

# COARSE-GRAIN MODELLING OF LIPID BILAYERS: A LITERATURE REVIEW

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## ABSTRACT

Particle-based computer simulation is a powerful tool to study the behaviour of membranes at molecular resolution. Atomic-level models have been employed for decades now, and have given an understanding of many membrane phenomena. However, these studies are computationally very expensive, for an enormous amount of calculation has to be performed to model the interactions between all atoms in the system. This problem can be tackled by adopting simplified, “coarse-grain” descriptions, in which the number of interacting particles is significantly reduced. In this review, we summarize and discuss the most representative work reported in the literature concerning coarse-grain computer models of lipid bilayers. Every model is analysed in terms of the force-field employed, parameterization procedure, and predictive power in relation to the corresponding experimental observables. We also highlight general advantages and drawbacks of the coarse-grain approach with respect to the traditional atomic-level methodology.

## INTRODUCTION

Lipid bilayers are extremely complex systems: they are characterized by a highly heterogeneous structure and dynamics, and display an astonishingly rich and biologically-relevant behaviour on a wide range of spatial and temporal scales [1]. The scope of this article is limited to the nanosecond to microsecond temporal scale, and to the nanometre spatial scale, as this is the realm of the models that we will consider. The nature of the modelling methodology further limits the treatment to *non-specific* membrane phenomena, in the sense that biochemical reactions will not be involved. It is important to note that these restrictions do not compromise in any way the possibility of obtaining a general understanding of bilayers: experiments have indeed shown that the most fundamental membrane properties depend exclusively on basic *physical* principles governing lipid structure and dynamics *at the molecular level* [2].

Experimental investigation of the physics of membranes has resulted in the characterization of a large body of bilayer features. The internal structure is resolved via electron density profiles [3], lipid dynamics is studied by lateral diffusion measurements [4], mechanical properties can be related to the measurements of elastic moduli [5], electrostatic properties can be quantified by estimating internal potentials [6], and even the trans-bilayer stress distribution can be qualitatively measured [7]. All of these membrane properties are crucially important in a vast number of physiological mechanisms. For example, the thickness of the inner hydrophobic core directly influences the conformation and function of embedded proteins [8], whereas lipid fluidity is central to membrane lateral organization [9] and trans-membrane transport processes [10]. The bilayer dipole potential is believed to affect the behaviour of integral proteins [11], membrane fusion [12, 13] and the modulation of molecule-membrane interactions in lipid rafts with effects on cells signalling [14, 15]. An even more important role is assigned to the trans-membrane lateral stress distribution, which is involved in protein folding [16], lipid synthesis [17], phase transitions and fusion [18–20] bilayer permeability [21], drug transport [22], anaesthetic potency [23–25] and modulation of protein channels [26–29].

Considering the hugely differing nature of the structures, interactions and phenomena present in lipid bilayers, it is clear that the development of realistic membrane models is a challenging task. In this review, we focus on particle-based computer models, which are typically simulated with the molecular dynamics method [30].

In particular, we will describe the two main approaches to the simulation of membranes. First, we summarize the basics of the traditional methodology, which involves an *atomistically-detailed* description of the system. Second, we describe the recently developed *coarse-grain* approach, which is based on a simplified representation: this is the main focus of this review, and therefore a number of representative coarse-grain models that have appeared in the literature will be described in some detail.

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## ATOMIC-LEVEL MODELLING

The traditional methodology employed to simulate lipid bilayers is based on an atomic-level (AL) representation: every atom of the system is explicitly represented as a point-mass. The inter-atomic interactions are described by molecular mechanics force-fields [31]: non-bonded interactions are modelled using Lennard-Jones and Coulomb potentials, whereas bond terms are considered via harmonic, angle and dihedral potentials.

Over the past two decades, several AL models of lipid bilayers have been developed and validated on experimental structural and dynamic data [32–39]. More recently, AL membrane simulations have been used to study important biological phenomena, such as undulations [40], self-diffusion [41], electrostatic interactions [42, 43], cholesterol function [44, 45], the permeation of small molecules [46, 47], the lateral pressure distribution [48–50] and the appearance of transient ordered domains [51]. Despite their popularity, AL membrane models are affected by a limiting efficiency issue: obtaining data comparable to the experimental measurements is hugely time-consuming, due to the computational cost inherent in the simulation of every atom in the system. This drawback of the AL approach makes difficult the study of (relatively) large-scale phenomena, such as membrane fusion or lipid rafts. Furthermore, there are efficiency issues associated even with the standard (relatively small) membrane sizes. For instance, it has become clear that several tens of nanoseconds are required for some crucial parameters (such as the lipid area) to converge [52]: even with parallel computing, several weeks of computation may be needed just to equilibrate the AL system. Also, the measurement of some properties such as elastic moduli or the lateral pressures, typically require extended simulation times to obtain accurate and precise data. Another issue is related to the prohibitive cost of simulating the fundamental phenomenon of the self-assembly of lipids into a bilayer from a random solution. With the single exception of Marrink *et al.* [53], all AL studies reported in the literature to date have been conducted on pre-assembled bilayers: these systems are therefore not guaranteed to be thermodynamically stable. A more general problem concerns the force-field reliability: AL lipid force-fields are still far from accurate, in terms of being able to *quantitatively* reproduce experimental data. For example, Benz *et al.* [54] conducted a thorough testing on the popular CHARMM and GROMACS force-fields via constant-pressure simulation, and concluded that neither parameter set can capture within experimental error the experimentally determined structure of a DOPC bilayer in the fluid state. Furthermore, de Vries *et al.* [55] showed through constant-volume simulation of a standard hydrated DPPC bilayer that the GROMOS parameter set yields a total pressure of about -140 bar (the proper equilibrium value being 1 bar). A refinement of the current lipid force-fields could in principle be performed by trial-and-error adjustments of the parameters, although in practice the computational cost associated with this procedure may be too high.

## COARSE-GRAIN MODELLING

A possible solution to the AL efficiency problem involves the use of simpler, *coarse-grain* (CG) models. The general CG strategy involves grouping together selected clusters of atoms into single super-sites, to reduce the number of interactions calculated, and hence

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also the computational cost (as the computing time scales with the square of the number of interaction sites present). A typical lipid molecule, which in reality comprises more than one hundred atoms, is thus typically reduced to a collection of only a dozen CG sites. The representation of water also undergoes a simplification process, that typically results in the replacement of groups of three/four water molecules by single CG units. To further improve efficiency, electrostatic interactions are highly simplified or completely absent.

In the following sections, we review the most representative coarse-grain models for biological membranes that have been reported in the literature, in chronological order. We focus on those CG models that retain a connection with specific chemical systems: these studies allow a direct comparison with the experimental results for the corresponding bilayer systems. However, a section is also devoted to a brief summary of “coarser”, idealized models: in this case, there is no effort to reproduce any particular real system, the objective instead being to capture general membrane phenomena (see *Idealized membrane models*). Other reviews of CG biomembrane modelling have been published by Nielsen *et al.* [56], Shillcock and Lipowsky [57], Muller *et al.* [58] and Venturoli *et al.* [59].

## SMIT AND GROOT MODELS

In the early Nineties, Smit and co-workers developed a seminal CG model of oil/water/surfactant systems [60, 61]: simulations showed for the first time the spontaneous formation of micelles. Some years later, Groot and Warren [62] discussed the use of the Dissipative Particle Dynamics (DPD) technique to simulate the dynamics of mesoscopic systems, and also proposed parameterization methods. The DPD technique is a coarse-grain scheme by construction: the forces due to clusters of individual molecules are lumped together to yield effective friction and a fluctuating force between the interacting sites. In particular, beads interact pairwise via a combination of three contributions: a conservative-repulsive, a dissipative, and a random force [63]. On these bases, Venturoli and Smit [64] employed DPD to model single-chain surfactant bilayers while Groot [65] simulated the spontaneous formation of surfactant micelles and the formation of polymer-surfactant mixtures. In all these early studies however, the parameters had not been related to molecules of specific chemistry. This issue was addressed by Groot and Rabone [66], who developed a model for phosphatidylethanolamine (PE) membranes; they also included similar models of non-ionic surfactants. The parameterization method of Groot and co-workers was subsequently used and extended by Smit and co-workers to develop a model of dimyristoylphosphatidylcholine (DMPC) lipids in water [67].

### *Force-field and parameterization*

Smit *et al.* [61] modelled idealized surfactant molecules as chains of identical Lennard-Jones sites.

Venturoli and Smit [64] employed different parameters to construct surfactants as linear molecules composed of one headgroup (hydrophilic) site and six to ten tail (hydrophobic) sites. Groot and Rabone [66] parameterized a DPD force-field to represent PE lipids. In

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particular, triplets of methyl groups were coarse-grained into individual tail beads, whereas the glycerol-headgroup region was described by three CG sites. Parameters were derived from compressibility and solubility data. Triplets of water molecules were collected into individual DPD solvent beads, the parameters being fitted to give the correct compressibility of water. Many subsequent DPD studies have employed this model of solvation [66].

A model of DMPC consisting of three hydrophilic head beads and two tails, each consisting of five hydrophobic tail beads was implemented by Kranenburg *et al.* [67]. The chain length of this model was varied by Kranenburg and Smit [68] to model the dilaureoylphosphatidylcholine (DLPC) and distearoylphosphatidylcholine (DSPC) lipid types. A common feature of the Smit and Groot CG membrane force-fields is the complete lack of electrostatic interactions. Groot [69] did extend the DPD methodology to incorporate electrostatics, obtaining realistic results for a cationic polyelectrolyte solution, but no biomembrane model has been developed to date.

### **Results**

The very simple oil/water/surfactant model of Smit *et al.* [61] was able to (qualitatively) reproduce experimental observations such as micelle formation, density profiles and order parameters.

Venturoli and Smit [64] obtained for the first time the self-assembly of (model) surfactant bilayers via DPD simulations. Studies on the effect of changes in the chain length and stiffness of the single-tail surfactants on the properties of the model membranes were carried out. The lateral stress profile across the model bilayer was also computed: the distribution is qualitatively reasonable. Groot and Rabone [66] made the first attempt to simulate a realistic biomembrane with DPD using a molecular-specific parameterization: the resulting CG membrane structure matched that of corresponding AL simulations, and the essential experimental thermodynamics was reproduced. They also included non-ionic surfactants to investigate morphology changes and bilayer rupture processes.

Smit and coworkers worked on further tuning of Groot's parameter set. Kranenburg *et al.* [70] studied the phase behaviour of model membranes and were able to induce interdigitation; the self-assembly process was also simulated [71]. Kranenburg *et al.* [67, 72] reproduced the experimental values of area per lipid and the hydrophobic thickness of a DMPC bilayer. The phase behaviour of bilayers comprising different lipid species was also characterized [68].

Kranenburg and Smit [73] also developed a DPD system composed of a DSPC bilayer incorporating model alcohol molecules, represented as idealized amphiphiles. The study reproduced the experimental phase diagrams, as well as the alcohol-induced interdigitated phase shown by experiments [74]. Smit's model has also been extended to study the structural changes resulting from the inclusion of a rod-like object taken as an idealized protein [75].

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## KLEIN MODEL

Klein and coworkers developed a model for simulating hydrated DMPC lipid bilayers which for the first time included an explicit, though incomplete, treatment of electrostatic interactions [76].

### *Force-field and parameterization*

In the Klein CG model, the 118 atoms of a DMPC lipid are reduced to a 13-site model. The two choline and phosphate head-groups were assigned charges of  $+e$  and  $-e$ , respectively: these are the only charges present in the force-field, and they interact via a dielectric constant set to  $\epsilon_r=78$ . The potentials employed were systematically parameterized in order to mimic structural properties obtained from atomistic simulations (radial distribution functions) and experimental data (density, surface tension).

Klein *et al.* modelled water through spherically symmetric sites each representing a loose grouping of three water molecules; site-site interactions were described using a Lennard-Jones potential, the parameters being chosen to reproduce the correct density and to have consistency with hydrodynamics. The electrostatic properties of water were not included in the solvent model [76].

### *Results*

Shelley *et al.* [77] qualitatively reproduced the density profiles of a hydrated liquid-phase DMPC bilayer; simulations were conducted at constant-volume. Lopez *et al.* [78] further simulated Klein's model and studied the lipid lateral diffusion: the CG diffusion coefficient was about two orders of magnitude higher than the experimental measurement.

The Klein model has been extended to incorporate the anaesthetic halothane inside the DMPC bilayer [77, 79]. A single site was used to represent each halothane molecule. The system studied was characterized by a 2:1 ratio of the phospholipid to halothane, equivalent to an atomistic simulation considered for comparison. After several adjustments of the parameters, the distribution of the halothane perpendicular to the membrane was brought into qualitative agreement with that found in the atomistic studies. Pickholz *et al.* [79] observed that increasing the anaesthetic concentration resulted in an increase of the lipid area and order parameters and a decrease in the inter-lamellar spacing.

Srinivas and Klein [80] studied the interaction of a synthetic pore-promoting "hydraphile" molecule with the CG phospholipid bilayer; the system was simulated for 5 ns, during which the initially fully extended trans-membrane hydraphile adjusted its end-to-end distance to match the bilayer thickness.

Srinivas *et al.* [81] employed Klein's CG model to simulate diblock copolymer self-assembly.

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The Klein bilayer was also extended to incorporate a model nanotube [56, 82]. In particular, the nanotube is modelled as a hydrophobic rod (made of sites identical to the lipid tail sites) capped at its termini with hydrophilic sites (identical to the water sites). Simulations were carried out in the NPT ensemble for several tens of nanoseconds to study the structure and dynamics of spontaneous insertion into the CG membrane [83]. First the nanotube fuses with a bilayer leaflet, then penetrates the interior while rotating to assume a transverse orientation.

Nielsen *et al.* [84] studied the lipid bilayer perturbations around the trans-membrane nanotube, focusing on the contact angle at the bilayer-nanotube interface and on the orientation of the lipid molecules in the vicinity of the inclusion.

Nielsen *et al.* [85] studied the trans-membrane peptide-induced lipid sorting (the phenomenon by which integral proteins attract the lipid type which better matches their hydrophobic surface) and the mechanism of L-to-inverted phase transition.

The spontaneous insertion of antimicrobial polymers has also been simulated: the average orientation of the antimicrobial molecules was found to be parallel to the bilayer plan [86].

## MARRINK MODEL

Marrink *et al.* [87] developed a CG model for lipid simulation which has become very popular due to its high efficiency, flexibility and simplicity.

### *Force-field and parameterization*

In the Marrink model, DPPC molecules were coarse-grained into 12 sites [87]. Water is represented by Lennard-Jones sites accounting for groups of four water particles. A trial and error procedure was used to optimize the parameters to reproduce the experimental densities of pure water and alkane systems around room temperature, the mutual solubility of oil and water, and the relative diffusion rates. Electrostatic interactions are only present between lipid headgroups, where they are treated through a Coulombic potential in a manner similar to the Klein model. A relative dielectric constant  $\epsilon_r = 20$  is employed for explicit screening [87].

### *Results*

Marrink's model showed spontaneous bilayers formation: the final structures were consistent with corresponding AL results, in terms of density profiles and order parameters. A number of elastic parameters were computed: results for the area compressibility modulus, bending rigidity and line tension were within an order of magnitude of the experimental data [87]. The calculation of the bending rigidity modulus proved particularly demanding: the simulation of undulatory modes (from which the bending rigidity can be extracted)

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required the simulation of a bilayer patch comprising 6400 lipids for 250 ns. The lipid lateral diffusion coefficient was also computed: it was found to be about four times larger than the experimental data [87].

The phase transformation into the gel phase was simulated by Marrink *et al.* [88]: the observed drop in lateral mobility by two orders of magnitude is consistent with experiments.

The Marrink CG model has been used to simulate a variety of phenomena and extended-systems, such as vesicle formation [89] and fusion [90], and mixed-lipid systems [91].

By increasing the temperature or reducing the hydration level, Marrink and Mark [92] simulated the complete transition pathway from a multi-lamellar to an inverted hexagonal phase: stalk intermediates were identified, in agreement with experimental observation.

Faller and Marrink [93] studied binary mixtures of two phosphatidylcholines of different chain lengths: the experimental phase behaviour was qualitatively reproduced. Shi and Voth [94] also employed Marrink's methodology to simulate a binary mixed system at the liquid-gel phase coexistence condition.

Dickey and Faller [95] studied the interaction of Marrink's bilayer with an alcohol. The Marrink model has also been extended to contain CG representations of polyamidine dendrimers [96] and membrane proteins [97, 98].

Recently, Adhangale and Gaver [99] employed the Marrink model to study a DPPC monolayer at the air/water interface.

## VOTH MODEL

Izvekov and Voth [100] developed a CG model for hydrated DMPC bilayers using a multi-scale approach in which explicit atomistic forces are propagated in scale to the coarse-grained level.

### *Force-field and parameterization*

The Voth model relies on a force-field which is obtained from a corresponding AL simulation via a so-called “force-matching” procedure. In particular, the force-matching yields potentials of mean force (PMFs) that are fitted using a spline interpolation of the AL forces, where atoms are grouped according to the chosen CG subdivision. This method is unique in the CG field, as it is not dependent on the matching of selected thermodynamic data, but it makes use of the calculated atomic forces from an underlying AL model.

Izvekov and Voth coarse-grained each DMPC lipid to a 13-site model, in a way similar to the Klein and Marrink models. Water molecules are represented explicitly through individual CG sites. Electrostatic interactions are not present in this CG force-field.

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## Results

A pre-assembled membrane bilayer comprising 64 DMPC molecules solvated by 1312 water sites was simulated in the NVT ensemble. Radial distribution functions and density profiles of the underlying AL model were reproduced [100].

The “force-matching” procedure has subsequently been applied to the study of a DMPC/cholesterol mixture simulated at constant temperature and pressure [101]. CG order parameters were consistent with the underlying AL data. CG diffusion coefficients turned out to be about four times higher than the corresponding experimental measurements.

Shi *et al.* [102] constructed a mixed AL-CG model of a membrane-protein system: in particular, an AL model of the gramicidin A ion channel was embedded in hydrated CG lipid bilayer. The system was simulated at constant temperature and volume for 10 ns; the radial distribution functions of the AL simulation employed in the “force-matching” parameterization were reproduced.

## IDEALIZED MEMBRANE MODELS

This section briefly presents CG models that are more phenomenological and simplistic than those previously summarized: bilayers are composed of amphiphiles with no specific chemical identity. These models are sometimes called “bead-and-spring” models, as the interactions represented often reduce to Lennard-Jones and harmonic potentials only. Electrostatic interactions are indeed typically not included. In some cases, even the solvent is sacrificed (see *Implicit-solvent models*).

### LIPOWSKY MODEL

In the late Nineties, Lipowsky and coworkers developed a simple, idealized CG bilayer model that proved capable of qualitatively capturing a number of fundamental membrane characteristics [103]. In particular, solvated aggregates of surfactant molecules were obtained employing only two types of Lennard-Jones sites: hydrophilic sites, used to describe both solvent and surfactant head-group particles, and hydrophobic sites, employed to model surfactant tail segments. Simulations of the model allowed bilayer self-aggregation, diffusion, interfacial tension and area compressibility to be studied. The trans-bilayer lateral pressure profile was also calculated: the distribution is qualitatively reasonable, apart from the unphysical negative pressure peak at the bilayer mid-plane. The Lipowsky model was further investigated in terms of undulations: in particular, from the spectral analysis of the bilayer shape fluctuations, Goetz *et al.* [104] were able to extract a value for the bending rigidity modulus.

Imparato *et al.* [105] extended the model to simulate a mixture of two different types of molecules: lateral diffusion was measured, and the activation barrier of flip-flop processes was estimated. Imparato *et al.* [106] investigated further the two-component membrane to study shape fluctuations and elastic properties. The Lipowsky model was employed by den

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Otter and Briels [107] to study the bilayer thermally-induced undulations and to ultimately extract the bending rigidity using different methods: undulatory modes either aroused naturally during equilibrium simulations, or were imposed through a number of non-equilibrium methods. The results of this work have proved consistent with the bending free energy prediction from the popular theory developed by Helfrich [108]. Boek *et al.* [109] performed additional simulations on Lipowsky's model to analyse structure factors: they propose refining the intermolecular potential parameters to yield fluctuation spectra that coincide with the atomistic results.

## OTHER BEAD-AND-SPRING MODELS

Loison *et al.* [110] proposed a model where amphiphiles are represented by linear tetramers, each composed of two solvophobic (tail) and two solvophilic (head) beads. A self-assembled bulk lamellar phase was investigated from a mechanical perspective. Pores, fluctuations and defects of the lamellar stack were also analysed [111, 112].

Stevens [113] developed a CG model where each lipid is composed of eleven beads, four in each aliphatic tail and three for the headgroup; the solvent is represented by particles equivalent to the headgroup sites. Stevens' model system spontaneously self-assembled into a lamellar bilayer; measurements of lipid lateral diffusion and material elastic parameters yielded qualitatively reasonable values [113]. Fusion simulations have also been performed: at the contact edge between liposomes, lipids were observed to splay their tails into the opposing leaflets, thus progressively producing a new hydrophobic core (a “stalk”) that eventually opened to complete the fusion process [114].

Lenz and Schmid [115] presented a simple CG bead-spring model with the aim of reproducing the main (gel-liquid) phase transition of biomembranes. Lipids are modelled as single-tail amphiphiles, each composed of six tail beads and one slightly larger head bead. Molecules are defined via bond and bond-angle harmonic potential; non-bonded interactions are taken into account via Lennard-Jones potentials. Solvent was represented by explicit “phantom” solvent beads: they behave exactly like head beads, except that they do not interact with each other. The model proved well suited for simulating lipid bilayers in the regime of the liquid-gel transition.

## IMPLICIT-SOLVENT MODELS

In this section we briefly consider a number of CG membrane models that have been designed to work without the presence of explicit solvent; for a thorough review, see Brannigan *et al.* [116].

Although water is generally regarded as an essential component of bilayer systems [2], in specific cases it may not play a fundamental role while still representing a computational bottle-neck. Hence, solvent-free models might be useful to gain insight into selected membrane phenomena at a very low computational cost.

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Whitehead *et al.* [117] developed a CG model for the bilayer hydrocarbon region only, based on the Gay-Berne model of liquid crystals [118]: in the absence of water and head-group, the lipid packing was maintained through the use of a restrain potential. The experimental phase behaviour of typical phospholipid bilayers was reproduced.

Noguchi and Takasu [119] represented lipids as rigid trimers consisting of one hydrophilic and two hydrophobic units interacting through multi-body potentials. This model has been used to simulate the self-assembly [119] and fusion [120] of vesicles, adhesion of nanoparticles to vesicles [121] and pulled vesicles [122].

Lyubartsev [123] developed a 10-site lipid model parameterized exclusively from corresponding AL structural data processed through the inverse Monte Carlo method [124]. Several simulations of the CG model obtained were performed, both within Monte Carlo and molecular dynamics simulations, such as a periodic sample of lipid molecules ordered in a bilayer, a free sheet of such a bilayer without periodic boundary conditions, formation of vesicle from a plain membrane and self-assembly of lipids [123].

Brannigan and Brown [125] developed a model of bilayers where entire lipids are represented by single soft spherocylinder. Through the combination of three simple pair potentials, a rich assortment of self-assembled phases was recovered, including micelles, fluid bilayers and gel-like bilayers. Brannigan *et al.* [126] extended the model to allow for variations in lipid length and simulations under constant surface tension conditions.

Brannigan *et al.* [127] developed a new model with flexible lipids that was employed to extract compressibility and bending moduli, and the lateral pressure profile. The pressure distribution is qualitatively reasonable apart from an unrealistic pronounced pressure trough located at the centre of the bilayer; interestingly, the curve is very similar to the result from the explicit-solvent model by Goetz and Lipowsky [103].

The model by Brannigan *et al.* [127]) was extended to incorporate multiple lipid species: in particular, the elasticity of idealized heterogeneous bilayers has been analysed [128].

## SUMMARY AND CONCLUSION

The traditional methodology for simulating biomembranes involves an atomic-level description of lipids and hydrating water. This approach has yielded fairly precise and accurate predictions of a number of experimental data. However, the associated large computational cost results in two major issues:

- collective, large-scale phenomena such as membrane fusion or micro-domain formation (lipid rafts) are intractable;
  - the reliability of the calculation of some important properties, such as the lipid area or the lateral pressure profile, is often undermined by insufficient sampling.
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Coarse-grain modelling techniques have shown a number of advantages over atomistic models:

- orders of magnitude more efficient, resulting in the possibility to study phenomena characterized by much larger temporal and spatial scales;
- enhanced sampling, resulting in statistically-reliable measurements;
- bilayers are usually self-assembled, which guarantees that the system is at thermodynamic equilibrium.

On the other hand, CG models are also affected by issues:

- limited force-field transferability;
- experimental data are typically captured at a qualitative level only;
- the over-simplification or complete lack of electrostatics precludes the proper representation of the membrane potential, which has indeed never been computed for CG models;
- no CG model published to date has proved able to reasonably quantify the transbilayer lateral pressure profile, which is crucial for the accurate modelling of many membrane processes.

There is a clear need, therefore, for CG models to be developed that incorporate electrostatic interactions more accurately. Such models will likely increase the range of membrane phenomena that may be accurately studied using the CG approach.

Considering that the CG field is still in its infancy, the preliminary results obtained so far are encouraging. In the future, we foresee that coarse-grain models will play an increasingly important role in the understanding of lipid membranes.

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