N_bX}\right)$$

$$- N_b = {PN_b \over X} \left(E + SX \over N_bD + n_b\right) - n_b,$$

where $P \equiv v_0/(\ell k_b)$, $E \equiv 2\pi \sqrt{2\sigma} \kappa \zeta / f_0$, $S \equiv \kappa_A \pi (r/R)^2 \ell / f_0$, $D \equiv \zeta v_0 / f_0$, $B \equiv k_b / k_h$, and $M \equiv 2\pi \ell R$. 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 $j_b \equiv J_b / k_h$ is given by $j_b = P(N_b)/(E + SX) / (N_b D + n_b)$.

**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 $F_t / F_b$ if $N_b / n_b$, where $D = 4\pi \eta m v_0 f_0^{-1} / [\ln(r/\lambda) + 1/2]$. Depending on the surface viscosity $\eta m$ of the membrane, three tubulation mechanisms can emerge: (i) tip pulling, where $f_b > F_b$, (ii) viscous drag, for which $F_b > f_b$, and (iii) hybrid extraction, such that $F_t \approx f_b$. Since hybrid extraction is a key limiting case, we shall determine its steady state solution $(\overline{X}, \overline{N}_b, \overline{\pi}_b)$ and its locus on the $\eta m \times \rho$ plane.

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

$$\overline{X} = P / D, \quad \overline{N}_b = E / 2D + \overline{PS} / 2D^2 \quad \overline{\pi}_b = E / 2 + \overline{PS} / 2D.$$ (11)

This leads to a current $I = \overline{\pi}_b - \overline{N}_b \sim P / D$ 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),

$$\overline{M} = (1 / \phi_b) (1 - \phi_b N_d / \overline{\phi}_b) / (1 - \phi_b),$$ (12)

with $\overline{\phi}_b \equiv (\overline{N}_b + \overline{\pi}_b) / (N_d \overline{X})$. Here, the tube length $\overline{X}$ and the number of stepping tracks $\overline{N}_b$ limit the population of bound motors $\overline{N}_b + \overline{\pi}_b$, so that Eq. (12) is physically relevant only if $\overline{\phi}_b < 1$. This constraint is violated at membrane viscosities (e.g., $\eta m \lesssim 10^{-9}$ Pa m s) for which $\overline{F}_b = \overline{f}_b$ requires an excessive number of bound motors. Discarding $\overline{\phi}_b \gtrsim 1$ 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 high ($P = 100$) processivities.

**Discussion.** What are the biophysical implications of Fig. 4? On the one hand, we note that the experiments of Refs. [15–19] remarkably fall into the viscosity range $\eta m \approx 10^{-10} - 10^{-9}$ 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 ($\eta m \approx 10^{-8}$ Pa m s) [20,21] and hence susceptible to the drag exerted by stem motors. For instance, tubulation in a neuron ($\eta m \approx 10^{-8}$ Pa m s) by kinesins ($P \approx 100$ at, say, $\rho = 500 \mu m^{-2}$) 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 $P \lesssim 10^6 \mu m^{-2}$. 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 $J_b \sim 1/\eta_m^\prime$, we expect that the accumulation of processive motors at the tip of nanotubes becomes less pronounced for increasing $\eta_m^\prime$. Fluorescence imaging experiments could tackle this issue, along the lines of Ref. [9].

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