Comment on: "Dynamics of Phospholipid Membranes beyond Thermal Undulations"

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ABSTRACT: I introduce an alternative interpretation for the short-time anomalous diffusion observed by Gupta et al. using neutron spin echo. The interpretation involves the Brochard-Lennon "red blood cell" mode to describe membrane thickness fluctuations, and yields an anomalous diffusion exponent 1/3 that is consistent with the experimental results.

The result of Gupta et al. of a distinct exponent, ν ≈ 0.26 ± 0.03, governing the (very short time) stretched exponential relaxation of the intermediate scattering function, and the transverse anomalous mean square displacement (MSD) of a membrane segment, is both intriguing and fascinating. It has been qualitatively interpreted by the authors as a molecular trapping-like effect that leads to powerlaw tails of escape waiting time distribution, as described by the continuous time random walk (CTRW) formalism. Their explanation, based on molecular dynamics simulations, is associated with the two-dimensional (2D) motion of lipids that is linked to local membrane density fluctuations. Here I would like to offer an alternative explanation.

There have recently been suggestions that membrane thickness fluctuations are detectable by neutron spin echo (NSE). Nagao and co-workers used a phenomenological expression for the relaxation rate, based on an elastic solid-like response to thickness deformations, which is added to the conventional Zilman-Granek (ZG) expression. Here I assume that for thickness deformations of wavelengths shorter than, or comparable to, the membrane half-thickness, a liquid-like response of the phospholipid tails is possible, within a mode similar to the Brochard-Lennon (BL) "red blood cell" mode. This mode corresponds to a peristaltic-like deformation of the membrane thickness with a distinct wavenumber k, and its relaxation rate ω scales as ~ k^6. The latter is a consequence of the bending energy of each of the two leaflets, which contributes ~ κ_m k^4 where κ_m is the bending modulus of a monolayer leaflet, and the material-conservative hydrodynamic flow of the hydrocarbon tails that contributes a factor of ~ k^2. The resulting relaxation rate takes the form ω = (κ_m d^3 / 24 η_{eff}) k^6, where d is the bilayer thickness, η_{eff} is the effective viscosity of the hydrocarbon tails, and the solvent viscosity has been neglected. Since obviously the hydrocarbon tails, being chemically bonded to their head-groups, are not truly free to flow independently of the head-groups, this effective hydrodynamic picture can only be relevant to peristaltic-like deformations of wavelengths shorter than the bilayer half-thickness. For such short wavelengths, by shearing the tails, they can be squeezed away from the narrow (bottleneck-like) regions of the deformation to fill space in the dilated regions. Notably, using continuous hydrodynamic approach is always a crude approximation at these molecular length-scales, nevertheless it has been proved useful time and again.
With this in mind, it is easy to deduce the time-dependent MSD of the thickness. Consider first the scaling hypothesis

\[ \langle (d(t) - d(0))^2 \rangle = \frac{k_B T}{\kappa_m} L^2 G(t/\tau_L) \quad (1) \]

where \( L \) is a membrane patch linear size, and \( \tau_L = \omega^{-1}(k = \frac{\pi}{L}) \approx \frac{\eta_{\text{eff}}}{\kappa_m d^2} t^6 \) is the longest bending relaxation time of this patch. Demanding that, at times \( t \ll \tau_L \), \( \langle \delta d(t)^2 \rangle \) become independent of \( L \), implies \( G(x) \sim x^{1/3} \) for \( x \ll 1 \), and so

\[ \langle \delta d(t)^2 \rangle \propto C \frac{k_B T d}{\kappa_m^{1/3} \eta_{\text{eff}}^{1/3}} t^{1/3}, \quad (2) \]

where \( C \) is a numerical prefactor, consistent with a power-spectrum \( \sim \omega^{-4/3} \) predicted by BL\(^5\). A more complete calculation involving an integral expression allows to evaluate the numerical prefactor, \( C \approx 0.149 \). As a consequence, the dynamic structure factor at large wavenumbers \( q \) decays as a stretched exponential with an exponent \( 1/3 \), \( S(q, t) \sim e^{-\left(\frac{t}{\tau_L}\right)^{1/3}} \), and a decay rate (arising from the single leaflet relative MSD, \( \langle \delta u(t)^2 \rangle = \frac{\langle \delta d(t)^2 \rangle}{2} \))

\[ \Gamma_q \approx 5.2 \times 10^{-5} \left( \frac{k_B T}{\kappa_m} \right)^{3/2} \frac{d}{\eta_{\text{eff}}} q^{-6} \quad (3) \]

The success to predict the anomalous diffusion (and stretching) exponent \( \nu = 1/3 \) is not sufficient to confirm this alternative explanation. The data of Gupta et al.\(^1\) for DOPC, for example, corresponds to an effective viscosity that is roughly \( \eta_{\text{eff}} \sim 1 \text{ mPa s} \), which is a relatively low viscosity but perhaps still reasonable given the data and parameter uncertainties. This effective viscosity has been deduced by taking, in Eq. (2), \( \kappa_m \approx 10 k_B T \), estimated as half of the long wavelength bilayer bending modulus, \( d \approx 3.6 \text{ nm} \), \( t \approx 3 \text{ ns} \), and \( \langle \delta d(t)^2 \rangle \approx 27 \text{ A}^2 \); using \( \kappa_m \approx 5 k_B T \), for instance, yields a larger value, \( \eta_{\text{eff}} \approx 4 \text{ mPa s} \). (The authors report on the 3D MSD \( \langle \delta r(t)^2 \rangle \), presumably deduced from \( S(q, t) \) following the relation \( S(q, t) = e^{-q^2 \langle \delta r(t)^2 \rangle / 6} \) for the case of independent particles motion, and thus I have used the relation \( \langle \delta r(t)^2 \rangle \approx 3 \langle \delta u(t)^2 \rangle = 3 \langle \delta d(t)^2 \rangle / 2 \) with \( \langle \delta r(t)^2 \rangle \approx 40 \text{ A}^2 \) for \( t \approx 3 \text{ ns} \) from the supporting information of Gupta et al.\(^1\), Fig. S2.) The dependence of the MSD on the phospholipid identity could perhaps be checked given knowledge of \( d \) and \( \kappa_m \) for each lipid, although this comparison might be hampered if \( \eta_{\text{eff}} \) is also sensitive to the lipid identity.

Despite the apparent consistency, the above interpretation implicitly assumes Gaussian statistics, thus contradicting the non-Gaussian behavior of \( \delta d(t) \) found by Gupta et al. during the early time regime where the small exponent \( \nu \approx 0.26 \pm 0.03 \) is measured. (The Gaussian statistics is recovered only during the time regime where the exponent \( \nu = 0.66 \) is observed, consistent with the ZG model.) This fundamental contradiction calls for further investigation of the non-Gaussian nature of the fluctuations. Could it be a consequence of the NSE technique, associated with these extremely short times, and not an inherent property of the system? Or, is there another process – associated with a CTRW powerlaw tail – that is similar to the suggestion of the authors but one that involves bilayer deformations and not 2D lipid diffusion? Swelling the bilayer with a suitable oil could be a useful way to distinguish between the different mechanisms due to the sensitivity of Eqs. (2) and (3) to \( d \).
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