Phospholipid membranes repulsion at \( nm \)-distances explained within a continuous water model.

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We apply a recently developed phenomenological theory of polar liquids to calculate the repulsive pressure between two hydrophilic membranes at \( nm \)-distances. We find that the repulsion does show up in the model and the solution to the problem fits the published experimental data well qualitatively and even quantitatively. Moreover, we find that the repulsion is practically independent of the temperature, and thus puts some extra weight in favor of the so-called hydration over entropic hypothesis for the membranes interactions explanation. The calculation is a good “proof of concept” example a sufficiently sophisticated continuous water model application to a non-trivial interaction on \( nm \)-size objects in water arising from long-range correlations between the water molecules.

The solvent induced forces play an important role in Nature, key nano- and bio-technological applications, drive various self-assembly phenomena in cells and membranes [1], vesicle-membrane, and -synapse fusion [2, 3], protein folding [4]. Understanding of these phenomena is crucial in a number of practically important applications such as drug design, drug transport optimization, and the design of nano-particles drug transport and delivery systems [5].

One of the most conceptually simple while still an important and an easily experimentally observable example of such interactions is provided by the short range repulsion between phospholipid membranes, originally discussed in [6, 7]. Since the original discovery there has been a lot of efforts to understand the nature of the repulsive forces, as described in [7] and the refs. therein. Most of the time the interactions are analyzed within some kind of a two-body approximation in such a way that the total water mediated pressure between the two parallel lipid membranes is represented as a the sum of the two components: the direct pressure, arising from the direct interactions between the opposing membranes, and the hydration component, associated with the interaction of the membranes with the intervening water molecules [8].

Since the membranes are hydrophilic, the exclusion of the water leads to the energy loss, and hence on the molecular level the hydration pressure can be associated with the orientation polarization of water near the membrane surfaces [9, 10, 11]. An alternative approach summarized in [12] suggests the dominant role the water molecules ordering next to the surfaces and thus emphasizes the water entropy contribution to the free energy of the system. None of the effects are easy to grasp within any kind of a simple continuous water model, which are normally designed to reproduce the effects of continuous electrostatics in polar solutes, e.g. [13, 14, 15]. The reason is that due to long-range electrostatic interactions between the molecular dipoles the correlations in water are collective and survive at very long distances up to 1\( nm \). Therefore the effects of the ordering may lead to cluster formations and phase transitions phenomena [16, 17, 18, 19, 20, 21, 22], appearance of strong and sufficiently long range interactions of non-electrostatics nature [4, 23, 24].

The alternative to the continuous solvation models is Molecular Dynamics (MD) [24] of the body of interest immersed in a tank of water molecules in a realistic force field or even within quantum mechanical settings. Though such an approach may in principle provide ultimately accurate predictions, the calculations are time consuming and pose a number of challenges stemming, e.g. from long relaxation times of water clusters. One possible way to bridge the “simulation gap” is to develop advanced of continuous solvation models, such as [22, 23, 26, 27] and test its limits to make sure the models include realistic and important interactions. In what follows we take the polar liquid phenomenology and calculate the repulsive pressure between two hydrophilic membranes at \( nm \)-distances. We find that the repulsion does show up in the continuous model and that the solution to the problem fits the available published experimental data well both qualitatively and quantitatively. The pressure turns out to be practically independent of the temperature, which strongly supports the hydration nature of the water-assisted interactions between the membranes. The interaction appears to be generic, should arise between any hydrophilic bodies and vanishes as soon as the objects in question are separated farther than \( R_D \sim 1nm \), the characteristic polarized water domain size identified in the model.

The continuous polar liquid model introduced in [23] is capable of describing both the short- and the long-range features of a polar liquid in a single theoretical framework. Originally it was applied to calculate...
water-assisted interactions of macroscopic bodies with hydrophobic interfaces of various shapes and charges. It was shown that the competition between the short range (hydrogen bonding) and the long-range dipole-dipole interactions of the solvent molecules leads to appearance of strong, long range and orientationally dependent interactions between the objects, which, in principle, can be responsible for various self-assembly processes in biological systems. Within the suggested model a polar liquid itself is characterized by a complicated fluctuating thermal state, ordered at sufficiently short scales within a single domain, and completely disordered at larger distances. This physical picture has far reaching consequences, especially at solvent-solute interfaces, where the ferroelectric film of solvent molecules may be formed [28]. In accordance with the MD simulations [20, 21] the vector model predicts the BKT-like topological phase transitions at solvent-solute interfaces [29, 30]. Most of our earlier research was confined to interactions of hydrophobic bodies. In this Paper we try the model and provide the solution to the phospholipid membranes repulsion problem, which is a hydrophobic bodies interaction example.

The model description of a polar liquid, e.g. water, proceeds as follows. Each of the molecules within the liquid (j = 1, 2, . . . , N) is assumed have a vector property: the static electric dipole moment d j = d 0 S j, where d 0 is its magnitude, and S j is the unit vector in expressing the orientation of the molecule. Having this in mind it is possible to develop a vector field theory in which the liquid is described by a local mean value of the molecular polarization vector s(r) = (d)/d 0, where (d) ≡ (d j) stands for the statistical average of molecular dipole moment d over a small but sufficiently large volume of the liquid containing macroscopic number of molecules. Accordingly, the model expression for the free energy functional is given by:

$$G[s(r)] = P_0^2 \int dV \sum_{\alpha,\beta=x,y,z} \partial s_{\alpha} \partial s_{\beta} +$$

$$+ P_0^2 \int dVV(s^2) + \int dV \frac{1}{8\pi} E_P^2 - \int dV \mathbf{P}(r) \mathbf{E}_e(r).$$  (1)

The polarization vector of the liquid, \(\mathbf{P} = P_0 s\) where \(P_0 = n_0 d 0\), \(n_0\) is the molecular density, and \(\mathbf{E}_e = -\nabla \varphi_c\) is the external electric field in the absence of the liquid. Similarly, \(\mathbf{E}_P = -\nabla \varphi_p\) is the polarization electric field produced by the polarization charges within the liquid characterized by the polarization charge density \(p_P = -\text{div} \mathbf{P}\). The polarization potential \(\varphi_p\) should be found from the Poisson equation \(\nabla^2 \varphi_p = -4\pi p_P\).

The Oseen’s like term in Eq. (1) provides a model description of the hydrogen bonds network deformation energy in the long wavelength limit. The value of the phenomenological parameter \(C \approx 10^{-15} \text{cm}^2\), as well as the specific form and characteristic values of the function \(V(s^2)\) describing the elastic energy of water polarization should be extracted from the experimental properties of the liquid as described in [23]. Typically the liquid polarization is small, \(s \ll 1\), and “the equation of state” function takes the usual Ginzburg-Landau form

$$V(s^2) \approx A \frac{s^2}{2} + Bs^4,$$  (2)

where \(A = 4\pi/(\varepsilon - 1) \approx 0.16, \varepsilon \approx 80\) is the (large) dielectric constant, and \(B \sim 1\). The parameter \(A\) characterizes the long-range interactions of the molecular dipoles, depending strongly on the temperature: \(A \propto (T - T_c)/T_c\) [22] and vanishes at \(T = T_c \approx 288 K\) roughly at the \(\lambda\)-transition point in supercooled water [16, 17, 18, 19]. On the contrary, the parameter \(B\) depends on the short-range physics and thus is practically independent of the temperature. The last two terms in Eq. (1) describe the long-range dipole-dipole interaction of molecules, and interaction energy of the liquid in the external electric field, produced by charges that reside inside or outside the liquid.

The cell membrane consists primarily of a thin layer of amphipathic phospholipids which spontaneously arrange so that the hydrophobic “tail” regions are shielded from the surrounding polar fluid, causing the more hydrophilic “head” regions to associate with the cytoplastic and extracellular faces of the resulting bilayer, as shown on Fig. (1). Typically the width of the lipid bilayer is up to 4 nm. Consider two membranes of the cross section area \(S\) separated by the water filled layer of width \(h\) from each other. Typically the membrane surfaces are comprised by molecular groups with no net charge, though with a considerable dipole moment. The lipid “heads” are hydrophilic, therefore water molecular dipoles arrange themselves in the direction of the lipid wall: \(s(\pm h/2) = \pm s_0, s_0 \sim 1\) (of course, \(0 < s_0 < 1\): the value of \(s_0\) depends on the dipole moments of lipid polar groups).

Since there is no external electric field in our system, \(\mathbf{E}_P = -4\pi \mathbf{P} = -4\pi P_0 s\) and the expression for the free

\[\text{Figure 1: Typical polarization of the water molecules between lipid membranes shown in green. Both the charges of the lipid polar groups and the polarization of the water molecules are schematically represented by the corresponding charge symbols.}\]
energy of the liquid reads

\[ G = SP_0^2 \int dz \left( \frac{C}{2} \left( \frac{ds}{dz} \right)^2 + U(s) \right), \tag{3} \]

where \( s = s_r \) is the only non-vanishing component of the average water molecules polarization and \( U(s) = V(s^2) + 2\pi s^2 \).

Variational minimization of the free energy \( \frac{\partial G}{\partial \delta s} = 0 \), with respect to the variations of the function \( s(r) \), gives the equation

\[ -\frac{C}{2} \frac{d^2 s}{dz^2} + \left( V'(s^2) + 2\pi \right) s = 0 \tag{4} \]

similar to the equation of motion of a particle of the mass \( C \) at the position \( s \) moving in one-dimensional quasi-potential \( U(s) \). Accordingly, the derivative \( ds/dz \) plays the role of the particle velocity and the variable \( z \) serves as the time. The solution is a well known 1d soliton

\[ \frac{ds}{dz} = \pm \sqrt{\frac{2}{C} \left( \epsilon + V(s^2) + 2\pi s^2 \right)}, \]

where the exact value of the “energy” is a constant to be found by matching the boundary conditions at the membrane surfaces \( s(\pm h/2) = s_0 \):

\[ \frac{h}{\sqrt{2C}} = \frac{\int_0^{s_0} ds}{\sqrt{\epsilon + U(s^2)}}. \tag{5} \]

The function \( \epsilon(h) \) simplifies in the large \( h \) limit: the main contribution to the integral comes the small \( s \) region where the integral diverges logarithmically, the function \( V(s^2) \) can be neglected altogether, \( U(s^2) \approx 2\pi s^2 \), and therefore

\[ \epsilon \approx 2\pi s_0^2 \exp(-h/\lambda), \tag{6} \]

where \( \lambda = \sqrt{C/4\pi} \ll h \) is the characteristic size of the soliton, \( \lambda \sim R_D \approx 0.15 \pm 0.25nm \), the characteristic water orientation domain size, first introduced in [22][23].

Eq. (8) can be used to transform the energy of the liquid layer to

\[ \frac{G}{SP_0^2} = 2C \int_0^{h/2} dz \left( \frac{ds}{dz} \right)^2 - \epsilon h = \]

\[ = \sqrt{2C} \int_0^{s_0} ds \sqrt{\epsilon + U(s^2)} - \epsilon h. \]

According to the standard definition the pressure, \( P = -S^{-1} \partial G/\partial h \), can be expressed as:

\[ P = -\sqrt{2C}P_0^2 \frac{dc}{dh} \int_0^{s_0} ds \sqrt{\epsilon + U(s^2)} + P_0^2(\epsilon + h \frac{dc}{dh}). \]

The integral in the r.h.s. can be evaluated using Eq. (6) and the asymptotic expression (6) for \( \epsilon(h) \), so that the pressure is given by

\[ P = P_1 \exp(-h/\lambda), \]

where the prefactor \( P_1 = 2\pi P_0^2 s_0^2 \). This is exactly the dependence observed in experiments [3]. The pressure is indeed positive, the membranes do repel each other, and the forces vanish exponentially quickely as soon as the membranes depart further apart than \( h \sim \lambda \).

The physical reason of repulsion is the formation of polarization charges in the middle of the water layer due to inhomogeneous water molecules alignment. The polarization charges are all of the same sign (positive for the example presented on Fig.1 and thus generate the electrostatic repulsion, which together with the hydrogen bonds network deformation energy is ultimately responsible for the repulsion of the membranes. For the maximum possible surface polarization, \( s_0 = 1 \), which corresponds to the large dipole moments of the lipid polar groups limit, we can estimate the maximum value of the prefactor: \( (P_1)^{\text{max}} \approx 3 \cdot 10^{10} \text{dyne/cm}^2 \). The value of the pressure obtained in this way agrees well with the results of the measurements reported for different types of the membranes: \( 5 \cdot 10^9 < (P_1)^{\text{exp}} < 5 \cdot 10^{10} \text{dyne/cm}^2 \) [5].

Few concluding remarks should be added here. First, the repulsion pressure depends essentially only on \( s_0 = \langle S_z \rangle \), \( z \)-component of unit vector \( S \) directed along the dipole moment of water molecule on the membrane interface \( \Gamma \). This quantity decreases slightly as the temperature rises, whereas any entropy-related effect should lead to the sharp increase of \( P \), as explained in [5].

Second, the model defined by Eq. (1) is very similar to the non-linear screening model introduced in [26][27] and was originally applied for the calculation of the electrostatic forces in water. The non-linear screening model does not contain the Oseen term responsible for the short-range ordering of the water molecules. The scale \( \lambda \) is the characteristic size of the water molecules domain (cluster) depends on \( C \) and thus can only appear in the complete model [1]. This makes our model apparently the minimal continuous model capable of predicting repulsion of hydrophilic membranes. We note that the separate problem interactions of hydrophobic objects has been also extensively studied within another class of two-scale continuous water models [24][31][32]. We leave the research on possible convergence of the approaches and the relation between the scales of the models for a future publication.

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