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Strong confinement, thermal fluctuations, and mobility of a tightly fitting vesicle in a very narrow microcapillary tube

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Abstract – We investigate theoretically the critical role of thermal fluctuations in maintaining a narrow gap between a very narrow capillary tube and a highly confined enclosed membrane vesicle. We quantitatively find that the size of the slender gap between a tightly fitting incompressible vesicle and an enclosing cylindrical tube depends on a subtle interplay between membrane area dilation and vesicle fluctuations. This work is therefore likely to be of crucial importance for investigating the paradigmatic properties of highly confined membrane vesicles inside a very narrow capillary tube. Additionally, fluid flow can also occur in this gap, giving rise to a finite vesicle mobility along a narrow capillary tube. Typically, for most (small to moderate) fluid velocities, we find that (in the vesicle fluctuation dominated regime) the gap size remains essentially insensitive to fluid flow. However, for relatively large fluid velocities, it is approximately found (in the fluid flow dominated regime) that the gap size grows with increasing fluid velocity as a power law, and we are able to evaluate the extra hydrodynamic pressure drop due to the presence of the vesicle, as well as the vesicle's relative mobility. This work is thus also likely to be highly relevant for considerations of the stalling and dynamic arrest of tightly confined vesicles in narrow constrictions. Possible applications of this work might thus also include biological transport, microfluidics, and drug delivery.

Introduction. – The properties of membrane vesicles in narrow constrictions are of great importance in various contexts, such as biology [1,2], microfluidics [3], and drug delivery [4,5]. In this letter we consider the behaviour of tight-fitting vesicles in very narrow, and highly confining cylindrical tubes, or microcapillaries. This will necessitate detailed consideration of the interplay between membrane elasticity, thermal fluctuations, and also low-Reynolds-number hydrodynamics.

Vesicles are typically very flexible, with a relatively low resistance to bending deformations [6,7]. However, due to incompressibility, vesicle configurations tend to conserve volume (V) [6–8]. On typical experimental timescales, a vesicle can therefore be considered as effectively impermeable, leading to a constant, fixed vesicle volume. Additionally, in the highly confined regime considered here, vesicles strongly resist changes in surface area (A) due to membrane stretching [9,10], governed by the elastic modulus K_A. In a highly confining capillary tube of narrow radius, therefore, the vesicle necessarily assumes a mean shape close to that of a spherocylinder [9–21], with a long cylindrical main portion accompanied by two hemispherical endcaps [15,20].

Conceptually, we therefore take as our starting point a vesicle of spherocylindrical shape that fits snugly (with no gap) inside a confining tube. Note that experimentally vesicles are often deflated somewhat before insertion into narrow capillaries in order to avoid any potential issues concerning vesicle rupture due to membrane lysis [18,22]. We can then calculate a new vesicle mean shape by turning on vesicle thermal fluctuations, and additionally an externally imposed fluid flow within the confining tube. This new mean spherocylindrical shape for the vesicle will necessary display a gap between the vesicle and the enclosing tube. For a tight fitting vesicle enclosed in a narrow cylindrical tube, the gap available for, *e.g.*, fluid flow is necessarily small. However, at non-zero temperature an entropic, steric repulsion operates between the membrane and the sphere due to the presence of vesicle membrane

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fluctuations [23–29]. These thermal fluctuations maintain a finite average gap size between the vesicle and the enclosing tube. Equally, an externally imposed flow field within the confining tube can also contribute to the production of a small gap, or lubricating layer, between the vesicle and the confining capillary tube. The existence of such a gap therefore enables fluid to flow around the vesicle and hence endows the vesicle with a finite mobility. In this work we estimate the size of this membrane gap self-consistently, and then use this result to calculate vesicle mobility using low-Reynolds-number hydrodynamics.

We will find that in the ultra-high confinement regime considered here, our analysis for the mean vesicle shape simplifies considerably. With a conserved volume constraint (and assuming no lysis), the dominant energetic contribution is given by area dilation (with curvature negligible), which must be balanced by vesicle fluctuations (around the mean shape) and imposed fluid flow (where applicable). We therefore study the crucial role of vesicle fluctuations, and also fluid flow, in maintaining a narrow gap between a vesicle and a confining capillary tube. Some of the fluid trapped in the tube between the vesicle and the enclosing capillary wall must flow past the vesicle if it is to move relative to the tube.

Despite associated experimental work on this topic being relatively sparse [22], related recent theoretical work can be found in [15,16], for example. Moreover, for stronger vesicle confinement in capillaries, it is typically found that the spherocylinder approximation for the mean vesicle shape agrees rather well with more complicated and involved theoretical treatments [12]. In what follows, we ignore any (necessarily sub-leading) effects of the vesicle's hemispherical endcaps, and only consider the dominant long cylindrical main body of our strongly confined vesicle.

Theory. –

Calculation of the vesicle gap size due to membrane thermal fluctuations. We now briefly outline our self-consistent mean-field theory of the radial vesicle fluctuations. The *average* radial extent of the fluctuations are controlled by the presence of the enclosing cylindrical constriction, or tube. This approach is analogous to Helfrich's steric theory for planar membranes [6,23], as well as previous work on a rod enclosing membrane [27]. Unless otherwise stated, we will work in units in which $k_{\mathrm{B}}T = 1$.

In order to describe the energetics of the cylindrically confined portion of our vesicle, we use the following Hamiltonian $H = H_V + H_A + H_C + H_S$ with area $A = \int \sqrt{g}\mathrm{d}\phi\mathrm{d}z$:

$$\begin{aligned} H_V &= \frac{K_V}{2V_0}(V - V_0)^2, \\ H_A &= \frac{K_A}{2A_0}(A - A_0)^2, \\ H_C &= \frac{\kappa}{2}\int c^2\sqrt{g}\mathrm{d}\phi\mathrm{d}z, \\ H_S &= \frac{\mathcal{C}}{2}\int (r(\phi,z) - \bar{r})^2\sqrt{g}\mathrm{d}\phi\mathrm{d}z. \end{aligned} \tag{1}$$

H_V imposes an energetic penalty for changes in vesicle volume (incompressibility), while H_A penalises membrane area stretching or dilation, with associated moduli K_V and K_A, respectively. H_C is the canonical Helfrich curvature Hamiltonian [6,7], containing a rigidity (κ) term involving the mean curvature (c), and g is the determinant of the metric tensor $\det(g_{ab})$. The steric Hamiltonian H_S contains a harmonic potential (with strength $\mathcal{C}$) that regulates the magnitude of the vesicle fluctuations to a narrow region about the average tube radius, $\bar{r}$. As we are dealing in this work with high confinement in a capillary tube, we can approximate the energy by computing the membrane Hamiltonian over the entire length of the long cylindrical main body of the vesicle, and can safely ignore the contribution of the vesicle endcaps.

We now write $r(\phi, z) = \bar{r} + \delta r(\phi, z)$ and expand the energy H, given by eq. (1), to quadratic order [8] in the radial perturbation $\delta r(\phi, z)$ about the average tube radius $\bar{r}$. The first-order perturbative contribution in δr must vanish so that $\bar{r}$ truly represents the mean vesicle shape, which naturally requires that we impose $\int \delta r \mathrm{d}\phi\mathrm{d}z = 0$.

Perturbatively, we can write for the vesicle volume V:

$$\begin{aligned} V &= \pi\bar{r}^2\bar{L} + \frac{1}{2}\int \delta r^2\mathrm{d}\phi\mathrm{d}z \\ &= V_0 + \pi r_0^2(\bar{L} - L_0) + 2\pi r_0 L_0(\bar{r} - r_0) \\ &\quad + \frac{1}{2}\int \delta r^2\mathrm{d}\phi\mathrm{d}z \end{aligned} \tag{2}$$

with $V_0 = \pi r_0^2 L_0$, and we have additionally expanded $\bar{L}$ around L_0 and $\bar{r}$ in the vicinity of r_0. Similarly, with $A_0 = 2\pi r_0 L_0$, we can write the vesicle area A perturbatively as

$$\begin{aligned} A &= 2\pi\bar{r}\bar{L} + \frac{1}{2\bar{r}}\int[\bar{r}^2(\partial_z\delta r)^2 + (\partial_\phi\delta r)^2]\mathrm{d}\phi\mathrm{d}z \\ &= A_0 + 2\pi r_0(\bar{L} - L_0) + 2\pi L_0(\bar{r} - r_0) \\ &\quad + \frac{1}{2\bar{r}}\int[\bar{r}^2(\partial_z\delta r)^2 + (\partial_\phi\delta r)^2]\mathrm{d}\phi\mathrm{d}z. \end{aligned} \tag{3}$$

We can thus see, by inspection of eq. (2) and eq. (3), that vesicle fluctuations δr do not contribute to leading order in the Hamiltonians H_V and H_A given by eq. (1) above. Additionally, and for reasons of simplicity, we impose in this work a "hard" incompressibilty constraint in what follows by effectively taking the $K_V \to \infty$ limit in H_V. This will prove useful in enabling us to eliminate $\bar{L}$ from our analysis a bit later on.

Using a convenient Fourier parameterisation of the radial fluctuations as $\delta r(\phi, z) = \sum_{n,m}\delta r_{nm}\times \exp\left(im\phi + \frac{2\pi inz}{\bar{L}}\right)$, with $q = \frac{2\pi\bar{r}}{\bar{L}}$, thus gives the perturbative expansion of the energy to quadratic order as

$$\begin{aligned} H &= \frac{\pi\kappa\bar{L}}{\bar{r}} + \frac{\pi K_A L_0}{r_0}(r_0 - \bar{r})^2 \\ &\quad + \frac{1}{2}\frac{2\pi\kappa\bar{L}}{\bar{r}^3}\sum_{n,m}\delta r_{nm}\delta r_{-n-m}K_{nm} \end{aligned} \tag{4}$$

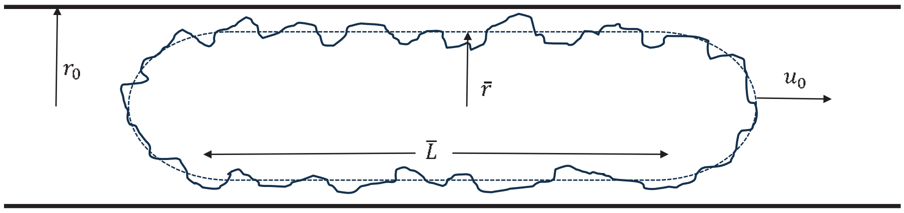

Fig. 1: Sketch of a tightly fitting fluctuating vesicle, of mean cylindrical radius $\bar{r}$ and average cylindrical length $\bar{L}$, enclosed in a narrow, highly confining, capillary tube of radius r_0. Additionally, under the effect of an externally imposed fluid flow, the vesicle moves with a steady velocity u_0 along the capillary tube axis. Note that the gap size between the vesicle and the enclosing tube has been exaggerated somewhat for purposes of illustration.

involving a Fourier mode kernel: $K_{nm} = \left(n^2q^2 + m^2\right)^2 - \frac{n^2q^2}{2} - \frac{5m^2}{2} + 1 + \frac{\mathcal{C}\bar{r}^3}{\kappa}$. The mean squared amplitude of the radial fluctuations, $\langle \delta r^2 \rangle$, depends on the parameter $\mathcal{C}$, as can be seen from $\delta^2 H$ in eq. (4). The presence of the constriction sterically constrains the vesicle radius, $r(\phi, z)$, to always remain less than or equal to the constriction radius r_0, as shown in fig. 1. Enforcing this constraint, via tuning the strength $\mathcal{C}$ of our harmonic potential as outlined below, is necessarily an approximate, phenomenological, treatment of the steric interaction. Thus, as is common to all theories that follow the spirit of the Helfrich approach, one should be cautious in relying too heavily on the numerical prefactors that appear in our final results. After integrating out the radial vesicle fluctuations we obtain the free energy F as follows:

$$F = \frac{\pi\kappa\bar{L}}{\bar{r}} + \frac{\pi K_A L_0}{r_0}(r_0 - \bar{r})^2 + \frac{1}{2}\sum_{n,m}\log\left(\frac{K_{nm}}{K_{nm}|_{\mathcal{C}=0}}\right). \quad (5)$$

In writing down eq. (5), we have chosen to normalise our free energy as follows. Physically, we wish to calculate the free-energy difference between the case when the constriction is present and when it is absent (and the vesicle is therefore unconstrained). For the unconstrained case the terms involving $\mathcal{C}$ that appear in K_{nm} must vanish ($\mathcal{C} \to 0$). Thus, for consistency, we choose our normalisation such that in the unconstrained limit, the fluctuation contribution to the free energy F from the steric potential vanishes.

Approximating the summations required in eq. (5) by integrals, we find that we can write our final expression for the confined vesicle free energy in the following suggestive form:

$$F = \frac{\pi\kappa_{eff}\bar{L}}{\bar{r}} + \frac{\pi K_A L_0}{r_0}(r_0 - \bar{r})^2, \quad (6)$$

where the "effective" bending modulus κ_{eff} is given as

$$\begin{aligned}\kappa_{eff} &\simeq \kappa + \frac{1}{4\pi}\int_0^\infty \mathrm{d}\rho \log(1 + \mathcal{C}\bar{r}^3/(\kappa\rho^2)) \\ &\simeq \kappa + \frac{1}{4}\sqrt{\frac{\mathcal{C}\bar{r}^3}{\kappa}} \quad (7)\end{aligned}$$

involving the variable $\rho = n^2q^2 + m^2$. Note that ultimately therefore, using this approach, all of the effects of the steric interaction between the vesicle and the constriction may be incorporated into an "effective" bending modulus κ_{eff}.

The physically self-consistent condition for the strength of the harmonic potential $\mathcal{C}$ required in order to describe the steric influence of the constriction can be quantitatively stated as $\bar{r} + \sqrt{\langle \delta r^2 \rangle} = r_0$, where $\langle \delta r^2 \rangle = \frac{\bar{r}^3}{2\pi\kappa L}\sum_{n,m} K_{nm}^{-1}$. For the physical situation considered here, we have strong vesicle confinement. Thus, the average radius of the vesicle is almost equal to the radius of the enclosing constriction ($\bar{r}/r_0 \simeq 1$) . The steric effects in this case should therefore also be very strong, with the strength of the self-consistent, confining, harmonic potential becoming very large ($\mathcal{C}\bar{r}^3/\kappa \gg 1$) in this limit. By again converting the required summations into integrals and changing variables, we can approximate the above consistency condition for $\mathcal{C}$ as follows:

$$\begin{aligned}\frac{(r_0 - \bar{r})^2}{r_0^2} &\simeq \frac{1}{4\pi\kappa}\int_0^\infty \mathrm{d}\rho \frac{1}{\rho^2 + \mathcal{C}\bar{r}^3/\kappa} \\ &\simeq \frac{1}{8}\sqrt{\frac{1}{\kappa\mathcal{C}r_0^3}}. \quad (8)\end{aligned}$$

Rearranging eq. (8), we obtain in this strong confinement limit $\mathcal{C} = \frac{r_0}{64\kappa}\frac{1}{(r_0 - \bar{r})^4}$. By substituting this obtained value of $\mathcal{C}$ into eq. (7) for κ_{eff}, we obtain to leading order in the gap size

$$\kappa_{eff}/\kappa = 1 + \frac{r_0^2}{32\kappa^2}\frac{1}{(r_0 - \bar{r})^2}. \quad (9)$$

In the strong confinement limit studied here, we can see from eq. (9) that the steric interaction contribution to κ_{eff} typically dominates the effective rigidity. Moreover, substituting this dominant value of κ_{eff} into eq. (6) for the vesicle free energy, we obtain (to leading order in the gap size)

$$F = \frac{\pi K_A L_0}{r_0}(r_0 - \bar{r})^2 + \frac{\pi r_0 L_0}{32\kappa}\frac{1}{(r_0 - \bar{r})^2}. \quad (10)$$

Note that a similar fluctuation contribution to the free energy that scales as the inverse squared gap distance, is well known for parallel flat membranes at small intermembrane separation [23–26]. In order to calculate the average radius $\bar{r}$ for the confined vesicle, we minimise the free energy F by using $\frac{\partial F}{\partial \bar{r}} = 0$, such that we find for the gap size due to fluctuations

$$\frac{r_0 - \bar{r}}{r_0} = \left(\frac{1}{32\kappa K_A r_0^2}\right)^{\frac{1}{4}}. \tag{11}$$

Notice the $\kappa^{-1/4}$, $K_A^{-1/4}$, and $r_0^{1/2}$ dependence of the gap size $r_0 - \bar{r}$, as displayed in eq. (11). Indeed, eq. (11) for the gap size, including the small (but crucially non-zero) correction due to vesicle membrane fluctuations, represents one of the primary testable predictions of this work. Moreover, one can evidently see that this result remains consistent as long as $\sim \kappa K_A r_0^2 \gg 1$. Furthermore, and as an important application of this work, we can utilise this result in order to calculate the mobility of a vesicle in a close-fitting tube, for example.

Application to fluid hydrodynamics, gap size and vesicle transport. In this section we apply ourselves to analysing the fluid hydrodynamics around a moving vesicle enclosed within a tightly fitting cylindrical constriction. In the limit of extreme vesicle confinement, as considered exclusively in this work, we find that a relatively crude hydrodynamical theory proves sufficient for our purposes. Moreover, a similarly modest hydrodynamic approach to the one taken in this work was found to be successful in describing the complimentary situation of the transport of solid bodies along tubular membrane tethers [29]. For a broader, and more comprehensive approach to modelling the hydrodynamics of vesicles in tubes, the reader should consult [11–17]. Our approximate hydrodynamical approach will allow us to calculate the transport properties of the highly constrained vesicle, such as its relative mobility, for example. In the "ultra-narrow gap" approximation of interest here, we can safely assume that the fluid flow in the gap can be described by the axial component u_z alone. In cylindrical coordinates, the low-Reynolds-number hydrodynamics of the fluid within the constriction, governed by Stokes' equation, along with the constraint of incompressibility, is as follows [30,31]:

$$\begin{aligned} -\frac{\partial p}{\partial z} + \frac{\mu}{r}\frac{\partial}{\partial r}\left(r\frac{\partial u_z}{\partial r}\right) &= 0, \\ \frac{\partial u_z}{\partial z} &= 0 \end{aligned} \tag{12}$$

with fluid velocity u_z, hydrodynamic pressure p, and viscosity μ. The incompressibility condition in eq. (12) can be satisfied straightforwardly by defining $u_z \equiv u_z(r)$. Using the method of separation of variables, the most general solution to eq. (12) can easily be shown to be $u_z(r) = \frac{a}{4\mu}r^2 + c\log r + d$, and $p(z) = b + az$, where a, b, c, and d are constants to be determined by the appropriate boundary conditions on the fluid. For convenience, we choose to work in the lab frame with respect to which the enclosed vesicle is moving. The boundary conditions satisfied by the fluid are thus as follows:

$$u_z(r)\Big|_{r=\bar{r}} = u_0,$$

$$u_z(r)\Big|_{r=r_0} = 0. \tag{13}$$

The presence of fluid inside the confining tube necessitates the addition of (z-dependent) pressure (p) and surface tension (σ) terms to the free energy in eq. (10) via H_F as follows:

$$H_F = \int p(z)\mathrm{d}V + \int \sigma(z)\mathrm{d}A. \tag{14}$$

Such fluid-induced z-dependent p and σ terms in H_F produce a further coupling to the first-order perturbation δr normal to the vesicle surface that goes like $\sim \int (p\bar{r}+\sigma)\delta r \mathrm{d}\phi \mathrm{d}z$. Within the context of our self-consistent (albeit approximate) calculational scheme (and given that we already impose $\int \delta r \mathrm{d}\phi \mathrm{d}z = 0$), we can see that in order for stability of our assumed mean spherocylindrical vesicle shape (around $\bar{r}$), we must take the combination $p\bar{r} + \sigma$ to be a constant (independent of z and ϕ). Concomitantly, and for the purpose of our approximate model, we can therefore simply write

$$\frac{\partial}{\partial z}\left(p\bar{r} + \sigma\right) = 0. \tag{15}$$

Ultimately, this necessary for self-consistency condition in our model can be seen to be equivalent to the usual force/stress balance considerations perpendicular to the vesicle surface, and will thus allow us to effectively fix the constant parameter a given above (in terms of the pressure gradient $\partial_z p$).

Stability to first-order perturbations tangentially, along the long cylindrical axis of our vesicle, requires the following balance between the surface tension σ and the fluid shear stress tensor T_{zr} [15,16]:

$$T_{zr} + \frac{\partial \sigma}{\partial z} = 0, \tag{16}$$

where $T_{zr} = \mu \partial u_z / \partial r$ [30,31].

By utilising all of the above boundary conditions, we can find all the integration constants required in order to completely describe the fluid flow around the confined vesicle:

$$\begin{aligned} u_z(r) &= u_0 \frac{\log r/r_0}{\log \bar{r}/r_0} + \frac{\partial p/\partial z}{4\mu \log \bar{r}/r_0}\big((r^2 - r_0^2)\log \bar{r}/r_0 \\ &\quad + (r_0^2 - \bar{r}^2)\log r/r_0\big), \\ \frac{\partial p}{\partial z} &= \frac{4\mu u_0}{\bar{r}^2 - r_0^2 + 2\bar{r}^2 \log \bar{r}/r_0}. \end{aligned} \tag{17}$$

In the narrow gap approximation, as $\bar{r} \to r_0$, we find from eq. (17) that the additional pressure drop Δp across the vesicle due to fluid flow is given by $\Delta p \simeq \frac{\mu u_0 L_0}{r_0(r_0 - \bar{r})}$ [15,16].

We additionally require that the volumetric flow rate (Q) of the fluid in the gap between the vesicle and the constriction must balance the volumetric flow rate of the fluid in the adjoining, cylindrical portions of the constriction, given by $Q = \pi r_0^2 \bar{u}$ (with some average fluid velocity $\bar{u}$). Thus, volumetric flow balance leads to

$$\pi r_0^2 \bar{u} = \pi \bar{r}^2 u_0 + 2\pi \int_{\bar{r}}^{r_0} u_z(r) r \mathrm{d}r. \tag{18}$$

As $\bar{r} \to r_0$, in the narrow gap approximation, we can obtain from eq. (18) that the relative mobility $u_0/\bar{u}$ of the vesicle is given by $\frac{u_0}{\bar{u}} \simeq 1 + \frac{(r_0-\bar{r})}{r_0}$ [15,16].

Now that we know $p(z)$ and $\sigma(z)$ from the above, we can use them to calculate H_F from eq. (14). By adding the u_0-dependent fluid flow contribution, H_F, to our preexisting free energy F given above by eq. (10) we get (to leading order in the gap size)

$$F = \frac{\pi K_A L_0}{r_0}(r_0 - \bar{r})^2 + \frac{\pi r_0 L_0}{32\kappa}\frac{1}{(r_0-\bar{r})^2} + \frac{3\pi}{2}\frac{\mu u_0 r_0 L_0^2}{(r_0-\bar{r})}. \tag{19}$$

Note that the pressure and surface tension terms in H_F do not contribute to leading order in the calculation of the vesicle gap size due to thermal membrane fluctuations, essentially because the steric term $\mathcal{C} \sim 1/(r_0 - \bar{r})^4$ dominates the governing fluctuation kernel K_{nm} given above. For large enough velocities u_0, if the fluid flow term in eq. (19) dominates over the term in the free energy due to vesicle thermal fluctuations, then the gap size obtained by minimising the free energy F with respect to $\bar{r}$ now becomes

$$\frac{r_0 - \bar{r}}{r_0} = \left(\frac{3\mu u_0 L_0}{4K_A r_0}\right)^{\frac{1}{3}}. \tag{20}$$

For lower velocities u_0, the expression for the gap size reverts to that given by eq. (11) above, due to vesicle membrane fluctuations.

Discussion. – In this letter, we have investigated theoretically the role of thermal fluctuations, and imposed fluid flow also, on the properties of a highly confined membrane vesicle inside a very narrow microcapillary tube. In the vesicle fluctuation dominated regime, and assuming values of $K_A \simeq 10^{-1}\,\mathrm{Jm}^{-2}$, $\kappa \simeq 10\,k_\mathrm{B}T$, and a capillary diameter of $\simeq 1\,\mu\mathrm{m}$ [1,6,9,18], we get from eq. (11) $\frac{r_0-\bar{r}}{r_0} \simeq 1\%$, which gives a gap size of $\simeq 5\,\mathrm{nm}$. Despite necessarily being relatively small, due to the ultra-strong vesicle confinement considered in this work, we should note that the calculated gap size is crucially non-zero, and, moreover, is comfortably sizeable enough to allow for the transport of large protein molecules [1,2], for example. In the fluid flow dominated case, and further assuming values of $\mu \simeq 10^{-3}\,\mathrm{Pas}$, and $L_0/r_0 \simeq 5$ [1,9,18], we get from eq. (20) $\frac{r_0-\bar{r}}{r_0} \simeq 1\%$–$3\%$ for $u_0 \simeq 10\,\mu\mathrm{ms}^{-1}$–$1\,\mathrm{mms}^{-1}$, for example. We can thus see that for vesicle velocities less than $\simeq 10\,\mu\mathrm{ms}^{-1}$, *the mean gap size is dominated by vesicle membrane fluctuations alone.* We also find that a typical additional pressure drop Δp across the vesicle due to fluid flow corresponds to $\Delta p \sim 10$–$10^3\,\mathrm{Pa}$ [16,32,33], while the relative mobility $u_0/\bar{u}$ of the vesicle can invariably be well approximated by $\frac{u_0}{\bar{u}} \sim 1$ in the high confinement limit.

The work presented here differs from most previous studies in that we focus exclusively on the ultra-strong confinement phase of a vesicle in a narrow capillary, while also including the effects of thermal vesicle fluctuations. Moreover, we find that in this highly confined approximation, the underlying physics, and our concomitant theoretical treatment, simplifies matters considerably compared to many previous, albeit more comprehensive, approaches. Furthermore, one of the main objectives of this work is the inclusion of thermal vesicle fluctuations, which leads to the presence of a thin lubricating layer between the vesicle and the confining tube wall, *even in the absence of any externally imposed fluid flow.* Indeed, the results presented here imply that the analogous $u_0 \to 0$ limit of all previous corresponding studies must be amended due to the presence of a fluctuation-induced gap, or lubricating layer. The novel calculation of the fluctuation gap presented here represents one of the central outcomes of this work, with the new result that the gap size $\not\to 0$ as the fluid velocity $u_0 \to 0$, unlike associated previous work [17,18], which ignore vesicle fluctuations and found that the gap size varied as $\sim u_0^{2/3}$ for small u_0.

We ignore any endcap effects in this work, which presumably represents a good approximation for the high confinement phase considered here, leading ultimately to a dominant free-energy contribution extensive in the length of the long cylindrical main portion of our vesicle (L_0). We also naturally assume that the deformations considered in this work lead to any possible induced surface tensions sufficiently below that required for vesicle rupture via membrane lysis. Indeed, using $\sigma_\mathrm{eff} \sim K_A(A - A_0)/A_0$ [1], we get an effective vesicle tension of $\sim 10^{-3}\,\mathrm{Jm}^{-2}$, well below typical lysis tensions of $\sim 10^{-2}\,\mathrm{Jm}^{-2}$ [1,2,18]. Moreover, we find that the hydrodynamically induced contribution $\Delta\sigma$ to the vesicle tension is typically in the range $\sim 10^{-5}$–$10^{-3}\,\mathrm{Jm}^{-2}$ [32,33].

Our approximate model free energy, given by eq. (19), represents one of the principal results of this work, and brings out the essential physics of the problem. Assuming volume conservation, or incompressibility, the mean shape of a highly confined vesicle in a narrow cylindrical tube, or microcapillary, is given by the competition between membrane stretch (or area dilation), steric vesicle fluctuations, and any imposed fluid flow also present. Moreover, our final approximate expression for the free energy should prove to be a useful reference point for future work in this area of study, with the additional advantage of being relatively easy to use.

Furthermore, our work is likely to be of importance, and highly relevant, for considering the stalling, clogging, jamming, and dynamic arrest of tightly confined vesicles in narrow constrictions. Possible wider applications of this work could hence potentially include biological transport [1,2], microfluidics [3], and drug delivery [4,5]. Finally, despite being presumably challenging, it would naturally be very interesting to see if future experimental work would be able to physically measure the gap size properties (and concomitant hydrodynamic mobility dependence) of highly confined vesicles in capillary tubes, as considered theoretically in this work.

To date, and to the best of our knowledge, the only experimental study of vesicle motion in capillary flow is due to [22]. In their study, the authors measured the effect of capillary confinement on the relative velocity. They showed that capillary confinement reduces the mobility, but did not measure the extra pressure drop.

In the strong confinement regime considered in this work, the steric effects on membrane fluctuations typically dominate over those due to fluid flow. The work of [34], for example, crucially relies on the extreme sensitivity of the nonlinear dynamics considered close to the TT-TB transition point, such that small perturbations due to thermal noise become correspondingly amplified.

We choose throughout this work to characterise the issue of relative vesicle size, and its concomitant ability to traverse the capillary tube, in terms of the lysis tension. An equivalent such characterisation of the vesicle could be given in terms of the reduced volume v (or area-to-volume ratio), defined as $v = \Omega/(4\pi R_0^3/3)$, where $R_0 = \sqrt{A/4\pi}$, for a vesicle of surface area A and enclosed volume Ω.

The work of [35] suggests that membrane viscosity could potentially play an important role in describing red blood cells in microfluidic flows. They find that membrane viscosity effects could potentially become comparable with those due to bulk fluid viscosity at smaller length scales, and are hence likely to become more important for smaller vesicles. We leave detailed consideration of this interesting problem to future work.

Finally, we include via Supplementary Material `Supplementarymaterial.pdf` (SM) a few illustration plots, where dependences of different quantities as a function of basic parameters can be presented. Also included in the SM is a comparison to previous hydrodynamic studies via the plotting of quantities from different models together, along with a brief discussion. Thus, the efficacy of our simple lubrication-type approximate model for the hydrodynamics can be illustrated through comparison with existing models.

* * *

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