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ARTICLE

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Multiscale modeling of lipids and lipid bilayers

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Abstract A multiscale modeling approach is applied for simulations of lipids and lipid assemblies on mesoscale. First, molecular dynamics simulation of initially disordered system of lipid molecules in water within all-atomic model was carried out. On the next stage, structural data obtained from the molecular dynamics (MD) simulation were used to build a coarse-grained (ten sites) lipid model, with effective interaction potentials computed by the inverse Monte Carlo method. Finally, several simulations of the coarse-grained model on longer length- and time-scale were performed, both within Monte Carlo and molecular dynamics simulations: a periodical sample of lipid molecules ordered in bilayer, a free sheet of such bilayer without periodic boundary conditions, formation of vesicle from a plain membrane, process of self-assembly of lipids randomly dispersed in volume. It was shown that the coarse-grained model, developed exclusively from all-atomic simulation data, reproduces well all the basic features of lipids in water solution.

Keywords Molecular dynamics · Multiscale modeling · Lipids · Membranes

Introduction

Molecular computer (MC) simulations have now become an important complement to experimental studies of bio-macro-molecular systems (Tielerman et al. 2001; Wang et al. 2001; Norberg and Nilsson 2003). Within a chosen theoretical model, computer simulations allow us to follow every detail in the molecular motion, providing valuable information for interpretation and understanding of experimental data. Lipid membranes is one of the examples where molecular simulations have shown to be especially fruitful. Lipid membranes provide the basic structural unit of living cells, and knowledge of their physical and chemical properties is very important for our understanding of how the whole cell is functioning. All-atomic molecular dynamics (MD) simulations of membranes became feasible in the last few years (Marrink and Berendsen 1994; Tieleman et al. 1997; Lindahl and Edholm 2000; Patra et al. 2003; Sum et al. 2003). These are, however, very time consuming simulations even if a small (a few nanometer) fragment of membrane is considered.

An often used way to reduce computer time expenses for simulations of large molecular systems in cases when all-atomic resolution is not principally important, is to use coarse-grained models. For instance, in the united atom model, each hydrocarbon group (CH_2) or (CH_3) is presented as a single interaction center. In a similar manner even bigger molecular fragments can be united in single interaction centers. Also, explicit description of the solvent may be excluded by considering effective solvent-mediated interactions (Lyubartsev and Laaksonen 1999). Developing of coarse-grained lipid model, which gives possibility to carry out simulations of bigger membrane fragments during longer time and which preserve properties of all-atomic model, would allow us to address to a much wider range of problems.

In the last few years, a number of coarse-grained lipid models with different levels of details have appeared (Goetz et al. 1999; Noguchi and Takasu 2001; Shelley et al. 2001; Marrink and Mark 2003; Kranenburg et al. 2003, 2004; Stevens 2004; Marrink et al. 2004). The common problem for such models is how to set up the interaction potentials for the united atom groups. For example, in some recent studies (Marrink et al. 2004; Stevens 2004), a Lennard-Jones potential was used to model interactions between all coarse-grain sites. Recently also an approach was developed, now called multiscale modeling, to derive interaction potentials for coarse-grained models from the atomistic simulations (Lyubartsev and Laaksonen 1995, 2004; Reith et al. 2003). In the application to lipid models, the main idea

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of this approach consists of the following steps. As a first step, an all-atomic molecular dynamics simulation of lipid molecules in water is carried out and radial distribution functions (RDF) between different lipid fragments are determined. Then, a 10-site coarse-grained lipid model is formulated. The interaction potential between the sites of the coarse-grained model is obtained by the inverse Monte Carlo method using radial distribution functions calculated in the all-atomic simulation. Finally, the coarse-grained model is used to simulate a substantially bigger lipid system. Previously this approach was applied to determination of the solvent-mediated potentials between ions and DNA in aqueous solution (Lyubartsev and Laaksonen 1997, 1999) as well as for computation of effective potentials between charged colloids (Lobaskin et al. 2001). For lipids, similar approach was considered in paper (Shelley et al. 2001) for parametrization of interaction between the lipid head groups while other interactions were empirically parametrized by Lennard-Jones like potentials.

In this work, the whole set of interaction potentials for a coarse-grained lipid model in implicit water is derived exclusively from atomistic MD simulations. Section 2 describes all computational details: atomistic MD simulations, construction of the coarse-grained lipid model, inverse Monte Carlo simulation for calculation of effective potentials. In Sect. 3, results of simulations of lipids using the calculated effective potentials are described and discussed. Conclusions are given in Sect. 4.

Theory. Building of the coarse-grained lipid model

Molecular dynamics (MD) simulation

The aim is to build a coarse grained lipid model which can be used for studies of mesoscale membrane properties, including mechanical elasticity, self-assembly, membrane fusion, etc. While local atomic motions are not very important in such studies, some basic features of lipid molecules like the presence of polar group and hydrophobic tails should be kept. A reasonable compromise may be the 10-site model displayed in Fig. 1. Two sites, corresponding to choline (N) and phosphate (P) groups represent the lipid polar head. The phosphate group is connected to two ester groups (CO), each of them being connected to a chain of three sites (CH) representing the hydrocarbon tails. To determine effective interactions between the sites of the coarse-grained model, we need to know RDFs between these sites. The RDFs can be computed from atomistic MD simulations of lipids in water.

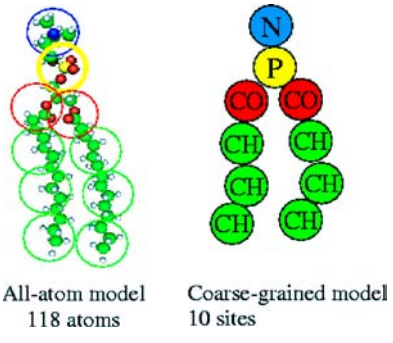

Fig. 1 All-atomic (**a**) and coarse-grained (**b**) lipid models

The MD simulation of lipids in water has been carried out for 16 DMPC lipids and 1,600 water molecules. Constant temperature and constant pressure Nosé-Hoover molecular dynamics algorithm [Martyna et al. 1996) was used with the temperature 312 K and pressure 1 atm. The lipids were described by the all-atomic CHARMM27 force field (Feller and MacKerell 2000). For water, flexible SPC model (Toukan and Rahman 1985). was used. The double time step algorithm was implemented with 0.2 fs short time step for intramolecular vibrations and intermolecular Lennard-Jones interactions within 5 Å distance, and long time step 2 fs for other interactions. The electrostatic interactions were treated by the Ewald summation method. Computational software was MDynaMix package (Lyubartsev and Laaksonen 2000).

The system was equilibrated during 2 ns and then run during 12 ns for the average collection. After initial equilibration, most of lipids were gathered in a cluster. Due to the small number of lipids and small system size (40 Å), these lipids cannot form any stable structure, and during the simulation some lipids or their fragments were often exposed to water, as it is seen in a typical snapshot of the system in Fig. 2. The self-diffusion coefficient of lipid's centers of mass was $7{\cdot}10^{-7}$ cm^2/s, which corresponds to the average displacement of about 6.5 Å during a nanosecond. Thus states of lipids in close contact as well as lipids surrounded by water were sampled well during this simulation.

The radial distribution functions were calculated between each pair of the centers of interaction sites in the coarse-grained model. The centers were set at the nitrogen and phosphorus atoms of the choline and phosphate groups, and at the center carbon atoms of the ester and hydrocarbon groups (that is carbons with numbers 1, 5, 9 and 13 in each tail, see Fig. 1). Additionally, distribution of distances between "bound" sites were computed to be used in determination of the "intramolecular" potential of the coarse-grained model. The two "CO" and six "CH" sites in the coarse-grained model were considered as equivalent, so the model included four different interaction sites (N,P,CO and CH) with ten different pairs of intermolecular potentials and four intramolecular bond potentials.

It is also possible to introduce bending potential into coarse-grained model as it was done in works (Kranenburg et al. 2004; Stevens 2004) to account for tail ridigity. In this work bending potential was however neglected. It is known that in pure solvent hydrocarbon chains have the fraction of gaushe conformations about 0.35 (Feller and MacKerell 2000), that is why after 4-5 covalent bonds (or less than 2 segments of the coarse-grained

model) such chains practically forget initial orientation. In principle, bending potential may be obtained from the distributions over angles in the same way as the bond potential.

The radial distribution functions were computed within separate "windows" of the length 2 ns and results obtained within different windows were compared with each other. No noticeable trend after initial 2 ns of the simulation was noticed. Thus the final RDFs, displayed in Fig. 3, are obtained in a well equilibrated system.

Inverse Monte Carlo procedure

The RDFs calculated in atomistic molecular dynamics simulations were used as input to the inverse Monte Carlo procedure to compute the effective potentials. The aim of this procedure is to obtain interaction potentials which, within the coarse-grained model in the implicit solvent, yield the same structural properties (RDF-s) as all-atomic molecular dynamics simulations in the explicit solvent. There exist different ways to reconstruct the effective potentials from (known) RDFs. In work (Soper 1996) Soper suggested an iterative procedure with series of Monte Carlo runs, during which corrections to the interaction potential are calculated as logarithm of the ratio between the simulated and reference RDFs. Such approach was used later in computation of effective potentials for coarse-grained models in a number of works (Shelley et al. 2001; Reith et al. 2003). The inverse Monte Carlo method suggested in paper (Lyubartsev and Laaksonen 1995), while computing corrections to the interaction potentials, takes into account cross-correlation terms of the radial distribution functions. Due to this reason the latter method provides better convergence in cases when one need to compute a set of different interaction potentials from a set of radial distribution functions, as in the case of the coarse-grained lipid model. A recent and more detailed description of the inverse Monte Carlo algorithm, used in this work, is given in paper (Lyubartsev and Laaksonen 2004).

The inverse Monte Carlo procedure has been run in the box of the same size and the same number of coarse-grained lipids as the corresponding atomistic MD simulation. Thus effects of the limited system size and small number of lipids on RDFs are fully taken into account. The intramolecular non-bonded interaction potentials were set the same as the corresponding intermolecular potentials. Additionally, charges $+1$ and -1 where prescribed to the choline and phosphate sites correspondingly. In the inverse MC procedure only the short range part of the effective potential (up to 20 Å distance) was varied, while the electrostatic interactions due to charges on the lipid head groups were treated by the Ewald method, with the dielectric permittivity of media $\varepsilon = 70$. The latter value was determined within the inverse Monte Carlo procedure itself by observing the asymptotic behavior of the effective potentials between the charged sites according to the procedure described by Lyubartsev and Laaksonen (2004). During the computations, both RDFs and effective potentials were tabulated with the grid resolution of 0.05 Å. The calculated short-range (non-electrostatic) parts of the effective potentials for all coarse-grained site pairs are presented in Fig. 4.

Mesoscale simulations

The effective potentials displayed in Fig. 4 provide the same RDFs for the coarse-grained lipid model in

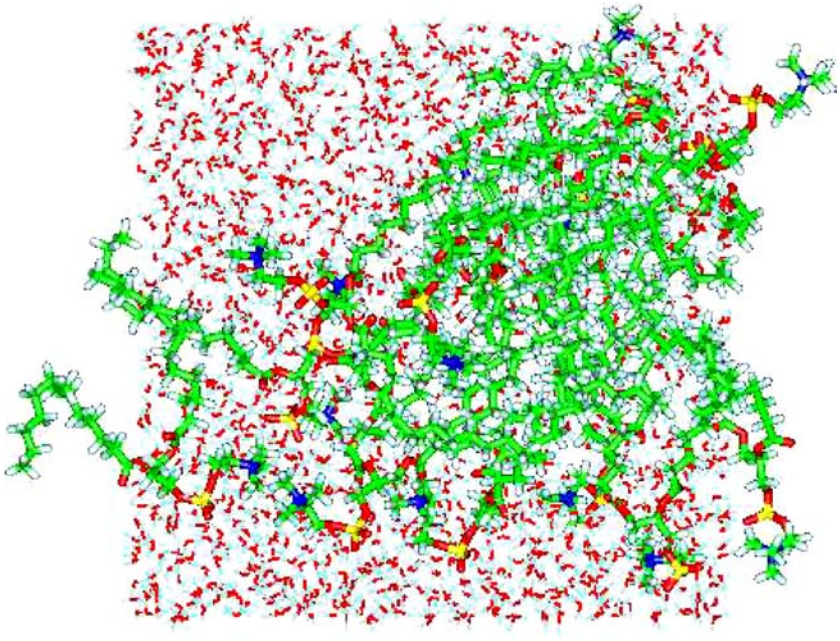

Fig. 2 A typical snapshot of atomistic MD simulations

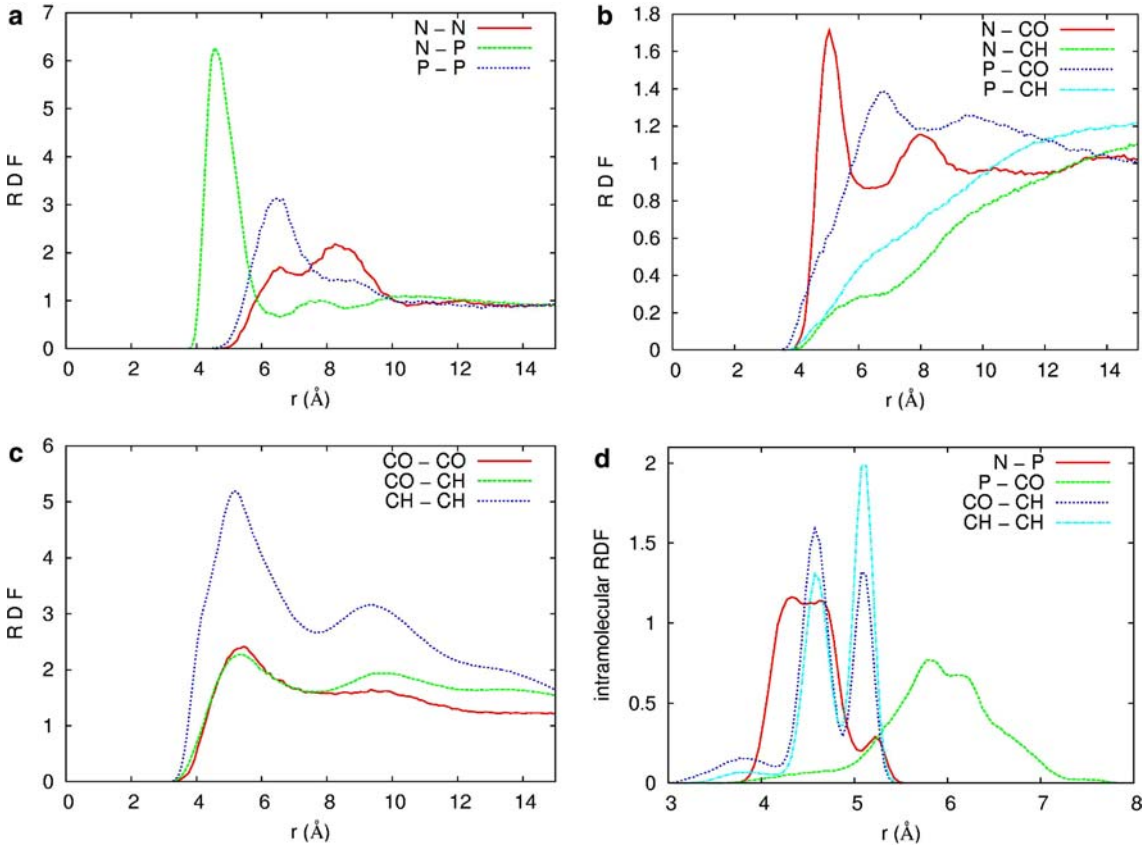

Fig. 3 Radial distribution functions (RDFs) between different lipid sites obtained in molecular dynamics (MD) simulations. Panel **d** shows distribution of intramolecular distances between the sites

continuum solvent as RDFs calculated in all-atomic molecular dynamics simulation, which are displayed in Fig. 3 (in fact, the differences between the MD and the coarse-grained RDFs are within the thickness of lines). Thus, for computation of structural properties, we can reach substantial saving of computational time, substituting the all-atom model by the coarse-grained model with effective potentials. We can also increase the size of the simulated system much beyond that what is possible in the atomistic simulations.

On the next stage, the computed effective potentials were used in Monte Carlo and MD simulations on a large scale. In these simulations, the effective potentials were tabulated as output from the inverse MC simulation without adjustment to any functional form. Monte Carlo simulations were carried out using standard Metropolis algorithm with trial moves of a single interaction site at each step. Such procedure is however inefficient in cases when molecules are gathered in well separated assembles. There is no "driving force" to move each cluster as a whole. That is why, a MD algorithm was also used to simulate the coarse-grained lipid model. In coarse-grained molecular dynamics simulations, the force acting on interaction centers was determined by linear interpolation of the effective potential between the nearest grid points. The temperature was kept constant by the weak coupling method (that is, by scaling particles velocities to the value corresponding to the average kinetic energy at given temperature).

In this work, the MD of the coarse-grained model should be considered as another (than Monte Carlo algorithm) way to sample the configurational space and to reach the thermodynamical equilibrium. To describe the real-time dynamics within a coarse-grained model, one must introduce friction and random forces, accounting for removed solvent and internal degrees of freedom, and run Brownian dynamics (or similar kind) simulations. Without friction and random forces, the dynamics is artificially accelerated and it brings the system to the equilibrium faster. Still it may keep qualitative feature of the real dynamics which may be reconstructed by scaling time by some factor as it was done in work (Marrink and Mark 2003). In the present work this factor is not specified and the time is reported as it appears in the MD equations.

The time step in MD simulation of the coarse-grained model was 10^{-14} s. This is a longer time step than that used in typical all-atom simulations. One can use a longer time step because in coarse-grained simulations the effective potentials are softer while masses of sites are larger than in all-atomic simulations.

Three types of simulations of the coarse-grained lipid model were performed: a lipid bilayer with periodic boundary conditions; simulations started from a sheet of lipid bilayer without periodic boundary conditions, and

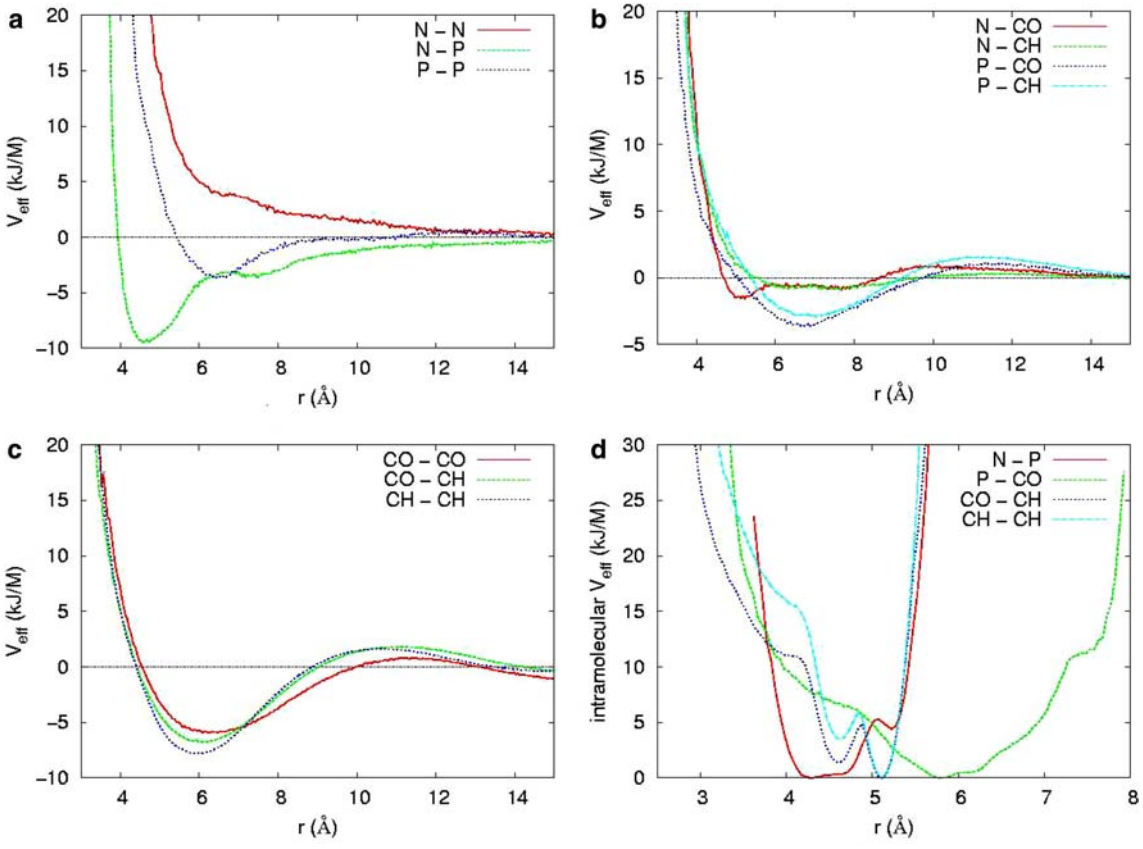

Fig. 4 Effective potentials between different sites of the coarse-grained model calculated by the inverse Monte Carlo simulations

simulations started from unordered configurations. In all cases, the temperature was 312 K.

Results and discussion

Simulation of an infinite lipid bilayer

In the start configuration, 392 coarse-grained lipid molecules were organized in a membrane bilayer with 14×14 lipids in each layer and periodic boundary conditions. The size of the simulation cell was chosen to provide the experimental value of 59 Å^2 for the area per lipid. The simulation was carried out by the Monte Carlo method. The results of this MC simulation of the coarse-grained model are compared with atomistic MD simulation of 98 DMPC lipids and 1,478 waters organized in the similar bilayer in a simulation box twice less in x and y directions than the size of the coarse-grained system (it was to expensive to run all-atomic MD simulation with 392 lipids). In the latter MD simulation, the same atomistic models for DMPC lipids and water were used as in the MD simulation of 16 lipids in water in which RDFs were calculated.

The results for the density distribution of different lipid sites along z direction (perpendicular to the membrane plane) are presented in Fig. 5. In the case of all-atomic molecular dynamics simulation, distributions of atoms representing centers of the coarse-grained units are shown. One can see that distributions of the coarse-grained model almost perfectly agree with the distributions of the corresponding sites in all-atomic simulation. The most noticeable difference is that the lipid tails region formed by "CH" sites is 1–2 Å narrower in the coarse-grained simulation leading to slightly thinner coarse-grained membrane comparing to the atomistic

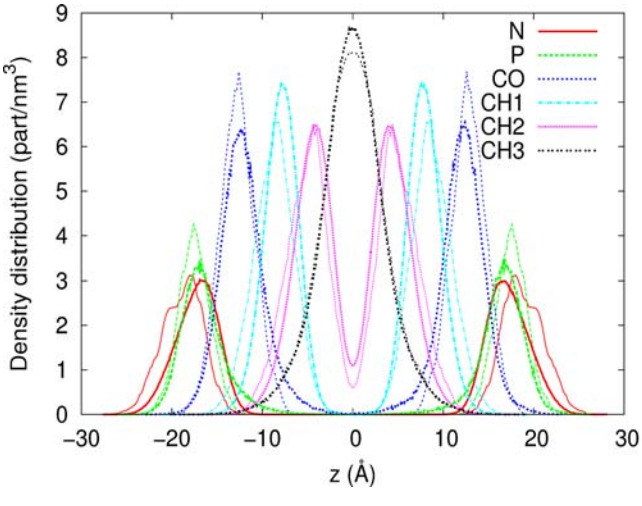

Fig. 5 Distribution density of sites of the coarse grained (*thick lines*) and corresponding sites of the atomistic (*thin lines*) lipid models relative to the membrane mid-plane

model. It is possible that introduction of angle bending potential in the coarse-grained model may improve this discrepancy.

A good agreement of the density profiles of all-atomic and coarse-grained models demonstrates, that effective potentials, calculated in a rather dilute phase (16 lipids per 1600 waters) of unordered lipids, work well in a condensed phase where the lipids are organized in a bilayer. In fact one cannot expect a priori that effective potentials, computed under some thermodynamic conditions, should provide correct properties of the system in other conditions (temperature, concentrations of species, etc), since the effective potentials themselves may depend on concentrations and temperature (Lyubartsev and Laaksonen 1997). Also, coincidence of RDFs does not necessary mean coincidence of other structural properties. The test with reproduction of the density profiles in plain bilayer shows however that these effects are small in the case of coarse-grained lipid model. This gives a hope that other properties computed for much bigger systems will be also realistic.

Formation of bicelles and vesicles

In the previous simulation, the initially prepared membrane bilayer structure was simulated under the periodic boundary conditions, which help to keep the structure. To study stability of the bilayer structure, the periodic boundary conditions were removed and a square sheet composed of 392 coarse-grained lipid molecules was simulated in a free space. In another simulation, the original bilayer fragment of 392 lipids was repeated three times in x and y - directions, and a piece of bilayer consisting of 3,528 lipids was simulated. Simulations were carried out by both the Monte Carlo and MD algorithms. Though both kind of simulations resulted in similar structures, the MD simulations turned out to be more efficient in sampling the configurational space and reaching the equilibrium configuration. Therefore all discussion below is given on the basis of results obtained in MD simulations.

During simulation of the smaller system (392 lipids), the membrane sheet almost immediately (faster that 100 ps) changed the shape from a square to discoid one (bicell), see Fig. 6. This change is quite expected since it decreases the contact area between the hydrophobic lipid tails and water (that is empty space in the coarse-grained model). After that, no substantial changes were observed. Within the membrane, these simulations produced almost the same structures as previous simulation with periodic boundary conditions.

A larger system initially also adopted the shape of a bicell of diameter about 350 ± 5 Å. This size of the bicell corresponds to the average area per lipid 56 Å^2, which is slightly less than the experimental value 59 Å^2. The slightly lower value of the area per lipid can be partially explained by the wave-like fluctuations of the membrane

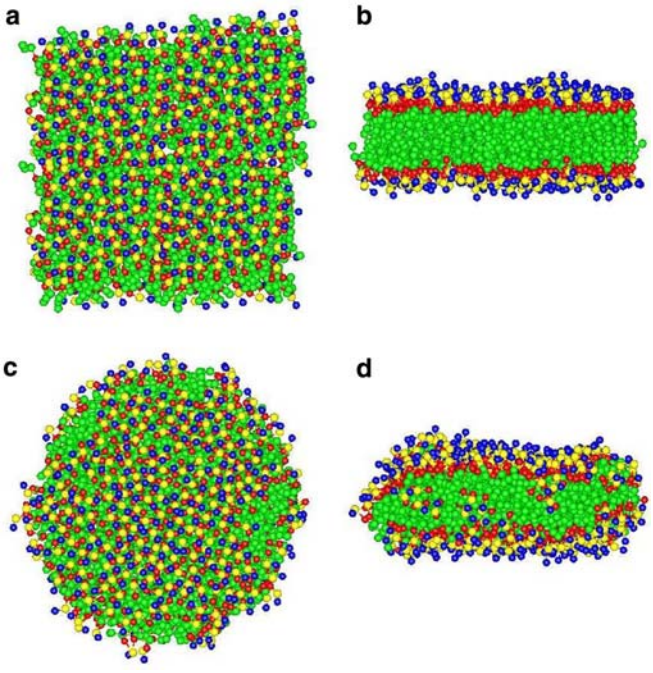

Fig. 6 Bicell formation starting from a square membrane sheet of 392 lipids. **a**, **b** are two views of the starting configuration, **c** and **d** is a typical equilibrium configuration

surface so that the "true" area of the surface exceeded the area calculated from measuring of the diameter.

After 0.5 ns of simulation, fluctuations of the membrane surface became stronger, it adopted a semispherical shape and then rather rapidly transfered to a spherical shape, see Fig. 7. Similar process of vesicle formation from a plain bilayer was observed in other coarse-grained simulations (Yamamoto et al. 2002; Marrink and Mark 2003). Just as in the case of bicell formation, this transition is driven by the minimization of the hydrophobic area (lipid tails) exposed to water. A defect in the form of a pore remained for a while in the place of membrane closure, with a pore surface formed by lipid headgroups. During the period of the pore existence, some lipids were moving from the inner vesicle layer to the outer one. Such a metastable state was also observed in the coarse-grained simulation (Marrink and Mark 2003) with Lennard-Jones type of effective potentials. Similarly to the work (Marrink and Mark 2003), the pore disappeared after about a nanosecond. After that the vesicle adopted a stable spherical conformation and the numbers of lipids in the inner and outer layers were constant: 1,478 and 2,050 correspondingly.

Densities of different lipid sites in the vesicle relative to its center of mass are displayed in Fig. 8. One can see similar distribution of the densities as in the plain lipid bilayer in Fig. 5. In the case of vesicle, densities of the inner and outer layers are different, the inner layer being more dense. It is possible to evaluate average area per lipid for the head groups of the inner and outer layers, evaluating their radii from Fig. 8 as 64 and 100 Å

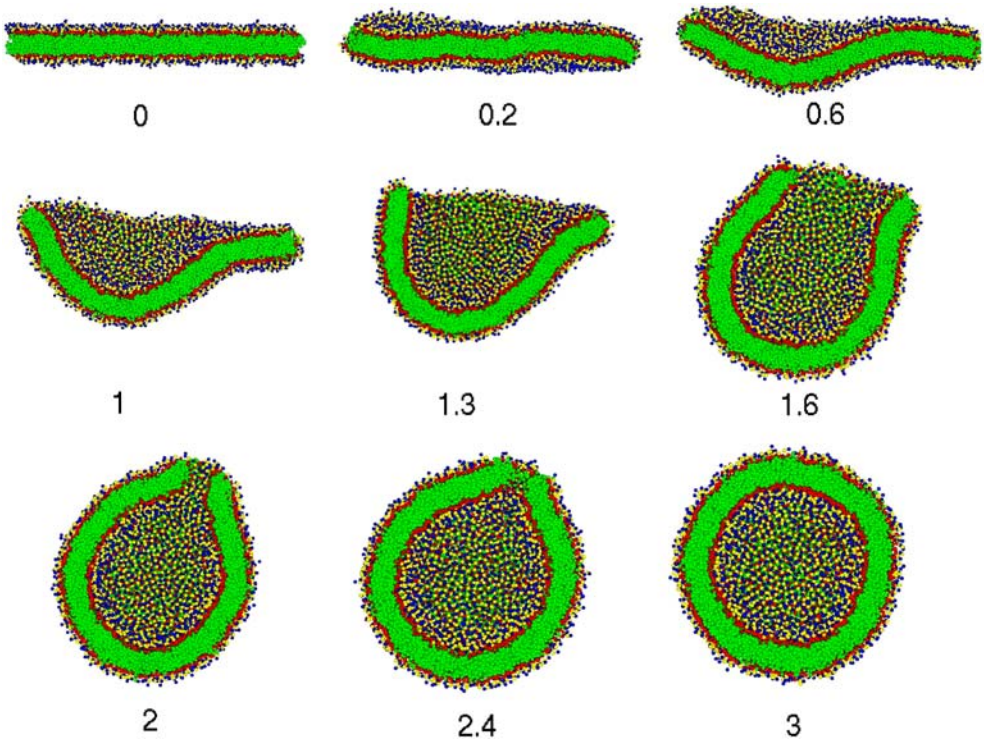

Fig. 7 Vesicle formation starting from a square membrane sheet of 3,522 lipids. A cross-section is shown at different time moments (non-scaled time is given in *ns*)

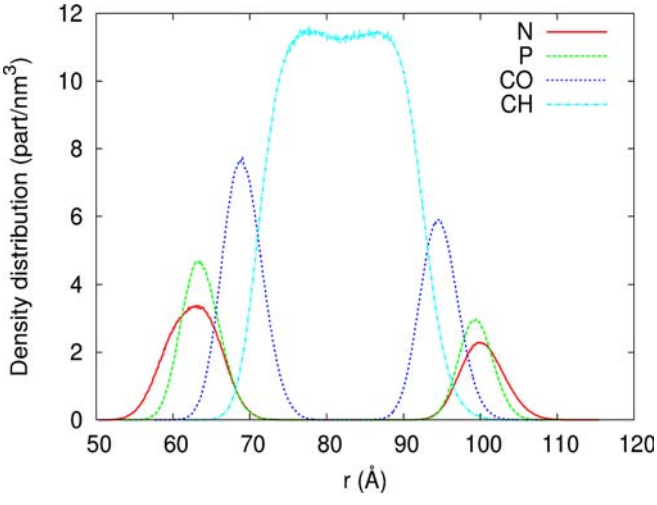

Fig. 8 Distribution density of sites of the coarse grained lipid model in a vesicle relative to its center of mass

correspondingly. For the outer layer, average area per lipid is 62 Å^2 which is slightly higher than in the plain bilayer. The inner layer is more dense with area per lipid 35 Å^2, which is even less than the area per lipid in the membrane gel phase. Clearly, in the inner layer lipid heads have much less place than in the plain membrane. Such a low area per lipid is achieved not only by denser packing but also by different shifts in the radial direction: one can see in Fig. 8, that the headgroup densities of the inner layer are wider than those of the outer layer or in the plain membrane (Fig. 5). It should be noted also that this unbalance of the area per lipid in the inner and outer layers may be partially caused by too fast vesicle closure in MD without explicit solvent. Introduction of friction forces in the frame of Brownian or Langevine dynamics, providing correct self-diffusion coefficient for coarse-grained lipids, may help to clarify this question.

Membrane self-assembly

Finally, several simulations to model membrane self-assembly have been run, starting from 392 or 1,000 lipids distributed randomly in a periodic cubic box of side 250 Å. In Monte Carlo simulations, lipids gathered in small clusters of 5–10 molecules after relative short time (about 10^8 MC steps). Then nearby located small clusters continued to unify into bigger ones but the process proceeded slower and slower and in the end six clusters were formed which became almost unmovable in the Monte Carlo simulation procedure. Some clusters had a characteristic bilayer structure but some smaller clusters had a spherical-like (micellar) form.

The initial stage of the molecular dynamics simulation of unordered lipid system was the same as in the Monte Carlo simulation: assembly of lipids in small clusters of 5–10 molecules and further unification of these clusters. A series of snapshots of one of MD runs is given in Fig. 9. For the smaller system (392 lipids), the process typically ends in several (5–10) nanosecond with bicell formation as in Fig. 9. Only in one run of total four the final structure was a vesicle of radius about 40 Å without any cavity inside.

The picture of self-assembly of the system consisting of 1,000 lipids was qualitatively the same. After 12 ns a

two separate entities were formed—a bicell of about 350 lipids and a small vesicle consisting of 650 lipids. They were stable during rather long simulation time, about 40 ns, until they come into contact. After reorganization, which took less than nanosecond, a larger vesicle, with the radius 62 Å, was formed. It is interesting to note, that area per lipid in the latter vesicle was about the same as in simulation of a bigger vesicle in the previous example: 64 $Å^2$ for the outer layer and 34 $Å^2$ for the inner layer.

Conclusion

The coarse-grained lipid model, presented in this work, has been developed exclusively on the basis of atomistic lipid model in water solution. The model has been constructed by the requirement that, for a small number of lipids dissolved in water, it reproduces the same structural properties (RDFs) as all-atomic MD. The coarse-grained model was then tested on a lipid bilayer and was shown to reproduce the same bilayer structure as the atomistic model. The coarse-grained model allows however simulations of much larger systems than all-atomic MD, and, for example, formations of bicelles and vesicles starting from different initial conditions have been demonstrated.

In comparison with similar coarse grained lipid models considered earlier (Shelley et al. 2001; Marrink and Mark 2003; Kranenburg et al. 2003), the present model does not include explicit water. Instead, the effect of water is taken into account by the solvent-mediated potentials. This provides even more substantial saving of computer time, than reducing the number of interaction sites on a lipid from more than a hundred to just a few. The hydrophobic character of lipid tails is mimicked by the attractive effective potential between them (see Fig. 4c). This fact is clearly demonstrated in all the examples where the lipid tail area exposed to water tends to decrease as long as steric limitations allow.

It is worth noting that in this work the effective potentials were calculated from MD simulations of only 16 lipids in water, which are unable to form any structurally stable complex like micelle or peace of bilayer. This gives a hope that the obtained coarse-grained model will not be biased to any specific phase. It is clear however that the effective potentials may depend on the lipid and water concentration in the original MD simulations and the corresponding phase. More studies may be needed to clarify this effect.

The MD algorithm implemented in this work was used to sample configurational space and to find thermodynamically equilibrium configurations; it was not intended to reproduce dynamical properties. Studying of dynamics in the frame of such coarse-grained model still seems to be feasible if one introduce friction and random forces with properly fitted parameters. Another option is to use local (Lowe-Andersen) thermostat (Lowe 1999) which was introduced to mimic the influence of solvent on dynamics of solute particles.

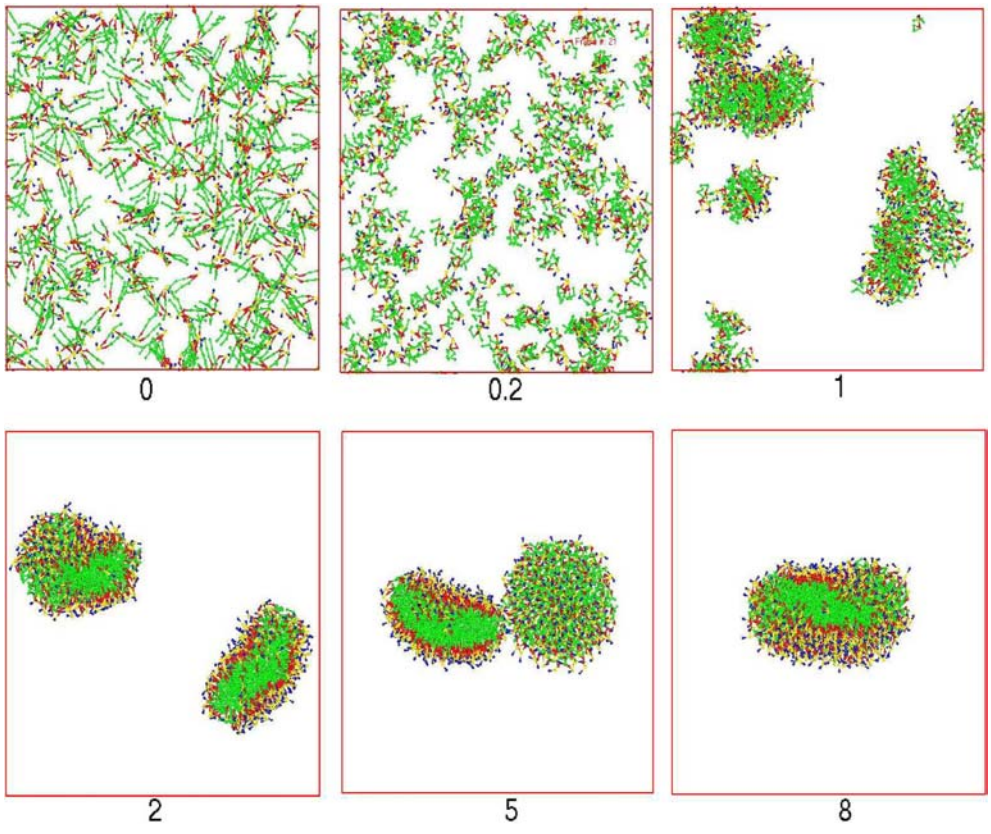

Fig. 9 Bicell formation starting from unordered structure. Non-scaled time of coarse-grained molecular dynamics (MD) simulation is shown in *ns*

The multiscale modeling approach to build coarse-grained models from atomistic simulations using inversion of RDFs is not limited to lipid molecules. In a similar fashion, coarse-grained models of other molecules can be developed and used in mesoscale simulations of biological or technological importance.

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