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Sudipta Gupta
Louisiana State University

Judith U. De Mel
Louisiana State University

Gerald J. Schneider
Louisiana State University

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Comment

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Reply to "Comment on 'Dynamics of Phospholipid Membranes beyond Thermal Undulation'"

Sudipta Gupta,*,† Judith U. De Mel,† and Gerald J. Schneider*,†,‡

†Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803, United States

‡Department of Physics & Astronomy, Louisiana State University, Baton Rouge, Louisiana 70803, United States

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Very recently, Granek[1] introduced an alternative interpretation of the short time behavior of the intermediate scattering function, $S(Q, t)$, determined by neutron spin echo (NSE) spectroscopy experiments by Gupta et al.[2] The interpretation is based on the Brochard−Lennon (BL) "red blood cell" mode.[3] The Comment assumes that only peristaltic-like deformation of the wavelength comparable to membrane half-thickness determines the intermediate scattering function at low Fourier time, which leads to

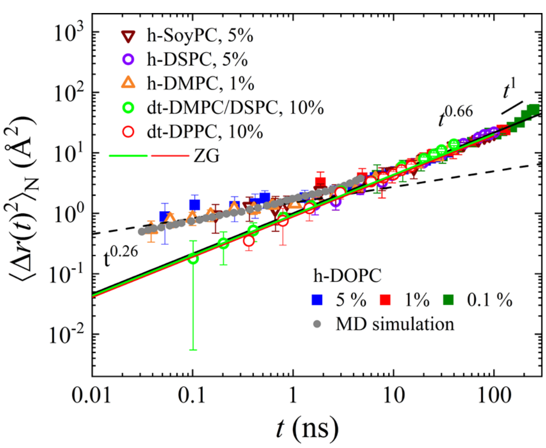

Figure 1. Normalized mean square displacement, $\langle \Delta r(t)^2 \rangle_N$, vs Fourier time, t, for 0.1%, 1%, and 5% h-DOPC, 10% h-DSPC, 1% h-DMPC, and 5% h-SoyPC samples, adopted from literatures.[2,8−10] The data for the 10% dt-DMPC/DSPC mixture and 10% dt-DPPC are calculated using $S(Q, t)/S(Q)$ from the literature.[8,9] The dashed lines represent the experimental power-law dependence, with filled circles from MD simulation for h-POPE.[10] The solid lines represent the calculation for the combination of ZG and thickness fluctuation for dt-DPPC (black) and dt-DMPC/DSPC (green), as explained in the text. Figure adopted from refs 2 and 4.

$$S(Q, t) \propto \exp(-(\Gamma_Q t)^{1/3}) \quad (1)$$

with $\Gamma_Q \simeq 5.2 \times 10^{-5} \frac{(k_B T)^3 d^3}{\kappa_m^2 \eta_{eff}} Q^6$. Despite the simplifications in this hydrodynamic approach, the exponent of 1/3 is very similar to 0.26 observed by Gupta et al.[2]

Granek emphasizes that his approach involves a Gaussian assumption, which contradicts the experiments. We agree with Granek's doubts and confirm that the most recent experimental results clearly invalidate this alternative explanation by eq 1.[4]

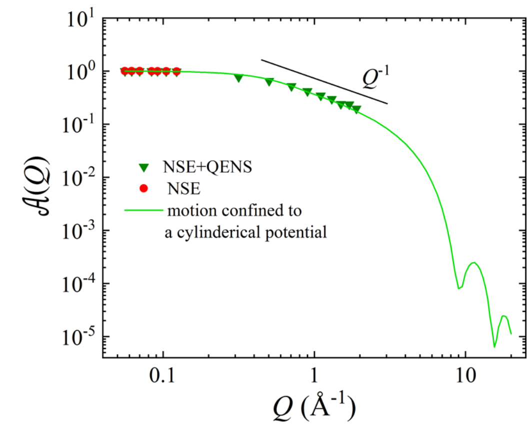

Figure 2. $A(Q)$ for h-DMPC obtained from NSE and QENS studies over a broad Q-range on protonated (h) DMPC.[4] Best description can be obtained by a motion confined to a cylindrical potential. Figure adopted from ref 4.

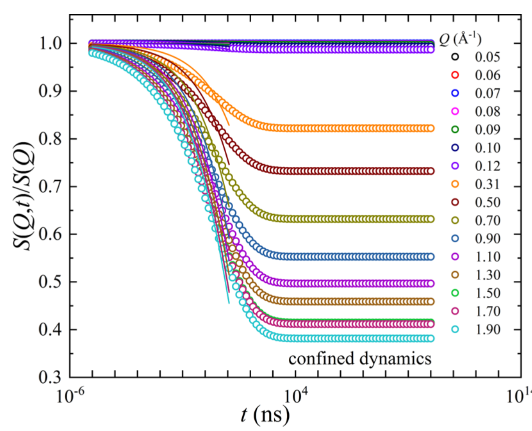

Figure 3. Normalized dynamic structure factor calculated for only the confined motion that is responsible for the observed dependency of the mean squared displacement (MSD).[4] Solid lines represent the fits following eq 1, with the relaxation rate, $\Gamma_Q \propto Q^6$. The Q-values are choosen based on the available data from NSE and QENS experiments.

First, we expand on the non-Gaussian nature. The explanation of Gupta et al. is based on the calculation of the mean squared displacement (MSD), $\Delta r(t)^2$, from[2,4−6]

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$$\frac{S(Q,t)}{S(Q)} = A \exp\left[-\frac{Q^2\langle\Delta r(t)^2\rangle}{6} + \frac{Q^4\alpha_2(t)}{72}\langle\Delta r(t)^2\rangle^2\right] \quad (2)$$

Here the second order expansion in Q^2 includes $\alpha_2(t) = \frac{d}{d+2}\frac{\langle\Delta r(t)^4\rangle}{\langle\Delta r(t)^2\rangle^2} - 1 > 0$, which indicates non-Gaussianity.

Such behavior could be caused by a single relaxation or the superimposition of two processes and deserves further attention. First, we exclude the argumentation that it could be an artifact from NSE. The NSE data displayed in Gupta et al.[2] are from three different NSE spectrometers, located at Spallation Neutron Source (SNS) at Oak Ridge National Laboratory (ORNL), USA; National Institute of Standards and Technology (NIST) Center for Neutron Research (NCNR), USA; and the Institut Laue-Langevin, France. The data from all these experiments point to a very universal behavior, which cannot be described by the traditional ZG model. We emphasize that these observations appear to be rather universal and apply at least to DOPC, DMPC, DSPC, DPPC, and SoyPC.[2,4] Further support comes from recent results by quasielastic neutron scattering (QENS) experiments, from the BASIS spectrometer at SNS-ORNL.[4] We summarize that several different NSE and QENS intruments independently verify a relaxation process beyond the traditional ZG model.[2,7]

Furthermore, we can compare the MSD of fully protonated lipids with liposomes in which the tails were contrast matched (dt-lipid) with the solvent.[4] As Figure 1 illustrates, if the tail motion is not visible for the NSE experiment, the short time relaxation behavior is not observed. Instead, it follows that $\langle\Delta r(t)^2\rangle_N \propto t^{0.66}$, which is expected from the membrane thickness fluctuations.[8,9] For the sake of a better visualization we have used the modified ZG expression including the thickness fluctuation model presented by Nagao et al. to calculate the MSD for dt-DMPC/DSPC and dt-DPPC.[8,9] More detailed explanations can be found in our recent work.[4]

The absence of the $t^{0.26}$-region experimentally verifies the fact that the observed short time behavior is related to the lipid-tail motion. The assumptions in the BL-mode require the existence in these samples as well. We emphasize that this excludes the explanation of the short time behavior by the BL-mode. We also note that the $t^{0.26}$-region is inherently coupled to the bilayer, which is additionally supported by the fact that it is not observed for microemulsions, like for those decorated with short polymers.[2]

In a next step, we need to explore the process underlying the observation of this short time behavior. In brief, the short time behavior can be described by the dynamics of a lipid-tail confined to a cylindrical potential. As illustrated by Figure 2, we can combine NSE and QENS data to follow the process over multiple orders of magnitude in length and time scales.[4] This elucidates the fact that the trapped motion corresponds to a highly confined relaxation of the fatty acid tails in the very crowded environment within the membrane bilayer and as a consequence causes the deviations from a Gaussian assumption. More details can be found in the literature.[2,4]

Independently of our interpretation of the experimental results, our description by a model-function allows extraction of the short time behavior. This result can be compared with eq 1. As Figure 3 illustrates, the assumption by Granek completely fails to describe the experimental results.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: g.sudipta26@gmail.com.
*E-mail: gjschneider@lsu.edu.

ORCID

Sudipta Gupta: 0000-0001-6642-3776
Gerald J. Schneider: 0000-0002-5577-9328

Notes

The authors declare no competing financial interest.

Abbreviations. DMPC: 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine; DSPC: 1,2-distearoyl-*sn*-glycero-3-phosphocholine; DPPC: 1,2-dipalmitoyl-*sn*-glycero-phosphocholine; DOPC: 1,2-dioleoyl-*sn*-glycero-phosphocholine; SoyPC: L-α-phosphatidylcholine; POPE: palmitoyl-oleoyl-phosphatidylethanolamine; dt: deuterated tail; h: protonated.

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