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Molecular dynamics simulations of lipid bilayers

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Abstract

Computer simulation methods are becoming increasingly widespread as tools for studying the structure and dynamics of lipid bilayer membranes. The length scale and time scale accessible to atomic-level molecular dynamics simulations are rapidly increasing, providing insight into the relatively slow motions of molecular reorientation and translation and demonstrating that effects due to the finite size of the simulation cell can influence simulation results. Additionally, significant advances have been made in the complexity of membrane systems studied, including bilayers with cholesterol, small solute molecules, and lipid-protein and lipid-DNA complexes. Especially promising is the progress that continues to be made in the comparison of simulation results with experiment, both to validate the simulation algorithms and to aid in the interpretation of existing experimental data.

Keywords: Molecular dynamics; Simulation; Force-field; Algorithm; Interactions

1. Introduction

The structure of a lipid bilayer in its biologically relevant, liquid-crystalline, state cannot be described by any single conformation of the molecules making up the membrane assembly. This inherent disorder leads to difficulties in developing simple models that can be used to visualize the system and to interpret experimental results. In the past decade, atomic-level models of the lipid bilayer have been developed as a useful tool for accomplishing these tasks. Molecular dynamics (MD) simulation, where particles representing lipid, water, and solute atoms are followed through time, has been used extensively because it simultaneously provides information on both the spatial organization and temporal dynamics of the system. This review will focus on MD simulations of lipid bilayer membranes described in the literature during the period from early 1999 to early 2000. For earlier reviews of the field of membrane simulation, the reader is referred to the following literature [1–7]. An overview of bilayer structure in general, covering mostly experimental results but also discussing bilayer simulations, is given by Nagle and Tristram-Nagle [8•].

The following discussion has been organized around the topics of: (1) pure lipid simulations, focusing on insights into lipid structure and dynamics and methodological developments; (2) membrane solute simulations, focusing on the interactions of small solute molecules and cholesterol, with their membrane environments; and (3) membrane-biopolymer simulations,

Abbreviations: DPPC, dipalmitoylphosphatidylcholine; DMPC, dimyristoylphosphatidylcholine; MD, molecular dynamics; NMR, nuclear magnetic resonance; PC, phosphatidylcholine; POPC, palmitoyloleoylphosphatidylcholine

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focusing on complex membranes containing proteins and DNA.

2. Pure lipid simulations

Increases in processor speed and the availability of parallel computers allowed major advances to be made in increasing the length scale and time scale accessible to bilayer MD simulations during the period of this review. With this increase in simulation duration, a growing number of reports have analyzed motions on the nanosecond time scale. Essmann and Berkowitz [9•] detailed the slow motion of the PC headgroup atoms and found that the orientation of water molecules compensates for the headgroup fluctuations to maintain a nearly constant membrane dipole potential. The long time scale of these headgroup motions was also emphasized in studies of headgroup interactions through charge pairing and water bridging in DMPC, where contact lifetimes on the order of a nanosecond were observed [10]. In a simulation of an especially large membrane patch, Lindahl and Edholm [11••] estimated the relaxation time of collective udulatory and peristaltic modes of motion. The long time scale for lipid reorganization, observed in these simulations, has important consequences in the study of the more complex membranes discussed in Section 5 of this review because the molecular translations and reorientations required to solvate incorporated species is presumably also on the multi-nanosecond time scale.

Membrane simulations with durations of 10 ns [9•,12•] and system sizes reaching 1024 lipids were reported [11••], allowing new comparisons between simulation results and experimental data. Examples include the calculation of Nuclear Overhauser Enhancement Spectroscopy (NOESY) cross-relaxation rates from a 10-ns simulation of DPPC and the subsequent interpretation of the underlying correlation functions in terms of lipid motions [12•], the determination of the diffusion coefficients for molecular rotation about the lipid long axis and for lateral translations [9•], and the computation of the bending modulus [11••] and area compressibility modulus [11••,13•]. An especially interesting comparison between simulation and experiment was the work of Tobias that focused on the wide variety of experimental data available from neutron scattering techniques [14••]. The interpretation of the relationship between lipid surface area and NMR S_{CD} order parameters was reconsidered based on the results of a DPPC simulation, where a new formula was proposed that reproduced the simulation area per lipid [15•]. A second study of the order parameters in DPPC, this one focusing on the S_{CC} order parameter [16•] and motivated by recent experimental results for this quantity [17], found significant differences between the conformations of the *sn*-1 and *sn*-2 fatty acid chains. Other interesting simulations motivated by specific experimental systems include a study of a hybrid bilayer formed from a DPPC monolayer and an alkanethiol self-assembled monolayer [18], and a study of solvent effects where water was replaced by dimethylsulfoxide (DMSO) in a simulation of DPPC [19]. An interesting observation from the latter simulation was that the dipole potential changed sign when comparing the aqueous and DMSO systems, a result that has implications for theories of the hydration force acting between membranes.

Several important methodological issues were addressed in the past year. Chiu et al. [20•,21] described a hybrid equilibration procedure combining configurational bias Monte Carlo (CBMC) with MD simulation to improve sampling efficiency. These methods could be especially useful for generating initial conditions of complex membranes where one wishes to equilibrate the lipids surrounding an incorporated solute. The same group also developed a hydrocarbon parameter set, by fitting to molecular volumes and heats of vaporization over a range of chain lengths, for use in lipid simulations [22•]. Especially encouraging was their finding that a single set of hydrocarbon parameters could reproduce both short chain and long chain experimental data. In a study to test parameterization, quantum mechanical calculations on indole and *N*-methylindole were carried out to study whether cation-π interactions, thought to be crucial in describing the attraction of aromatic amino acids for the membrane interface, can be described using simple point charges placed on atomic centers [23]. The authors concluded that much of the interaction is captured for point charges approaching perpendicular to the aromatic ring, however, agreement between the quantum mechanical results and force field calculations were less satisfactory for other directions of approach.

Most MD simulations of lipid bilayers have focused on the liquid crystalline state, however, one simulation of gel state DPPC was reported where the authors carried out a systematic study of the effects of force truncation and boundary conditions on structural parameters such as area per molecule, bilayer repeat spacing, chain tilt, and fraction gauche bonds [24•]. They concluded that gel phase simulations require a fully flexible simulation cell during the equilibration period and that Ewald summation techniques are superior to truncation methods, and showed that equilibration of chain torsions near the headgroup region can be a very long process in the gel state.

The most pressing issue in the development of bilayer simulation methods over the past 5 years has

been the choice of boundary conditions in constant pressure simulations, where the size and/or shape of the simulation cell is allowed to adjust. In principle, this type of simulation can provide a powerful technique for determining membrane structural parameters, such as the surface area per molecule. The argument among practitioners of membrane simulation has centered on the appropriateness of applying an isotropic pressure (typically 1 atm) in both the directions parallel and perpendicular to the membrane surface. Employing an isotropic pressure tensor is equivalent to imposing a condition of zero surface tension, γ, on the lipid interface. It has been suggested that zero surface tension is the appropriate state for an unstressed bilayer at its free energy minimum and thus that an isotropic pressure is the correct ensemble for MD bilayer simulations [25]. Others have argued, based on the confining effects of periodic boundary conditions [26–28] or comparison with monolayer systems [29], that a bilayer (at least on the length scale of a typical MD simulation) may have a finite surface tension at the surface area per molecule that minimizes its free energy. Unfortunately, there is little guide from experiment or elsewhere on its precise value, and the value of γ calculated from constant area simulations has been observed to depend sensitively on the force field employed and the method of calculating long-range coulombic interactions [30]. Consequently, the majority of constant pressure lipid simulations have been done with $\gamma = 0$, or with only the cell dimension perpendicular to the membrane allowed to adjust against atmospheric pressure (the NPAT ensemble, for constant particle number, normal pressure, surface area, and temperature). Substantial progress on this problem has been achieved recently. Feller and Pastor showed, via a series of DPPC simulations differing only in their value of the applied surface tension, that the area per molecule and other structural parameters depended sensitively on the value of γ applied [13•]. Importantly, their comparisons with fixed area simulations showed that, when systems at approximately equal surface areas were examined, there was no difference in structural or dynamic properties due to choice of ensemble. Thus, the value of the applied surface tension (or fixed surface area) is much more important than whether one uses a fully flexible simulation cell or one with a fixed area. Lindahl and Edholm carried out a series of fixed area simulations and analyzed the calculated surface tensions in terms of the energetic and entropic contributions from various interactions between lipid headgroups, fatty acid chains, and water [31•]. They find the surface tension calculated from simulation to be a sum of large terms of opposing signs and interpret this result as explaining the sensitivity of γ to simulation setup. Finally, in an ambitious series of simulations where 64, 256, and 1024 DPPC molecules were simulated under isotropic pressure, Lindahl and Edholm observed that the area per molecule increased uniformly as the number of lipid molecules was raised [11••]. This explicit demonstration of system size-dependent behavior in a constant pressure simulation is consistent with earlier observations of Feller and Pastor [26] where the calculated surface tension decreased with larger system size in a series of constant area simulations. Combining the work of the two groups results in clear evidence for a size-dependent surface tension present in lipid simulations over the range from 18 to 1024 molecules. By extrapolating to infinite sized membranes, Lindahl and Edholm estimate that a standard sized membrane simulation consisting of 64 lipids will have an area per molecule that is $\sim 2–3$ Å^2 too small when simulated at $\gamma = 0$. The results of Feller and Pastor, using smaller systems, suggest the effect could be somewhat larger. Clearly, constant pressure simulations of lipid bilayers are more complicated than those on isotropic systems and the artifacts inherent in a uniform pressure tensor, while only a few percent of the total area, are large enough to influence lipid structure and dynamics.

3. Membrane-solute simulations

Both the transport of small solutes and their effects on membrane structure have been studied extensively with MD simulation. Pohorille and colleagues [6,32•] have recently published a review of their work and others in the field, providing a useful overview of the theories and simulation strategies that have been applied to membrane permeation. Many simulation studies have focused on the role of spontaneously arising free volume with the membrane, including the works of Xiang [33] and Xiang and Anderson [34] where MD simulations of noble gases in a model membrane were used to study the fundamental properties of membrane transport. Another target of membrane simulation has been the interaction of anesthetics, such as a recent study of halothane in a DPPC bilayer [35•]. The halothane was observed to localize within the hydrocarbon core and to change the bilayer structure, lowering the fatty acid chain order parameters at the center of the membrane.

Several simulations of phospholipid bilayers containing cholesterol were reported during the period of this review. Smodyrev and Berkowitz [36] performed simulations with DPPC/cholesterol ratios of 8:1 and 1:1 and compared these results with those of a pure DPPC bilayer under indentical conditions of temperature and hydration. They found a significant decrease in lipid surface area, thus reproducing the experimen-

tally observed 'condensing' effect that cholesterol has on membrane lipids, along with an increase in chain order as measured by the deuterium order parameters and a decrease in the gauche fraction. This same group also examined the differences between a 1:1 mol ratio mixture of DPPC and cholesterol sulfate and the aforementioned 1:1 mixture of DPPC and cholesterol, and found the condensing effect and ordering of alkyl chains was less pronounced with cholesterol sulfate [37]. A study of a DMPC/cholesterol bilayer, focusing on the effects of cholesterol on the membrane/water interface, suggests that the addition of cholesterol disrupts Coulombic interactions between lipid headgroups and increases lipid–water interactions [38].

4. Membrane-biopolymer simulations

The number of complex membrane simulations reported in the literature has exploded recently, and now likely surpasses the reports of 'simple' bilayer systems (described in the previous sections) in most journals. Simulations of lipid bilayers containing peptides species have recently been thoroughly reviewed by Forrest and Sansom [7], thus we will not attempt to cover all published works but focus only on a few observations.

Two studies of melittin in phospholipid bilayers have recently been reported. A single peptide was followed for 500 ps and observed to induce disorder in the lipid chains, with the magnitude of this effect different for the two halves of the bilayer [39]. A second MD simulation studied a membrane pore formed by four melittin molecules initially embedded in a lipid bilayer, however, over the course of the simulation the aggregate decayed into a trimer and an isolated monomer [40]. This relatively long melittin simulation (5.8 ns in length) shows convincingly that significant trajectory must be obtained before concluding that an initial membrane structure is thermodynamically stable. Another important methodological issue is raised by the melitin simulation in Bachar and Becker [39], that is how does one allow surface densities on the upper and lower monolayer to adjust independently when the peptide insertion is not symmetrical? Some bilayer simulations have employed fully flexible simulation cells [41], but the majority imposed orthorhombic symmetry on the system that could introduce artifacts into the membrane structure.

An especially active area of research has been the study of proteins forming ion channels spanning the lipid membrane. During the period of this review, simulations of a gramicidin channel [42], a variety of K^+ channels [43•,44,45], a synthetic Leucine-Serine ion channel [46], a proton channel [47], and other helical peptides that associate in lipid bilayers to form ion channels [48–50], have been reported. A number of these simulations have explicitly followed the dynamics of ion or water permeation through the channel [43,45,51•] and identified structurally significant features that influence this process. Molecular dynamics simulations have also been used to test channel protein structures generated by homology modeling [52,53], to compare the effect of a bilayer membrane with other solvent environments [54•], and to investigate alternative model-built structures as initial conditions [55•]. In the latter it was observed that simulation results for the protein structure are sensitive to details of the starting structure, at least on the nanosecond time scale.

Finally, the first report describing an MD simulation of a lipid–DNA complex was reported by Bandyopadhyay et al. [56•]. This system, a hydrated lipid bilayer composed of a mixture of the cationic lipid dimyristoyltrimethylammonium propane (DMTAP) and the neutral lipid DMPC, with a DNA strand intercalated between bilayers, was motivated by experimental studies on these compounds and the potential application of lipids as DNA carriers for gene transfer therapies.

5. Conclusions

Improvements in simulation protocol, such as the particle mesh Ewald summation (PME) that allows efficient calculation of Coulombic interactions [57], and constant pressure methods that allow flexibility in the size and shape of the simulation cell [58], have dramatically improved the accuracy of membrane simulations in the recent past. These tools, as well as the continual refinement of potential energy parameters, have advanced the field of bilayer simulation to the point where quantitative agreement between simulation and experiment has been achieved by numerous groups for most positions of the fatty acid chain order parameters (the quantity most often used to benchmark lipid simulations). Further progress is likely needed before similar convergence will be observed in headgroup and water structure. As examples, few if any simulations have been able to reproduce the splitting of the two unique order parameters observed experimentally for C2 of the *sn*-2 chain, and the magnitudes and origins of the membrane dipole potential have varied widely among reported simulations.

A review of lipid bilayer simulations in this journal from 3 years past predicted orders of magnitude increases in the length scale and time scale accessible to atomic-level MD simulation [2]. Certainly this pre-

diction has come true and at present it seems clear that the increased computational power and algorithmic advances needed to sustain this growth will continue, at least for the near future. This increase in computational power will be especially useful in studying the lipid–protein complexes of significant biological interest. These simulations suffer not only from poor sampling due to the small number of solute molecules being followed, but also from long relaxation times inherent in equilibrating a lipid solvent environment. It is critical that in the drive to increase the complexity of systems under study, the accumulated knowledge gained from pure lipid simulations, e.g. long equilibration times and sensitivity of results to treatment of electrostatic interactions, is not overlooked.

Acknowledgements

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