Communication

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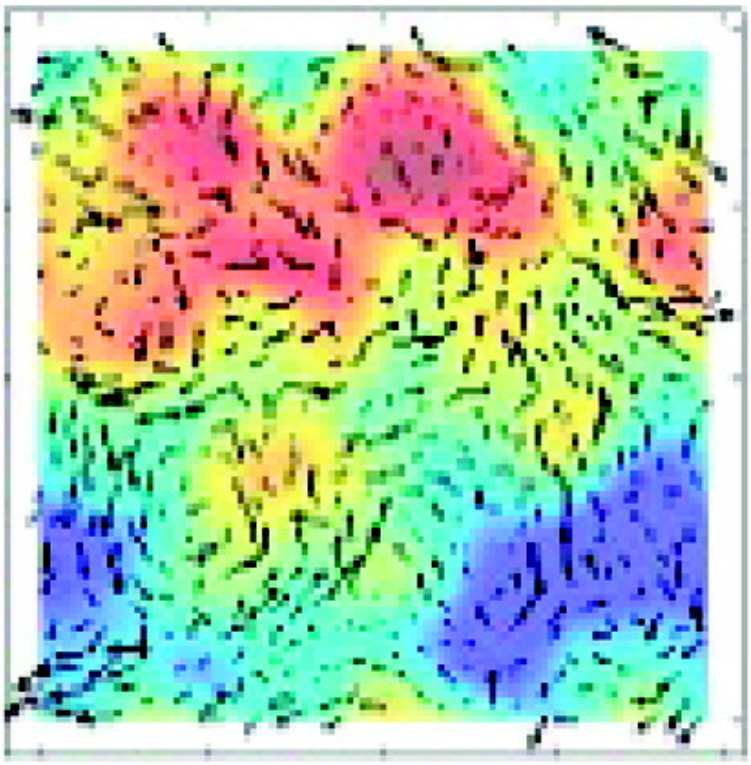

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Lateral Diffusion in Lipid Membranes through Collective Flows

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Cellular membranes bustle with dynamic phenomena at a wide range of time and length scales.[1] Indeed, membrane dynamics lies at the core of a variety of cellular processes such as signaling, formation of lipid rafts, and cell death. While models for membrane structure have been constantly evolving,[1−3] and even the dynamics of proteins is in many ways understood,[4−6] the dynamics of lipids has received much less attention. Overall, one could say that there is no mature model for membrane dynamics. Even mechanisms of seemingly simple dynamic processes are far from well understood, such as the case of lateral diffusion, that is, the motion of lipids in the plane of the membrane.

Different experimental techniques applied for a given membrane yield lipid lateral diffusion coefficients that differ by 2 orders of magnitude.[7−9] This is usually interpreted as a result of diffusion gauged over different time scales. It has been thought that short-range techniques such as QENS measure the rapid rattling-in-a-cage motion, where a lipid is confined to a cage formed by its neighbors, while long-range techniques such as FRAP probe the slower motion manifested as random-walk-like displacements over much larger scales. While the nature of the rattling-in-a-cage motion has been confirmed by atomistic simulations,[10] and the random walk of lipids has been observed over scales of ∼100 nm,[11] very little is known about the mechanism of how lipids actually diffuse. The successful interpretation of QENS backscattering experiments[12,13] in terms of a "jump model" has lent some support to the picture that lateral diffusion would consist of nearly instantaneous, discrete jumps, where a lipid molecule moves out of its cage, moving a distance comparable to its own size. However, no direct experimental or computational evidence for the jumps as a dominating mechanism exists. Meanwhile, following the ideas of Ayton and Voth,[14] one is tempted to assume that density fluctuations and other collective effects would have an important role to play in lateral diffusion.

In this work, we propose a mechanism for the lateral diffusion of lipids in the membrane plane. We find little or no evidence for a jump-diffusion model in terms of two clearly distinct regimes, that is, rattling and jumps. Instead, the in-plane motion of a lipid with its nearest neighbors is observed to be strongly correlated: the lipid and its neighbors move as a loosely defined cluster. What is more, we observe that such transient local clusters are a manifestation of the concerted motions of lipids at much longer scales. The motion of lipids is correlated at least over tens of nanometers, and the concerted displacements of lipids yield flow patterns not previously reported for lipid membranes. These findings highlight the collective nature of lipid dynamics at mesoscopic scales, providing a novel view for lipid diffusion.

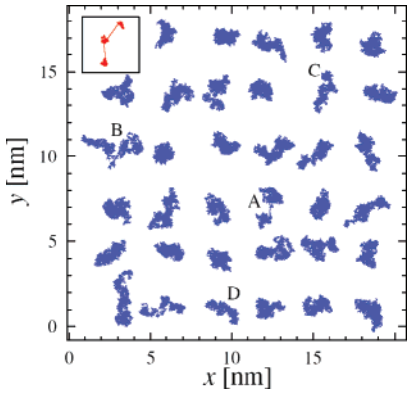

Figure 1. Examples of CM trajectories in plane of the bilayer from the lower monolayer of system 1152-RF. The last 30 ns are shown. The red inset shows an example of what a trajectory could look like if the diffusion were jump-dominated (suggestive only; scales in the inset not shown).

We have performed extensive atomistic molecular dynamics (MD) simulations of dipalmitoylphosphatidylcholine bilayers in the fluid phase (323 K). We performed MD simulations for four bilayers. The first system (128-PME) consists of 128 lipids, the second and third (1152-PME and 1152-RF) of 1152 lipids, and the fourth (4608-RF) of 4608 lipids. PME refers to particle mesh Ewald electrostatics, and RF to reaction field electrostatics. The 128-PME system was simulated for 100 ns, 1152-PME for 10 ns, 1152-RF for 40 ns, and 4608-RF for 8 ns. The last 80, 8, 30, and 6 ns of 128-PME, 1152-PME, 1152-RF, and 4608-RF, respectively, were used for analysis. All systems were fully hydrated by 28.55 water molecules per lipid and yielded consistent results. Below we focus on the results of the larger systems. The simulations were performed using GROMACS.[15] Detailed description of the simulation protocol and validation of the model are given in Supporting Information.

To gain insight into the possibility of jumps, we first inspected the lateral trajectories of all individual lipids in all four systems. Examples of center of mass (CM) trajectories covering the last 30 ns of the 1152-RF simulation are shown in Figure 1. The relation $l^2 \sim 4Dt$ for the distance l traveled by the lipid during time t, with $D = 1.5 \times 10^{-7}$ cm^2/s and $l = 0.7$ nm (linear size of a lipid), suggests that if jump diffusion were the dominating mechanism, we should observe, on the average, four discontinuous jumps per lipid. Figure 1 suggests that most trajectories do not contain such jumps: the trajectory labeled A contains one of the fewer than five rapid jump-like events observed in this simulation. Probability densities confirm that there is only a handful of 100 ps intervals where a lipid moves a distance of 0.7 nm or longer. Indeed, instead of observing thousands of discontinuous jumps in the four in-plane

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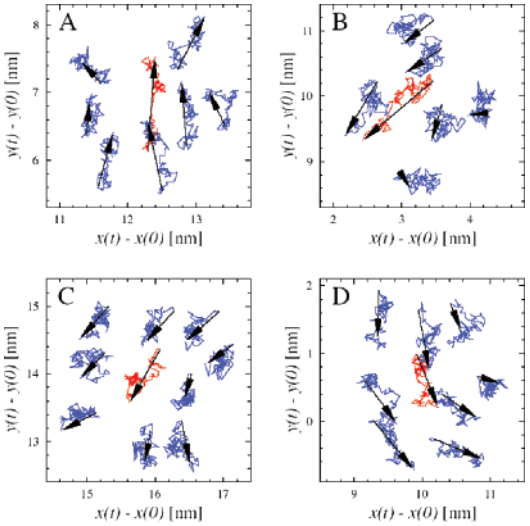

Figure 2. Trajectories of neighboring lipids during 1 ns time intervals. The red trajectory in each panel is part of the trajectory labeled A, B, C, or D in Figure 1. For each lipid, the 1 ns interval was chosen to be the one during which the lipid migrates the longest distance. These are 17.45−18.45, 24.63−25.63, 25.86−26.86, and 34.61−35.61 ns for A, B, C, and D, respectively. The blue trajectories are those of the nearest neighbors, that is, the lipids whose CM is within 1 nm of that of lipid A, B, C, or D at any time during the 1 ns interval. The black arrows indicate the total displacements during the 1 ns period.

trajectories we analyzed, we identified fewer than 10 such events. Clearly, lateral diffusion is not dominated by jumps. The recent data by Bockmann et al. are in line with this view.[16]

How does a lipid move in relation to its neighbors? Are the motions correlated, and if so, what is the range of the correlations? To illustrate the motion of a lipid with respect to its nearest neighbors, we focus on the four labeled trajectories from Figure 1. Figure 2 depicts the motion of each of the lipids, together with its nearest neighbors, during a 1 ns interval. These data suggest that a lipid's movement is correlated with its neighbors'; we see the lipids moving as loosely defined local clusters, confirming the earlier observation by Ayton and Voth based on a coarse-grained model (11). This seems to be typical of lipid dynamics. Lipids do not appear to jump out of cages composed of their nearest neighbors. Panel A of Figure 2, for instance, depicts one of the most distinct jump-like movements in the whole series of simulations. The panel clearly shows that most of the nearest neighbors move along with the relatively rapidly migrating central lipid.

We have established that 1 ns displacements of individual lipid molecules are strongly correlated with those of their nearest neighbors'. How about correlations at longer length scales? How do the loosely defined dynamic clusters interact? Are there concerted lipid motions in membranes? Figure 3 shows the lateral CM displacements of all lipids in a given monolayer of 1152-PME or 1152-RF for 50 ps, 500 ps, 5 ns, and 30 ns. The arrows denoting the displacements show a 2D streaming pattern or flow field, highlighting the presence of concerted motions. This is a very intriguing observation which has not been reported before in the context of lipid membranes. To ensure that the flow patterns are not an artifact of the finite system size, we performed a simulation on a system measuring 39.5 nm × 39.5 nm (4608-RF). The study confirmed the existence of concerted motions.

Our results provide a novel view for the mechanism of lateral diffusion of lipids in membranes. It is predominately continuous, and the motions of neighboring lipids are intimately correlated. The correlations persist over tens of nanometers, manifesting themselves

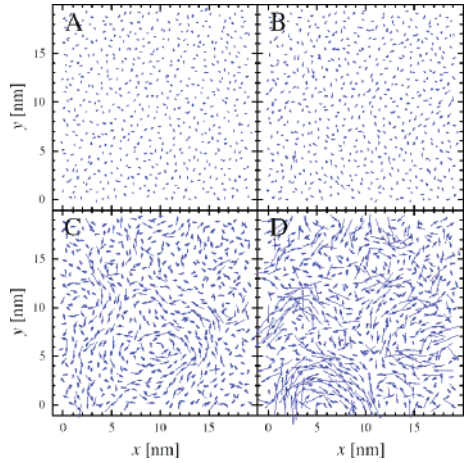

Figure 3. Lateral CM displacements of lipids during different time intervals. Panels A, B, and C show data from the upper monolayer of the 1152-PME system: A depicts a 50 ps interval from 5.00 to 5.05 ns, B a 500 ps interval from 5.0 to 5.5 ns, and C a 5 ns interval from 5 to 10 ns. In panel D, we show displacements from the lower monolayer of the 1152-RF system, during a 30 ns interval from 10 to 40 ns.

as 2D flow patterns that presumably originate from thermal density fluctuations together with local short-time momentum conservation despite the dissipative nature of the membrane embedded in a water bath. It is likely that these flow patterns affect the molecular mechanisms of several key processes in membranes. For example, they should influence membrane fusion, local pore formation, and the dynamics of raft mixtures. Lipid flows may also have an effect on signaling and affect the structure and function of membrane proteins by contributing locally to lateral pressure profiles in the membrane, and affect the assembly of complexes of membrane proteins.

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Supporting Information Available: Simulation details, system setup, and additional results. This material is available free of charge via the Internet at http://pubs.acs.org.

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