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Computer Simulation of Lipid Membranes: Methodology and Achievements[1]

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Abstract—Rapid development of computer power during the last decade has made molecular simulations of lipid bilayers feasible for many research groups, which, together with the growing general interest in investigations of these very important biological systems has lead to tremendous increase of the number of research on the computational modeling of lipid bilayers. In this review, we give account of the recent progress in computer simulations of lipid bilayers covering mainly the period of the last 7 years, and covering only several selected subjects: methodological (development of the force fields for lipid bilayer simulations, use of coarse-grained models) and scientific (studies of the role of lipid unsaturation, and the effect of cholesterol and other inclusions on properties of the bilayer).

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INTRODUCTION

Biomembranes are very complex heterogeneous systems consisting of many different types of lipids, sterols, proteins, carbohydrates and various membrane associated molecules which are involved in a variety of cellular processes; consequently, membranes play an active part in the life of the cell, they exist as dynamic structures. Lipid molecules differ with respect to the type of hydrophilic head-group and occur with a wide variety of hydrophobic hydrocarbon chains of fatty acids (FAs). Usually the most abundant phospholipid in animal and plants is phosphatidylcholine (PC): it is the key building block of membrane bilayers. Cholesterol (CHOL) molecules are essential component of mammalian cell membranes playing an important role in formation of heterogeneites (known also as rafts) which are supposed to be responsible for cell signaling. Knowledge of physical-chemical properties of lipid bilayers is a key element of our general understanding of biomembrane functioning, which is one of the greatest challenging problems in biophysical and biomedical sciences.

A characteristic feature of lipid bilayers is that, in a physiological form, they exist in a liquid crystalline (fluid) state which implies a relatively high degree of disorder. Experimental measurements of structural and dynamical properties are obtained as averages over a large number of lipids and over a certain time interval, which not always can give an unambiguous picture of individual lipids and their interactions.

During the last decades computer simulations have become a well established tool of modern investigations of molecular structure. Monte Carlo (MC) or molecular dynamics (MD) can provide three-dimensional real-time imaging of the system with atomistic-level resolution, and hence can give essential structural and dynamical information which otherwise is hardly accessible by any experimental method. The first attempts of computer simulations of model bilayers composed of amphiphilic molecules with atomistic resolution were made by 30 years ago [1–3]. The amount of works on simulations of lipid membrane systems has increased tremendously, and a number of reviews appeared accounting for this in the past decade [4–15] and more recently [16–30]. The rapid development of the accessible computer power has made simulations of more and more complicated systems feasible, and allowed also increase the size of the simulated systems. Now simulation of an order of hundred fully hydrated lipids during a few hundred nanoseconds can be considered as a routine.

In this review, we give account of the recent development in computer simulations of lipid bilayers covering mainly the period of the last 7 years. About three hundred papers have been chosen but this is a moderate part of the simulation studies performed recently in this active area of research. It is beyond the scope of this review to touch upon other topics and types of membrane systems. Unfortunately, as a result a number of important areas are not represented here sufficiently (or even mentioned). Some reviews can be enumerated here in this respect, e.g. reviews devoted to computer simulation studies of protein—nucleic

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acid complexes [31], membrane proteins [32], biomolecular folding [33], protein folding [34] and unfolding [35], large conformational changes in proteins [36], infrared spectra in peptides and proteins [37], blood coagulation proteins [38], thermodynamic properties of biomolecular recognition [39], biomembrane dynamics and the importance of hydrodynamic effects [40], block copolymers having biocompatible and functionalizable properties required for mimicking cell membranes [41], etc. The absence of some references in our review is related with an existence of many excellent above-mentioned and similar reviews.

Throughout this review, notation of $N : k(n–j)cis$ for describing the structure of each hydrocarbon chain of lipids will be used, where N refers to the total number of carbon atoms in the chain, k is the number of the methylene-interrupted double bonds (i.e., one methylene group is localized between each pair of double bonds), whereas *cis* refers to the conformation around the double bonds; letter "*n*" means that so called "*n* minus" nomenclature is used, i.e., the position "*j*" of the first double bond is counted from the methyl, CH_3, terminus of the chain (with the methyl carbon as number 1). The first double bond extends from the *j*th carbon to the *(j + 1)*th carbon from the end. For brevity, the fragment $(n - j)cis$ in the notation is frequently omitted.

Some of the commonly occurring types of FA chains and PC molecules discussed in the text are listed below, with the given systematic name, trivial name in paranthesis (if it exists), and shorthand designation:

Saturated FAs: dodecanoic (lauric, 12 : 0); tetradecanoic (myristic, 14 : 0); hexadecanoic (palmitic, 16 : 0); octadecanoic (stearic, 18 : 0); eicosanoic (arachidic, 20 : 0).

Monounsaturated FAs: *cis*-9-hexadecenoic (palmitoleic, 16 : 1(n-7)*cis*); *cis*-9-octadecenoic (oleic, 18 : 1(n-9)*cis*).

Polyunsaturated FAs with methylene—interrupted double bonds: *cis*-9,12-octadecadienoic (linoleic, 18 : 2(n-6)*cis*); *cis*-9,12,15-octadecatrienoic (α-linolenic, 18 : 3(n-3)*cis*); *cis*-5,8,11,14-eicosatetraenoic (arachidonic, 20 : 4(n-6)*cis*); *cis*-5,8,11,14,17-eicosapentaenoic (20 : 5(n-3)*cis*); *cis*-4,7,10,13,16,19-docosahexaenoic (22 : 6(n-3)*cis*).

PC molecules: 1,2-dilauroyl-sn-glycero-3-PC (DLPC), 12 : 0/12 : 0 PC; 1,2-dimyristoyl-sn-glycero-3-PC (DMPC), 14 : 0/14 : 0 PC; 1,2-dipalmitoyl-sn-glycero-3-PC (DPPC), 16 : 0/16 : 0 PC; 1,2-distearoyl-sn-glycero-3-PC (DSPC), 18 : 0/18 : 0 PC; 1,2-dioleoyl-sn-glycero-3-PC (DOPC), 18 : 1(n-9)*cis*/18 : 1(n-9)*cis* PC; 1-palmitoyl-2-oleoyl-sn-glycero-3-PC (POPC), 16 : 0/18 : 1(n-9)*cis* PC; 1-stearoyl-2-oleoyl-sn-glycero-3-PC (SOPC), 18 : 0/18 : 1(n-9)*cis* PC; 1-palmitoyl-2-linoleoyl-sn-glycero-3-PC, 16 : 0/18 : 2(n-6)*cis* PC; 1-stearoyl-2-linoleoyl-sn-glycero-3-PC, 18 : 0/18 : 2(n-6)*cis* PC; 1-palmitoyl-2-linolenoyl-sn-glycero-3-PC, 16 : 0/18 : 3(n-3)*cis* PC; 1-stearoyl-2-linolenoyl-sn-glycero-3-PC, 18 : 0/18 : 3(n-3)*cis* PC; 1-palmitoyl-2-arahidonoyl-sn-glycero-3-PC (PAPC), 16 : 0/20 : 4(n-6)*cis* PC; 1-stearoyl-2-arahidonoyl-sn-glycero-3-PC (SAPC), 18 : 0/20 : 4(n-6)*cis* PC; 1-palmitoyl-2-eicosapentaenoyl-sn-glycero-3-PC (PEPC), 16 : 0/20 : 5(n-3)*cis* PC; 1-stearoyl-2-eicosapentaenoyl-sn-glycero-3-PC (SEPC), 18 : 0/ 20 : 5(n-3)*cis* PC; 1-palmitoyl-2-docosahexaenoyl-sn-glycero-3-PC (PDPC), 16 : 0/22 : 6(n-3)*cis* PC; 1-stearoyl-2-docosahexaenoyl-sn-glycero-3-PC (SDPC), 18 : 0/22 : 6(n-3)*cis* PC.

Some other types of lipids abundant in living cells and discussed in this review are phosphatidylethanolamine (PE), sphingomyelin (SM), phosphatidylserine (PS), and phosphatidylglycerol (PG).

FORCE FIELD DEVELOPMENT

Proper parametrization of the force field (FF) defining molecular interactions is ongoing problem in molecular simulations. A good FF should provide agreement with all available experimental data within the simulation and experimental uncertainty. As simulations becoming longer, uncertainties caused by the equilibration stage and statistical error are decreasing. Experimental techniques are also improving. At some point, the FF which earlier provided satisfactory agreement with experimental data, may begin to show discrepancies. This in turn may initiate further improvements of the FF leading to better description of the molecular interactions and better agreement between computer simulations and experimental results.

In simulation of lipid bilayers, two families of FFs were typically used in recent years: GROMOS [42–44] and CHARMM [45, 46]. GROMOS employs united atoms approach representing each of non-polar CH, CH_2 and CH_3 groups of hydrocarbons as a single particle which allows to reach about 3-fold speedup comparing to all-atomic simulations. There exists several versions of the GROMOS FF which essentially fall into two groups, one with original GROMOS non-bonded parameters (for example, 45A3 and similar parameter sets [44]), and Berger modification [47] which is the most frequently used. In the latter one, besides modification of the non-bonded interaction parameters, the Ryckaert–Bellemans potential is implemented to describe torsion rotations of the hydrocarbon chains of lipids. GROMOS FF is fully supported in GROMACS simulation package [48]. An overview over the different types of analysis implemented in the GROMOS++ software has been given in ref. [49].

The CHARMM FF [46] describes all hydrogens explicitly. Additionally, it has a more detailed description of intramolecular interactions, including Urey-Bradley term for covalent angles and a richer variety of

parameters for dihedral angles. CHARMM parameters for lipids were introduced first in ref. [50] (within the Charmm22 parameter set, often denoted also as C22), were updated in ref. [13] (Charmm27, or c27 parameter set), updated again in ref. [51] (C27r parameter set). Besides the original CHARMM software, the CHARMM FF is native in the NAMD simulation package [52]. It is also implemented in a number of other simulation packages.

Another frequently used FF for biomolecular simulations, AMBER (known also as GAFF, or Generalized Amber Force Field [53]) was also extended to include lipid parameters [54].

Several methodological studies were devoted to validation of different FFs used in bilayer simulations. The average area per lipid defined in constant pressure—zero tension simulations, is a parameter which is most often used to define the quality of a FF. Area per lipid is one of the most fundamental properties of a lipid bilayer and one of the most common ways to determine whether the bilayer system has reached equilibrium. When the area per lipid reaches a stable value, other structural properties (density distributions, NMR order parameters) are usually not changing either. Simulated area per lipid can be also compared with experimental values available from X-ray or neutron diffraction and volumetric data. A collection of average lipid areas for several bilayers composed from different lipids and computed from different FFs, as well as experimental areas, is available in Table 1 of paper [55]. More reliable validation of a FF can be done by comparison of simulated and experimental structure factors as it was shown in paper [56]. Additional important source of data for validation of a FF used in lipid bilayer simulations is NMR bond order parameters.

In ref. [44], the 45A3 GROMOS parameter set, as well as few other versions of the GROMOS FF, were tested in simulations of 16 : 0/16 : 0 PC bilayer at 323K, by comparison with experimentally known average membrane area per lipid, NMR bond order parameters and lipid lateral diffusion. In ref. [56], comparison of simulated and measured in X-ray or neutron diffraction structure factors was made for 18 : 1(n-9)/18 : 1(n-9) PC lipids. In ref. [57], 14 : 0/14 : 0 PC bilayer was simulated using Berger parameter set [47] at 30 and 50°C and comparison with similar set of experimental data has been made. A common conclusion from these as well as some other studies [58-60] can be made that while giving a fair representation of the bilayer structure and dynamics, the GROMOS FF still has some small, but going beyond possible computational or experimental error differences for the electron density profile (or the structure factor), area per lipid and some other properties.

Two new updates of GROMOS parameter set have been proposed [61, 62]. In the first one (called 43A1–S3 parameter set) some additional revision of parameters was made on the basis of ab initio computations and fitting to thermodynamical data for liquid alkanes [61]. These corrections improved agreement with experiment for the area per lipid for a number of lipids in comparison with other versions of the GROMOS FF. Then the G53A6 parameter set of the GROMOS FF which greatly improved the fluidity of 16 : 0/16 : 0 PC lipid bilayers was reported [62]. Specifically, the repulsion between choline methyl groups and non-ester phosphate oxygens was enhanced by increasing van der Waals radius for this particular interaction. The structural properties of 16 : 0/16 : 0 PC bilayers (area and volume per lipid, electron density profiles, bilayer thickness and hydration, ordering and conformation of acyl chains) were in very good agreement with the experiment [62]. The ability of this parameter set [62] to reproduce the structural and hydration properties of common phospholipids of varying length and degree of unsaturation of the acyl chains, i.e., pure bilayers of 12 : 0/12 : 0 PC, 14 : 0/14 : 0 PC, 18 : 1(n-9)*cis*/18 : 1(n-9)*cis* PC, and 16 : 0/18 : 1(n-9)*cis* PC in a liquid crystal phase was examined in ref. [55]. The simulations demonstrated that the set [62] is well suited for the simulation of PC bilayers in the biologically relevant liquid-crystalline phase. The structural properties of the bilayers were validated using a broad range of experimental data for each lipid. Critically, the extent of hydration of the lipid headgroups was found to be in agreement with NMR, X-ray, and neutron diffraction as well as infrared spectroscopic data. The work [55] underlines the fact that to validate simulation models, especially those used to model lipid bilayers, there is a critical need to examine a range of experimental data as opposed to focusing on a single parameter, such as area per lipid alone.

The CHARMM FF, describing all hydrogens explicitly, and having a richer variety of parameters for dihedral angles, many of which being developed on the basis of quantum-chemical calculations, may seem to have advantages in accurate description of lipid bilayers. However, detailed investigations have shown that the CHARMM FF, including its CHARMM27 version [13], have also non-negligible disagreements with experiment [56]. Moreover, it was found that such fundamental parameter as the average area per lipid, is underestimated in constant-pressure simulations, and in some cases the bilayer goes to the gel phase at conditions corresponding to the liquid crystalline phase [63–66]. This was the reason that many recent bilayer simulations employing CHARMM27 FF were done either in the NVT ensemble, or with a fixed area per lipid, or under non-zero surface tension [56, 67–70]. One of the reasons of such behavior can be traced to too strong preference for *trans*-conformations in the saturated alkane chains of lipid tails described by the CHARMM27 FF [51, 60, 66].

Further update of CHARMM torsion parameters for alkane chains has been suggested, known as c27r parameter set [51]. Revision of parameters was made

on the basis of ab initio recomputation of the torsion potential energies for short alkanes, which lead to some decrease of the energy difference between *trans*- and *gauche*-conformations. Later studies have demonstrated however that c27r parameter set still does not reproduce the correct area per lipid in simulations at zero surface tension [68]. Another way to improve parameters was to recalculate charges of the lipid headgroup, which was suggested by Sonne in papers [65, 71]. In these works, the charges were computed within the ab initio Hartree-Fock approach for an ensemble of typical lipid conformations taken from a molecular dynamics trajectory, and then averaged. Though recalculation of charges has brought result for the area per lipid closer to the experiment, its value was still about 4–5 Å^2 too low, both for DPPC [65] and DMPC [72] lipids. In ref. [73], simulations of bilayers composed of DPPC, POPC and PDPC lipids, with atomic charges derived in ref. [65] and with alkane torsion parameters described by c27r parameter set, also provided good agreement with experimental data for these types of lipids.

In ref. [66], an empirical way of gradual change of the energy difference between *trans*- and *gauche*-conformations of alkane chains, by scaling of the 1–4 electrostatic interactions (between atoms separated by exact three covalent bonds) was suggested. It was shown however that the scaling parameter, which most closely reproduces the experimentally known *gauche*-*trans* ratio in liquid alkanes, still provides a too low area per lipid for DMPC bilayer. However, after recomputation of atomic charges in the same manner as in work [65], a 100 ns simulation of DMPC bilayer at 303K has shown the area per lipid in perfect agreement with experiment, both in the case of using TIP3P and SPC water models. Very good agreement was also demonstrated for other experimentally measurable bilayer properties such as bond order parameters, electron density and the structure factor [66]. The model developed in ref. [66] has been recently applied also to DPPC and POPC bilayers [74], and the calculated membrane area per lipid molecule, as well as order parameters showed a good agreement with the experimental values.

The reason by which modification of charges based on ab initio computations for the whole lipid headgroup [65, 66] provides a significant improvement for the simulation results, can be rationalized from the following. In the original derivation of FF parameters, the charges of individual atomic groups constituting a lipid molecule were fixed as +1 for the choline group, −1 for the phosphate, and 0 for the rest. When these groups are gathered in a single molecule, some redistribution of charges occurs, leaving charge +0.76 on the choline group, −0.89 for the phosphate and +0.13 for the esters. Such redistribution leads also to decrease of "in-plane" lipid dipole moments and increase of the dipole moment normal to the membrane surface. Both factors favor to repulsion between the lipid headgroups and thus to increase of the area, bringing it in agreement with the experiment.

As another line of modification of the CHARMM FF for lipids, it was suggested to use a united atom description of hydrocarbons in lipid tails with similar to the Ryckaert-Bellemans torsion potential but with modified parameters [75]. However simulations using this model were carried out at constant area per lipid and comment was made that behavior of the average area and surface tension is similar to that for the unmodified all-atom CHARMM FF.

The CHARMM22 and CHARMM27 FFs were recently implemented in the GROMACS simulation package [76] to allow comparisons of the lipid CHARMM27 FF with other lipid FFs or lipid—protein FF combinations.

The most recent update of the CHARMM FF, the C36 parameter set, was presented in ref. [77] and validated on six lipid types: 12 : 0/12 : 0 PC, 14 : 0/14 : 0 PC, 16 : 0/16 : 0 PC, 18 : 1/18 : 1 PC, 16 : 0/18 : 1 PC and 16 : 0/18 : 1 PE. The changes included reparameterization of partial atom charges and torsion potentials on the basis of ab initio computations, as well as revision of some Lennard-Jones parameters. Properties as average area per lipid at zero tension, structure factors, NMR order parameters, dipole electrostatic potential, showed certain improvements relative to the previous C27r parameter set. A modification of the C36 FF for CHOL, called C36c, has been also reported [78]. The new parameters in the C36c modification should enable more accurate simulations of lipid bilayers with CHOL, especially for those interested in the free energy of lipid flip/flop or transfer of phospholipids and/or CHOL [78]. A set of CHARMM-based parameters of molecular mechanics FF for neutral articaine, a potent and widely used local anesthetic, was presented in ref. [79]. Up–to–date overviews of the CHARMM FFs were given in refs. [80, 81]: a limited presentation on the historical aspects of FFs was given, including underlying methodologies and principles, along with a brief description of the strategies used for parameter development.

Following ideas discussed in papers [65, 66], a new all-atomistic force field called Slipids has recently been developed for fully saturated phospholipids [82] and for lipids containing a single double bond in one or two tails [83]. The parameterization has been largely based on high-level ab initio calculations in order to keep the empirical input to a minimum. The FF's ability to simulate lipid bilayers in the liquid crystalline phase in a tensionless ensemble was tested in simulations of DLPC, DMPC, and DPPC [82], as well as POPC, SOPC, POPE, and DOPE bilayers [83]. The new force field reproduces many experimentally measurable properties of lipid bilayers such as area per lipid, NMR order parameters, and structure factors, including their temperature dependence. Compatibility of Slipids FF with Amber FF for amino

acids (often used to model membrane proteins) was also demonstrated [83].

Some earlier simulations of lipid bilayers were performed with Amber FF [84, 85]. Recent simulations carried out within the standard Amber94 set of parameters [86, 87], as well as using its newer version known as GAFF, provided average lipid area below the experimental value for DMPC and DOPC lipids [88]. Some additional modifications of the GAFF FF, including recomputations of atomic charges, were made in paper [59]. However, the average area per lipid in constant pressure simulations of DOPC bilayer still remained below experimental, and additional surface tension should be applied to maintain the correct area. The GAFF FF seems to need further optimization to reproduce correct bilayer structure for a tensionless membrane.

Polarizable FFs have been also constructed and applied for different systems such as lipids and lipid bilayers [89]. This area has been relatively untouched by FF developers with particular focus on polarizable, non-additive interaction potential models. Recent applications and developments of such FFs in classical MD simulations are discussed in review [89].

There exist also other than FF factors affecting simulation results. Finite system-size effects in MD simulations of lipid bilayers are subject to much discussion in the membrane simulation community. In ref. [90], system-size effects on the structure of a DOPC bilayer are investigated by performing MD simulations of small and large single bilayer patches (72 and 288 lipids, respectively), as well as an explicitly multilamellar system consisting of a stack of five 72-lipid bilayers, all replicated in three dimensions by using periodic boundary conditions. The analysis [90] demonstrates that finite-size effects are negligible in simulations of DOPC bilayers at low hydration. A similar MD simulations study was performed for DPPC saturated bilayers composed of 72 and 288 lipids to examine system size dependence on dynamical properties [91].

Efforts are underway towards development of advanced computer simulation techniques with the purpose to alleviate some bottlenecks of the standard MD simulation algorithms. For instance, preferred conformations of the glycerol region of DPPC have been explored using replica exchange MD simulations and compared with results of the standard MD approaches as well with experiment [92]. It was found that due to too slow isomerization rates of the key torsions on the timescale of atomistic MD simulations, the standard MD is not able to produce an accurate equilibrium conformer distributions from reasonable trajectory lengths, e.g., on the 100 ns timescale. Replica exchange MD, however, provides a quite efficient sampling due to a rapid increase in the isomerization rate with temperature [92]. Another example is accelerated MD which is an enhanced sampling technique that facilitates conformational space sampling by reducing the barriers separating various low-energy states of a system. The first application of the accelerated MD method on POPC and DMPC lipid membranes was recently presented [93]. Different properties of DMPC bilayers from MD simulations accelerated with graphical processing units have been described in ref. [94]. This contribution suggests the suitability of applying emerging graphical processing units technologies to studies of an important class of biological environments, that of lipid bilayers and their associated integral membrane proteins.

Concluding discussion of this section on methodological issues in lipid bilayer simulation, it might be constructive to bring attention to the treatment of long-range corrections to the Lennard-Jones potential. While importance of correct treatment of the long-range electrostatic forces is well recognized [95, 96], and vast majority of lipid bilayer simulations implement Ewald summation method, the role of long-range corrections to the Lennard-Jones forces is less appreciated. Most of molecular dynamics simulations employ a force cutoff distance of 10–14 Å, out of which van–der–Waals interactions are neglected. Though the attractive part of the Lennard-Jones potential may seem to be small at such distances, its total contributions to the energy and especially pressure are not negligible. They can be evaluated by assuming that the pair correlation function $g(r)$ is equal to 1 beyond the cutoff distance $r > R_{cut}$ [97] for all atom pairs. Application of these expressions to a DMPC lipid bilayer described by the CHARMM27 FF results in a correction for pressure of −360 bar for $R_{cut} = 10$ Å which decreases to −130 bar for $R_{cut} = 14$ Å. Using of a transition region for the Lennard-Jones potential modifies the formulas but does not remove the need for the correction which can still be of order of hundred atmospheres. There exist also a more accurate isotropic periodic sum (IPS) approach [98, 99] which takes into account long-range corrections to the Lennard-Jones potential for inhomogeneous systems. It is however important to have in mind that in principle more correct methods to compute intermolecular interactions not necessarily lead to improvement of the results, since they may occur not consistent with older FFs optimized without such corrections. Taking or not taking into account the long-range corrections (known also as dispersion corrections) in simulations of lipids may change the surface tension by several *dyn/cm* per leaflet [96] which may lead to noticeable difference in computed average areas per lipid. Different treatments of out-cut-off corrections may also explain some differences in results for the simulated bilayers computed in different works implementing the same FF.

Finally, it should be mentioned [81] that even the most accurate FF is only as good as the computational design with which it is applied. Careful calculation setup requires understanding of the strengths and the weaknesses of the applied FF.

COARSE GRAINED SIMULATIONS

Properties of lipid membranes can be studied at different time and length scales. For some properties it is important to take into account all details of the system, considering explicitly all atoms including hydrogens. Other properties require much larger length and time scale than that where atomistic simulations are possible. Examples are undulations of membrane surface, formation of different aggregates as micelles, vesicles, lamellar or hexagonal phase transformations, problems related to domain formation at the membrane surfaces, etc. In such cases, one needs to simplify description of individual lipids, so that groups of atoms are lumped into pseudo-particles resulting in a coarse-grained (CG), or mesoscopic, description of a bilayer. CG models are emerging as a practical alternative to all-atom simulations for the characterization of membrane phenomena over long length and time scales. Several reviews and discussions appeared describing different aspects of CG, or multiscale modelling of bilayers [26, 27, 100–111].

There exists a large variety of CG models of lipids differing by the level of details, account for the solvent and the way how interaction potentials are defined. It is rather common to unite groups consisting of 2–5 heavy atoms into a single CG site. Further, while some of CG models use explicit 'coarse-grained' water, other models are formulated to use in implicit solvent, where the effect of solvent (water) is described by effective potentials. One of the most widely used explicit solvent CG models is based on the MARTINI FF [112, 113]. The MARTINI FF employs essentially a four-to-one mapping, i.e., on average four heavy atoms are represented by a single interaction center. The interaction potential consists of Lennard-Jones and eventually electrostatic terms, which are tuned to reproduce experimental partitioning data. The MARTINI FF was generalized to include protein models [114], carbohydrates [115], and peptides [116]. For the later, a big multipole water (BMW) model for water has been suggested resulting in a new BMW-MARTINI FF [116].

During a few latest years the MARTINI FF has been used in a large variety of studies: formation of lipid domains and rafts by spontaneous separation of lipid mixture into a liquid-ordered and a liquid-disordered phase [117], monolayer collapse [118], lipid self-assembly and vesicle formation [119], flip-flop motions of CHOL and lipids in membrane [120], nanoparticle transport and accumulation in lipid bilayers [121–124], fluid-gel transformations of a DPPC bilayer in the presence of nanoparticles [125], sol-gel phase transitions of a DPPC bilayer [126], spontaneous curvature and stability of asymmetric bilayers [127], membrane curvature and lipid packing [128], freezing of small lipid vesicles [129], mixtures of 16 : 0/16 : 0 PC and 18 : 2(n-6)*cis*/18 : 2(n-6)*cis* PC [130], interleaflet interaction and asymmetry in phase separated lipid bilayers [131], thermal fluctuations in shape, thickness, and molecular orientation in lipid bilayers [132], ternary bilayer mixtures of 16 : 0/16 : 0 PC, 18 : 1(n-9)*cis*/18 : 1(n-9)*cis* PC, 18 : 2(n-6)*cis*/18 : 2(n-6)*cis* PC, and 20 : 4(n-6)*cis*/20 : 4(n-6)*cis* PC [133], phase behavior of saturated lipids as a function of temperature and tail length [134], behavior of micelles made out of 1,2-dihexanoyl-sn-glycero-3-phosphocholine lipids [135], voltage-sensitive dyes with a lipid membrane [136], and surfactant micellization [137].

It is still worth to note, that MARTINI FF has certain limitations, for example approximate description of the electrostatic interactions via shifted electrostatic potential which is cut at 12 Å, and dielectric permittivity set to 15. Also, CG water in the MARTINI FF freezes at normal temperature, which is typically counterweighted by introduction of artificial "antifreeze" particles [113]. In order to improve properties of water in the MARTINI FF, as well as to provide better description of electrostatic and polarization interactions, a polarizable CG model for water has been introduced in recent paper [138].

A CG model for lipids and proteins in water solution, build initially on similar principles as MARTINI FF with 10 : 1 mapping (counting all atoms), and refined by atomistic simulations, is described in a series of works by Schulten group [139, 140]. This model was used to study selfassembly of lipoprotein systems [141, 142] and the effect of proteins on membrane curvature [140, 143, 144].

In refs. [145, 146], another CG lipid model with explicit water was considered, in which CG sites of lipids were presented as ellipsoidal particles interacting by Gay-Berne potential with embedded charges on the head group and dipoles at the ester groups. Water was presented as a one-site spherical particle with a dipole. This model provides a CG description of hydrated bilayer in more details than MARTINI FF. In paper [146] this model was used to study membrane electrostatics, pressure distribution, spontaneous curvature, water permeation and some other properties of 14 : 0/14 : 0 PC and 18 : 1/18 : 1 PC bilayers.

Another class of CG lipid models do not treat water explicitly. Instead, effective solvent-mediated potentials between lipid sites are used [147, 148, 149, 150]. Potentially, such models can be used for simulations of very large lipid systems since computer time is not spent for simulation of water. Parameterization of such models is however more difficult. In some cases, a Lennard-Jones potential or its modifications are used to describe CG sites [147, 151, 152]. In a more consecutive approach, effective potentials for CG simulations are derived from fully atomistic simulations of lipids in water. There exist two main approaches to derive CG potentials from atomistic simulation. One is based of the force-matching procedure in which expression for the pairwise CG FF is fitted to reproduce the n-body potential of mean force for the CG

sites in the atomistic system [153, 154]. This approach was used for multiscale simulations of DMPC bilayers [150], DMPC—CHOL lipid mixtures in plain bilayers as well as liposomes [150, 155], and DOPC–DOPE lipid mixtures [156]. A hybrid algorithm with a part of CG interaction potential presented by the Gay-Berne potential was also considered [157].

In another approach the effective potentials between lipid CG sites are derived from the structural properties of lipids simulated in atomistic details. Radial distribution functions between sites of different lipids, as well as distributions of intramolecular distances are used for parameterization of inter- and intramolecular potentials. Computations of the effective potentials can in this case be carried out using the inverse Monte Carlo [158] or inverse Boltzmann [159] methods. Effective potentials, computed in work [149] from atomistic simulations of DMPC lipids, were used to describe processes of spontaneous formation of bicells, micelles and multilammelar structures [160, 161]. In ref. [162], the iterative inverse Boltzmann approach was used to derive effective potentials for CG 16 : 0/16 : 0 PC lipid model which are suitable for description of both liquid crystalline and amorphopus states of this lipid. In ref. [163], the inverse Monte Carlo method was used to derive effective potentials for a two-dimensional model of lipid—CHOL domain forming mixtures.

We mention also a number of other CG lipid models built on different principles and which were used to study different systems and problems such as pore formation under tension [164], protein interactions in membranes [165, 166], interactions of membrane protein–lipid complexes [167], behavior of CHOL in membrane [168], phase transitions in lipid monolayers and bilayers [169], process of self-assembly and gel-phase transition [170], simulations of membranes under tension [171], topology change processes of a membrane [172], large-scale systems employing models with chemical specificity [173] (in particular, DPPC in non-lamellar phases [174]), rafts across bilayers [175], self-assembly of the complex lipid mixtures found in the outermost layer of the skin [176], pressure control in the fluids density functional theory calculations of lipid bilayers [177], role of inertia and CG on the transverse modes of lipid bilayers [178], etc.

BILAYERS: LIPIDS WITH SATURATED AND UNSATURATED CHAINS

It was mentioned that a typical biological membrane contains many species of lipid molecules, with different head groups and hydrocarbon tails. The most commonly occurring FA chains may contain 1–6 carbon–carbon double bonds of the *cis* configuration in different positions. In most cases, at least half of the FA chains are unsaturated. The double bonds of polyunsaturated (PU) chains are, as a rule, methylene-interrupted.

The PU FA tails of lipids are of great importance for the structure and functioning of biomembranes [179–186]. Docosahexaenoic acid, 22 : 6(n-3)*cis*, is the longest and most unsaturated FA commonly found in nature.

A number of animal and plant species, tissues or organs may be cited which contain membranes with one or several unsaturated lipid chains as their main component. PU FAs play a key role in membrane metabolism and the control of gene expression. It has been observed that membranes that are active metabolically, have high levels of PU FAs; 22 : 6(n-3)*cis* chain and other PU FAs have been linked to the great number of biochemical processes, to an enormous variety of human afflictions, chronic diseases. Key transcription factors are regulated by (n-3) PU FAs, which in turn control levels of proteins involved in lipid and carbohydrate metabolism. 22 : 6(n-3)*cis* acid has been established as a key controller of hepatic lipid synthesis [187], 22 : 6(n-3)*cis* acid and related FAs reduce colon cancer risk and inflammatory disorders of the intestine [188]. PU FAs of the (n-3) series have immunosuppressive effects which make these molecules candidates for treating inflammatory symptoms associated with cardiovascular disease, obesity, arthritis, and asthma [189]. 22 : 6(n-3)*cis* FA is highly concentrated in the central nervous system and is essential for proper neuronal and retinal function [190]. The potential role of many oxidation products of 22 : 6(n-3)*cis* FA on induction of apoptosis in cancer cells is reviewed in ref. [191].

Evidently the basis (and primary cause) of these and similar phenomena is the specific chemical structure of PU FA chains (in particular, 22 : 6(n-3)*cis*) having methylene-interrupted *cis* double bonds, which results in their specific physical properties, which are in its turn cause their specific functioning in living organisms. Nevertheless, full understanding of the effects of lipid unsaturation on various physical properties of membranes at the molecular level, affecting their functioning, is not yet achieved. The mechanisms of many biological functions of PU FAs remain a subject of much debate.

Many theoretical investigations (during the period of last 7 years) were devoted to the various properties of unsaturated and PU FA chains of different lipid molecules in bilayers; several FA chains most frequently studied by molecular simulations and corresponding references are enumerated below: 22 : 6(n-3)*cis* [181, 192–204], 22 : 5(n-3)*cis* [192], 20 : 4(n-6)*cis* [64, 195, 198, 200–203, 205, 206], 18 : 3(n-3)*cis* [195, 198, 200, 201, 203], 18 : 2(n-6)*cis* [64, 195, 198, 200–203, 207], 18 : 1(n-9)*cis* [54, 55, 59, 64, 74, 88, 181, 194–196, 198, 200–203, 205, 208–231].

MD simulations and experiment (both small-angle neutron and small-angle X-ray scattering) were combined to determine the pre*cis*e structure of bilayers composed of POPG (a lipid commonly encountered in bacterial membranes) [231]. Experiment and simu-

lation were used to develop a one-dimensional scattering density profile model suitable for the analysis of experimental data. To study mixed bilayers of neutral and charged lipids, MD simulations of a POPC bilayer containing 23 mol % POPG were performed [232]; nearly one-half of all the POPG lipids were found to be involved in hydrogen bonding with POPC lipids. Similarly, MD simulations of lipid bilayers consisting of a mixture of cationic dioleoyloxytrimethylammonium propane and neutral DMPC lipids were performed [233]. Adding unsaturated lipids into DMPC bilayers was found to promote lipid chain interdigitation and to fluidize lipid bilayers.

The molecular organization in model membranes composed of 18 : 1(n-9)*trans*/18 : 0 PC, 18 : 1(n-9)*cis*/18 : 0 PC, 18 : 0/18 : 0 PC was compared by MD simulations [228]. It is shown that acyl chain order in 18 : 1(n-9)*trans*/18 : 0 PC in the liquid crystalline state is much closer to that of 18 : 1(n-9)*cis*/18 : 0 PC than that of the substantially more ordered 18 : 0/18 : 0 PC, which is attributed to the reduced energy barrier to rotation about the C–C single bonds next to either a *trans* or *cis* carbon double bond. All-atom MD simulations for a series of mixed fluid systems of DOPC and DPPC at seven different molar ratios of lipids were carried out in [230]. In the binary system, DPPC acts as an ''order-preferring'' agent, which efficiently modulates behavior of DOPC; studies of lateral heterogeneity in cell membranes are important since they help to understand the physical origin of lipid domains and rafts.

Cardiolipin is a key lipid component in the inner mitochondrial membrane, where the lipids are involved in energy production and mechanisms in the apoptotic pathway. Cardiolipin has a unique dimeric structure with two negatively charged phosphatidyl moieties attached to a glycerol group and four acyl chains. Three cardiolipin—POPC bilayers with different lipid compositions were simulated by MD [221] to investigate cardiolipin and its effect on the structure of lipid bilayers. MD simulation of three models of cardiolipin containing membranes using a new set of parameters for tetramyristoyl and tetraoleoyl cardiolipins has been developed in the framework of the united-atom CHARMM27-UA and the all-atom CHARMM36 FFs [234]. The physicochemical properties of the bilayers were determined and compared with previously reported data.

A large number of researches is traditionally involved in the computer simulation studies of saturated lipid bilayer systems. In ref. [235], DPPC bilayer systems were investigated, and the convergence of structural and dynamical properties with the system size and with the MD simulation time were studied. Atomistic MD simulations of the gel phase and melting transitions of DPPC bilayers in water reveal the dependency of many thermodynamic and structural parameters on the initial system ordering. A gel phase DPPC system was created in ref. [236] and it was observed that a very high ordering of the gel phase in the starting system is necessary to observe behavior which reproduces experimental data. Atomistic simulation of mixed-lipid bilayers of saturated-tail lipids was performed in ref. [237]. Coarse grained MD simulations have been used to study the structure, dynamics, and stability of membranes composed of model bolalipids, consisting of two DPPC lipids covalently linked together at either one or both tail ends [238]. Bolalipids are tetraether lipids found in Archaea bacteria, conferring stability to these bacteria by spanning across the cytoplasmic membrane. It was found [238] that bolalipid membranes differ substantially from a normal lipid membrane, with an increase in thickness and tail order, an increase in the gel-to-liquid crystalline phase transition temperature, and a decrease in diffusivity of the lipids.

MD simulations of DMPC model system in the fluid phase was combined with several experimental methods [239]. The combination of experiment and simulation offers a powerful set of tools to investigate the lipid structure and dynamics. Whereas experiments are essential for FF validation and developments, simulations help to interpret and complement experiments and can, in turn, initiate further experimental studies. Similarly, combined MD simulations and experiments of fluid phase DPPC bilayers were performed in ref. [240].

For a literature on MD simulation studies of several fully hydrated bilayers (e.g., DPPC, DPPE) in a gel phase, see also [74, 217, 241, 242]. The gel to liquid-crystal phase transitions of fully hydrated bilayers were studied in ref. [241, 243, 244]. It should be mentioned also series of MD simulations of a ceramide bilayer [245–247], and sphingomyelin ceramide bilayers [248]. Ceramide is the simplest molecule in the class of glycosphingolipids composed of a sphingosine backbone and acyl moiety. It plays significant roles in cell signaling, apoptosis, binding of hormones, toxins, and viruses, and many other biologically important functions.

BILAYERS: STEROLS, ANESTHETICS AND OTHER INCLUSIONS

Cholesterol

Sterols are essential constituents of mammalian cell membranes, one of them is CHOL. The significance of CHOL in biological membranes has been known for a long time. A large number of experimental and theoretical studies has been devoted to unravel the modes of action of this molecule (for recent reviews see, e.g., refs. [24, 27, 186, 249–254]).

CHOL's preference for specific fatty acid chains was investigated in MD computer simulations [197] of a lipid bilayer membrane consisting of CHOL and 18 : 0/22 : 6(n-3)*cis* PC in a 1 : 3 ratio. Three bilayer systems were studied by MD in ref. [199]: 18 : 0/

22 : 6(n-3)*cis* PC, 18 : 0/22 : 5(n-6)*cis* PC, and 18 : 0/22 : 6(n-3)*cis* PC with 25 mol % CHOL. It was found that the distribution of lateral stress within the hydrophobic core of the membrane is sensitively dependent on the degree of chain unsaturation and on the presence of CHOL. Replacing (n-3) fatty acids with (n-6) chains, or incorporating CHOL into the membrane, shifts the repulsive lateral chain pressure away from the lipid/water interface toward the bilayer interior [199]. MD simulations [255] performed on DMPC, POPC, and DAPC bilayers showed that in high PU FA content bilayers CHOL is capable of assuming different orientations within a bilayer simultaneously. The results of MD simulations of the bilayers of DOPC–CHOL mixtures [256] are consistent with a partial ordering of phospholipid acyl chains by the rigid fused-ring structure of CHOL. An unexpected result of this study is the observation of a high concentration of acyl-chain methyl groups in the polar headgroup region of liquid-disordered membranes. The condensing effect of CHOL in DOPC lipid bilayers was systematically investigated via atomistic MD simulation in ref. [257]. Fourteen independent 200 ns simulations, spanning the entire range of CHOL mole fraction in DOPC bilayers (0, 1.95, 5.08, 10.16, 14.84, 20.31, 25, 30.08, 35.16, 39.84, 44.92, 50, 57, and 65.63 mol %) were performed. The results showed that the total area of a PC–CHOL bilayer is primarily determined by the molecular packing in the CHOL sterol ring region.

Free energy profile of a pair of CHOL molecules in a leaflet of POPC bilayers in the liquid-crystalline phase has been calculated in ref. [258] as a function of their lateral distance using a combination of NPT-constant atomistic MD calculations and the thermodynamic integration method. This free energy function may be used as a reference when coarse grained potential model is investigated for this two-component system.

MD simulations of DPPC, POPC, and DAPC membranes were performed to explore the energetics and mechanism of passive CHOL flip-flop and its dependence on chain saturation [259]. The resulting paths indicate that CHOL prefers to tilt first and then move to the bilayer center where the free energy barrier exists. The barrier is lower in DAPC than in DPPC or POPC, and the calculated flip-flop rates show that CHOL flip-flop in a polyunsaturated bilayer is faster than in more saturated bilayers.

Systematic MD simulations were applied in ref. [260] to study partitioning of solutes between water and membranes. The potentials of mean force were derived for six different solutes (ethanol, ammonia, nitric oxide, propane, benzene, and neopentane) permeating across 20 different lipid membranes containing one out of four types of phospholipids (DMPC, DPPC, POPC, POPE) plus a CHOL content of 0, 20, 30, 40, and 50 mol %. The simulations showed that the partitioning is more sensitive to CHOL (i) for larger solutes, (ii) in membranes with saturated as compared to membranes with unsaturated lipid tails, and (iii) in membranes with smaller lipid head groups.

To elucidate the molecular mechanism of the reduction in water leakage across the membranes by the addition of CHOL, water permeability of DPPC and palmitoyl–SM bilayers in the absence and in the presence of CHOL (0, 10, 20, 30, 40, and 50 mol %) have been studied by MD simulations [261]. An enhanced free energy barrier was observed in these membranes with increased CHOL concentration, and this was explained by the reduced cavity density around the CHOL in the hydrophobic membrane core and this was found to be the main reason to reduce the water permeability.

Isomolar semigrand canonical ensemble simulations, performed at fixed difference in chemical potential between DPPC and DOPC, have been performed to assess the tendency of DPPC and DOPC to demix in the presence of CHOL [262]. The relative affinity of DPPC and DOPC for high CHOL bilayer environments in simulations is explicitly shown to depend on the degree of CHOL alignment with the bilayer normal, suggesting that a source of the cooperativity is the composition dependence of CHOL tilt angle distributions.

A statistical mechanical model of CHOL–phospholipid mixtures that is able to rationalize almost any critical mole fraction value previously reported for sterol superlattice formation as well as the observed biphasic changes in membrane properties was recently presented in paper [263]. According to this model, the extent and the type of sterol superlattices, and thus the lateral distribution of the entire membrane, should vary with CHOL mole fraction in a delicate, predictable, and nonmonotonic manner, which should have profound functional implications.

An all-atom MD simulation of lipid bilayers with different CHOL–SM molar ratios was reported in ref. [264]. Five hydrated systems were built with molar CHOL/18 : 0–SM ratios of 0/100 (pure SM), 20/80, 30/70, 35/65, and 40/60. The results revealed structural and dynamic changes suggesting the random distribution of lipids along the bilayer planes is supplanted at CHOL concentrations above 30 mol % by the formation of a liquid-ordered phase, which is thought to be the precursor to lipid raft formation. The packing of molecules in the bilayer is shown to be associated with the hydrogen bonding between CHOL and SM. The molecules tend to migrate toward distributions in which a SM molecule forms on average one hydrogen bond with a CHOL molecule [264]. The translocation of CHOL, ceramide, and diacylglycerol in a POPC bilayer and a raft (1 : 1 : 1 palmitoyl–SM, POPC, and CHOL) bilayer was investigated [265] using MD simulations. CHOL was shown to have a large (54 kJ/mol) free energy of exchange between the POPC and raft bilayer, and therefore, it strongly prefers a more ordered and rigid raft bilayer over a more

liquid POPC bilayer. MD simulations of GM1–SM–CHOL and GM1–POPC bilayers have been performed [266]; GM1 (monosialo-gangliosides) form a microdomain with SM and CHOL and are deeply involved in the aggregation of some peptides on neural membranes. GM1 molecules in the GM1–SM–CHOL membrane were condensed, whereas those in GM1–POPC membrane scattered. That is, the formation of GM1 cluster was observed only on the GM1–SM–CHOL mixed membrane [266].

MD simulations were used [267] to consider 1,6-diphenyl-1,3,5-hexatriene fluorescent probes in a fluid hydrated DPPC bilayers with 5 and 20 mol % CHOL. It was shown that while the fluorescent probe affects a number of membrane properties, the perturbations induced by the probe depend on the concentration of CHOL in the membrane. The fluorescent probe was found to influence the mass density distribution of lipids across the membrane and to promote the ordering of acyl chains around the probe. Yet, these perturbations get relatively weaker for increasing CHOL concentration.

To clarify the role of glycosphingolipids in the dynamics of CHOL-rich lipid rafts, lipid membranes that contain varying amounts of galactosylceramide, SM, CHOL, and POPC were considered by MD simulations [268]. The results indicate that increasing the portion of galactosylceramide molecules greatly slows down the lateral diffusion. MD simulations were used to characterize the influence of CHOL on the interaction between the anticancer drug doxorubicin and a DPPC–CHOL lipid bilayer (0, 15 and 30% CHOL) [269]. It was shown that the drug greatly affects local membrane structure by attracting DPPC headgroups, curving the membrane, and allowing water penetration. The effect of CHOL on doxorubicin translocation is not only quantitative. Not only does doxorubicin prefer to be inside the bilayer without CHOL present, it actually flip-flops very rapidly (10^3 times faster) compared to its release from the bilayer [269].

Anesthetics

Another important membrane inclusions can be anesthetics (e.g., lidocaine, benzocaine, articaine, halothane, hexafluoroethane, short chain alcohols like methanol, ethanol, 1-alkanols) [79, 270–278]. The specific molecular mechanism of action of anesthetics and details of their interactions with biological membranes are, to a large extent, unknown or poorly understood. For instance, lidocaine–family drugs are widely used as local anesthetics in medical treatment to prevent or relieve pain. Clearly, the lidocaine—membrane (and other anesthetics) interaction perturbs the bilayer structure. It is speculated [272] that this change in the local order will also affect the lipid protein (ion channel) interaction which is claimed to be essential for the anesthetic activity. It was demonstrated in ref. [276] that addition of local anesthetic benzocaine increases disorder in the membrane. A thermodynamic study of benzocaine insertion into DPPC and DPPS bilayers by means of MD was carried out [279]. It was shown that an increase in the DPPS fraction of the lipid bilayer facilitates the insertion of the benzocaine into the bilayer, an observation that could be related with the activity of certain drugs that depend on the lipid composition of the cell membrane. It was shown [280] for benzocaine, lidocaine, and tetracaine that the charged form of these drugs are oriented at the interface as one of the lipids, while the neutral form can easily cross the interface, entering the membrane (DPPC) in agreement with most experimental results.

Since the action of general anesthetics was known to be pressure dependent, MD simulations of such a molecule, halothane, embedded in a DMPC membrane, performed under physiological conditions and also at elevated pressures were carried out [281]. The results clearly show that at high pressures the halothane molecules tend to cluster together. Further, it was shown [282] that the solvation of halothane by the DMPC membrane and bulk water are both pressure dependent, with an increased pressure driving halothane into the membrane. A possible mechanism for pressure reversal of general anesthetics from computer simulations is discussed in ref. [283]. Recent paper [277] contains an account of a series of simulations of PC bilayers discussing a possible effect of halotane general anesthetic on K^+ ion channel.

A series of atomic-scale MD simulations of POPC membranes in aqueous solution with ethanol, whose concentration was varied from 2.5 to 30 mol % (lipid–free basis) have been performed [284]. It was shown that at concentrations below the threshold value of 12 mol % (30.5 v/v %) ethanol induces expansion of the membrane, accompanied by a drop in the membrane thickness as well as disordering and enhanced interdigitation of lipid acyl chains. These changes become more pronounced with increase in ethanol concentration, but the bilayer structure of the membrane is maintained. Above the threshold concentration the appearance of multiple transient defects in the lipid/water interface eventually gives rise to desorption and assembly of some of the lipids into non-bilayer structures within the membrane interior. These structures, being small and irregular, resemble inverted micelles and have a long-lived character. Furthermore, formation of the non-bilayer structures is accompanied by mixing of lipids that belong to the opposite membrane leaflets, thereby leading to irreversible changes in the membrane structure [284].

To investigate the effect of 1-alkanols of various carbon chain lengths onto the structure and dynamics of DMPC bilayers, long-time MD simulations were performed [285]. All investigated 1-alkanols assembled inside the lipid bilayer within tens of nanoseconds. Their hydroxyl groups bound preferentially to the lipid carbonyl group and the hydrocarbon chains

stretched into the hydrophobic core of the bilayer. The studies showed that all 1-alkanols drastically affected the bilayer properties. Insertion of long-chain 1-alkanols decreased the area per lipid while increasing the thickness of the bilayer and the order of the lipids. The bilayer elasticity was reduced and the diffusive motion of the lipids within the bilayer plane was suppressed. On the other hand, integration of ethanol into the bilayer enlarged the area per lipid. The bilayer became softer and lipid diffusion was enhanced [285].

MD simulations have been carried out to scan the interdigitation effect at the (5S)-1-benzylo-5-(1H-benzimidazol-1-ylo-methylo)-2-pyrrolidinone/DMPC system [286], and partial interdigitation was observed.

Another action mechanism discussed in the literature is the change of electrostatic potential inside membrane (called also dipole potential). It was demonstrated by MD simulations that addition of lidocaine to DMPC membrane causes noticeable increase, by up to 200 mV, of the dipole potential [273, 278] which may affect the work of ion channels and result in anesthetic action.

Small Molecules

One of the key membrane functions is the regulation of the transport of small molecules across the membrane. Behavior of small solutes [287] is widely discussed. While the membrane transport, as a rule, involves special channel forming peptides and proteins, various small, uncharged molecules, such as O_2, CO_2, water, NO, CO, etc., can permeate in small amounts the cell membrane without the aid of any transmembrane proteins. In ref. [288], the effects of the hydrocarbon chain length of lipid molecules on the permeation process of small molecules (O_2, CO, NO, and water) through lipid bilayers were investigated. MD simulations of three saturated lipid bilayer systems were performed: DLPC, DMPC, DPPC [288].

Cell membranes need to be hydrated by water for their proper functioning. As a matter of fact, water is an essential constituent of biomembranes. Therefore, it is important to understand the structural and dynamical properties of water molecules located at the interface with lipids and other biomolecules. MD computer simulations were performed to study the orientational dynamics of water next to bilayers containing DLPC with different hydration levels [289], next to bilayers of DOPC and DOPS [212], next to DOPC bilayer [290]; see also review [291] concerning simulations of aqueous solutions next to phospholipid membrane surfaces. It was shown [292] that water at the DPPC membrane surface is substantially more ordered than bulk water, due to a loss of hydrogen bonding between water molecules, coupled with an alignment of lipid and water dipole moments. Ordering of the water leads to a gradient in the effective dielectric permittivity. Water permeability for a bilayer composed of a 2 : 2 : 1 molar ratio of ceramide NS 24 : 0 (ceramide 2)—CHOL—free FA 24 : 0 was estimated with extended ensemble MD in ref. [247].

The interaction of dimethylsulfoxide molecule ($(CH_3)_2SO$) with gel-phase bilayers of ceramide 2 was investigated in ref. [246]. The liquid-crystalline phase of ceramides is expected to be markedly more permeable for solutes than the gel-phase structure.

Another long-standing problem in membrane biophysics is related to the ion permeation across protein-free lipid membranes. Pore formation in lipid membranes and subsequent pore-mediated ion transport, salt-induced effects in plasma membrane, the electrostatic properties of membranes are also traditionally attractive topics for computer simulation studies (see, e.g., [293–305] and the literature lists). MD simulations of biologically realistic transmembrane potential gradients across a DMPC bilayer are presented in ref. [306]. These simulations are the first to model this gradient in all-atom details, with the field generated solely by explicit ion dynamics.

MD simulations considering how mono- (NaCl) and divalent ($CaCl_2$) salts affect properties of inner and outer membranes of mitochondria were described in ref. [307]. This work seems to be the first computational study concerning mitochondrial membrane properties in the presence of salt. Six different membrane systems mimicking mitochondrial membranes with and without salt were studied. Three of them corresponded to the inner membrane and three to the outer one. The membranes were composed of PC, PE, and cardiolipin. Linoleic chain was used as the acyl chains of the lipids, i.e., two chains in PC and PE and four chains in each cardiolipin. The main focus of the study was on the basic modifications induced by ions to the bilayer. It was discovered that the influence of salt on the structural properties is rather limited, only weakly affecting lipid packing, conformational ordering, and membrane electrostatic potential. The changes induced by salt were found [307] to be more prominent in dynamical properties related to ion binding and formation of ion-lipid complexes and lipid aggregates, as rotational diffusion of lipids is slowed down by ions, especially in the case of $CaCl_2$. In the same spirit, lateral diffusion of lipids is slowed down rather considerably with increasing concentration of $CaCl_2$. The effects of bilayer composition (cationic dimyristoyltrimethylammoniumpropane to neutral DMPC lipid fraction) and of NaCl electrolyte concentration on the dynamical properties of these systems were studied in ref. [308]. It was noted that the systems having low cationic lipid content are able to retain cationic ions in their carbonyl region for very long times, whereas systems with higher cationic lipid content lack this ability. To study the effect of PEGylated (PEG is poly-(ethylene glycol)) lipid density, salt concentration, and the interaction with KCl and $CaCl_2$ salts in addition to NaCl, MD simulation have been used [309]. It was found that addition of salt slightly expands the PEG layer and expands the region

of the PEG layer where the Na^+ ions are located. For the liquid crystalline membrane, the PEG polymer also penetrates deeper into the membrane when salt is added [309].

Large Penetrants

Some of the penetrants (e.g., drug molecules) are comparatively large. To reach their biological target, drugs have to cross cell membranes, and understanding passive membrane permeation of large drugs [287] is therefore very important. Behavior of fluorescent probes [310] in a lipid bilayer from computer simulations is also widely discussed.

Another penetrants are surfactants. MD simulations of bilayers consisted of a single tail cationic surfactant behenyl trimethyl ammonium chloride with stearyl alcohol as the cosurfactant were reported [311]. MD simulation was recently applied to investigate the bilayer properties of catanionic vesicles composed of an ion pair amphiphile hexadecyltrimethylammonium-dodecylsulfate and a double-tailed cationic surfactant ditetradecyldimethyl-ammonium chloride [312]. Structural information regarding membrane elasticity and the organization and conformation of surfactant molecules was obtained.

Six molecules of $(CF_3)_2$—benzoic acid with deprotonated carboxyl groups were inserted into the MD simulation box containing a lipid bilayer with DMPC molecules [313]. MD simulations confirmed the intuitive expectation that $(CF_3)_2$ —benzoic acid molecules are oriented in the lipid bilayer according to their amphiphilic properties, which also allows for favorable hydrogen bonding within the lipid headgroup region.

MD simulations and X-ray diffraction analysis study of several 18 : 1(n-9)*trans* / 18 : 1(n-9)*trans* PE membranes containing free FAs were performed in ref. [314]. The study was aimed at understanding the interactions of several structurally related FAs with biomembranes, which is necessary for further rational lipid drug design in membrane-lipid therapy. FAs able to affect biophysical properties of cell membranes, in turn will also alter localization and/or function of membrane protein involved in the regulation of cellular processes. For the above reasons, FAs or other lipids could be a tool to modulate pathophysiological conditions via cell membrane properties [314].

A coarse grained MD method was used in ref. [315] to model the permeation properties of flat DPPC bilayers with various amounts of incorporated monopalmitoyl-PC lysolipid (i.e., PC molecule with one 16 : 0 chain). The enhanced permeability of the membranes at their gel to liquid-crystalline phase transition was explored. A peak in the permeability was shown to coincide with the phase transition temperature from the gel to liquid-crystalline state when lysolipid is present. This peak in permeability correlates with a jump in the area per lipid near the same temperature as well as increased fluctuations in the lipid bilayer free volume.

The effects of the bioflavinoids (ion-channel modifiers) genistein and daidzein on DOPC and diphytanoylPC bilayers as determined by volume measurements, X-ray scattering, and MD simulations were reported [316]. Both bioflavinoids inserted into the hydrocarbon region of both DOPC and diphytanoylPC near the carbonyls of the lipids and both decreased the bilayer thicknesses. The long axes of both bioflavinoids were oriented nearly parallel to the plane of the bilayer with their carbonyl groups preferentially pointed toward the proximal surface.

Transmembrane lipid translocation (flip-flop) processes can also be discussed in this context. These processes are involved in a variety of properties and functions of cell membranes; flip-flops are one of the least understood dynamical processes in membranes. In ref. [317], the atomic-scale MD simulations were performed on DMPC bilayer. It was shown that the computational approach can actually provide a substantial insight into the mechanism (or one of the mechanisms) associated with lipid flip-flops.

One of the methods to introduce foreign molecules into cells is electroporation. Electric fields can induce pore formation and other structural defects in lipid membranes. The mechanism of pore formation by direct MD simulations of DOPC bilayers with applied electric fields of different strengths was investigated in ref. [211], that of asymmetric membranes DOPC—DOPS was studied in ref. [213, 318].

An important contributor to the thermodynamic driving force is the available free volume across a membrane. Thus, the diffusion properties of the penetrants are obviously related to the properties of the free volume clusters (e.g., their size, shape, orientation, etc.) present in the membrane, and therefore a detailed analysis of the voids can also provide some information on the permeability properties of the membrane. Such a study was performed for bilayers composed of 18 : 0/18 : 1(n-9)*cis* PC, 18 : 0/18 : 2(n-6)*cis* PC, 18 : 0/18 : 3(n-3)*cis* PC, 18 : 0/20 : 4(n-6)*cis* PC and 18 : 0/22 : 6(n-3)*cis* PC molecules in ref. [200]. It was found that the preformed cross-membrane channels are not broad enough to let small molecules, such as water, go readily through them, however, they are likely to facilitate the permeation of such molecules across the membrane.

Effects of various nanostructured materials (nanoparticles) on lipid membranes are also widely discussed [319] including carbon nanotubes [320–322], gold [323] and other nanocrystals [324], fullerenes [325], etc. Many hydrophobic nanoparticles are found to be able to transverse a membrane, with some nanoparticles even causing damage to the membrane, thus potentially leading to cytotoxic effects. Though lipid membranes have been very intensively studied by computer simulations during last decade, in general

modelling translocation of nanoparticles through a lipid membrane is a significant challenge.

CONCLUSIONS

Computer simulations of various lipid membrane systems allow to elucidate at the molecular level the detailed relations between the chemical structure and physical properties of various lipid molecules and membrane inclusions, to explain individual peculiarities of natural objects, to make forecasts concerning their behavior, etc. An understanding of the molecular basis of various physical properties of lipids and other membrane constituents allows one to narrow down the list of hypotheses under consideration about the possible functions of various components (such as acyl chains) in lipid membranes, e.g., the maintenance of proper bilayer fluidity and permeability, of the activity of membrane-bound enzymes, etc. Thus, together with the continued improvements of force fields and significant development of the simulation methodologies, algorithms and mutually complementary methods, rapid advances in computing power, the long-term prospects of computer simulations in membrane studies seem to be highly promising.

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