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Lipid tempering simulation of model biological membranes on parallel platforms

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ABSTRACT

In this report we have tested a parallel implementation for the simulation of lipid bilayers at the atomistic level, based on a generalized ensemble protocol where only the torsional degrees of freedom of the alkyl chains of the lipids are heated. The results in terms of configurational sampling enhancement have been compared with a conventional simulation produced with a widespread molecular dynamics code. Results show that the proposed thermodynamic-based multiple trajectories parallel protocol for membrane simulations allows for an efficient use of CPU resources with respect to the conventional single trajectory, providing accurate results for area and volume per lipid, membrane thickness, undulation spectra and boosting significantly diffusion and mixing in lipid bilayers due to the sampling enhancement of *gauche/trans* ratios of the alkyl chain dihedral angles.

1. Introduction

Molecular dynamics simulation is an important computational tool for the study of biomolecular systems, such as biological membranes, that have lipid bilayers as main constituents [1]. The recent development of high performance massively parallel computing environments (HPC) exploiting high speed communication links has nowadays made possible parallel simulations in the time range of hundreds of nanosecond of lipid bilayers of the extension of tens nanometers. In spite of the indisputable and tremendous gain in the performance with respect to early serial applications, computational scientists still face a severe length-scale and a time-scale problem in membrane simulation. The current limits in length and time scale in fully atomistic simulations (20–30 nm and $\simeq 1$ μs respectively) severely restrain the possibility of studying key properties of bilayers like the bending rigidity via determination of the undulation spectrum and/or cooperative transport phenomena. Both these properties are intimately connected with important biological situations including endocytosis, lipid raft formation and stability, membrane fusions an membrane trafficking [2,3].

As stated, flat lipid bilayers under periodic boundary conditions provide a simple and effective model system for biological membranes. Nonetheless, in order to avoid size effects [1], the simulations of a hydrated bilayer at the atomistic level requires a number of atoms in the order, at least, of tens of thousands, resulting in a high wall-time even resorting to efficient parallel algorithms such the as the domain decomposition method (DDM) [4-6].

Typically, on the CRESCO3 HPC platform [7] a relatively small system, such as a hydrated lipid bilayer of 36 molecules of palmitoyl oleoyl phosphatidylcholine (POPC) per leafleat (about 17,000 atoms), can run with a maximum speed of 20–25 ns per day using the popular GROMACS Molecular Dynamics (MD) program [5,8] exploiting at most 160 processors with an efficiency of less than 50%. This is so since, after a certain processor number, the inter-domain communication overhead dominates over the time spent in the computation of the forces within each domain. In other words, in DDM schemes there is an *optimal domain size* (ODS/DDM) for a given HPC configuration. The ODS/DDM is in the order of few hundreds atoms on most of the common CPU-based or GPU-based HPC architectures [9].

The saturation problem on parallel platform can be obviously circumvented by simply increasing the size of the sample, i.e. by increasing the number of ODS domains to be assigned to each processor. In this way, the simulation speed in terms of ns/day remains roughly independent on the size of sample, provided that number of available cores is equal to or greater than the number of ODS domains. If, on one hand, large samples allow, by taming fluctuations of ensemble averages, a faster convergence of key static membrane properties such as mean lipid area, head-to-head thickness, bending rigidity and undulation spectra, a wider surface requires longer traveling times for a diffusing component thus increasing significantly the equilibration times for, e.g., perfect mixing of a two component system under

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scrutiny [10]. The transport problem is so acute in the membrane simulation practice, that, trading model accuracy in exchange for computational speed, approaches have been developed using the *coarse-grained* models, where larger molecular units are considered as single particles [11].

In this report we investigate on the effectiveness of using advanced Hamiltonian Replica exchange schemes (HREM) with selective scaling of specific degrees of freedom of the system [12-16] as a mean for boosting configurational sampling in simulations of model membranes at the atomistic level. Enhanced sampling techniques for membrane simulations has been recently reviewed by Mori et al. [17]. Standard temperature REM in membrane systems has the obvious drawback that the simulation must be performed in conditions of *constant volume*, in order to preserve the integrity of the system and avoid catastrophic behavior at high temperatures. While it has been recognized [18,19] that the existence of sharp cooperative transitions (such as phase transitions) can lead to temperature exchange bottlenecks in REM schemes and significantly reduce the sampling efficiency, nonetheless standard temperature REM methods have been recently used as an expedient to gain insights on the sol-gel transition in coarse grained lipid bilayer models as a function of temperature in conditions of constant pressure, pushing the upper temperature limit (390 K) slightly beyond the water boiling point [20]. Enhanced sampling techniques have been employed to study the conformational landscape of proteins embedded in biological membranes [21,22]. To our knowledge, the only *genuine* replica exchange scheme (i.e. a simulation scheme for *enhanced sampling* of a target thermodynamic state) of a membrane bilayer system to date was proposed by Mori et al. [23] in the context of NPγT simulations. Their generalized ensemble (GE) approach is based on exchanges between few replicas spanning the surface tension (γ) space, rather than the temperature space, from zero tension of the target replica to higher tensions, obtaining a moderate gain in the convergence time of structural parameters.

On the other hand, recent studies have highlighted the key importance of lipid flexibility and entanglement in shaping the transport and undulation phenomena in biological membranes [24,3]. These molecular properties, in turn, have time scale dynamics that are essentially dictated by the free energy barriers separating *gauche* and *trans* states for the dihedral conformation of the torsion around the sp^3 bonds of the alkyl chains in the hydrophobic interior of the bilayer. One can hence infer that, by selectively scaling, along the replica progression, the energy terms implied in these barriers (i.e. dihedral potentials and 1–4 Coulomb and Lennard-Jones interactions), the jump rate for *gauche trans* interconversion can be exponentially increased in the hot replicas, thereby enhancing diffusion and area/volume modulation throughout the GE, in condition of *constant pressure*, without necessarily triggering phase transitions due to the fact that most of the degrees of freedom of the system remain at the target temperature. Along precisely this line of reasoning, a biased torsional potential with user adjustable parameters, for example, has been recently used to boost conformational sampling in the lipid phase by McCammon and coworkers without observing catastrophic cooperative phenomena [24,25]. Their approach, termed "accelerated MD" (aMD), is actually equivalent to a single standard Umbrella Sampling simulation [26] with a torsional bias potential and, while useful for speeding up diffusion and conformational sampling, has the well known limitations in the acquisition of the average properties due to the high energetic noise produced by the bias potential when re-weighting back to the unbiased system [17].

In this paper we shall describe and test on a POPC atomistic-level bilayer system, a rigorous, parameter free, torsional tempering scheme in the context of a genuine replica exchange simulation, allowing to collect, in few ns or tens of ns time span on the target state, a manifold of equilibrium configurations statistically out of the reach of conventional (single trajectory) simulations. The present report is organized as follows. In the section Theoretical background, we briefly summarize the theoretical aspects of the HREM technique, with emphasis on torsional tempering for membrane simulations. In the Methods section, we succinctly describe the system and the various parallel simulation techniques used in our contribution. In the section Results, we compare configurational properties such as volume and area fluctuations, diffusion and bilayer structure obtained using the HREM approach as opposed to the conventional single trajectory technique. In the Conclusions section conclusive remarks are presented.

2. Theoretical background

2.1. Hamiltonian Replica Exchange and solute tempering schemes

"Solute tempering" was introduced originally by Liu and Berne [27]. These authors developed a variant of the temperature replica exchange method (T-REM) whereby the solvent-solvent interaction energy is rescaled along the replica progression such that it vanishes in the exchange probability. This partition was strictly defined for the "real" solvent. In the Hamiltonian Replica exchange method [12,13], rather than globally scaling the temperature of the system as in T-REM, each state in the generalized ensemble is characterized by its own potential energy function. A flexible and efficient solute tempering scheme has been recently formalized [15] in the context of HREM. This approach relies on the definition of independent scaling factors for each of additive components of the total potential energy of the system. Following Ref. [15], the potential energy function of the *m*-state in HREM can hence be compactly written as

$$V_m(X) = \mathbf{c}_m \cdot \mathbf{V}(X) \tag{1}$$

where X represent a configuration of the system and where the components of the vector $\mathbf{V}(X)$ correspond to the individual additive terms in the system potential energy, i.e. $V(X) = \sum_i V_i(X)$. The $\mathbf{c}_m$ vector is the scaling vector for state *m*, where the *i*-th component is the scaling factor in the *m* state for the $V_i(X)$ additive term. In the target (unscaled) state, all the components of the $\mathbf{c}$ vector are equal to 1, so that $V_m(X) = V(X)$. The transition probability in a replica exchange scheme with the state potential energy given by Eq. (1) is given by

$$P = \min(1, e^{\beta \Delta \mathbf{c} \Delta \mathbf{V}}) \tag{2}$$

with $\Delta\mathbf{c} = \mathbf{c}_{m+1} - \mathbf{c}_m$ and $\Delta\mathbf{V} = \mathbf{V}(X_{m+1}) - \mathbf{V}(X_m)$. From Eq. (2), it is easy to see that only the potential terms V_i that are scaled (i.e. those corresponding to components $c_m^{(i)} \neq 1$) will affect the exchange probability. Also note that all replicas are simulated at the same inverse temperature β and when all components of the $\mathbf{c}$ vector are scaled coherently (i.e $V_m = c_m V$), one recovers the standard Hamiltonian REM with the scalar scaling factor βc_m playing the role of a scaled inverse temperature.

With this powerful formalism, in a single accepted replica exchange event, the vector $\mathbf{c}$ can be swapped instead of the coordinates (thereby keeping, as in T-REM, the communication overhead at a nominal level) and local scaling can be implemented in a very general fashion using an appropriate, user defined partition of the system and/or of the potential function $V(x)$. By limiting the scaling to selected portions of the overall potential energy, the system can be surgically heated on few relevant degrees of freedom, therefore limiting the number of replicas in the GE also when implementing a very small scaling factor *c* corresponding to very high local temperature *T*/*c*.

In a solute tempering scheme, for example, the "solute" and the "solvent" are by definition the part of the system which will be scaled and the unchanged part, respectively. In HREM implementations based on Eq. (1) [28-32], any subset of atoms out of the N system atoms can be selected, thus defining the "solute". This subset may include disconnected portions of real solute, as well as selected solvent molecules. The scaling factor *c* for the additive component of the so defined "solute"-" solvent" potential can be chosen at will and can involve different contribution of solute, solvent or solvent-solute potential. In the EDU-REM implementation (Energy Driven Undocking Replica Exchange