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# Vibrational lifetimes of hydrated phospholipids

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**Abstract** – Large-scale *ab initio* molecular-dynamics simulations have been carried out to compute, at human-body temperature, the vibrational modes and lifetimes of pure and hydrated dipalmitoylphosphatidylcholine (DPPC) lipids. The projected atomic vibrations calculated from the spectral energy density are used to compute the vibrational modes and the lifetimes. All the normal modes of the pure and hydrated DPPC and their frequencies are identified. The computed lifetimes incorporate the full anharmonicity of the atomic interactions. The vibrational modes of the water molecules close to the head group of DPPC are active (possess large projected spectrum amplitudes) in the frequency range 0.5–55 THz, with a peak at 2.80 THz in the energy spectrum. The computed lifetimes for the high-frequency modes agree well with the recent data measured at room temperature where high-order phonon scattering is not negligible. The computed lifetimes of the low-frequency modes can be tested using the current experimental capabilities. Moreover, the approach may be applied to other lipids and biomolecules, in order to predict their vibrational dispersion relations, and to study the dynamics of vibrational energy transfer.



Much research is currently focused on understanding the biological activities that are performed by biomolecules. The static view of such molecules, as obtained from, *e.g.*, Bragg X-ray diffraction, provides only an incomplete window into the properties of such complex molecules. It is, therefore, evident that such a window is insufficient for understanding a wide range of biological activities [1,2]. Hence, attention has turned to dynamical properties, and in particular the time scales over which a biomolecule performs a specific activity, or takes part in a phenomenon, as it is generally recognised that any knowledge about the dynamics and characteristic time scales of biomolecules actions sheds light on many processes in which they participate. The characteristic time scales for various biomolecules have a broad spectrum. For example, the typical time scales for global DNA twisting, DNA bending and protein folding are, respectively, $\sim 1$ ps, 0.1 ps–10 ps and 10 $\mu$s–10 s [3–5]. Another example is photosynthesis, the understanding of its microscopic details requires insight into and knowledge about all the time scales that are relevant to the process [6].

Biological membranes are dynamic entities that are involved in processes that occur at various time and length scales [7]. Motions in lipid bilayers range from the long-wavelength undulation and bending modes of the bilayer, with typical relaxation times of nanoseconds and lateral length scales of several hundred lipid molecules, to the short-wavelength density fluctuations in the picosecond range on nearest-neighbor distances of lipid molecules (see [7] and references therein). Local dynamics in lipid bilayers, *i.e.*, dynamics of individual lipid molecules such as vibrations, rotations, librations (hindered

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rotation), and diffusion, have been investigated by, *e.g.*, incoherent neutron scattering and NMR to determine the short-wavelength translational and rotational diffusion constant [7,8].

The characteristic time scales are also relevant to the vibrational energy transfer across lipid membranes, a very important phenomenon in many biological processes that have been studied extensively [9,10]. Thus, there have been several recent studies of the dynamics and characteristic time scales of lipid-like assemblies, lipid membranes and the associated molecules [11–15]. Experimentally, femtosecond, time-resolved studies of biomolecules that probe energy dynamics in biomolecules provide important information about and insight into the functions of biomolecules, which cannot be obtained from static experiments [16–20] alone. Information about what takes place at the membrane's surface is crucial to understanding the viral infection and targeted drug delivery.

Recent experiments [21] have indicated that hydration of lipid headgroups by water enables efficient energy transfer across membrane leaflets on sub-picosecond time scales. The extended vibrational modes that emerge upon hydration underlie this phenomenon [22]. The dynamics of membrane-associated proteins and their affinities to downstream components might be affected by coupling to the vibrational dynamics of the lipid bilayer membrane [23]. Advances in two-dimensional IR spectroscopy have made it possible to probe the vibrational coupling between lipids and the associated proteins [24]. Predicting the vibrational properties of lipid bilayer membranes is, however, a nontrivial task due to the system size and the interactions with nonbonded solvent molecules, and because under physiological conditions cellular membranes function at relatively high temperatures.

In a harmonic approximation, the phonons do not scatter and, therefore, they have infinite lifetimes. In the vibrational density of state, or the vibrational spectrum, they exhibit peaks that are of delta-function type. At nonzero temperatures, the phonons scatter and, thus, have finite lifetimes due to the anharmonic interactions, leading to a shift in the phonon spectrum and broadening of the phonon peaks. Moreover, in contrast to bulk crystals at low temperatures for which estimation of the vibrational lifetimes based on harmonic and third-order anharmonic lattice dynamics calculation is reasonably accurate [25], for biological membranes at the relevant temperatures higher-order events must be taken into account. There have been several femtosecond laser-based studies that attempted to address the dynamics of model biological membranes, such as water-lipid interactions [11–15] and transmembrane proteins [26,27].

In this letter we present the results of extensive calculation of lifetimes of vibrational modes of pure and hydrated dipalmitoylphosphatidylcholine (DPPC), which belongs to the most ubiquitous membrane phospholipid family, phosphatycholine. To our knowledge, this is the first time that such properties of the DPPC are computed. While there are recent experimental data for the high-frequency regime, no data exist yet for the low-frequency region.

Several methods have already been developed for predicting the vibrational lifetimes, including the perturbation method [28], the normal mode analysis [26,27,29], and the spectral energy density (SED) analysis [30–33]. The perturbation method is used in the frequency domain and uses Fermi's golden rule to calculate the three-phonon scattering rates that result from lattice anharmonicity. The temperature effect can be included only implicitly by tuning the phonon occupation number based on the phonon density of states at zero temperature [22].

Our calculations utilized *ab initio* molecular-dynamics (AIMD) simulations and the SED analysis [15]. Typically, anharmonic lifetimes calculation is limited to three-phonon scattering events, which is a good assumption only at low temperatures. On the other hand, the normal mode analysis and the SED method map the MD trajectories onto each individual phonon normal modes, which makes it possible to derive the spectral phonon relaxation time from either the phonon population decay in the time domain, or the phonon linewidth in the frequency domain. Thus, all order phonon processes are taken into account in the MD simulation as the atoms evolve dynamically using the full anharmonicity of the interatomic interactions, which is implemented in SED approach and, thus, the lifetimes predicted by this method include the effect of $n$-phonon scattering events. As such, the SED method is a robust approach for calculating the vibrational lifetimes. The method does not require any adjustable parameters and can be readily integrated with AIMD simulations in order to extract the fully anharmonic phonon frequencies and the associated phonon scattering rates for individual modes [30–33]. Moreover, since the SED is obtained directly from the projected atomic velocities correlation functions, there is no distinction between normal and umklapp phonon scattering processes. Both effects are fully included in the calculations of the phonon lifetime.

The ground state of pure DPPC and DPPC with hydration of its headgroup by 50 water molecules were also calculated using density functional theory (DFT) and the SIESTA code [26]. The calculated ground state structures were used as the starting configuration for the AIMD simulations at $T = 310$ K, the temperature of human body. The calculations were performed within the generalised gradient approximation for the exchange correlation energy functional, with Perdew-Burke-Ernzerhof parametrization. The simulation time was about $\sim 3$ ps with a time step $\Delta t = 0.1$ fs, which is about one-hundredth of the shortest vibration period in this system [22,34]. The temperature was held constant with the Nosé-Hoover thermostat.

We determined the relaxation time scales of the vibrational modes using the SED [15,30] $\Phi(\omega)$, the average kinetic energy, as a function of the frequency $\omega$ and wavenumber. The calculations were based on computing the projected velocity time series of all the atoms on the

eigenvectors of the vibrational modes. The peaks of the calculated SED $\Phi(\omega)$ of the DPPC and DPPC plus water were modelled by the Lorentzian function (see below),

$$L(\omega,\nu)=\frac{I_0}{[2\tau(\omega-\omega_c)]^2+1}. \quad (1)$$

Here, $I_0$ is the peak amplitude, $\nu$ is the index of the vibrational mode, $\omega_c$ denotes the frequency at the peak's centre, and $\tau$ is the mode's lifetime. We determined all the modes that are mostly active at temperature $T=310\,\mathrm{K}$, as well as their lifetimes.

To calculate the full vibrational modes of the DPPC and hydrated DPPC, we used Troullier-Martins–type pseudopotentials along with double-$\zeta$ singly polarized basis set. The coordinates of the atoms of a single lipid were relaxed using the conjugate-gradient method until the maximum force exerted on the atoms was less than $0.007\,\mathrm{eV/\AA}$. To this end, the molecule was placed in a unit cell with dimensions much larger than its own size. As a consequence, only the Gamma point in the reciprocal space was needed for energy integration. The vibrational properties were studied within the linear response regime. Each atom was displaced from its equilibrium position, obtained after relaxation, by a small value, 0.2 bohr. Then, the forces exerted on every atom were calculated and the force constants matrix was constructed, which was then diagonalized in order to obtain the vibrational modes and the eigenfrequencies.

Let us define the average kinetic energy of normal mode ($\omega$) as (at the Gamma point) [30,35]:

$$T(\omega)=\frac{1}{4\tau_0}\left|\frac{1}{2\pi}\int_{-\tau_0}^{\tau_0}\dot{q}(\nu;t)\exp(-i\omega t)\mathrm{d}t\right|^2, \quad (2)$$

where $\omega$ is the angular frequency, $2\tau_0$ is the integration time scale, and $q(\nu;t)$ is given by

$$q(\nu;t)=\frac{1}{\sqrt{N}}\sum_{j=1}^{N}\sqrt{m_j}\mathbf{e}(\nu)\cdot\mathbf{u}_j(t), \quad (3)$$

where $m_j$ is the mass of atom $j$, $\mathbf{u}_j$ is its displacement vector, $N$ is the number of atoms, and $\mathbf{e}(\nu)$ is the mode polarization. It can be shown that the SED function is a linear superposition of $3N$ Lorentzian functions with their centers at the fully anharmonic vibrational frequency $\omega_c$ [29,34]:

$$\Phi(\omega)=2\sum_{\nu=1}^{3N}\langle T(\omega,\nu)\rangle=\sum_{\nu=1}^{3N}L(\omega,\nu), \quad (4)$$

where $L(\omega,\nu)$ is given by eq. (1), with $I_0$ representing the combination of the coefficients as the weighting factors for the Lorentzian functions.

Figure 1 presents the calculated SED in which panel (a) indicates that the active vibrational modes of pure DPPC at 310 K have frequencies 1.11, 2.96, 37.40, 40.74, 41.85 and 87.03 THz with lifetimes, respectively, of 0.86, 0.54, 0.51, 1.17, 0.81 and 1.00 ps. Figure 1(b) indicates that the active vibrational modes of hydrated DPPC at 310 K have frequencies 2.80, 4.40, 37.60, 42.00 and 87.60 THz, with lifetimes, respectively, of 0.75, 0.86, 1.41, 0.52 and 0.69 ps. A comparison of figs. 1(a) and (b) indicates that hydration produces blue-shift in the energy spectrum of the two systems. For example, the peak frequencies 41.85 THz and 87.03 THz for the pure DPPC have shifted to 42.00 THz and 87.60 THz, respectively, for the hydrated DPPC.

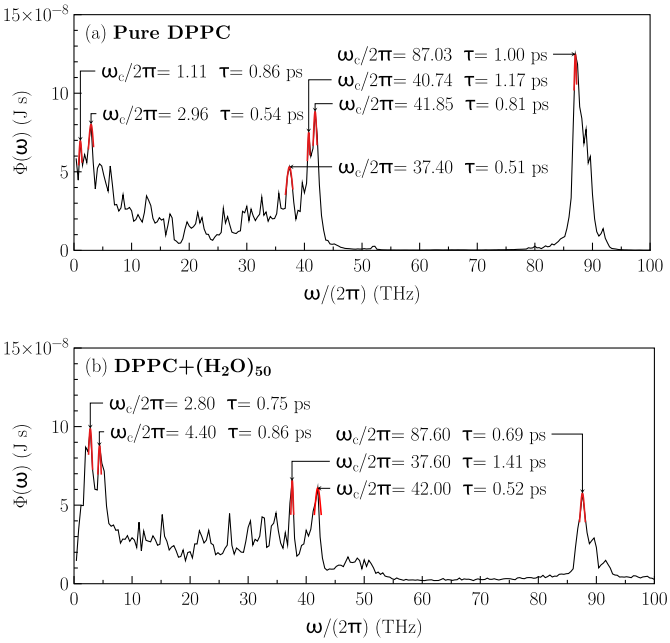


Fig. 1: (Colour on-line) Spectral energy density and vibrational lifetimes of the pure (a), and hydrated (b) DPPC. The peaks were estimated by fitting $\Phi(\omega)$ to the Lorentzian function. Panel (b) indicates that the active vibrational modes of hydrated DPPC at body temperature have frequencies 2.80, 4.40, 37.60, 42.00 and 87.60 THz, with the lifetimes, respectively, of 0.75, 0.86, 1.41, 0.52 and 0.69 ps.

To examine the frequencies at which both the lipid and water molecules contribute to the SED, we calculated their SED separately. Figure 2 presents the results. As shown in fig. 2(b), water is active in a wide range of frequencies, from 0.5 THz to 55 THz, with some peaks around 2.80 THz and 48.75 THz. In the range 45–55 THz, the main contribution to the total SED is by water, whereas as indicated by fig. 2(a), the lipids are active mainly at frequencies 4.40, 5.20, 37.60, 42.00, and 87.58 THz. The multiplication of the SEDs for lipid and water molecules are given in fig. 2(c), which presents the active modes of the lipid + water molecules system.

We also checked that the locations of the peaks in the SED are in agreement with the calculated density of states of the phonon frequencies obtained by harmonic lattice dynamics computations, indicating that the phonon frequency shifts due to anharmonic effects are negligible. We found that integrating beyond 3 ps, which is

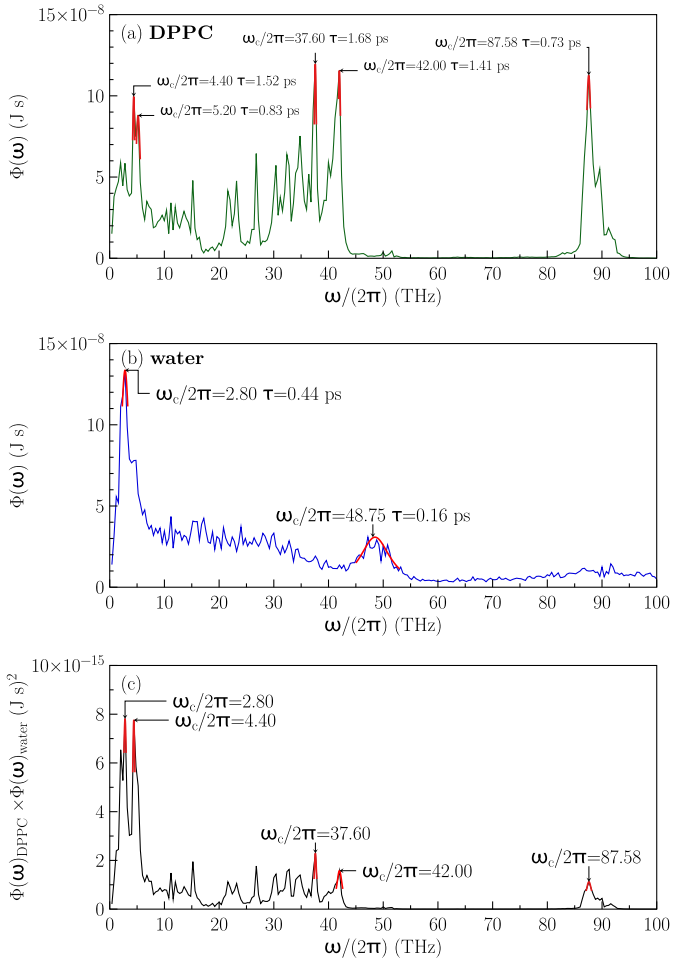


Fig. 2: (Colour on-line) Decomposition of the spectral energy density of DPPC plus water into the spectrum of DPPC and water molecules and the corresponding vibrational lifetimes of DPPC (a), and water (b). Panel (c) shows the product of the two spectral energy densities.

approximately six times greater than the longest phonon lifetime, does not change the predicted phonon properties. In fig. 3 we present two vibrational modes of DPPC + water system at frequencies of about 0.70 THz and 0.83 THz, which are spatially extended modes, demonstrating the ability of our computational approach for identifying the entire vibrational density of states. The water molecules are not shown there.

A comparison of some of our results with the experimental data is also instructive. As discussed earlier, we found for the peak in the SED of the hydrated DPPC with frequency 87.60 THz a relaxation time of 0.69 ps, which is in agreement with the relaxation time measured using time-resolved sum frequency generation. The experimental value for the lifetimes in the high-frequency range 83.94 THz–89 THz were reported to be (sub-)picoseconds [20]. We note that the estimated relaxation times, particularly for the low-frequency modes, are affected when neighbouring lipid molecules are considered.

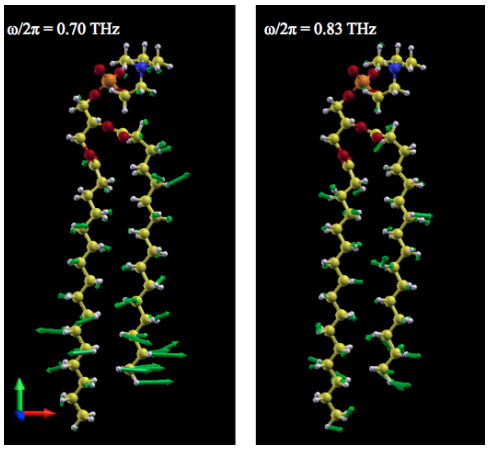


Fig. 3: (Colour on-line) Two vibrational modes at frequencies of about 0.70 THz (left) and 0.83 THz (right) of the DPPC + water system, as examples of the ability of the method to identify and compute the entire vibrational density of states. The water molecules are not shown.

In contrast to the high-frequency vibrational modes that are often localised, low-frequency modes extend over neighbouring lipid molecules and the surrounding interfacial water [22]. Physically, the local vibration of a few atoms including the H-bonds will be almost independent of the other lipids. However, for vibrations with long wavelengths the mean-free path of such modes will be on the order of the lipid length and, hence, there will be interactions with other lipids, too.

Summarizing, we employed *ab initio* molecular-dynamics simulations to calculate the lifetimes of the vibrational modes of the lipid and lipid/water systems. Our results for high frequencies agree well with the recent experimental results, while the computed lifetimes of the low-frequency modes can be tested experimentally. The computational method can be used to further investigate the system and to gain insight into energy transfer in other biomolecular systems. In addition, the approach may be used to compute the same properties for other types of polymers, a long-standing problem.

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