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Crossover from picosecond collective to single particle dynamics defines the mechanism of lateral lipid diffusion

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ABSTRACT

It has been widely accepted that the thermally excited motions of the molecules in a cell membrane is the prerequisite for the cell to carry its biological functions. On the other hand, the detailed mapping of the ultrafast picosecond single-molecule and the collective lipid dynamics in a cell membrane remains rather elusive. Here, we report all-atom molecular dynamics simulations of a 1,2-dipalmitoyl-sn-glycero-3-phosphocholine bilayer over a wide range of temperature. We elucidate a molecular mechanism underlying the lateral lipid diffusion in a cell membrane across gel, rippled and liquid phases using an analysis of the longitudinal and transverse current correlation spectra, the velocity auto-correlation functions, and the molecules mean square displacements. The molecular mechanism is based on the anomalous ultrafast vibrational properties of lipid molecules at the viscous-to-elastic crossover. The macroscopic lipid diffusion coefficients predicted by the proposed diffusion model are in a good agreement with experimentally observed values. Furthermore, we unveil the role of water confined at the water-lipid interface in triggering collective vibrations in a lipid bilayer.

1. Introduction

The plasma membranes separates the inner compartment of a cell and the extracellular fluid and therefore is responsible for a multitude of physiological functions [1]. These functions include but are not limited to passive and active transport, nutrient uptake and waste discharge, signalling and cell communication. All these functions are possible because the plasma membrane is fluid and dynamic in nature [2]. Due to thermal fluctuations, the constituents of the cell membrane exhibit complex movements at different time (from picoseconds to minutes) [3] and form both transient and stable structural elements at different length scales (from nanometers to microns) [4,5]. The biological relevance and the paramount importance of the lipid membranes structures at different length scales have been well recognized and reflected by the raft model [5-9]. However, much less attention has been devoted to a systematic study of membrane dynamics at different time scales despite its fundamental importance for various biological processes [3].

Phospholipids, being the most abundant component of a cell membrane, consist of two hydrophobic fatty acid chains and a hydrophilic head group. They are thought to play a crucial role in mediating nearly all complex phenomena in a cell membrane that involve, among others, the vibrational or translational motions of molecules [10-12]. However, while substantial efforts have been directed towards understanding the biological phenomena consequential to these motions, the lipid dynamics itself has received much less attention despite its overarching role in a myriad of cell functions. Among the most studied phenomena is the lateral diffusion of lipid molecules with the pioneering works dating back to the late 1970s and early 1980s [13-17]. Lipid diffusion, or the membrane fluidity, plays a crucial role in processes like protein diffusion, heat transfer, and solution penetration [18-26]. There have been considerable efforts to propose and refine models to explain lateral lipid diffusion coefficients observed experimentally by different techniques [13,14,16-18,23,24,26-32]. The well-explored free area theory of lipid diffusion [27,28], which is based on the consideration of a lipid "particle" performing a random walk in two dimensions, and other obstacle-based models [11,33,34] have been reasonably successful in predicting the lateral diffusion coefficients. However, to predict the diffusion coefficients for various phases of a given lipid, a different set of empirical constants and correction

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coefficients [29] is required for each phase, which limits the universality of such approaches. As a result, the understanding of the physical origin of the lipid lateral diffusion and related biological processes in a cell remain elusive.

As we have previously shown [35], short-lived nanometer-scale lipid nanoscopic domains and transient pores form due to thermal collective motions of lipid molecules within the lipid bilayer, which facilitate passive molecular transport across the bilayer. The fact that the molecular transport through bio-membranes of cells heavily relies on the dynamics of lipids implies that individual and collective dynamics of lipids are closely interconnected. For instance, macro processes such as heat transfer and passive transport of molecules primarily stem from the cell mechanics, which is a combination of the elastic waves propagation (collective dynamics) and other competing processes such as diffusion (individual dynamics). The latter is responsible for the intra-leaflet lipid bilayer transport and molecules (protein-protein, lipid-protein) interaction since leaflet's individual molecules are able to move in lateral direction similar to 2D liquids. Therefore, the knowledge about lipid membrane motions may help to reveal the biological functions of a cell membrane at the molecular scale.

Here, we have performed all-atom molecular dynamics (MD) simulation of a 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) bilayer over a wide range of temperature covering both gel, rippled, and liquid phases. Through the analysis of the transverse current correlation spectra we have determined the evolution of the propagating transverse phonon mode and its thermally-triggered phononic gap [35,36] as a function of temperature. The combination of transverse phononic gap temperature dependence and the concurrent calculation of molecules' mean square displacements (MSDs) allows us to propose a new analytical representation of the temperature-dependent lateral lipid diffusion coefficient, which accurately describes the experimentally observed values across all lipid phases. Further analysis of the velocity autocorrelation functions (VACFs), DPPC optical phonon modes, and neighboring water MSDs helps understanding the interconnection between the water dynamics adjacent to the lipid bilayer, which is assumed to govern the external molecule binding [37], and lipids collective dynamics.

2. Theory

2.1. Current correlation spectra and phonon gaps

Collective molecular motions in lipid membranes are supported in the form of compression waves (longitudinal vibrations) and shear waves (transverse vibrations). The existence of collective density excitations for wavelengths down to a few lipid molecular spacings is correlated with the oscillatory behavior of both the longitudinal $C_L(Q,E)$ and transverse $C_T(Q,E)$ current correlation spectra, whose direct analysis can give access to the membrane properties originating from the collective molecule motions. For example, the longitudinal and transverse lipid membrane motions are associated with nanoscale density fluctuations, whose parameters can be deduced from the analysis of the projection of the lipid molecule currents along and perpendicular to the direction of the wavevector $\overrightarrow{Q}$ parallel to the membrane plane [35]. In general, the site-site current correlation spectra are defined as the time Fourier transforms of the corresponding current correlation functions:

$$C_\alpha(\overrightarrow{Q}, E) \equiv \int_{-\infty}^{+\infty} dt \quad e^{iEt} < \vec{J}_\alpha^*(\overrightarrow{Q}, t) \cdot \vec{J}_\alpha(\overrightarrow{Q}, t) > \tag{1}$$

where $\alpha = (L,T)$ and current correlation functions:

$$\vec{J}_L(\overrightarrow{Q}, t) = \frac{1}{\sqrt{N}} \sum_k \widehat{\overrightarrow{Q}} (\widehat{\overrightarrow{Q}} \cdot \vec{v}_k(t)) e^{-i\overrightarrow{Q} \cdot \vec{r}_k(t)} \tag{2}$$

$$\vec{J}_T(\overrightarrow{Q}, t) = \frac{1}{\sqrt{N}} \sum_k \widehat{\overrightarrow{Q}} \times \vec{v}_k(t) e^{-i\overrightarrow{Q} \cdot \vec{r}_k(t)} \tag{3}$$

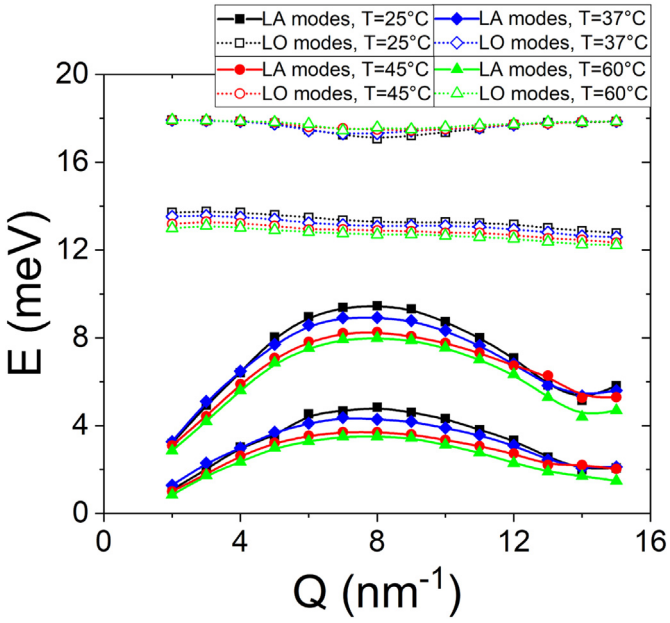

Fig. 1. Temperature evolution of longitudinal acoustic (LA) and optical (LO) vibrational modes. The momentum transfer vector Q lies parallel to the membrane surface, or perpendicular to the lipid tails. As temperature increases, both vibrational modes are softened, which results in a decrease of the energy at which they get excited. Every mode is dubbed "Longitudinal" (either acoustic or optical) as they are obtained from the fit of the longitudinal current correlation spectra, $C_L(Q,E)$.

$\widehat{\overrightarrow{Q}}$ is the unit vector along $\overrightarrow{Q}$, N is the total number of atoms, $\vec{r}_k(t)$ and $\vec{v}_k(t)$ are positions and velocities of atom k.

It is noteworthy, that the experimental exploration is primarily focused on probing the dynamic structure factor $S(Q,E)$. However, MD simulation gives a direct access to the longitudinal current correlation spectra, $C_L(Q,E)$, which can be expressed as $C_L(Q,E) = E^2 S(Q,E)/Q^2$. The oscillatory behavior of the $C_L(Q,E)$ can be described by a set of $C_L(Q,E)$ peaks at corresponding Q-values. It is widely accepted that the peaks can be determined by the Damped Harmonic Oscillator (DHO) model [38-40]. Positions of $C_L(Q,E)$ peaks as a function of Q-values define vibrational modes commonly known as dispersion relations.

Certain vibrational modes can be collectively excited in lipids, which are able to interact with sound or light and can be strongly coupled with each other under specific conditions. In Fig. 1, we presented the temperature evolution of the compression waves in DPPC lipid bilayer calculated by MD. Every longitudinal dispersion curve (LA or LO) in Fig. 1 corresponds to a single set of DHO peaks at various Q-values obtained from the fit of longitudinal current correlation spectra, $C_L(Q,E)$ (see Methods section for details). The so-called in-phase rattling movements of lipids at lower energies exist in the form of longitudinal acoustic (LA) vibrations, which is commonly associated with sound in the long wavelength limit ($E = 0$, $Q = 0$). Such LA modes have been routinely observed experimentally using, *e.g.* inelastic X-ray scattering [35,41,42]. Similarly, the out-of-phase rattling oscillations define longitudinal optical (LO) vibrational modes, which are able to interact with light at corresponding frequencies (or energies). The experimental evidence for the LO mode was provided by inelastic neutron scattering [43] Also, multiple optical modes were observed in DMPC lipid membrane by far infra-red spectroscopy [44] and confirmed by MD simulation [45].

At the same time, it is of particular importance to examine the evolution of the transverse current correlation spectra $C_T(Q,E)$, where the anomalous dynamic behavior is observed. In contrast to $C_L(Q,E)$, $C_T(Q,E)$ spectra converge to finite values in the low-energy limit (see Fig. 2a). This implies that $C_T(Q,E)$ spectra can not be fitted with the use