Solvent hydrodynamics enhances the collective diffusion of membrane lipids

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The collective motion of membrane lipids over hundred of nanometers and nanoseconds is essential for the formation of submicron complexes of lipids and proteins in the cell membrane. These dynamics are difficult to access experimentally and are currently poorly understood. One of the conclusions of the celebrated Saffman-Debrück (SD) theory is that lipid disturbances smaller than the Saffman length (microns) are not affected by the hydrodynamics of the embedding solvent. Using molecular dynamics and coarse-grained models with implicit hydrodynamics we show that this is not true. Hydrodynamic interactions between the membrane and the solvent strongly enhance the short-time collective diffusion of lipids at all scales. The momentum transferred between the membrane and the solvent in normal direction (not considered by the SD theory) propagates tangentially over the membrane inducing long-ranged repulsive forces amongst lipids. As a consequence the lipid collective diffusion coefficient increases proportionally to the disturbance wavelength. We find quantitative agreement with the predicted anomalous diffusion in quasi-two-dimensional dynamics, observed in colloids confined to a plane but embedded in 3D solvent.

The study of lipids, as building units of the cell membranes, has been intensive since their discovery in 1925 [1]. While the membrane equilibrium structures are relatively well understood, the collective dynamics of lipids is still relatively unexplored [2–4]. The strong coherence between lipid displacements observed from few to hundred nanometers over less or about hundred of nanoseconds [2, 3, 5] is essential to the membrane fluidity and is crucial to biological functions such as the formation of nanometric pores [4], the kinetics of submicron complexes (lipid rafts) [5], protein transport, transduction or gating mechanisms [6]. This mesoscopic spatio-temporal scale is difficult to access experimentally [2, 3, 5, 7–10], being too large for neutron scattering or spin echo [10] but too fast and small for standard fluorescence labeling techniques [11]. At the nanometric border of this “mesoscale gap” [10] quasi-elastic neutron scattering (QENS) experiments [7, 12, 13] have recently measured two relaxation mechanisms: one compatible with a fast, purely diffusive lipid motion and a slower, ballistic mode, which was interpreted as nanometric currents of lipids propagating with velocities much smaller than the thermal value $(k_B T/m)^{1/2}$. Molecular simulations [2, 14] are consistent with this view, which implies that lipids diffuse in a coordinated, hydrodynamic-like, fashion instead by discrete “jumps” out from molecular cages. Coarse grained (CG) models with two-dimensional (2D) hydrodynamics find that the correlations between lipid displacements [2] span over more than 10 nm and microseconds [2, 5]. Correlations beyond 10 nm were also inferred by QENS experiments [3].

Since 1975, the elegant Saffman-Delbrück theory [15, 16] has been used to describe the interaction between the membrane and solvent hydrodynamics. Its great merit is to show that the solvent’s tangential friction slows down the collective motion of lipid flow patterns if their wave-length $\lambda$ is larger than a certain cut-off distance: the Saffman length $\lambda_S$. This length $\lambda_S = \eta_m / (2 \eta)$ (proportional to the ratio between the surface viscosity and the solvent viscosity) is typically in the micron scale. Therefore, it is currently thought that, at submicron scales, the momentum-exchanged with the solvent is negligible so lipid dynamics approximately conserves the in-plane momentum, as in 2D hydrodynamics. For these scales, all-atom molecular dynamics (MD) [17] are prohibitive, while continuum fluid dynamics [16] does not resolve lipid motions. Therefore, different CG models have been used to study collective motions in the mesoscale domain [2, 5, 18, 19]. Albeit, these works focused on momentum-conserving, 2D hydrodynamics.

In this Letter we use Martini-MD simulations [18] and CG models equipped with an immersed boundary description of the 3D-hydrodynamics [20] to show that the solvent hydrodynamics strongly enhances the collective diffusion of lipids at all scales, even below $\lambda_S$. Notably, the momentum exchanged with the solvent in the normal direction spreads over the membrane acting like a repulsive hydrodynamic force between lipids. As a consequence, the collective diffusion increases without bounds with the disturbance wavelength. This type of anomalous collective diffusion is in quantitative agreement with the quasi-2D hydrodynamics observed in colloids confined in a plane and surrounded by solvent [21], recently analyzed in several works [22–24]. In membranes, this phenomena introduces a so far unexplored intermediate dynamic regime which significantly enhances the collective diffusion at short times (over about 100ns) and affects a wide range of scales, from nanometers to microns.

Models with hydrodynamics. We solve the dynamics of membranes in periodic cubic boxes of sizes up to $L \approx 88$nm using three different computational techniques and two membrane models (more details in Sup-
FIG. 1: (a) Averaged velocity field evaluated from lipid displacements $\delta \mathbf{r}_2 = \mathbf{r}_2(\Delta t) - \mathbf{r}_2(0)$ with respect to a central tagged lipid at $\Delta t = 400$ ps. (b) and (c) are pictorial illustrations of the models taken from simulations. (b), MD corresponds to the MARTINI model for DPPC with explicit water [18] and BD and BDHI simulations (c) to the Cooke-Deserno model [25]. The arrows drawn in (c) sketches normal momentum from the solvent spreading over the membrane.

Both lipid models are depicted in Fig. 1. Simulations with greater resolution detail correspond to molecular dynamics (MD) using the Martini force-field [26] and solved by the GROMACS package [27, 28]. Following the Martini description [29], water molecules are explicitly resolved while the membrane is formed by Dipalmitoylphosphatidylcholine (DPPC) lipids. Simulations were performed at temperature $T = 310K$. The coarser membrane description, hereafter referred to as CG model, is based on the “dry membrane” model by Cooke and Deserno [25] which implements lateral lipid-lipid interactions to stabilize the bilayer without explicit water. The CG membrane matches the compressibility and dominant peak in the static structure factor of the MD (Martini) model (see SI). Two different dynamics were implemented in the GC simulations. On one hand, we used the standard pure Brownian dynamics (BD) method, whereby lipids random displacements are completely uncorrelated. The second approach is based on an implicit hydrodynamic solvent solved by the FLUAM package [30]. It basically consists on an immersed boundary description in fluctuating hydrodynamics [20, 31, 32]. Lipid beads are treated as immersed particles and exchange momentum with the solvent’s fluctuating momentum-field. We worked in the Stokesian limit [20] where momentum propagates instantaneously (no fluid-inertia). This description is equivalent to Brownian hydrodynamics with the Rotne-Prager-Yamakawa mobility and we shall refer these simulations as Brownian dynamics with hydrodynamic interactions, BDHI.

These three models (MD, BD and BDHI) treat momentum transfers in quite different ways. While the BD model provides a vanishing correlation between lipids displacements, BDHI conserves momentum and lead to strong in-plane correlations. In BDHI, any force acting on a lipid is transferred to the fluid and, like in the Saffman model [15, 16], the fluid-lipid coupling is determined by the no-slip constraint (see [31, 32]). The MD model also conserves total momentum but this is exclusively transferred by intermolecular collisions (either lipid-water or lipid-lipid interactions). A first comparison between models is shown in Fig. 1 by plotting the relative lipid-velocity field around a tagged lipid. As expected, the BD scheme shows no trace of correlations. But notably, despite their differences, MD and BDHI yield a remarkably similar vortical pattern of correlated motions spanning over more than 10 nm. It seems that momentum conservation is what really matters to match MD and BDHI models. At first glance, the flow pattern of Fig. 1 is similar to that found in prior DPD 2D-simulations [2, 5], however relevant differences shall be soon highlighted.

The lipid self diffusion offers quantitative comparison between models and experimental values. Figure 2 shows the lipid mean square displacement of the lipid’s head bead (see Fig. 1) projected in the plane, MSD$(t) = \langle (r_i^h(t) - r_i^h(0))^2 \rangle$ along with the self diffusion coefficient $D_s(t) = MSD/(4t)$. All models present three dynamic regimes, similar to those observed in membranes in the fluid-phase [10, 12]: a short-time diffusion is followed by a sub-diffusive regime which finally leads to a slower long-time diffusion regime. The intermediate sub-diffusive regime approximately extends from 0.01 ns to 10 ns and is characterized by MSD$(t) \sim t^\alpha$ with a sub-diffusive exponent $\alpha \approx 0.55$ quite similar in all models. Fig. 2
and plotted against indicate strong collective effects. A way to analyze these correlations is provided by the collective intermediate scattering function \( F_c(q,t) \) obtained from the time-evolution of the Fourier transform of the spatial correlations in lipids density,

\[
F_c(q,t) = \langle \rho(q,t) \rho(q^*,0) \rangle ,
\]

where \( q \) is a wavevector in the membrane plane and we assume that the system is isotropic in the plane, so that \( F_c(q,t) = F_c(q,t) \). Figure 3(a) shows exemplary results for \( F_c(q,t) \). We find that \( F_c(q,t) \) can be fitted using a two-relaxation model,

\[
\frac{F_c(q,t)}{S(q)} \approx A_1(q) \exp[-t/\tau_1] + A_2(q) \exp[-t/\tau_2],
\]

where \( S(q) = F_c(q,0) \) is the static structure factor. The relaxation times \( \tau_1^{-1} \equiv D_1(q)q^2 \) and \( \tau_2^{-1} \equiv D_2(q)q^2 \) introduce two effective diffusion coefficients \( (D_1 > D_2) \) related to short-time and long-time relaxation mechanisms. A similar two-relaxation model has been used in QENS experiments to fit \( F_c \) at \( q = 0.5 \text{Å}^{-1} \) and the scattering spectra (see Supporting Information of Ref. [7]). For \( q = 0.5 \text{Å}^{-1} \) Armstrong et al. find \( \tau_1 = 1/(D_1q^2) = 0.05 \text{ns} \) and \( \tau_2 = 1/(D_2q^2) = 0.9 \text{ns} \) which provide \( D_1 = 80 \text{Å}^2/\text{ns} \) and \( D_2 = 4.5 \text{Å}^2/\text{ns} \). At the equivalent wavenumber \( q\sigma \approx 4 \) (with \( \sigma = 8 \text{Å} \)), BDHI simulations yield respectively \( D_1 \approx D_s^{(s)} = 75 \text{Å}^2/\text{ns} \) and \( D_2 \approx D_s^{(s)} = 6.4 \text{Å}^2/\text{ns} \) in excellent agreement with these experiments. Our CG correctly capture the collective dynamics at molecular wavelengths and now we analyze larger scales.

The values of \( D_1 \) and \( D_2 \) for the BD and BDHI models are plotted in Fig. 3(b) against \( q\sigma \). We start by analyzing the short-time collective diffusion, \( D_1 \). At molecular wavelengths \( q\sigma > 2 \) all models yield a qualitatively similar trend \( D_1(q) \approx D_0/S(q) \). In MD, we find that \( D_0 \approx 4 \text{nm}/\text{ns} \) agrees with the peak of \( D_s^{(s)} \) at short times (inset of Fig. 2). The dynamics of larger density fluctuations \( (q\sigma < 1) \) is however strongly modified by hydrodynamic correlations. Figure 3(b) reveals an anomalous increase of the short-time diffusion as \( q \) decreases. The trend we observe \( D_1 \approx 1/q \) is strongly reminiscent of the anomalous collective diffusion in colloids confined to move in a plane but embedded in 3D solvent, a set-up which usually called quasi-two-dimensional (q2D) [23, 24]. Under hydrodynamic interactions the short-time diffusion is expressed as \( D_1 = [H(q)/S(q)] D_0 \), where \( H(q) \) is called the hydrodynamic function [34]. Notably,
under q2D dynamics, it has been proved [22] that $H(q)$ diverges like $H(q) = 1 + (qL_h)^{-1} + O(q)$. The anomalous diffusion is already felt at molecular scales because the “hydrodynamic length” $L_h = \sigma/(3\phi)$ is of molecular size ($L_h = 0.44$nm for BDHI and 0.53nm for MD, calculated using the lipid head surface fraction $\phi \approx 0.6\text{Å}^{-2}$ and 0.3Å$^{-2}$, respectively). Figure 3(b) shows that the q2D theory agrees extremely well with our results for $D_1$ for $q\sigma > 0.4$. Deviations at larger $q$ are expected because the theory [22] only considers the Oseen contribution of solvent’s mobility (only valid at long distances, see e.g. Ref. [24] for a study with purely repulsive colloids).

In view of the different ways BDHI and MD models carry out momentum transfer, we need to validate this phenomena against the more detailed MD model. The hydrodynamic function $H_1(q) = D_1(q)S(q)/D_0$ permits to compare MD and BDHI models in one single master-curve, which is shown in Fig. 4. The agreement is extremely good and both models agree remarkably well with the q2D theory (i.e., quantitatively, without fitting parameters). This central result shows that hydrodynamic interactions between the membrane and the ambient fluid leads to a significant enhancement of collective lipid diffusion compatible to that observed in colloidal q2D dynamics [22]. While in colloids, the confinement arise from an external force field [24], in membranes, it arises from the internal elastic forces acting in normal direction to the plane. These forces transfer normal momentum to the surrounding fluid which spreads tangentially over the membrane. This mechanism is sketched with with arrows in Fig. 3(c). The resulting collective drag acts like a long-ranged repulsive force $f_{\text{q2D}}$ between lipids. Technically, this force is a form of thermal drift [35] arising in the presence of a mobility gradient $f_{\text{q2D}} = k_BT\nabla \cdot \mathcal{M}$. In q2D, the resulting current is proportional to the (lipid) density fluctuations [36], being controlled by the Oseen’s contribution of the solvent’s mobility $\mathcal{M}_{3D}$. The solvent is incompressible so $\nabla \cdot \mathcal{M}_{3D} = 0$, but a non-zero divergence appears when evaluated in the plane ($z = 0$ and $\mathbf{r} = \mathbf{r}^\parallel$) simply because $\nabla_{\parallel} \cdot \mathcal{M}_{3D} = -\partial_z \mathcal{M}_{3D} \neq 0$. Particles confined to move in the plane are thus exposed to a repulsive hydrodynamic force $f_{\text{q2D}} = k_BT\nabla_{\parallel} \cdot \mathcal{M}_{3D}(\mathbf{r}^\parallel, z = 0)$ which is long ranged $f_{\text{q2D}} \propto 1/\ell^2$ because $\mathcal{M}_{3D} \propto 1/\ell$ [24, 36, 37].

As an important aside, we note that the long time collective diffusion coefficient $D_2$, reaches a roughly constant value independent on $q$ [see Fig. 3(b)] for BD and BDHI models. This means that at long times (about 100ns) the dynamics will gradually recover its normal diffusive character. Remarkably, in both models (BD and BDHI) $D_2$ coincides (within error bars) with the long-time self diffusion coefficient $D_s^{(1)}$. This result proves that the q2D anomalous diffusion does not generally lead to a divergent long-time diffusion ($D_s^{(1)} \sim 1/q$) in contrast with what it has been pointed out by some authors [23]. Our MD simulations are not long enough to resolve the long-time regime (SI) and we cannot confirm a similar outcome $D_s^{(1)} \rightarrow D_s^{(2)}$ in this case.

Conclusions. From the standpoint of membrane modeling, we show that a coarse dry membrane model equipped with the fluctuating immersed boundary method (FIB) [20, 31, 32] reproduces the correlations of lipid’s displacements observed in molecular representations with explicit solvent molecules. This type of CG model with implicit hydrodynamics will allow to explore a significantly larger range of the huge spatio-temporal scales present in membrane dynamics. In passing, we note that FIB methods are also able to correctly describe the shape fluctuations of a membrane [38], however, to the best of our knowledge they have not been so far used to study lipid dynamics.

From the perspective of lipid membrane dynamics, present findings indicate that below 100nm and 100ns the highly correlated pattern of lipid displacements is mainly a consequence of hydrodynamic interactions with the solvent. Normal (out-of-plane) momentum, exchanged between the incompressible fluid and the membrane elastic forces, induces long-ranged repulsive hydrodynamic interactions in the plane which strongly enhance the short-time collective diffusion of lipids at small wavenumbers $q\sigma < 1$. Notably, this phenomena is not described by the Saffman theory [15, 16] which otherwise explains the slowing down of large lipid disturbances (above one micrometer) due to the action of the solvent tangential friction. An unified view of the solvent-membrane hydrodynamics, from nanometers to microns will require taking this novel effect into consideration.

Finally, some remarks on the experimental verification of this new phenomena are due. According to our observations, lipid’s density patterns will initially decorrelate over short times of order $\tau_c \sim 1/(q^2D_1)$. For $q\sigma < 0.1$ (i.e. $q < 1.4\text{nm}^{-1}$) the intermediate scattering function
drops a 20%, i.e. to $F_c(q, \tau_s)/S(q) \approx 0.8$ after $t \approx \tau_s \sim 10\text{ns}$. The anomalous diffusion yields $D_1 \approx D_0/(qL_h)$ so the initial decorrelation propagates with a characteristic velocity $v_{q2D} = qD_1 \approx D_0/L_h \sim 2\text{nm}/\text{ns}$. Interestingly, this velocity is quite compatible with the ballistic relaxation velocities measured in QENS experiments (see SI of Ref. [7]). At larger scales, propagating at speed $v_{q2D}$, the anomalous diffusion should lead to an appreciable decorrelation of micron-size fluctuations in about one micro-second. This gives an idea of the experimental difficulty in measuring this collective effect. Experimental confirmation of this fast, but strong, transient regime might come from spin-echo experiments at low wavenumber $[7, 13]$ or from high time resolution fluorescence correlation spectra [1] performed in vesicles; a spherical geometry for which the theory for $q2D$ diffusion has been recently derived [39]. The strong enhancement of collective diffusion might prove to be relevant for the formation of nanopores [4] or on the kinetics of lipids and proteins complexes [5, 6].

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