Thermal Casimir effect in lipid bilayer tubules

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We calculate the thermal Casimir effect for a dielectric tube of radius R and thickness δ formed from a membrane in water. The method uses a field-theoretic approach in the grand canonical ensemble. The leading contribution to the Casimir free energy behaves as $-k_BTL\kappa_c/R$ giving rise to an attractive force which tends to contract the tube. We find that $\kappa_c \sim 0.3$ for the case of typical lipid membrane t tubules. We conclude that except in the case of a very soft membrane this force is insufficient to stabilize such tubes against the bending stress which tends to increase the radius.

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Lipid bilayers in water exhibit a huge variety of geometries and in cell biology even more varied structures arise. In order to understand where biological mechanisms, such as molecular motors and cytoskeletal structures, are determinant in the stability of biological structures, one must first understand the role of the basic physical interactions in pure model membrane systems. There has been much study of lipid bilayer shape using standard continuum mechanics [1,2]. This basic approach is also complemented by more microscopic studies based on lipid-lipid interaction models [2,3]; this approach is of course ultimately necessary to fully understand the physics of bilayers.

In certain muscle cells, structures known as t tubules are found. These are basically cylindrical tubes whose surface is composed of a lipid bilayer. Similar structures may also be mechanically drawn off bilayer vesicles. The stability of these tubular structures requires an explanation. The basic continuum theory (where the native curvature is zero) [1,2] predicts that the free energy of a tube of length L and radius R is

$$F_b(L,R) = \frac{k_BT\kappa_bL}{R}, \tag{1}$$

where the above expression is strictly speaking the excess free energy with respect to a flat membrane of the same area $A=2\pi RL$ and the subscript b refers to mechanical bending. Various experimental and theoretical estimates for the bending rigidity κ_b defined as above (our $\kappa_b=\pi\kappa_b'$, where κ_b' is the conventionally defined rigidity) can be found in the literature; experimental estimates [2] lie between 10 and 100 although certain theoretical models predict regimes where κ_b is of order 1 [3]. The values of κ_b depend of course on the composition of the bilayer and on the experimental protocol used to measure it. One crucial element in both theoretical and experimental determinations of κ_b is whether the tube is attached to a reservoir of lipid or not, i.e., whether the statistical ensemble is grand canonical or canonical. Clearly if there is no reservoir then any increase in the surface area of the tube will lead to a less dense lipid surface concentration, in this case water may be able to come in contact with the internal layer composed of the hydrophobic heads and so lead to a significant increase in free energy. If upon changing the area of the tube, lipids can flow into the tube wall to maintain the local optimal packing, then the free energy cost will be substantially different. This bending free energy is positive and hence in the absence of external forces or extra constraints it tends to make a tube structure expand. We note that when lipid tubes are drawn from a vesicle the mechanically applied tension can of course overcome this free energy barrier [4]. A natural question, motivated by the fact that such structures occur in cells, is whether other physical mechanisms could lead to their formation and explain their stability. A possible explanation put forward is that that electrostatic effects involving surface charges and ions (salt) in the surrounding medium could play a role [5–7]. Certain experiments however showed a relative insensitivity of the equilibrium tube structure to the concentration of salt [6], although there exist systems with highly charged head groups where the salt concentration does appear important in determining the stability of the tubules [8]. Another explanation has been put forward in terms of the geometry of the lipid, notably the tail having a structure such that there is a preferred orientation of the tails next to each other, giving rise to a chirality which stabilizes the tubes [9–13].

In this paper we investigate the possibility that a static van der Waals or thermal Casimir force could provide an attractive force across the tube leading to its stabilization. We adopt a continuum model where the lipid bilayer is modeled as a layer of thickness $\delta \approx 5$–10 nm and of dielectric constant $\epsilon_M \approx 2\epsilon_0$. The surrounding water is also treated as a dielectric continuum of dielectric constant $\epsilon_W \approx 80\epsilon_0$. We shall also adopt a model where the lipid tube is fixed at each end to a flat lipid reservoir and so work in the grand canonical ensemble. The behavior of systems composed of layers of varying dielectric constants was first studied by Lifshitz and coworkers [14,15]. The formalism developed is an elegant way of taking into account van der Waals forces in a continuum theory. Two types of van der Waals forces are accounted for in theses theories, firstly zero frequency van der Waals forces whose nature is classical, and secondly the frequency dependent ones due to temporal dipole fluctuations. In terms of thermal field theory the former correspond to modes with

zero Matsubara frequency and the latter to the modes of nonzero frequencies. These latter terms require information about the frequency dependence of the dielectric constants, whereas the former only requires the static dielectric permittivity. In this paper we will calculate the contribution of the zero-frequency mode, alternatively known as the thermal Casimir effect. The quantum Casimir effect corresponding to the modification of the ground state energy of the electromagnetic field has been intensively studied in the case of idealized boundary conditions in a variety of geometries including spheres and cylinders [16]. The thermal Casimir effect investigated here has a similar mathematical structure though the corresponding effective spatial dimension is one less. The temperature dependence of the full Casimir effect in a simplified model of a solid dielectric cylinder (and sphere) has been recently examined using a heat kernel coefficient expansion [17]. In our analysis of the diffuse limits we make use of summation theorems for Bessel functions which were introduced for the study of the Casimir energy for cylinders with light-velocity conserving boundary conditions [18].

We find that the thermal Casimir effect gives a contribution to the excess free energy of the tube relative to that of the flat plane of

$$F_c(L,R) = -\frac{k_B T L \kappa_c}{R} + O\left(\frac{\delta}{R^2}\right), \tag{2}$$

with

$$\kappa_c = \frac{\Delta^2}{64}[3\log(\Lambda\delta) + 0.02954] + \Delta^4 B(\Delta^2), \tag{3}$$

with $\Delta = (\epsilon_W - \epsilon_M)/(\epsilon_W + \epsilon_M)$ and where numerically we find that $B(\Delta^2)$ is only slowly varying with $B(0) \sim 1/8$. Here $\Lambda \approx \pi/a$ is the large wave-number, ultraviolet, cutoff which is phenomenologically expressed in terms of microscopic cutoff a corresponding to the molecular size below which the continuum picture of the dielectric medium breaks down. It is not a priori clear whether the cutoff a should be associated with the water or the lipid or indeed both; we discuss this point later. In this expression the coefficient of Δ^2 is dominated by the logarithmic term, the constant contribution being typically only of order 1%, and the (estimated) $O(\Delta^4)$ term is of comparable size for large enough Δ.

We note that the sign of F_c is negative and that it has the same functional form as the bending free energy F_b, meaning that the thermal Casimir force tends to collapse the tube and so helps to stabilize the system against the bending forces. We shall show later that with reasonable physical parameters $\kappa_c \approx 0.3$–0.5. We conclude that it is unlikely that the Casimir attraction is able to overcome the repulsion due bending that is predicted by current theories and measured by experiment. However, the results of this paper are important for several reasons.

We show that the thermal Casimir effect tends to contract the tube structure.

The presence of the microscopic cutoff in κ_c shows that the physics is ultimately dominated by the short scale or ultraviolet physics. This means that weak electrolyte concentrations will have little effect on the system as verified by experiments [6] given that there are no strong surface charges.

Further attractive interactions will be generated by the nonzero frequency Matsubara modes.

At a technical level we use the Pauli van Vleck formula to evaluate the arising single body path integrals. This technique is direct and well suited to layered systems.

In what follows we shall sketch the calculation of the thermal Casimir free energy in the absence of electrolyte. The full calculation is rather lengthy and it will be presented in the general case with electrolyte in a more detailed longer paper [19].

The partition function for the zero frequency (static) fluctuations of electrostatic field in a medium of varying dielectric constant $\epsilon(\mathbf{x})$ is given by [20]

$$Z = \int d[\phi] \exp\left(-\frac{\beta}{2}\int d\mathbf{x}\, \epsilon(\mathbf{x})(\nabla\phi)^2\right). \tag{4}$$

In the model we shall consider the function $\epsilon(\mathbf{x}) = \epsilon(r)$ where r is the radial coordinate from the center of the tube. The total length of the tube is L and the coordinate along the length of the tube is denoted by $z \in [-L/2, L/2]$. At the extremities of the tube are two flat bilayers which act as a reservoir for the material from which the tube is made. We consider the limit $L \gg R$ so as to be able to neglect edge effects where the tube meets the reservoir. The interior of the lipid tube is taken to be at $R_1 = R - \delta/2$ and the exterior at $R_2 = R + \delta/2$. In terms of the coordinate r we thus have

$$\epsilon(r) = \epsilon_W, \quad r < R_1 \text{ and } r > R_2,$$

$$\epsilon(r) = \epsilon_M, \quad R_1 < r < R_2. \tag{5}$$

Using the radial symmetry of the problem we express the field ϕ in cylindrical coordinates as

$$\phi(r,z,\theta) = \sum_{n=-\infty}^{\infty} \sum_k X_{n,k}(r) \exp(ikz) \exp(in\theta). \tag{6}$$

The functional integral now factorizes into a product of noninteracting path integrals. Taking the limit of L large we find

$$F(R, \epsilon_W, \epsilon_M, \delta) = -k_B T L \sum_n \int \frac{dk}{2\pi} \ln(Z_{n,k}(R, \epsilon_W, \epsilon_M, \delta)), \tag{7}$$

where

$$Z_{n,k}(R, \epsilon_W, \epsilon_M, \delta) = \int d[X] \exp\left(-\frac{\beta}{2}\int_0^\infty \epsilon(r) \times \left[\left(\frac{dX}{dr}\right)^2 + \left(\frac{n^2}{r^2} + k^2\right)X^2\right]\right). \tag{8}$$

As we are only interested in the dependence of the free energy as a function of R we may work with the free energy normalized with respect to that of pure water with no tube. In

this model it is equivalent to subtracting off the free energy of a system where $\epsilon_W = \epsilon_M$. This regularized free energy is thus

$$F(R,\epsilon_W,\epsilon_M,\delta) = -k_B T L \sum_n \int \frac{dk}{2\pi} \ln\left(\frac{Z_{n,k}(R,\epsilon_W,\epsilon_M,\delta)}{Z_{n,k}(R,\epsilon_W,\epsilon_W,\delta)}\right). \tag{9}$$

In order to evaluate the individual kernels we make use of the Pauli van Vleck formula which is exact for quadratic actions. If $S[t_1,t_2,X]$ is an action quadratic in X, as is the case here, the Pauli van Vleck formula gives

$$\begin{aligned} K(t_1,t_2;X,Y) &= \int_{X(t_1)=X}^{X(t_2)=Y} d[X]\exp(-S[t_1,t_2,X]) \\ &= \left(-\frac{1}{2\pi}\frac{\partial^2 S[t_1,t_2,X_{cl}]}{\partial X\,\partial Y}\right)^{1/2} \\ &\quad \times \exp(-S[t_1,t_2,X_{cl}]), \end{aligned} \tag{10}$$

where X_{cl} is the classical path minimizing the action $S[t_1,t_2,X]$ given by $\delta S[t_1,t_2,X]/\delta X = 0$ and with the condition that the end points are fixed at X and Y. If the action S is quadratic then $S[t_1,t_2,X_{cl}]$ is a quadratic form in X and Y and it only remains to evaluate the resulting (ordinary) Gaussian integrals after obtaining the necessary expressions for $S[t_1,t_2,X_{cl}]$, one obtains [19]

$$\begin{aligned} \frac{F(R,\epsilon_W,\epsilon_M,\delta)}{Lk_BT} &= \frac{1}{R_1}g(\Lambda R_1,\Delta) + \frac{1}{R_2}g(\Lambda R_2,-\Delta) \\ &\quad + h(R_1,R_2,\Lambda,\Delta) + m(\Lambda,\Delta), \end{aligned} \tag{11}$$

where $\Lambda = \pi/a$ is the ultraviolet cutoff corresponding to the length scale a. In Eq. (11) we have

$$g(x,\Delta) = \frac{1}{2\pi}\sum_n \int_0^x du\, \ln[1 + \Delta u (I_n(u)K_n(u))'],$$

$$\begin{aligned} h(R_1,R_2,\Lambda,\Delta) = \frac{1}{2}\int_0^\Lambda \frac{dk}{\pi}\sum_n \ln[1 &+ \{4\Delta^2 k^2 R_1 R_2 I_n'(kR_1) I_n(kR_1) K_n'(kR_2) K_n(kR_2) \\ &/(1 + \Delta k R_1 [I_n(kR_1)K_n(kR_1)]') \\ &/(1 - \Delta k R_2 [I_n(kR_2)K_n(kR_2)]')\}], \end{aligned}$$

$$m(\Lambda,\Delta) = -\frac{1}{2}\int_0^\Lambda \frac{dk}{\pi}\sum_n \ln(1-\Delta^2), \tag{12}$$

where I_n and K_n are the modified Bessel functions [21]. The contribution $Lk_BTg(\Lambda R,\Delta)/R$ is the free energy of an isolated cylinder of length L, radius R and dielectric constant ϵ_M in a medium of dielectric constant ϵ_W. Thus the first two terms in Eq. (11) are the respective separate contributions of the inner and outer cylindrical regions that form the layer of thickness $\delta = R_2 - R_1$; the term $Lk_BTh(R_1,R_2,\Lambda,\Delta)$ is the contribution from the interaction between the cylinders. The function $g(x,\Delta)$ diverges as $x \to \infty$ and so this term in the free energy must be regulated by taking a nonzero cutoff a. Viewed as a Taylor expansion in Δ we find that the $O(\Delta)$ term of g is independent of R and thus in the free energy the contributions proportional to Δ cancel. This to be expected on physical grounds since by examining the limit of a diffuse system one can see that any term proportional to Δ must be a self-energy term [19]. The term of order Δ^2 can be evaluated to be

$$g(x,\Delta) = -\frac{1}{256}\Delta^2[6\log(x) + 30\log 2 + 6\gamma - 11] + O(\Delta^4). \tag{13}$$

This term is the leading term in the diffuse limit and the derivation uses Bessel function summation theorems exploited in [18]. The same form for the high temperature expansion for a solid dielectric cylinder was obtained in [17].

The function h is finite in this same limit and the term m, though divergent, is independent of R and cancels when the free energy of the bulk in the reservoir is subtracted. The $O(\Delta^2)$ contribution to $h(R_1,R_2,\Lambda,\Delta)$ is given by

$$\begin{aligned} &h(R-\delta/2, R+\delta/2, \Lambda, \Delta) \\ &\quad = \frac{3}{64}\frac{\Delta^2}{R}\frac{1-y^2}{y^2}\int_0^\infty dz \frac{y^2 z^4 - 1}{(1+z^2y^2)^{1/2}(1+z^2)^{5/2}}, \end{aligned} \tag{14}$$

where $y = \delta/2R$.

Taking account of the bulk reservoir and imposing overall conservation of surface area, the relevant free energy is that of the tube less the free energy of a flat membrane of the same area

$$F_c(R,\epsilon_W,\epsilon_M,\delta) = F(R,\epsilon_W,\epsilon_M,\delta) - 2\pi R L F_f, \tag{15}$$

where F_f is the free energy per unit area of a flat membrane, which is be given by

$$F_f = \frac{1}{2\pi L}\lim_{R\to\infty}\frac{1}{R}F(R,\epsilon_W,\epsilon_M,\delta), = -\frac{k_BT}{16\pi\delta^2}\sum_{m=1}^\infty \frac{\Delta^{2m}}{m^3} \tag{16}$$

and can be computed directly in a planar geometry by a variety of methods [15], including the path integral technique used here [20]. The contribution to F in this limit arises only from the functions h and m in Eq. (11) and the latter cancels identically. After subtraction, the dominant contribution, $h_C(R,y,\Lambda,\Delta)$, from h is the leading $1/R$ term, and we find to $O(\Delta^2)$:

$$h_C(R,y,\Lambda,\Delta) = \frac{3}{64}\frac{\Delta^2}{R}[\log(y) + 2\log 2 - 1/2]. \tag{17}$$

Putting our results together we find that κ_c, as defined by Eq. (2), is given by

$$\kappa_c = \frac{\Delta^2}{64}\left[3\log\left(\frac{\pi\delta}{a}\right) + 6\log 2 + 3\gamma - 4\right] + \Delta^4 B(\Delta^2), \tag{18}$$

where the constant inside the bracket is evaluated to be 0.02954… . An important point here is the exact cancellation of the $\ln(R)$ terms coming from g and h, giving a leading order behavior of $F_c \sim 1/R$. The function $B(\Delta^2)$ receives

TABLE I. For various values of Δ and δ/a we compare the prediction of Eq. (18) with numerical integration and deduce a numerical value for $B(\Delta^2)$. Owing to small systematic errors in the numerical calculation of the Bessel functions there is a negligible discrepancy for very small Δ but $B(\Delta^2)$ is seen to be a constant function from evaluations at larger Δ. We see that the result for F_c from Eq. (18) is in very good agreement with the full calculation. Various values of δ and a were used but typically $\delta=1$–10 nm.

Δ	δ/a	$O(\Delta^2)$ coeff. of $1/R$ from Eq. (18)	Coeff. of $1/R$ from numerics	$B(\Delta^2)$
78/82	10^3	-0.342	-0.443	0.123
78/82	10^2	-0.244	-0.346	0.123
0.6	10^3	-0.1361	-0.1520	0.123
0.6	10^2	-0.0972	-0.0162	0.123
0.2	10^3	-0.0151	-0.0162	
0.6	10^3	-0.0038	-0.0040	

contributions from both the g and h terms in Eq. (12) with $B(0)\neq 0$. Note that there are no odd terms in Δ in the leading $1/R$ behavior of F_c as, to leading order, one may set $\delta/R=0$ in the leading order behavior of g and in the denominator of the second term in the logarithm of the integral defining h. This is a consistent parametrization whilst $\delta \gg a$. The limit $\delta\to 0$ must be taken carefully and when $\delta < a$ the separation of F in Eq. (12) into contributions from functions g and h is not useful since h develops the compensating ultraviolet divergence to that in g and we find $\lim_{\delta\to 0}F_c=0$, as expected; in essence, the larger of δ and a acts as the ultraviolet cutoff on the integral defining h. We note that the dependence of κ_c on the membrane thickness δ is considerably different from that predicted for the mechanical bending energy, which is [2,22] $\kappa_b\sim\delta^2$ and is verified experimentally [22] if an offset of the measured lipid layer thickness δ is used. Of course κ_b as measured experimentally should be $\kappa_b+\kappa_c$ and the form predicted here for κ_c is compatible with the qualitative behavior seen in measurements [22].

In Table. I, for various values of Δ and δ/a, we compare the prediction of Eq. (18) with the result of numerical integration and deduce a numerical value for $B(\Delta^2)$. Owing to small systematic errors in the numerical calculation of the Bessel functions there is a tiny discrepancy for very small Δ but $B(\Delta^2)$ is seen to be a constant function from evaluations at larger Δ and we see that $B(0)$ is plausibly $1/8$.

The physical value of the ultraviolet cutoff length can only be determined phenomenologically. This is because the model is an effective field theory in which the dynamics of the molecular electric dipoles is described by the dielectric constant which is a static long-range parameter. The field modes with large-k and n probe the static short distance properties of the model and so a more refined field theory is needed for these scales. It is unclear whether the molecular nature of the lipid has an effect on the ultraviolet cutoff but it would seem most likely that the effective value of ϵ_W at short scales (i.e., the microscopic details of water) is dominant in this calculation.

From Table I we see that for a lipid bilayer tube in water with $\delta=10$ nm and $a=0.1$ nm we find $\kappa_c=0.346$. If we were to include the contributions from the modes with non-zero Matsubara frequencies, a calculation in progress, we can expect at most a factor of two or so enhancement based on past experience of similar calculations [15], and so $\kappa_c\sim 1$ is a likely largest value. These magnitudes are at the lowest end of those for κ_b for known lipid bilayers in water [2,3]. However, Würger [3] calculates κ_b for surfactant films, analyzing the role of hydrophobic tails, as a function of the tail length and the area per molecule, and finds a wide range of values for κ_b (again $\kappa_b=\pi\kappa_b'$, with κ_b' from Ref. [3]) including values small enough, corresponding to soft interfaces, to be balanced by our result. Thus it is conceivable that there can be small tubes formed from very soft membranes in water for which the bending forces tending to expand the radius are compensated by the Casimir attraction, and the tube is stabilized by subleading $O(1/R^2)$ forces.

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