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Computer Simulation Studies of Model Biological Membranes

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ABSTRACT
This Account is focused on computer simulation studies of model biological membrane systems with potential applications in biomedical research. In the past decade, classical molecular dynamics has provided novel insights into the properties of model biomembrane systems, including the nature of the DNA−lipid interactions, the effect of pore-forming transmembrane peptides on the lipid environment, and the partitioning of volatile anesthetic molecules. Such simulations, employing full atomic detail, are typically restricted to systems of dimensions less than ∼10 nm. Simplified models of the coarse-grain type have been intended to bridge the gap between full atomistic detail and the mesoscopic (micron) regime. The use of such models is illustrated with the example of anesthetics in a phospholipid bilayer.

Introduction

Biological membranes are composed of a complex (organized) mixture of lipids, proteins, and carbohydrates. These sheetlike structures form the different compartments within the cell and the boundary that separates living cells from their environment.[1] In the past decade, the usual view of lipids as a mere fluid medium for membrane-bound proteins[2] is fading out, and a new picture in which lipids have a functional role is emerging.[3,4] From (complex) lipid "rafts"[4] in plasma membranes to (mere) large scale phase separation[5] in lipid mixtures, this new view is in large part based on the notion of microdomain formation and lateral organization of membrane heterogeneities. Cholesterol is an essential component of biomembranes and plays an important role in the formation of microdomains.[5] Cholesterol seems to be crucial in the sorting of membrane heterogeneities and specially in the formation of the so-called lipid rafts[4] in plasma membranes, which are rich in cholesterol and sphingolipids and are thought to act as platforms for adhesion and signaling. Glycolipids, whose headgroups are attached to oligosaccharides, form an important class of lipids that play a fundamental role in cell−cell and cell−matrix interactions. They not only function as specific recognition sites but also form a soft cushion between cells and tissues as a result of their unique swelling behavior, preventing nonspecific adhesion. This indicates a complex interplay between weak generic forces and strong specific forces.[6] Recent experiments[6] of synthetic glycolipids with headgroups composed of lactose oligomers at interfaces have shown that these represent quite realistic models for the glycocalix. Lipid−peptide and peptide−peptide interactions in membrane environments play a fundamental role not only in the folding of natural proteins or association of synthetic peptides but also in the mechanisms of action of toxins and antimicrobial peptides or other peptides with lytic activity, which are lethal to the cells.[7] Because of the different scales of time and length involved in the processes of insertion and assembly, peptide aggregation in membranes and the formation of pores is an important and challenging problem.

The development of novel algorithms[8] and the revolutionary advances in computer hardware technology that took place during the last two decades have permitted computer simulations of complex biological membranes to advance at a similar pace as and in connection to experiment in biomedical applications.[9] Computer simulations provide a unique tool to analyze biomembrane properties from an atomic perspective with a level of detail missing in any other technique. The excellent agreement with experiment obtained in classical molecular dynamics (MD) simulation studies[10−18] on simple model membranes consisting of lipid bilayers in the biologically relevant fluid lamellar phase have permitted new applications to membrane systems of a considerable degree of complexity. These more complex systems usually consist of the introduction of additives or foreign (bio- or nonbio-) molecules, such as small amphipathic molecules or other solutes, membrane peptides or proteins, or other biopolymers, into a simple model lipid bilayer. Such studies have provided invaluable information about the nature of lipid−lipid,[15] DNA−lipid,[19] peptide−lipid,[9,20] and peptide−peptide[1,9] interactions. It would be of great interest in future studies to investigate at a microscopic level the kinds of fundamental problems described in the previous paragraph, in which very different types of forces are

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present or diverse lengths and temporal scales are involved. Simplified models of the coarse grain type could be useful for this kind of application and have been successfully applied earlier to polymers and more recently to surfactants.[21]

In coarse grain models, solute and solvent sites are usually represented as a group of atoms that interact in an effective way, reducing in this way the computer time needed for the calculations. Coarse grain models can be adjusted to mimic a specific system instead of a general phenomenon.[22] They have been shown to successfully describe collective phenomena occurring at mesoscopic scales,[22−25] which have only been reached very recently by atomistic simulations[26,27] after sacrificing an accurate treatment of the long range (electrostatic) forces.

In this Account, we focus on multicomponent membranes with potential applications in biomedical research in which computer simulation, classical MD in particular, has been applied successfully to get new insights into their behavior. Specifically, we will discuss the nature of DNA−lipid complexes that may be relevant in gene therapy, the effect of a pore-forming bundle of peptides on the lipid environment, and the partitioning of anesthetic molecules within model membranes. The possible utility of a simplified model of the coarse grain type to study the effects of anesthetics in phospholipid bilayers is also illustrated. Some other aspects of lipid bilayer simulations are described in the Account by Pastor et al. (this issue).

DNA−Lipid Complexes

DNA−lipid complexes are important biomedical materials because of their potential use as vectors in gene therapy.[28] These complexes are effective carriers and deliver DNA to the nucleus of living cells, where damaged or missing genes are replaced. Currently, the most common method of gene delivery is by means of viral carriers of DNA.[29] However, the risk involved in the clinical applications of the latter points to lipid−DNA complexes as a potential alternative. Recent developments in the field have selected a few cases (binary mixtures of suitable cationic and neutral lipids) with the adequate properties.[30] For instance, mixtures containing the unsaturated neutral DOPC and the cationic DMTAP lipid formed a novel multilayer structure with alternating lipid bilayers and DNA monolayers.[31,32] There, the hydrated DNA molecules are intercalated between each pair of lipid bilayers in the water region. In each layer, the DNA strands are parallel to one another, forming a two-dimensional smectic phase. Similar structures have been also observed in binary mixtures of the saturated neutral lipid DMPC and the cationic DMTAP with DNA.[33,34] When one of the lipids has the tendency to adopt a negative curvature at the lipid−water interface, there is a second kind of liquid crystal structure, which consists of an inverted hexagonal phase that performs better for gene therapy purposes than the lamellar case.[30]

Recent all-atom MD simulations of lipid−DNA complexes containing DMPC and DMTAP lipids[19] have obtained interesting insights into the nature of the lipid−DNA interactions and the role of the lipid interface in the formation of these complexes. This simulation was carried out in the fluid lamellar phase of the complex ($T = 50$ °C) at the isoelectric point (the mixing ratio for which the DNA and lipid charges cancel each other) and contained 24 DMPC, 20 DMTAP, 1003 water molecules, and a DNA duplex d(CCAACGTTGG)$_2$.[19] Unless otherwise stated, all of the atomistic simulations reported herein were performed using the PINY_MD program[8,35] with the latest all-atom CHARMM force field[13,36] for the different components of the biomembranes and a rigid TIP3P water model.[37] Figure 1 shows the configuration of this system after 5.5 ns. The presence of the DNA intercalated between the two lipid−water interfaces, which were initially nearly flat, produces significant undulations of the membrane surfaces. This indicates a strong interaction between the lipid interface and the DNA. In particular, these calculations revealed that the phosphate groups of the DNA can interact directly or via bridging water molecules, with either the choline group of the neutral DMPC lipids or the cationic lipids with equal probability. The negative charges of the DNA phosphate groups are, thus, screened

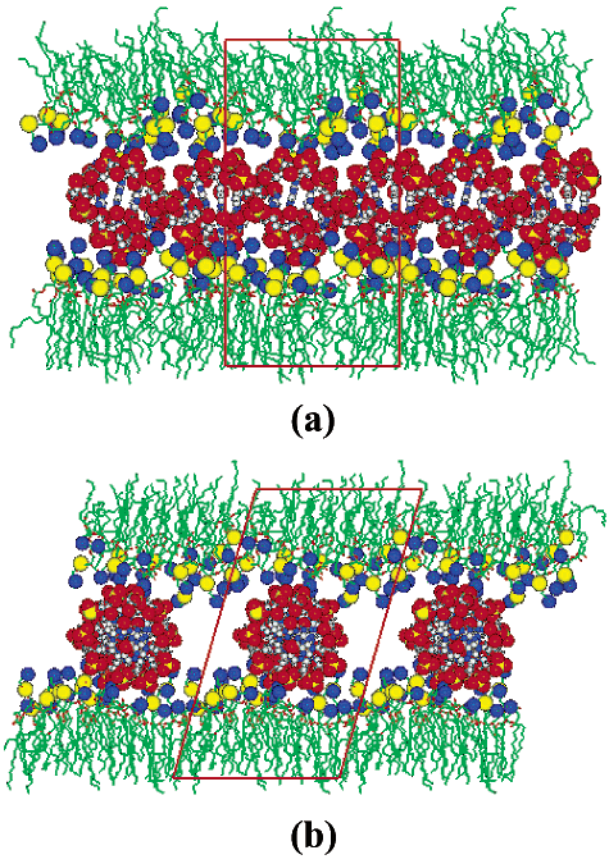

FIGURE 1. Configuration of the DMPC/DMTAP−DNA complex taken from an MD simulation after 5.5 ns.[19] The details of the simulation can be found in ref 19. Two different views are shown: (a) perpendicular to, and (b) along, the DNA axis. The DNA and the lipid headgroup P and N atoms are drawn as spheres, whereas the lipid chain atoms are drawn as sticks. The atom coloring scheme is N, blue; O, red; P, yellow; C (DNA), gray; C (lipid), green; and H, dark gray. For clarity, the water molecules and the lipid H atoms are not shown. The (central) simulation cell is shown in red.

by both lipid species. This behavior is due to the electrostatic interactions taking place at the lipid bilayer surface. At the interface, three different kinds of interactions were observed,[19] namely: PC group−PC group via the formation of P^--N^+⋯P^--N^+ charge pairs linking the negatively charged phosphate groups (P^-) and the positively charged choline groups (N^+), typical of pure (PC) lipid bilayers;[15,38] P^- groups of the DMPC molecules and the N^+ of the TAP groups (N^+⋯P^--N^+ charge pairs); and N^+ of both the PC and the TAP groups of the lipids with the anionic DNA phosphates. The interactions between the P^- groups of the DMPC molecules and the N^+ of the TAP groups cause a reorientation of the PC headgroup dipole moments (denoted by $P^- \rightarrow N^+$) away from the lipid−water interface, in agreement with NMR experiments on similar systems,[39] thereby pushing the covalently bonded choline groups out of the interface, which then become available to interact with the anionic DNA phosphates.

Pore-Forming Peptides

The incorporation of relatively large membrane proteins, such as those forming pores that function as ion channels, in membranes is expected to modify the physical properties of the lipid bilayer. However, because of the fundamental importance of these proteins, most of the effort of the experimental and theoretical works has been devoted to the study of the effects of the lipid environment on the structure, dynamics, and function of membrane proteins. For instance, recent notable successes of computer simulation in the area of transmembrane channels include the KcsA K^+ channel[40] and the *Escherichia coli* aquaglyceroporin GlpF,[41] shown at full atomic detail. The difference between the hydrophobic length along the membrane normal of the lipid bilayer and the protein (hydrophobic mismatch) and the membrane curvature have been identified as the key factors for this interplay between structure and function.[1,9,42]

Recent experiments have been focused on the study of the influence of simple membrane peptides on the membrane properties in an effort to get more insights into the structure and dynamics of model membranes. The effect of incorporating small membrane proteins or model transmembrane peptides into lipid bilayers changes the phase behavior of the water−lipid system[43,44] and can even promote nonbilayer phases.[43] For instance, single transmembrane peptides can decrease the temperature of the phase transition and increase the orientational order of the lipid chains.[45] Other NMR experiments performed on a mostly hydrophobic cationic peptide showed that the order parameters of the hydrophobic region were significantly modified neither by the peptide in DMPC lipid bilayers nor in DMPC/DMPS (5:1) but that the peptide affects the membrane interface by rotating the headgroup dipoles in a direction away from the membrane plane as a result of the (sign of the) "bound" surface charges.[46] In these experiments, even though a major influence is expected to occur on the lipids located closer to the peptide, the formation of lipid−protein complexes was ruled out at least in the time scale of the experiments ($\approx 10^{-5}$ s).[46] Systematic NMR and ESR spectroscopy studies using hydrophobic polypeptides of different lengths,[43] however, indicate that peptides can induce a hydrophobic mismatch that perturbs the bilayer in a systematic manner. Differences obtained for peptides with different shapes indicate also that the topology of the peptide surface modulates the effect of hydrophobic mismatch.[43,45]

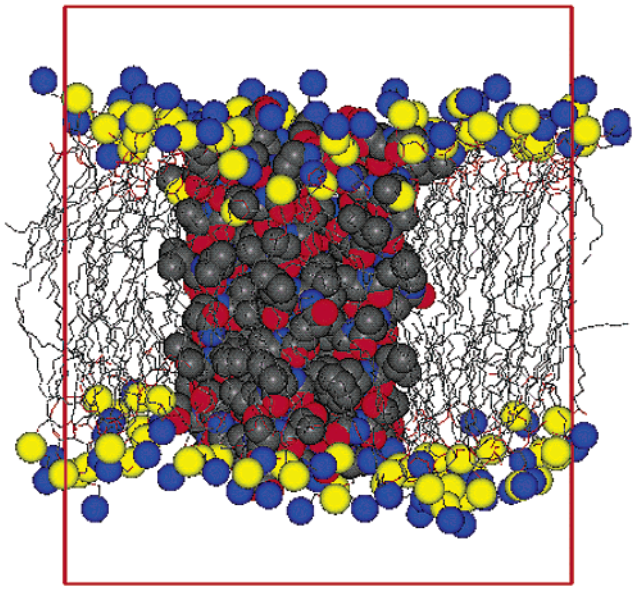

FIGURE 2. Configuration of the 5×M2−DMPC system taken from an MD simulation after 2 ns.[47] The details of the simulation can be found in ref 47. The lipid molecules are shown as balls and sticks except the N and P atoms of the headgroups, which are displayed as blue and yellow spheres, respectively. For clarity, the water molecules and hydrogen atoms are not shown. The coloring scheme for the M2 helices is N, blue; O, red; C, gray; and S, yellow. The radii of the spheres correspond to the atomic van der Waals radii of the different species. The C-terminus (synaptic or extracellular[48]) is located at the bottom of the bundle.

In Figure 2, we show a snapshot of a recently performed atomistic MD simulation[47] of the transmembrane homopentameric bundle of the α-helical M2 segments that are thought to form the pore region of the nicotinic acetylcholine receptor (nAChR) ion channel.[48] The nAChR is the neurotransmitter-gated ion channel responsible for the rapid propagation of electrical signals between cells at the nerve−muscle synapse.[49] Previous simulation studies on the nAChR were focused exclusively in peptide−peptide interactions of simplified models or the effects of the α-helices environment on the secondary structure.[50] To investigate the effect of the presence of pore-forming peptides on the properties of the lipid environment, the peptide bundle was embedded in a fully hydrated DMPC lipid bilayer in the fluid lamellar phase, L_α, at ambient conditions ($T = 303$ K and $p = 1$ atm) with a lipid/peptide molar ratio of 19:1.[47] The M2 segments are characterized by the sequence GSEKMSTAISVLLAQAVFLLLTSQR and correspond to the δ subunit of the native nAChR ion channel of the *Rattus norvegicus*.[48] Preliminary results[51] indicate that the main effect of the incorporation of the pentameric bundle into the DMPC lipid bilayer consists

of an increase of the bilayer thickness and the orientational order of the DMPC lipid acyl chains. The orientational distribution of the lipid dipole moments with the membrane normal, which is broader and has a smaller average orientation than that corresponding to the pure DMPC lipid bilayer, indicates a perturbation of the $P^- \rightarrow N^+$ dipoles at the membrane interface. The presence of the peptide bundle renders the otherwise symmetric lipid bilayer asymmetric. Consistently, the behavior of lipids located in the two different leaflets differed. The calculation of the different properties for the lipids as a function of their distance from the bundle center of mass indicated that, on average, the effect is stronger for those lipids located closer to the peptides. For these lipids, for instance, the orientation order parameters are higher. Interestingly, specific lipid−peptide interactions and the formation of lipid−peptide complexes mainly between the Lys^+ (K) residues located at the external surface of the bundle and the negatively charged lipid phosphate groups have been identified and seem to be responsible for the inhomogeneous effect observed as a function of the distance to the peptides, as compared to the homogeneous effect observed in the other monolayer.

Anesthetic Partitioning into Phospholipid Bilayers

The interaction of small molecules with biological membranes is a basic issue in the understanding of the mechanisms of general anesthesia and, specifically, the search for the site of anesthetic action (lipid bilayer membrane or membrane proteins?), which is still unresolved.[52,53] Recent computer simulations[54] on inhaled (volatile) anesthetics (halothane, $CF_3CHBrCl$) at concentrations higher (mol fraction of 50%) than those clinically used to study their effects on the (pure) lipid bilayer membranes have shed some light onto this problem. The most relevant observation is a nonuniform distribution of the anesthetic molecules (initially located in the lipid bilayer hydrophobic region) along the axis perpendicular to the lipid−water interface. This indicates that the halothane molecules are located preferentially in the upper region of the lipid acyl chains, below the carbonyl groups. This has been observed to affect the membrane interior by reducing the order of the lower half of the hydrocarbon chains and increasing the number of gauche defects and the mobility of the lipid chains. The presence of the halothane molecules modified not only the hydrocarbon region of the system, as compared with the pure lipid bilayer membrane, but also the interface by inducing a reorientation of the lipid headgroup $P^- \rightarrow N^+$ dipole moments. In this calculation,[54] the $P^- \rightarrow N^+$ orientational distribution changed from being almost uniform to a distribution with a most probable orientation of 120° with the membrane normal, −30° with the membrane surface pointing toward the lipid bilayer interior and away from the water phase. This change may alter the electrostatic properties of the membrane interface, such as the membrane potential (the electrostatic potential across the membrane interface) of the mixed system. Similarly, the area available per lipid molecule increases, and this is accompained by a concomitant reduction of the spacing between the lamellae. In contrast, when a similar molecule, C_2F_6, is introduced in a pure lipid bilayer membrane,[55] the mixed system exhibits a remarkable perturbation of neither the membrane interior nor the interface. In this case, the C_2F_6 molecules are evenly distributed along the hydrocarbon region with a higher probability at the bilayer center. The C_2F_6 compound, which is known to produce two of the key effects of anesthesia (amnesia and analgesia) but it is not an immobilizer, is more hydrophobic and lacks the small dipole moment of halothane.

To illustrate the differences existing between the distributions of both types of molecules in a model membrane, we depict in Figure 3 the configurations of two very recent simulations[56] of a polyunsaturated SDPC lipid bilayer[18] with halothane and with the nonimmobilizer C_2F_6 after 2 ns. The simulations were carried out at $T = 30$ °C and $p = 1$ atm, where the pure SDPC lipid bilayer is in the fluid lamellar phase,[18] with 16 halothane/C_2F_6 molecules and 64 SDPC molecules (mol fraction of 25%).[56] Figure 3a indicates that the halothane molecules in the SDPC lipid bilayer have the tendency to move toward the membrane interface, below the carbonyl region, although there are also some molecules remaining at the membrane center (methyl trough). Conversely, the distribution emerging from Figure 3b shows that the C_2F_6 molecules are more probably located at the membrane interior and closer to the membrane center.

The study of the effect of anesthetics and nonimmobilizer in highly unsaturated lipid bilayers is particularly relevant in biology as a result of the essential role of fatty acids with cis double bonds. Recent simulations on the fully hydrated mixed (saturated/polyunsaturated) chain SDPC lipid bilayer with the highly unsaturated docosahexaenoic fatty acid (DHA) in the biologically relevant fluid lamellar phase[18] provided interesting insights into the origin of the special properties of these complex lipid systems. In these systems, the presence of the polyunsaturated chains, which have an enhanced tendency to visit the lipid−water interface, increases the disorder of the membrane.[57] This is due to the different intramolecular conformation and dynamics[18,38,57] of the polyunsaturated chains compared to those of the better-studied saturated chains. In fact, the distinct conformations of the DHA chain have a different (and inhomogeneous) effect on the order parameters of the saturated chains. The most linear conformations of DHA increased the order, whereas the nonlinear conformations decreased the order of the bottom part of the saturated chains.[57]

Coarse Grain Models of Phospholipids

The utility of coarse grain (CG)-type models to study collective phenomena in model membranes is well-established.[24,25] In early studies, however, the parameters of the model were not fitted to specific systems. Here, we will describe a simplified model of the coarse grain type,[22]

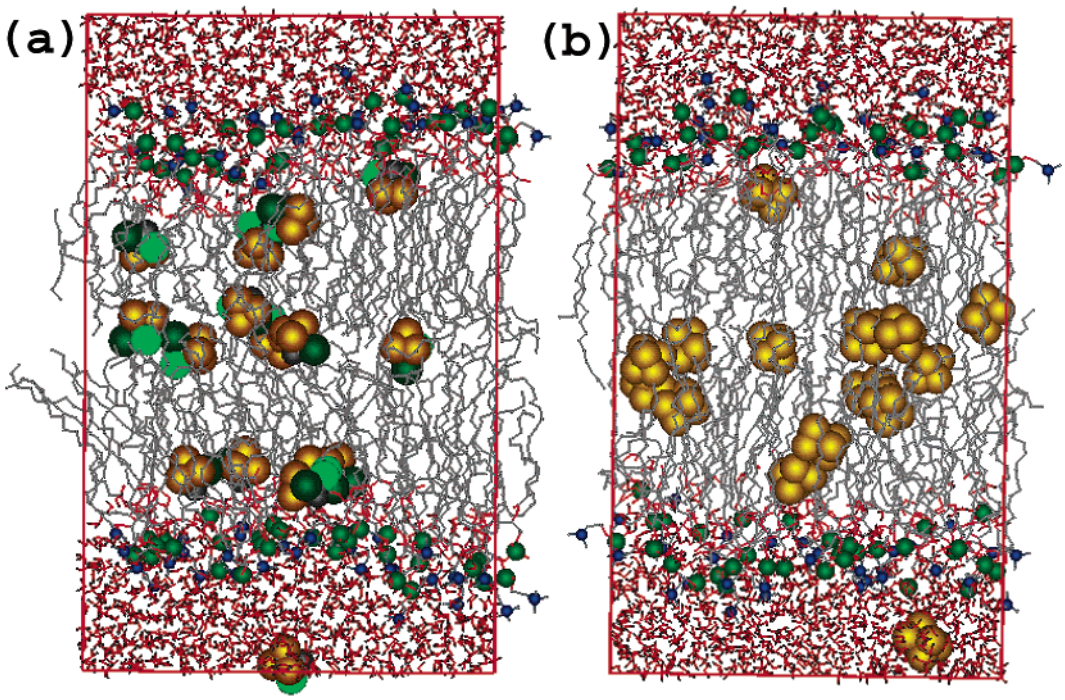

FIGURE 3. Configurations of the halothane−SDPC (a) and C_2F_6−SDPC (b) systems taken from MD simulations after 2 ns.[56] The details of the simulations can be found in ref 56. The water and SDPC lipid molecules are shown as balls and sticks except the N and P atoms of the lipid headgroups, which are displayed as blue and green spheres, respectively, to highlight the interface. For clarity, the hydrogen atoms of the lipids are not shown. Halothane and C_2F_6 molecules are depicted with the atomic van der Waals radii (F, yellowish; Cl, light green; Br, dark green; H, gray).

which has been constructed to mimic specific phospholipids and has been successfully applied to model a few complex systems.[22,23] In this approach, all of the molecular components, including the solvent, are considered explicitly. In the model, the CG waters, represent clusters of three water molecules and are spherically symmetric and interact via a Lennard−Jones potential with the parameters chosen to match a number of the properties of water (i.e., CG water should adopt the correct density, remain liquid within the desired interval, and be consistent with hydrodynamics). The CG model for the DMPC lipids is as follows (see Figure 4). The lipid chains are represented by one site for each triplet of methylene or methyl atoms (SM and ST). Harmonic bond length and bond angle potentials are used to link sites together forming the hydrocarbon chain and to maintain the stiffness and tail length, respectively, and Lennard−Jones interactions are used for the nonbonded interactions. The hydrophilic region of the lipids is built in a similar way, and the main feature is that the beads representing the choline (CH) and the phosphate (PH) groups have a charge of $+e$ and $-e$, respectively, and a dielectric constant of 78 is used for the electrostatic interactions. A single CG site (GL) represents the glycerol backbone (CH_2CHCH_2) that links the two chains and the headgroup together. The number of interaction sites for the CG model of DMPC is thus considerably reduced (by 1 order of magnitude; from 118 atoms to 13 interaction sites), and the number of charged sites in the CG model is two per lipid molecule instead of the 118 charged atoms of the all-atom DMPC. This, in turn, reduces considerably the computer time consumed in the calculation of the long-range interactions. For all of the components, the different interactions were parametrized on the basis of the corresponding radial distribution functions (RDFs), $g_{\alpha\beta}(r)$, obtained from atomistic simulations. These RDFs were used as the starting point. The method to reconstruct the CG Hamiltonian from the RDFs[22,58] uses the potential of mean force $[V_{\alpha\beta} \propto - k_B T \ln(g_{\alpha\beta}(r))]$ as the initial choice for the effective interaction potentials between the different CG sites. The parameters are then adjusted iteratively until the RDFs or other desired quantities are appropriately matched within the pertinent accuracy. The model constructed in this way has been shown to reproduce semiquantitatively the density profiles of the different components/sites in the direction normal to the interface of a preassembled DMPC lipid bilayer at room temperature, even though it produces pressures that are somewhat too high.[22] This CG model also self-assembles into a lipid bilayer system from a random initial configuration.[22,23,59] The coarse grain simulations were performed using the CM^{3}D program.[60]

To investigate whether this type of model can be used to study more complex biological membranes, the CG model for the DMPC lipid bilayer was generalized to include interactions with a foreign molecule,[23] for example, the anesthetic halothane, at conditions similar to those of the fully atomistic simulations[54] described in the previous section. The results obtained showed that a careful parametrization and, consequently, a necessity of gathering the adequate data for the full parametrization is vital in order for the CG model to be predictive. The refining of the parameters (basically, the depth of the well

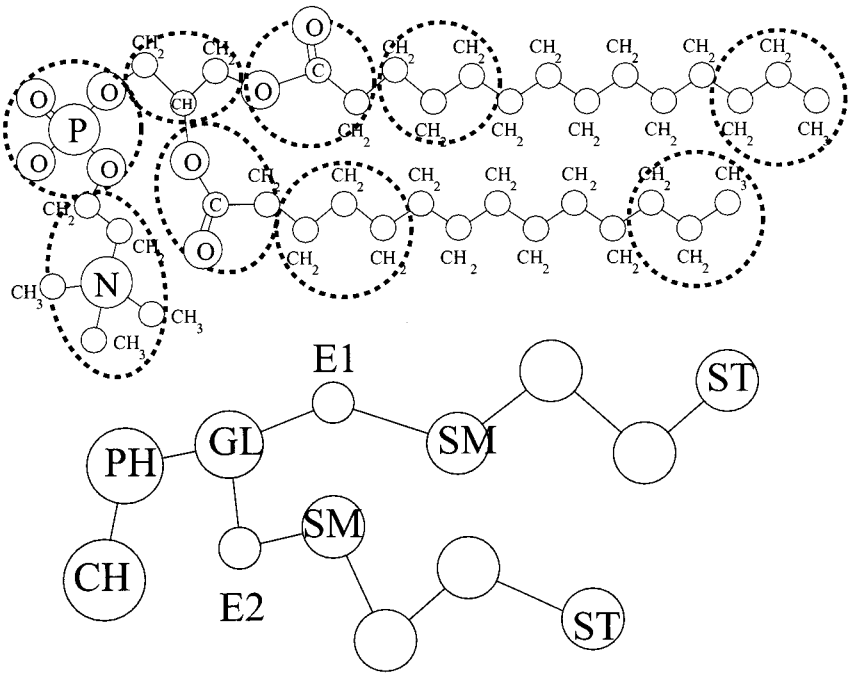

FIGURE 4. Atomistic (top) and coarse grain (bottom) squematic representations of the molecular structure of DMPC. For the sake of clarity, the hydrogen atoms are not explicitly shown in the sketch of the atomistic model.

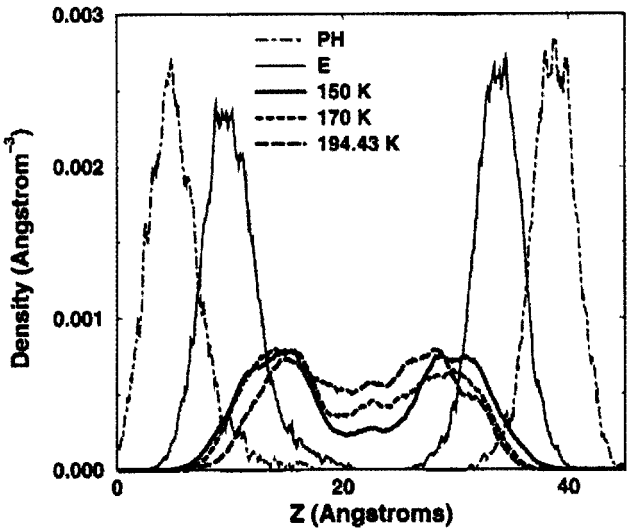

FIGURE 5. Density profiles along the membrane normal for the coarse grain simulation containing halothane.[23] The details of the simulation can be found in ref 23. Curves are given for the phosphate groups (PH), the ester groups (E), and three choices of the H−S interaction parameter ϵ_{SH} (ϵ_{SH} = 150, 170, and 194.43 K).

of the Lennard−Jones interactions of halothane with the lipid chain groups, ϵ_{SH}, and with the choline group) leads to reasonable agreement with the existing atomistic data, especially concerning the density profiles of the halothane distribution along the membrane normal.[23] In Figure 5, the density profiles for the ester groups (E, O_2CCH_2) and the phosphate groups of the DMPC lipid and that corresponding to the halothane molecules for three values for the ϵ_{SH} parameter are shown for the CG model.[23] The differences obtained in the distributions corresponding to the three values of ϵ_{SH} illustrate the sensitivity of the model to the parameters. The nonuniform distribution for the halothane molecules obtained in the atomistic study[54] resembles that of the CG model with the shallowest halothane tail (H-S)−CG interaction potential. It is interesting to point out that by fine-tuning a single parameter of all of the CG interactions of the solute (solute−hydrocarbon chain in this case), one can go from a behavior typical of an anesthetic (ϵ_{SH} = 150 K) to that typical of a nonanesthetic molecule (ϵ_{SH} = 170, and 194.43 K).

Concluding Remarks

We have considered in detail three examples that illustrate the current ability of fully atomistic computer simulations to describe model membranes with potential applications in biomedical research. Here, computer simulation has been successfully applied to get new insights into the properties of multicomponent systems with a considerable degree of complexity. The nature of DNA−lipid interactions, the interplay between functional membrane peptides and their lipid environment, and the effect of foreign molecules on model membranes are timely topics in membrane science. These and related studies have provided invaluable information about the nature of lipid−lipid, peptide−lipid, and peptide−peptide interactions, which have been possible as a result of the full atomistic detail available from this kind of computer simulation.[40,41]

In most of the cases of biological interest in which particular molecular interactions play a fundamental role, however, very different types of forces are present, or diverse lengths and temporal scales are involved, thus making necessary a complete description covering full atomistic detail up to mesoscopic scales. This is the case, for instance, in processes such as peptide insertion and assembly, peptide aggregation in membranes and pore-

formation, microdomain formation and lateral organization of membrane heterogeneities, and in glycolipid systems, in which weak generic forces and strong specific forces are responsible for the formation of a soft cushion between cells and for recognition, respectively. Even though the revolutionary advances in computer hardware technology and state-of-the art simulation methodologies of the past decade indicate that longer time and length scales will be progressively achieved, there is still a need for less refined models of biomembrane systems. Simplified models of the coarse grain type, which have been successfully applied to polymers and surfactants, could perhaps be useful for this kind of application. As an example, to illustrate the possible utility of coarse-grain models, we have described the partitioning of the anesthetic halothane in a model phospholipid bilayer. The successes achieved to date suggest that in the next few years, it will be useful to continue to pursue both fully atomistic and coarse-grain approaches to membrane systems.

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Note Added after ASAP Posting

The final sentence was inadvertently omitted from the Acknowledgment published with this article in the ASAP version posted on the Web 05/03/02. The corrected version was posted 5/30/02.

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