Volume-Energy Correlations in the Slow Degrees of Freedom of Computer-Simulated Phospholipid Membranes

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Abstract. Molecular dynamics simulations of phospholipid membranes reveals striking correlations between equilibrium fluctuations of volume and energy on the nanosecond time-scale. Volume-energy correlations have previously been observed experimentally at the phase transition between the L_α phase and the L_β phase, but not in the fluid L_α phase. The correlations are investigated in four membranes, with correlation coefficients ranging between 0.81 and 0.89. An experimentally single parameter test is proposed.

Keywords: Molecular dynamics simulation, Phospholipid membrane, Single parameter description
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Biological membranes are an essential part of living cells. They not only act as passive barrier between outside and inside, but play an active role in various biological mechanisms. The major constituent of biological membranes are phospholipids. Pure phospholipid membranes often serve as a models for the more complex biological membranes. Close to physiological temperatures membranes undergo a transition from the fluid L_α phase (often referred to as the biologically relevant phase) to an ordered gel phase L_β. In the melting regime, at the transition temperature T_m, the response functions such as heat-capacity, volume expansion coefficient and area expansion coefficient increase dramatically. Also, the characteristic time for the collective degrees of freedom increases and becomes longer than milliseconds. Heimburg et. al. found that the response functions are connected so a single function describes the temperature dependence of all of them. Experiments indeed shows that heat capacity and volume expansion coefficient of DMPC can be superimposed at T_m [1] (see also [2, 3]).

The fluctuation-dissipation (FD) theorem connects response functions to equilibrium fluctuations. The isobaric heat capacity c_p can be calculated from enthalpy fluctuations as follows: $c_p = \langle(\Delta H)^2\rangle/(Vk_BT^2)$, where $\langle\ldots\rangle$ is an average in the constant temperature and pressure ensemble and Δ is deviation from the average value. Similarly, volume fluctuations are connected to the isothermal volume compressibility by the expression $\kappa_T = \langle(\Delta V)^2\rangle/(Vk_BT)$. If the response functions were described by a single parameter, fluctuations are also described by a single parameter [1, 4] and the microstates were connected via the relation $\Delta H_i = \gamma^{vol}\Delta V_i$. At constant pressure this relation applies if and only if $\Delta E_i = \gamma^{vol}\Delta V_i$ (where E is energy), which is the relation investigated below. This situation is referred to as a that of a single-parameter description [4]. A single-parameter description applies to a good approximation for several models of van der Waals bonded liquids as well as for experimental super-critical argon [5].

Molecular dynamics simulation is not a good method for investigate the "single parameter"-ness of membranes at T_m, since the relaxation time for collective motions exceeds typical simulation times. However, we show below that a single parameter description is not only feasible at the phase transition, but also in the fluid L_α phase approaching T_m. We discusss how this can be tested in experiments.

It is not trivial that a single parameter is sufficient. Simulations of water and methanol show no "single parameter"-ness, since competing interactions destroy the correlation. Contributions to volume and energy fluctuations from hard core repulsion compete with directional hydrogen bonds [5]. Membranes are complex anisotropic systems and one cannot give an a priori reason for why volume and energy should be correlated.

A membrane may be perturbated via three thermodynamic energy bonds. A change of the enthalpy dH can be written as a contribution from a thermal bond, a mechanical volume bond and mechanical lateral (or area) energy bond, $dH = dE + pdV + \Pi dA$ where E is internal energy, p is pressure, V is volume, Π is surface tension of the membrane and A is the membrane area. The natural ensemble to consider is the constant T, p and Π ensemble since water will act as a reservoir. If a single parameter controls the microstates, for all states i one would have $\Delta E_i = \gamma^{vol}\Delta V_i = \gamma^{area}\Delta A_i$ where the γ's are constants.

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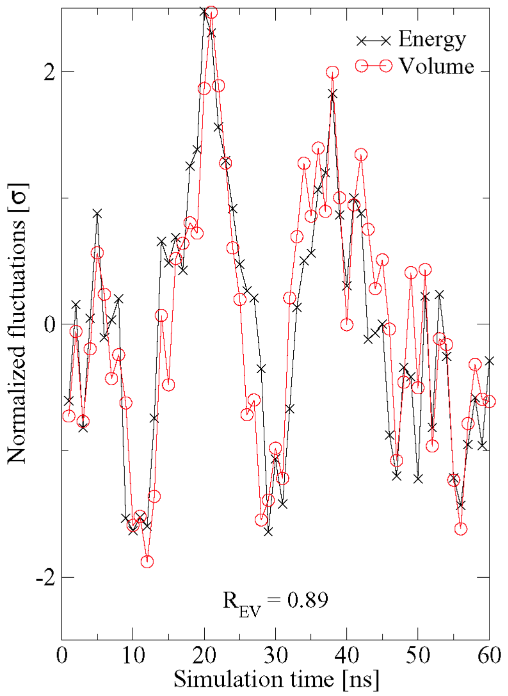

FIGURE 1. (Color online) Normalized fluctuations of energy (×) and volume (○) for a DMPC membrane at 310 K. Each data point represents a 1 ns average. Energy and volume are correlated with a correlation coefficient of $R = 0.89$.

In general, the microstates may of course be controlled by several parameters. An interesting question is how many parameters are sufficient to describe the membrane thermodynamics to a good approximation. This question is addressed below by investigating molecular-dynamics simulations of different phospholipid membranes.

An overview of the simulated systems is found in table 1. The simulated systems include different head groups (both charged and zwitterions) and temperatures. All simulations was carried out in the constant pressure, temperature ensemble. The membranes are fully hydrated and in the fluid L_α phase. The simulations were performed using the program NAMD [6] and a modified version of CHARMM27 all hydrogen parameter set [7, 8]. More simulation details have previously been published [8, 9].

Striking correlations between time-averaged equilibrium fluctuations of volume and energy on the nanosecond time-scale of a DMPC membrane at 310 K are shown on Figure 1. If $\overline{E(t)}$ is the energy averaged over 1 nanosecond and $\overline{V(t)}$ is the volume averaged over 1 nanosecond then

$$\Delta\overline{E(t)} \simeq \gamma^{vol}\Delta\overline{V(t)} \tag{1}$$

where $\gamma^{vol} = \sigma_E/\sigma_V$ is a constant, σ is the standard deviation and Δ is difference from the thermodynamical average value. Equivalent results are found for the remaining membranes. Table 1 shows correlation coefficients between volume and energy, $R = \langle\Delta\overline{E}\Delta\overline{V}\rangle/\sqrt{\langle(\Delta\overline{E})^2\rangle\langle(\Delta\overline{V})^2\rangle}$ ranging between 0.81 and 0.89.

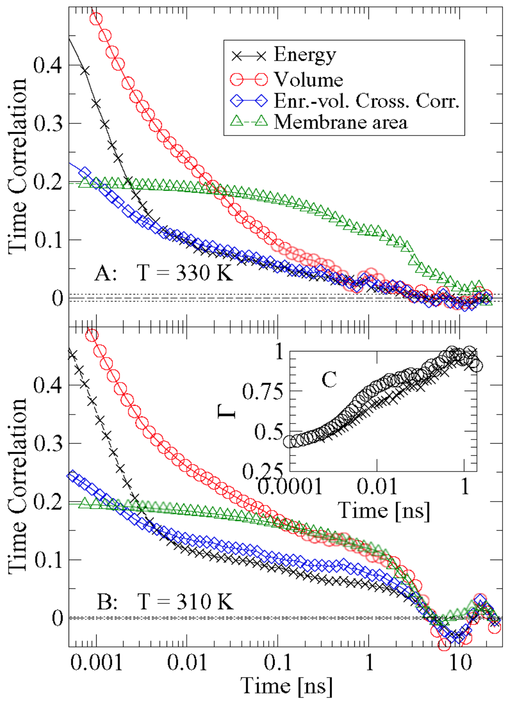

FIGURE 2. (Color online) Time correlation functions of potential energy C_{EE} (×), total volume C_{VV} (○), membrane area C_{AA} (△) and cross correlation between energy and volume C_{EV} (◇). Time correlation for membrane areas are scaled by a factor 0.2. Panel A shows data for a DMPC membrane at 330 K and panel B for a DMPC membrane at 310 K. The inset (C) displays $\Gamma = C_{EV}/\sqrt{C_{EE}C_{VV}}$ at 310 K (○) and 330 K (×). Γ approaches unity at $t \simeq 1$ ns meaning that volume and energy become strongly correlated on this timescale. Color online.

The correlation depends on the time scales considered. This can be investigated by evaluating $\Gamma(t) = C_{EV}(t)/\sqrt{C_{EE}(t)C_{VV}(t)}$ where $C_{AB}(t) = \langle\Delta A(\tau)\Delta B(\tau + t)\rangle/\sqrt{\langle(\Delta A)^2\rangle\langle(\Delta B)^2\rangle}$ is a time correlation function. $\Gamma(t) = 0$ implies that energy at time τ is uncorrelated with volume at time $t + \tau$ whereas $\Gamma(t)$ close to unity implies strong correlation. $\Gamma(t)$ is plotted in the inset of figure 2. At short time (picoseconds) Γ is around 0.5 but approaches unity at $t \simeq 1$ ns.

The "single parameter"-ness between volume and energy is connected to the experimental finding of Heimburg et. al. [1] since the slow collective degrees of freedom (at $t > 1$ ns) are the same ones which give rise to the dramatic changes of the response functions at T_m. There are some indications of this. Figure 2 shows time correlation functions of energy, volume and membrane area of

TABLE 1. Data from simulations of fully hydrated phospholipid membranes of 1,2-Dimyristoyl-sn-Glycero-3-Phosphocholine (DMPC), 1,2-Dimyristoyl-sn-Glycero-3-Phospho-L-Serine with sodium as counter ion (DMPS-Na) and hydrated DMPS (DMPSH). The columns lists temperature, correlation coefficient between volume and energy, average lateral area per lipid, simulation time in equilibrium (used in data analysis) and total simulation time.

	T **[K]**	R	A_{lip} **[Å^2]**	t **[ns]**	t_{tot} **[ns]**
DMPC	310	0.885	53.1	60	114
DMPC	330	0.806	59.0	50	87
DMPS-Na	340	0.835	45.0	22	80
DMPSH	340	0.826	45.0	40	77

DMPC membranes at 330 K and 310 K. The time constant and the magnitude of the slow fluctuations increase when the the temperature is decreased. γ^{vol} in equation 1 is 9.3×10^{-4} cm^3/J. This is the same order of magnitude as $\gamma^{vol} = 7.721 \times 10^{-4}$ cm^3/J calculated from experimental data of $C_p(T)$ and $\kappa_T^{vol}(T)$ at T_m [1].

Both the volume and energy time correlation functions show a two step relaxation at 310 K for DMPC (Figure 2B). As temperature is lowered toward T_m the separation is expected to be more significant. It makes sense to divide the dynamics into two separated processes, a fast and a slow collective process. Our simulations suggest that slow degrees of freedom can be described by a single parameter.

To see the "single parameter"-ness of the L_α phase, the fast degrees of freedom have to be filtered out. Experiments must deal with macroscopic samples where fluctuations are small and difficult to measure (the relative fluctuations scales as $1/\sqrt{N}$ where N is the number of molecules). It is therefore difficult to do the same analysis as we have done here. It is easier to measure response functions.

Fast fluctuations can be filtered out by measuring frequency dependent response functions. The slow collective degrees of freedom will show as a separate peak. The frequency dependent Prigogine-Defay ratio $\Lambda_{Tp}(\omega)$ has been suggested as a test quantity for "single parameter"-ness [4]. If $c_p''(\omega)$, $\kappa_T''(\omega)$ and $\alpha_p''(\omega)$ are the imaginary parts of the isobaric specific heat capacity per volume, isothermal compressibility and isobaric expansion coefficient respectively then

$$\Lambda_{Tp}(\omega) = \frac{c_p''(\omega)\kappa_T''(\omega)}{T_0[\alpha_p''(\omega)]^2}. \qquad (2)$$

In general $\Lambda_{Tp} \geq 1$ and only have the value of unity if a single parameter describes the fluctuations. $1/\sqrt{\Lambda_{Tp}}$ can be related to a correlation coefficient.

In summary, we found strong volume-energy correlations of the slow collective degrees of freedom in molecular dynamics simulations of different phospholipid membranes in the L_α phase. An experimental test was suggested.

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