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Review

Computer simulations of lipid membrane domains

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ABSTRACT

There is great diversity in the composition and structure of biological lipid membranes. We are beginning to appreciate the crucial role of lipids in many cellular processes, and characterize some of the lateral structures within membranes that could play a role in the activity of lipids. Simulations probe molecular level interactions between single molecules, which provide complementary information to experiments. Lipid membrane simulations have reached an exciting point, where the time and length scales of our simulations are approaching experimental resolutions and can be used to interpret experiments on increasingly complex model membranes. The focus of this review is on recent molecular simulations of domain formation in lipid bilayers. We highlight a number of recent examples where simulations are used in collaboration with experiments. We review recent simulation studies on lipid–lipid interactions related to domain formation and on lipid–protein interactions relevant for lipid raft function.

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1. Introduction

Lipid mixing is a fundamental problem in cellular biology. How lipids self associate and interact with membrane proteins is crucial for many cellular functions. Life contains great diversity in the structure and composition of membranes between organisms, organelles, and intracellular compartments. An important example is the gradient in the composition of some mammalian membranes, from the endoplasmic reticulum (0–5 mol% cholesterol) to the plasma membrane (25–40 mol% cholesterol) [1]. This is thought to play an important role in the trafficking of membrane proteins and lipids. At the heart of membrane domains are lipid–lipid, lipid–protein, and protein–protein interactions, which are difficult to probe at the single molecule level. Next generation spectroscopic techniques and computational modeling are nearing overlap in resolution, spatially and temporally, making future avenues of research and collaboration possible.

Abbreviations: MD, molecular dynamics; CG, coarse-grained; DPD, dissipative particle dynamics; DAPC, diarachidonyl-PC; DMPC, dimyristoyl-PC; DOPC, dioleoyl-PC; DPPC, dipalmitoyl-PC; POPC, palmitoyl-oleoyl-PC; PSM, palmitoyl-sphingomyelin; PMF, potential of mean force

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The lipid raft hypothesis was initially conceived to explain the difference in membrane sorting between the apical and basal sides of epithelial cells [2], although the existence of lipid domains had been suggested based on earlier work [3–5]. The idea of membrane sorting, with cholesterol–sphingomyelin interactions as an organizing principle, changed the way lipid membranes had been traditionally viewed, with a much-enhanced, bioactive role for specific lipids [6]. The current prevailing hypothesis is that rafts are small, dynamic domains in membranes enriched in cholesterol, sphingomyelin (or other saturated lipids), and specific membrane proteins [7]. Because of the functional implications of rafts for cellular signaling and for signaling related disease, there has been considerable research and debate on the existence and characterization of rafts [6,8]. While lipid rafts remain somewhat controversial, larger specialized domains have been characterized, such as caveolae [9]. On a smaller scale, the existence of 'shell' lipids has been observed, with specific lipids co-crystalizing with a membrane protein [10]. Lipid rafts would fit between these extremes, encompassing ordered structures on an intermediate scale (~10–100 nm). Much current research is focused on understanding the physicochemical basis for lipid domain structure and on the functional roles of lipid domains.

Cholesterol is a central part of the lipid raft hypothesis and is an interesting lipid in many other regards, given its simple chemical structure. There is a clear phylogenetic divide for sterols: cholesterol is only found in mammals, while plants have phytosterol, fungi have ergosterol, and prokaryotes do not have higher sterols [11]. From a biochemical perspective, cholesterol is known to affect the phase behavior, mechanical properties, and structural properties of lipid bilayers [12]. Cholesterol broadens the gel–liquid phase transition of for instance DPPC, by preventing packing at low temperatures, disrupting gel formation, and inducing order in the liquid-phase at higher temperatures [12]. The incorporation of cholesterol into phospholipid membranes induces the well-characterized cholesterol condensing effect; the bilayer becomes thicker, the lipid tails become more ordered (or aligned) and the area per lipid is reduced. This results in the bilayer becoming stiffer, preventing membrane bending and bilayer deformation. Cholesterol's influence on membrane structure has broad implications on the mechanism of lipid rafts in cells. Local membrane properties would affect transmembrane protein localization and activity. Experimentally, it has been demonstrated that the membrane environment can directly affect integral membrane protein function and localization [13,14].

Due to the difficulty of studying lipid mixing in live cell membranes (with possibly thousands of unique lipid species [15]), model lipid systems have been used extensively to understand lipid mixing. *In vitro* membrane systems exhibit a rich phase behavior for simple binary and ternary lipid mixtures containing cholesterol, including regions of liquid–liquid phase co-existence [16,17]. It has been observed that cholesterol induces phase separation in ternary lipid mixtures with saturated and unsaturated lipids [16]. Fig. 1 shows an example of a ternary phase diagram of a giant unilamellar vesicle. The edges of the triangle are the composition of each respective lipid, so the point in the middle of the triangle is a 1:1:1 ratio of the three lipids. The shaded region in the middle of the diagram indicates liquid-ordered–liquid-disordered phase coexistence. Tie-lines determine the composition of each phase: the ordered phase is rich in PSM and cholesterol, the disordered phase is rich in DOPC.

It is important to remember that cellular membranes are much different than these simple model systems, with non-equilibrium processes, large protein content, and cytoskeleton effects in cells. But, if we do not understand the basic physiochemical driving forces for lipid mixing in simple systems, then understanding cellular membranes is unlikely. Using different experimental techniques, different lipid phase diagrams and corresponding tie-lines have been proposed for the same system [10]. A good example is the binary phase diagram for DPPC and cholesterol, where the existence of a liquid–liquid phase coexistence region is disputed [16]. Large visible domains can be observed in model membranes, but not in cell membranes, which may limit the applicability of *in vitro* phase behavior measurements to biological lipid rafts. Using giant plasma membrane vesicles large domains were visible at low temperatures, but not at higher temperatures, and fluorophore partitioning suggested liquid-ordered–liquid-disordered phase coexistence [18]. It has been shown that near the critical point in the phase diagram, compositional fluctuations in model membranes result in transient domains with a correlation length of ca. 20–50 nm [19]. Using sub-diffraction limit stimulated emission depletion fluorescence spectroscopy cholesterol-meditated trapping of raft associating lipids was observed in live cells [20]. More recent work showed that the partitioning of fluorescently labeled lipid analogs between liquid-ordered and liquid-disordered model membranes was not correlated with their trapped diffusion in live cell membranes [21]. At this level of detail it is not well understood how lipids behave—how they diffuse laterally in the membrane and self-associate.

Molecular dynamics simulations are increasingly used to study lipid systems. We refer the reader to other more comprehensive reviews on earlier work in the field of lipid simulations [22–30]. Atomistic MD simulations follow the motions of each atom in the simulation using an empirical force field. Simulations of lipid systems can provide complementary information to experiments: macroscopic behavior is difficult to simulate and generally easy to observe in experiments, while molecular and atomistic details and energetics are directly observed in simulations and generally hard to obtain from experiments. Currently, atomistic simulations are on the order of hundreds of nanoseconds to a few microseconds, for box lengths of tens of nanometers, or hundreds of lipids. Undoubtedly, a large reason for the interest in simulations is the pace of growth in computer power, where simulations that took a month five years ago, now take a few days. The size and length of simulations expands each year. Current state-of-the art coarse-grained simulations already match the hypothetical size of 10–100 nm for lipid rafts, while detailed atomistic simulations can be done on a length scale of ca. 20×20 nm on reasonably standard computers. Many important molecular level details related to lipid domain formation have been determined from MD simulations.

One route around the small time and length scales accessible to simulations is to use a coarse-grained model. Coarse interaction sites, or beads, that encompass a number of atoms, replace specific chemical details. Due to the bias of our lab, we will focus on the MARTINI model [31], and others with similar resolution. While some details are lost, simulation time scales are increased by roughly 2 to 3 orders of magnitude, compared to similar atomistic simulations. Many recent models using dissipative particle dynamics (DPD) have a similar resolution (for example [32]), or chemical mapping, as the MARTINI model.

In this review, we will focus on recent molecular level computer simulations on lipid bilayers that relate to aspects of domain formation and the lipid raft hypothesis, emphasizing work on lipid–lipid and lipid–protein interactions. For this purpose, we accept a rather vague definition of lipid raft, as we are focused on defining the underlying structural and dynamical basis for domain formation, and their mechanism of action. Due to the vast literature on lipid membrane simulations and this general definition, we tried to narrow our focus and we acknowledge and apologize for undoubtedly missing other important contributions. We will conclude with what we believe are the most significant hurdles in the field and interesting short term future directions for lipid simulations.

2. Part 1: Lipid–lipid interactions

MD simulations can provide valuable insight into the structure and dynamics of lipid bilayers over a range of length scales and time scales, although constrained by the size and availability of computers. Domain formation implies that lipids are preferentially demixing laterally in the plane of the membrane. Two important considerations for modeling lipid mixing are the ability to reproduce the

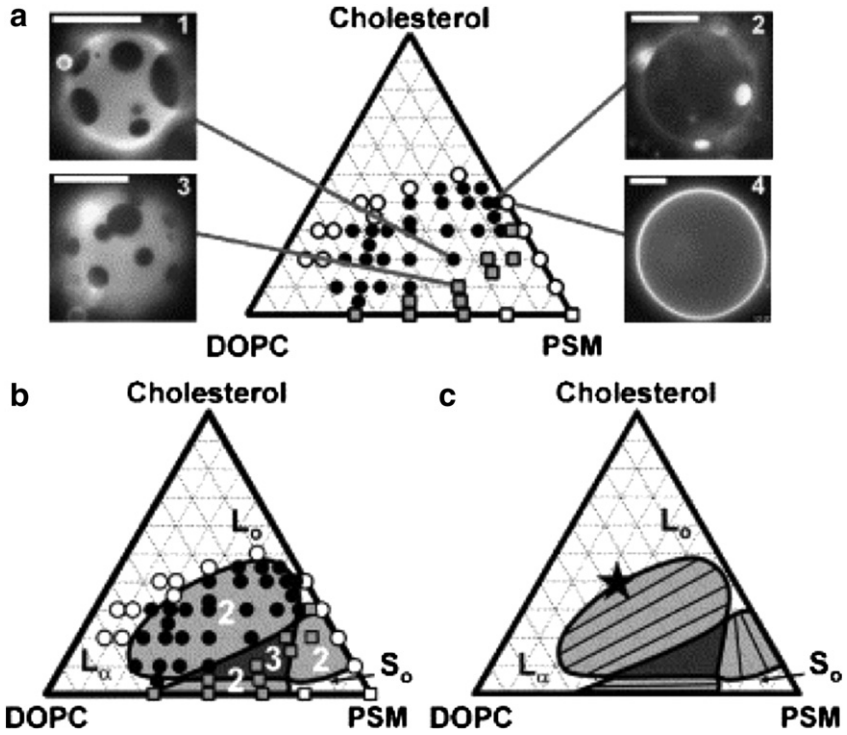

Fig. 1. (a) Phases observed by fluorescence microscopy of GUVs containing mixtures of DOPC, PSM, and cholesterol at 25 °C. White symbols denote that membranes are in one uniform phase, either liquid (circles) or solid (squares). Black circles denote coexisting liquid phases, and gray squares denote coexisting solid and liquid phases. (b) Fluorescence microscopy data are consistent with a speculative underlying phase diagram that includes a region of three-phase coexistence. (c) Speculative location of tie-lines and a miscibility critical point (star). Reproduced from Veatch and Keller [16].

correct structural properties of the different bilayer phases and understanding the diffusion of lipids in the bilayer, which affects the time scale required to observe lipid mixing. We review recent simulations investigating both of these properties of model membrane systems. For bilayers, how quickly lipids can move from one leaflet to the other could affect the bilayers' phase behavior, and overall cellular cholesterol trafficking. We will discuss recent simulations on cholesterol and other lipids' flip-flop, or translocation. With advances in computer power and the development of coarse-grained force fields, domain formation in lipid bilayers can now be directly observed. We will also describe recent CG simulations on domain formation in model bilayers.

2.1. Phospholipid bilayer simulations

In order to study bilayer domain formation, it is important for the model to be able to reproduce key structural properties of pure bilayers as well as their phase behavior. One problem is knowing *a priori* what the 'important' properties are, both within a single lipid and collectively with the other lipids and water. Lattice and continuum models are routinely used to model bilayer phase behavior [33,34], but lack specific chemical details. At the other end of the spectrum, polarizable atomistic simulations and quantum level models have been used on lipid systems, but are currently limited to short time and length scales, with as an extreme example the very detailed simulation of melting of a single lipid in vacuum using Born–Oppenheimer MD [35]. A general problem for molecular simulations and especially atomistic models, is determining phase changes, which due to their collective nature occur slowly.

Atomistic simulations have been used to study the self-assembly of lipids into bilayers and detergents into micelles [29,36–39]. Gel phases have been characterized using atomistic [40] and CG simulations [41,42]. Atomistic simulations estimated the gel–liquid transition temperature for DPPC and DSPC for one particular force field to be only 5–6° lower than experimental values [43], which is in better agreement than previously thought [44,45]. Other more subtle phases have been observed as well, including a hexagonal phase [46], cubic phase [47], and ripple phase [48]. Atomistic and CG simulations have been used in conjunction with X-ray scattering or neutron scattering experiments on lipid bilayer structure determination [49–52].

CG simulations are more amenable to the study of phase behavior due to the long time and length scales that can be simulated. How much chemical detail is required to reproduce complex phase behavior is not known. The phase diagram of a DMPC–cholesterol mixture was determined using DPD simulations and compared quite well to experimentally determined phase diagrams [32,53]. The model also reproduced many properties of the bilayer compared to atomistic models. Using a type of computational 'calorimetry' the phase behavior of a range of saturated PC bilayers was determined using the same DPD model and MARTINI CG simulations [54]. These studies suggest that CG models can model complex membrane phase transitions, although future work is needed to fully explore CG models' lipid phase behavior.

2.2. Lipid lateral diffusion

Slow lateral diffusion is one of the major hurdles for MD simulations of lipid mixtures. As an example, if the lateral diffusion coefficient of a lipid is 10^{-7} cm^2/s then on average a lipid will move ~1 nm in a 25 ns simulation [55]. An obvious constraint is the diffusion coefficient for lipid lateral diffusion, which has been shown to be slow, but dependent on lipid composition, and bilayer phase. At the molecular level it is not clear how lipids diffuse within the membrane. Quasi-elastic neutron scattering experiments estimated lipid diffusion coefficients were 2 orders of magnitude larger than methods like fluorescence spectroscopy [56,57]. Therefore, it was thought that a lipid would 'rattle' in its 'cage' and then have discrete jumps from one site to an adjacent site.

Falk et al., showed that lipid diffusion is strongly correlated, up to tens of nanometers in length, in a pure DPPC bilayer [58]. This matched previous mesoscale simulations from Ayton and Voth that showed density fluctuations and collective motions were important [59]. This is in contrast to the 'jump models' of diffusion. Collective diffusion of lipids has important consequences on the lateral segregation of lipid domains. A more recent neutron scattering study on a DMPC bilayer did not show lipids rattling in a cage, and jumping models were not supported [60]. Rather, using newer instruments it was shown that collective flows of neighboring lipids occur on the nanometer scale. This confirmed the predictions made by MD simulations mentioned above.

Using a combination of MARTINI CG MD simulations, DPD simulations, and atomistic simulations, the diffusion of lipids in model 'raft' bilayers was investigated [61]. It was shown that lipids undergo short lived collective motions and no evidence for discrete 'jumps' was observed [61]. It was found that lipids in the liquid-ordered phase have slower diffusion, and the domain can move as a whole. Correlated motion of lipids and their neighbors was found to occur over 1–10 nm length scales and the ca. 1 μs time scale in both liquid-ordered and liquid-disordered phases.

Understanding lipid diffusion, and its collective nature is important for the function of lipid rafts, the trafficking of lipids, and the interpretation of experimental tracking experiments. Future work on bilayers of varying composition and larger time and length scales will be useful.

2.3. Cholesterol mixtures

Computer simulations of lipids have developed hand-in-hand with the study of cholesterol containing bilayers. Initially such simulations explored interactions between sterols and other lipids, focusing on local interactions that were often interpreted in terms of highly stylized umbrella or other models, as more systematic studies at a length scale where domains might form or that allowed detailed explorations of multiple concentrations and temperatures have been out of reach until recently. Previous work has shown that the condensing effect of cholesterol on phospholipid bilayers can be reproduced both with AA and CG models and has been reviewed in [28]. To our knowledge, atomistic simulations have not been used to directly observe lipid domain formation in membranes, due to computational constraints. If a small domain is considered around 10 nm in diameter, this is already a reasonably large simulation by today's standards, not to mention the other lipids surrounding the domain. As of 2012 several atomistic simulations at this level have been reported at conferences but have not been published yet. Directly simulating lipid de-mixing remains a major challenge. Starting from a preformed domain might also be a problem, as this might not be the equilibrium distribution, and risks representing an artificial metastable state.

Combining neutron scattering with molecular dynamics simulations, cholesterol's effect on the distribution of the terminal methyl groups of DOPC was studied [62]. The results showed significantly more disorder in the DOPC bilayer than was previously thought based on X-ray scattering profiles, with methyl groups reaching the head group region. Incorporating 33 mol% cholesterol dramatically decreased the extent of the broad methyl density due to the ordering of the bilayer and straightening of the lipid tails. Atomistic simulations reproduced both the extent of the DOPC tail's disorder and the effect of cholesterol on reducing the disorder.

Olsen and Baker investigated the difference between 40 mol% cholesterol and oxysterol on a lipid membrane, showing dramatic differences between them [63]. They extended this work to study oxysterol and cholesterol mixtures [64]. Other recent atomistic simulations studied interactions involving glycolipid interactions in model membranes [65–67], phosphoinositides [68], sphingomyelin [69], diacylglycerol [70,71], cholesterol [72], and other sterols [73,74]. More complex mixtures such as a model yeast membrane [75], bacterial model membranes [76], and asymmetric cholesterol and sphingomyelin mixtures [77] have also been simulated recently.

de Joannis and coworkers used semi-grand canonical ensemble simulations to investigate cholesterol:DOPC:DPPC mixtures [78]. In this method, single lipids change between being either a DOPC or DPPC, using a Monte-Carlo exchange procedure, based on the inputted chemical potential difference between the two lipids. For ideal mixing, changing the chemical potential difference between DOPC–DPPC will result in a linear change in the molar ratio of the two lipids. At low cholesterol content, near ideal mixing of DPPC and DOPC was observed, while non-ideal mixing above 16 mol% cholesterol showed preferential interactions between DPPC and cholesterol. Their results qualitatively matched experimentally determined tie lines of a typical ternary phase diagram. This is encouraging for the study of lipid domains using atomistic simulations.

Free energy calculations of lipids binding to bilayers of different compositions have implications for understanding the driving forces for domain formation. We have determined the excess chemical potential for a single cholesterol molecule in different membranes compared to water. Umbrella sampling simulations to determine the potential of mean force to move cholesterol from its equilibrium position to bulk water have been conducted by our group and a few others. By using water as a reference state, a lipid's free energy of exchange between two bilayers with different compositions is determined, or rather, cholesterol's preferential localization. Zhang and Berkowitz found that cholesterol has a ca. 61 kJ/mol free energy difference between a SSM (stearic sphingomyelin) bilayer and water, compared to 54 kJ/mol for POPC [79].

We found that cholesterol has a gradient in its excess chemical potential with respect to cholesterol content in a DPPC bilayer: 89 kJ/mol, 40 mol%; 86 kJ/mol, 20 mol%, and 80 kJ/mol, 0 mol% [80] (Fig. 2). Cholesterol had a 67 kJ/mol free energy difference between a DAPC bilayer and water [80], and 132 kJ/mol for a 1:1:1 mixture of cholesterol:POPC:PSM [81]. From these results, we concluded that cholesterol has a preference for more ordered and rigid bilayers and the lowest preference for a bilayer with polyunsaturated fatty acid tails. An interesting corollary to this work, we found that DPPC has the opposite preference as cholesterol, with a strong preference for a pure DPPC bilayer, followed by 20 mol% and then 40 mol% cholesterol:DPPC mixtures [82].

2.4. Cholesterol flip-flop

An important aspect of the lipid raft hypothesis and domain formation is cholesterol's localization. Phospholipids have a well-documented asymmetric distribution with phosphatidylethanolamine (PE) and phosphatidylserine (PS) concentrated on the inner leaflet while the external leaflet is enriched in phosphatidylcholine (PC) and sphingomyelin [1]. An active area of research on lipid rafts is trying to understand domain coupling across the asymmetric membrane leaflets. There has been considerable debate over cholesterol's distribution across the asymmetric plasma membrane. How quickly cholesterol can exchange between leaflets is an important consideration for assessing its transbilayer distribution and the effect on domain formation. Recent experimental evidence is split on the subject, with some studies showing rapid flip-flop, so cholesterol would equilibrate between the two leaflets, although not necessarily to equal concentrations [83,84]. But slow cholesterol flip-flop was predicted by Garg et al., which suggests that cholesterol is actively transported and could maintain a non-equilibrium distribution across the bilayers leaflets [85].

We used both atomistic and coarse-grained simulations to study cholesterol flip-flop in a range of lipid bilayers, from a poly-unsaturated DAPC bilayer to a rigid and ordered 40 mol% cholesterol:DPPC bilayer and a model 'raft' bilayer (1:1:1 ratio of cholesterol:PSM:POPC) [80,81] (Fig. 2). The free energy barrier for cholesterol flip-flop was much lower in the polyunsaturated DAPC bilayer than in a DPPC bilayer, and

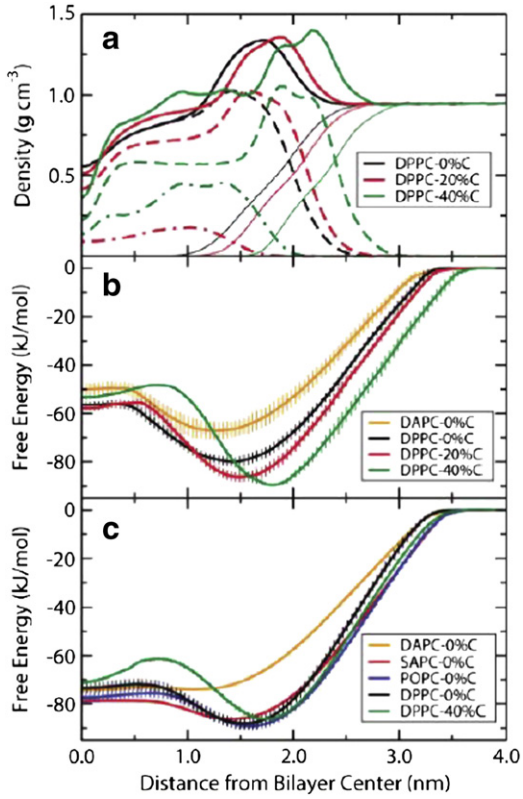

Fig. 2. Cholesterol free energy profiles. (a) Partial density profiles of the all-atom 0, 20, and 40 mol% cholesterol and DPPC bilayers. Total density is solid thick lines, water density is solid thin lines, DPPC density is thick dashed lines, and cholesterol density is dot-dashed lines. (b) PMFs for cholesterol partitioning in the all-atom bilayers. (c) Coarse-grained PMFs for cholesterol partitioning from water to the center of various bilayers. Both AA and CG PMFs were set equal to zero in bulk water. Error bars are the standard error from the mean of the two leaflets' cholesterol PMFs.
Reproduced from ref. [80].

the highest in the raft bilayer. CG simulations were used to directly observe cholesterol flip-flop and atomistic simulations provided specific chemical details of the mechanism. These results matched previous estimates based on MARTINI simulations in conjunction with neutron scattering data [51]. Another study using a different atomistic model showed similar free energy barriers for cholesterol flip-flop [86]. With an implicit model of a DPPC bilayer the rates of flip-flop for cholesterol and other steroids were estimated to be on the order of microseconds to milliseconds, depending mostly on the polar substituents [87]. For cholesterol (10^4 s^{-1}), the rate constant was on the same order of magnitude as the atomistic simulations mentioned above.

Fast flip-flop for ceramide and diacylglycerol in DPPC and DAPC bilayers was estimated using CG simulations [88]. We determined free energy profiles for cholesterol, diacylglycerol and ceramide flip-flop across atomistic models of a POPC bilayer and a lipid raft mimic (1:1:1 ratio of cholesterol:PSM:POPC)[81]. All the molecules had orders of magnitude slower flip-flop across the ordered bilayer than the POPC bilayer, with cholesterol faster than diacylglycerol and ceramide the slowest. We note that the mechanism for flip-flop suggested by both atomistic and CG simulations for flip-flop of lipids with small, polar head groups, like cholesterol is similar to a solubility-diffusion model. This is in contrast to phospholipid flip-flop, and other charged molecules, where flip-flop proceeds through pore formation, which is difficult to model with CG force fields [89] and likely implicit models.

2.5. CG domain formation

Due to the enhanced sampling, CG models have been used to directly observe domain formation in model membrane systems. With molecular level detail one can simulate bilayers large enough and for long enough to directly observe domain formation in ternary lipid mixtures. Fig. 3 illustrates examples of domain formation using CG models under various conditions, as discussed below.

In a series of work, Marrink and coworkers have used the MARTINI model to investigate various aspects of lipid domain formation. Phase separation of ternary lipid mixtures of bilayers and small vesicles was shown to occur, matching experimentally observed liquid-ordered domains (high DPPC and cholesterol content) and liquid-disordered domains (high polyunsaturated DLiPC content and low cholesterol) (Fig. 3) [90]. Interleaflet domain coupling was observed, and linked with elastic theory, predicting a small surface tension drives bilayer registration [90]. As well, fast cholesterol flip-flop in the disordered phase, and slow flip-flop in the ordered phase was observed agreeing with results mentioned above.

Perlmutter and Sachs extended this approach, simulating asymmetric ternary lipid mixtures (Fig. 3) [91]. Matching previous results, they found that in the DLiPC:DPPC:CHOL symmetric bilayers liquid-ordered–liquid-disordered coexisting domains were directly observed. Domain formation in one leaflet induced ordering in the opposite leaflet composed of pure unsaturated lipids, and increased the local lipid curvature. With longer saturated lipids domain anti-registration was observed [91].

Pantano et al. used the CG model of Shinoda and coworkers [92] to study domain registration in bilayers composed of mixtures of single chain polymers, with identical tails, but with either a charged or neutral polar head group [93]. Domain formation was observed due to the clustering of the charged head groups cross-linked with an ion. Registration of the domain was shown to occur from thickness mismatch and local bilayer curvature. The results suggest that domain registration cannot be explained simply by the minimization of the interfacial energy due to the surface tension between the leaflets.

Schäfer and Marrink investigated lipid partitioning to the domain interface using phase-separated ternary mixtures of DPPC:DLiPC:cholesterol [94]. It was shown that POPC partitions to the domain interface and reduces the line tension of the domain interface at low concentrations (3 mol%). PLiPC was shown to partition to the liquid-disordered phase and lyso-PPC had a slight preference for the interface.

Muddana et al. used MARTINI simulations and confocal microscopy to investigate the effect of non-lipid amphiphiles on lipid phase separation [95]. Vitamin E partitions to the domain boundaries, and promotes lipid mixing or disrupts domain formation. This is in contrast to benzyl alcohol and Triton-X, which both promoted phase separation. Benzyl alcohol partitioned to the disordered phase and caused increased bilayer thinning, which would increase the tendency to demix. Triton-X went into both liquid-ordered and disordered phases, but had a stronger ordering effect on the saturated lipid than the unsaturated lipid, which would promote phase separation. This study illustrates how CG simulations combined with experiments can be used to explain macroscopic phase behavior at the single molecule detail. How non-lipid amphiphiles influence membrane phase behavior has implications on cell membranes (e.g. in the mechanism of vitamin E function), as well as on model studies that use these molecules as tools, such as membrane protein extraction by detergents.

Ternary mixtures of saturated lipids, unsaturated lipids and cholesterol were recently studied using the MARTINI model with different lengths of tails and numbers of double bonds [96]. Both monosaturated and di-unsaturated lipid, and varying tail lengths, were simulated and domain formation characterized. Complete phase separation was only observed for bilayers with the di-unsaturated tails, although non-ideal mixing was found for mixtures with one saturated and one unsaturated tail.

Baoukina and co-workers carried out a series of simulations of monolayers and bilayers [97]. Following simulations of monolayer mixtures that showed no clear domain formation [98,99], a recent paper studied the properties of two types of large monolayers (80 nm × 80 nm, ca.

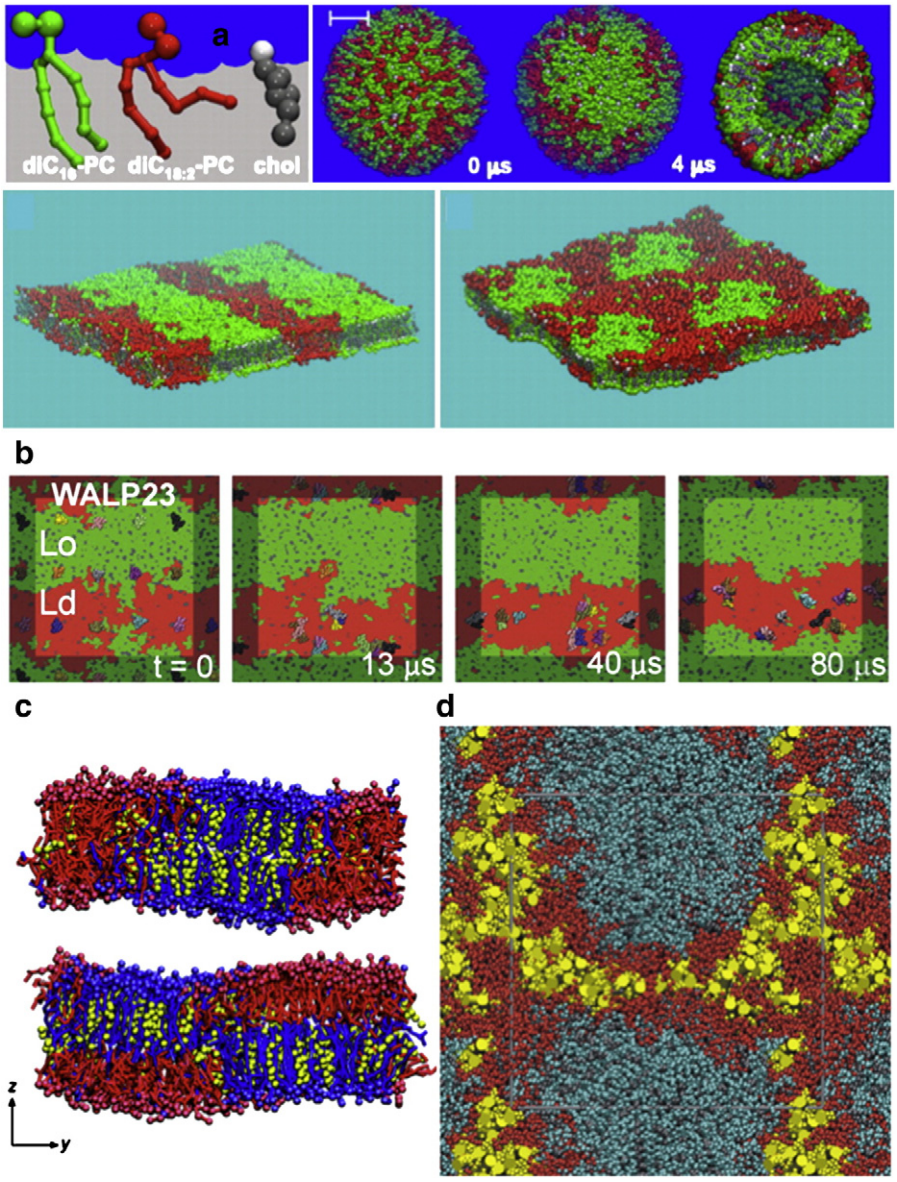

Fig. 3. Raft formation in several simulations, including a lipid mixture in vesicles and bilayers (A, from ref. [90]), partitioning of WALP23 in different phases (B, from [110]), an asymmetric bilayer (C, from [91]), and a peptide-containing phase-separated membranes (D, from [117]).

9000 lipids) on a time scale of 25 μs. The first consisted of a mixture of DPPC, POPG and DOPC (3:1:1) and showed a transition from a homogeneous liquid-expanded (LE) to a mixed liquid-condensed (LC) state upon quenching from 310 K to 290 K. The second consisted of a mixture of DPPC, DOPC and cholesterol (5:3:4), which showed a transition from liquid disordered (Ld) to liquid ordered (Lo). From these simulations, the properties of individual domains, including their composition, partial areas, diffusion coefficients, line tensions, and the kinetics of growth could be calculated. Fig. 4 shows four snapshots of the process of domain formation for the cholesterol-containing monolayer. This process significantly differs from the other monolayer and can be described as spinodal decomposition versus nucleation and growth.

Although this is a monolayer study, with surface tension as additional variable and an air–alkane chain interface instead of a monolayer–monolayer interface as in a bilayer, these properties are likely relevant for lipid bilayers as well. In a follow-up study, the same compositions were studied in lipid bilayers [100]. Four corresponding snapshots for the cholesterol containing bilayer are shown next to the monolayer snapshots in Fig. 4. Although the bilayers are smaller, at 40 nm × 40 nm, the phenomenology is very similar, and the same structural and dynamical properties were calculated. Increasing the temperature in the bilayer simulations produced similar effects as increasing the surface tension in monolayers. Thus this side-by-side comparison of monolayers and bilayers supports the strong similarity between monolayers at a similar surface density as a bilayer and gives detailed insight into the structure and composition of domains at a regime where phase coexistence occurs.

3. Part 2: Lipid–protein interactions

The interaction of membrane proteins with lipids is important, but their relationship is not well-understood. Two possible cellular functions of lipid rafts are the sorting and localization of membrane associating proteins, and the modulation of the activity of specific integral membrane proteins. An important example for the localization and clustering of proteins is provided by G-protein coupled receptors (GPCRs), whose functions may be mediated by lipid rafts [13]. The transmembrane GPCR protein binds to a lipid anchored G-protein upon specific stimulus. Lipid phase behavior and composition may influence the probability of this interaction. Another possible mechanism

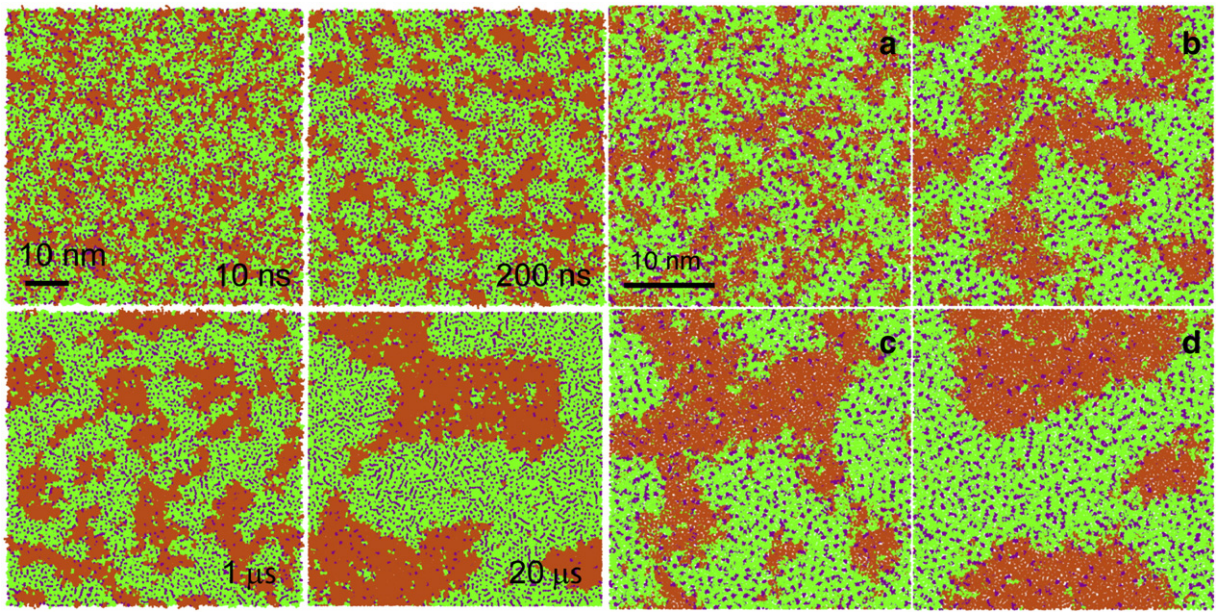

Fig. 4. Transformation into Lo and Ld phases in a DPPC:DOPC:cholesterol 5:3:4 mixture in a bilayer and a monolayer at 290 K. In all panels, DPPC is shown in green, DOPC in orange, and cholesterol in purple. The left four panels are simulation snapshots of a monolayer at 30 mN/m. The right four panels (a, b, c, and d) are snapshots of a bilayer at 10 ns, 500 ns, 2 μs and 11 μs, respectively.
The left four panels are reproduced from ref. [97]. The right four panels are reproduced from [100].

by which rafts modulate membrane proteins is by directly affecting the activity of transmembrane proteins. Increasing evidence has shown that the activity of ion channels and transporters is affected by the membrane environment and lipid composition [101]. Recently, voltage gated ion channels were shown to respond to small changes in the mechanical properties of the membrane [102]. Therefore, the movement of proteins into and out of lipid rafts, or membrane regions with different mechanical properties, would affect their activity. Lipid domain formation may also play an important role in the activity of antimicrobial peptides [103], cell-penetrating peptides [104], in pathogen entry [105], lung surfactant function [106], and large-scale membrane remodeling [107].

Here we briefly review a selection of recent biophysical studies on the interaction of lipids with model peptides, with a number of studies combing experiments and computer simulations. Studies specifically addressing lipid–transmembrane protein interactions using simulations will be discussed. The effect of bilayer mechanical properties on the conformational changes of integral membrane proteins studied using simulations will be reviewed. A number of studies on other lipid–peptide interactions, such as lipid-anchored proteins, will be summarized.

3.1. Lipid–model peptide interactions

Single pass transmembrane peptides are interesting as model systems for lipid–protein interactions. A well-studied class of model peptides are the WALP and KALP peptides and variants of these, which contain flanking tryptophan or lysine, and proline, with variable lengths of alanine and leucine repeats [108,109]. These systems are used to study basic interactions between lipids and proteins, such as hydrophobic mismatch; how the system responds when the hydrophobic bilayer slab and the hydrophobic peptide are different lengths. The simplicity of the peptides, and the model bilayers commonly used, illustrates our gap in understanding these fundamental biological problems.

Using the MARTINI CG model and confocal microscopy experiments, the incorporation of model peptides into membranes composed of liquid-ordered–liquid-disordered phase coexistence was investigated (Fig. 3) [110]. It was found that the peptides partition to the liquid-disordered phase regardless of the hydrophobic mismatch. By using a CG model they were able to determine the free energy of exchange for a WALP peptide between the liquid-ordered phase and the liquid-disordered phase, as well as the entropy/enthalpy decomposition. They found the peptide had a lower free energy in the liquid-disordered phase than the liquid-ordered phase, which matched confocal microscopy images of the peptides concentrating in the disordered phase. They found that the preference for the disordered phase was due to a favorable enthalpy. It was shown that hydrophobic mismatch caused WALP31 to cluster more in the disordered phase than the shorter WALP23 peptide.

Combining atomistic simulations and experiments it was shown that hydrophobic mismatch is cholesterol dependent [111]. Model peptides of different lengths were incorporated into mono-unsaturated PC lipids of different lengths, with varying levels of cholesterol, to investigate negative (length of the peptide is shorter than the bilayer thickness) and positive hydrophobic mismatch. Without cholesterol the bilayer could more easily deform under negative mismatch, or the helix tilt under positive mismatch. Cholesterol incorporation prevented the PC lipids from accommodating hydrophobically mismatched peptides, and induced domain formation of the mismatched peptide. This could explain the sorting of integral membrane proteins from the ER to the plasma membrane, where a gradient in cholesterol is observed.

Gramacidin is a model antimicrobial peptide that can dimerize to form cation channels in membranes. In its most common form, each monomer only spans half the bilayer, so that two are required to form a full channel. The free energy for dimerization, and therefore channel conductance, depends on the local membrane environment, which makes it a nice probe for the effect of bilayer properties on protein interactions. Recent simulations showed that pure PC bilayers deform to accommodate the dimer structure [112]. The deformation profiles for the MD simulations differed from those predicted from continuum theories, which shows that atomistic details can be necessary to accurately model lipid–peptide interactions.

The free energy for 3 different TMD dimers' association was determined in different membrane environments [113]. It was found that in general the strongest dimerization was in a POPC membrane compared to the shorter DMPC and longer DEPC (20:1-PC).

3.2. Lipid–transmembrane protein interaction

The ion channel Kv1.2 in a POPC bilayer was simulated for 500 ns, and the diffusion of the lipids around the protein was investigated [114]. Two types of lipid diffusion were observed, with lipids near the protein (within 3 nm) diffusing more slowly, with a similar diffusion coefficient of the protein, and lipids far away from the protein, which had diffusion coefficients similar to a pure POPC bilayer. This suggests that small 'domains' can be formed with a single transmembrane protein in a pure POPC bilayer.

The effect of transmembrane protein (NaK channel) crowding on lipid and protein diffusion in lipid bilayers was studied using the MARTINI model [115]. Protein crowding was shown to significantly reduce the diffusion of both proteins and lipids. In protein free systems, hundreds of nanoseconds are needed to observe normal, uncorrelated diffusion, while with high protein content (1:50 protein: lipid), millisecond simulations would be needed. This work is a stark reminder of the challenges facing simulations of lipid domains in membranes.

Using MARTINI simulations it was shown that rhodopsin aggregates in bilayers, especially when there is large hydrophobic mismatch [116]. This approach was extended to study membranes with high concentrations of model peptides and protein in mixed bilayer systems (Fig. 3) [117]. The peptides and rhodopsin preferentially partitioned to the liquid-disordered phase. High peptide concentrations were shown to increase non-ideal mixing in a ternary system. As well, the diffusion coefficient for the peptides was roughly 10 times reduced in the membrane with high peptide concentration over a dilute case.

The quaternary structure of some membrane proteins is important for their function. A good example is the oligomerization of GPCRs, like the $GABA_B$ receptor, in their functioning. Recently, the dimerization of rhodopsin (class A GPCR) was studied using MARTINI simulations [118]. Using both long time scale simulations, and multidimensional umbrella sampling calculations, the free energy for rhodopsin dimerization was determined. The MD simulations provided molecular level details for the most stable dimer interface, which matched previous experimental predictions. This illustrates the potential use for simulations in determining the oligomerization of membrane proteins, and the molecular driving forces for the preferred orientations. For lipid rafts, understanding how oligomerization depends on the membrane composition is now a realistic endeavor.

Other recent atomistic and CG simulations have focused on aspects of the interaction between lipids and integral membrane proteins. Using atomistic simulations the interaction of specific co-crystallized lipids with aquaporin-0 were investigated [119]. Hydrophobic mismatch interactions were investigated using semi-grand canonical MD simulations with both AA and MARTINI models [120]. Using a CG model the interaction of DOPC and DOPE with MsbA, an ABC transporter [121], annular lipids around the protein and detailed molecular packing details were determined. Cholesterol binding to specific sites on GPCRs was shown using atomistic [122] and MARTINI CG simulations [123]. Binding of cardiolipin to both cytochrome bc_1 [124] and cytochrome *c* oxidase [125] of the respiratory chain proteins was characterized using MARTINI simulations. Using both atomistic and CG simulations negatively charged phosphatidylinositol 4,5-bisphosphate binding to Kir2.2 potassium channel was characterized, with binding sites matching experimental predictions [126].

3.3. Conformational changes in membrane proteins

Mechanical properties of lipid bilayers are important for many aspects of transmembrane protein structure and function. We will focus on recent attempts to relate bilayer lateral pressure profiles to the conformation changes of membrane proteins. Many transmembrane proteins are known to change conformations for their function, which would necessarily perturb the lipids in the surrounding membrane. From the changes in the surface area exposed to the lipid environment in different conformations, the work to deform the lipid membranes' structure can be determined using the lateral pressure profile of the bilayer. This could explain the difference in activity of proteins in raft or non-raft bilayers, because the two bilayer domains will have different local lateral pressure profiles, so the work to change conformations will change.

Niemela and coworkers determined the lateral pressure profile across a pure POPC bilayer and two model 'raft' bilayers composed of 1:1:1 and 2:1:1 ratios of POPC:PSM:cholesterol [127]. Using a crude estimate for the shape of MscL in the open and closed conformations, and the lateral pressure profile they estimated the work due to membrane deformation to be 1–2 kT in a pure POPC and PSM bilayer, compared to 4–11 kT in the 'raft' bilayers. This matched another estimate using POPC of 1.7 kT, from a different force field [128]. Both of these estimates assumed simple shape changes, i.e. from cylindrical to conical, which is an obvious approximation.

Ollila et al. recently showed that using a more accurate description of the change in membrane shape through MARTINI CG simulations of MscL in a lipid bilayer the actual membrane contribution to gating is ca. 35 kT [129]. This suggests that membrane deformation could be a dominant energetic component in the functioning of some integral membrane proteins. Future studies into the effect of membrane composition on the gating mechanism would be interesting. This approach could be applied to other channels and transporters that undergo conformational changes, and whose activity is affected by the lipid composition.

3.4. Other protein–lipid domain studies

The clustering of the lipid anchor region of H-ras in phase separated bilayers was investigated using the MARTINI model [130] (Fig. 5). H-ras, is a GTPase with multiple lipid modifications, and is an integral part of many crucial cellular signaling pathways. Experimentally, the clustering of Ras into lipid mediated clusters has been observed [131], although the physical basis for the clustering is not understood. MARTINI simulations showed that the H-ras anchor partitioned to the domain interface, with the palmitoyl tails preferring the liquid-ordered domain and the farnesyl tail interacting with the disordered domain [130]. The line tension of the domain interface was reduced in the presence of the H-ras anchor. A subsequent study by the same group showed that clusters still formed without cholesterol, but were not as stable [132].

Also using MARTINI, the partitioning of complete H-ras, N-ras, cholesterol-anchored Hedgehog protein, and lipid-anchored transmembrane model peptides in ternary lipid bilayers was investigated (Fig. 5)[133]. The lipid anchor had a large effect on the partitioning behavior of the different proteins, between the liquid-ordered and liquid-disordered phases. Ganglioside lipids caused the formation of nano-domains with the lipid-anchored peptides, which had a large preference for the liquid-ordered phase.

Clustering and domain formation of negatively charged lipids with cationic peptides is important for a number of important biological processes. Atomistic simulations of K-ras interactions with bilayers composed of POPC and POPG showed preferential interactions between the cationic lysine residues and the negatively charged POPG [134]. The K-ras peptides were shown to induce POPG clustering in the mixed bilayer. Two cationic penetrating peptides rich in arginine residues, were shown to cluster POPG in mixed POPG and POPC bilayers using atomistic MD simulations [135]. Ionic proteins were shown to cluster with negatively charged PIP2 lipids in STED microscopy and MARTINI simulations [136]. Electrostatic calculations have previously shown how PIP2 lipids and specific protein domains cause lateral structures [137]. Antimicrobial peptides and other cationic peptides are also likely to modify the local lipid structure by selectively binding to anionic lipids. This type of process will no doubt be the subject of many future simulation studies of increasingly complex membrane models and processes.

4. Summary and future directions

This review presents a large variety of recent simulations on aspects of membrane domains. The overarching theme of contemporary membrane domain computer simulations is the cooperative and collective nature of lipid membranes. It matters what each individual lipid is doing for its own energy and conformation, but each lipid also affects its neighbors' conformations and their energies. Determining this synergy is a multi-body problem. Molecular simulations are beginning to probe these details, but the complexity of even model membranes makes a detailed quantitative understanding very challenging.

Atomistic simulations have been used to obtain detailed information on cholesterol containing mixed lipid bilayer systems. Many earlier simulations have characterized the condensing effect of cholesterol on lipid membranes. Free energies for moving lipids out of the membrane, and across the membrane, have been calculated [79–81,86]. Simulations have shown that cholesterol, and other lipids with small, polar head groups can flip-flop orders of magnitude faster across disordered, cholesterol free bilayers, than ordered and rigid bilayers with high cholesterol content [80]. From a single lipid's free energy for desorption from different model membranes, cholesterol has been shown to have a strong preference for more ordered and rigid environments, which could be a physicochemical driving force for raft formation [80]. Semi-grand canonical ensemble simulations have reproduced qualitative trends of a ternary phase diagram [78]. The chemical potential difference of individual lipids in various membrane environments and the difference in rates for flip-flop, illustrate how bilayers' collective properties affect individual lipid's thermodynamic and kinetic behavior.

Many interesting problems in membrane biology beyond the reach of atomistic simulations can be studied using coarse-grained models. Large-scale CG systems have been used to directly observe domain formation in a variety of multi-component lipid mixtures. These systems have been used to investigate a number of important domain related problems: domain coupling between bilayer leaflets [91], line acting lipids [94], other amphiphile's partitioning [95], different types of phospholipid [96], monolayer demixing compared to bilayers [97], and many lipid–protein interactions.

Lipid rafts are thought to function through membrane protein–lipid interactions. MD simulations have provided valuable insight into a number of important aspects related to raft function. Free energy calculations for transmembrane and model peptide interactions in lipid bilayers have been conducted using CG models [118]. Simulations and experiments on model transmembrane helices have been used to investigate aspects of the hydrophobic mismatch, important for protein localization and function [110,111]. Lipid-anchored peptide and protein distribution between liquid-ordered and liquid-disordered phases has been investigated using MD simulations [130,133]. The packing and dynamics of lipids with respect to transmembrane proteins have found 'shell' lipids whose diffusion and conformations are different compared to bulk lipids [114]. Mechanical properties of membrane phases have been used to estimate the work required to deform the membrane during transmembrane protein conformational changes [129].

Two major hurdles for MD simulations of lipid domains are overcoming the sampling problem, and parameterizing and validating lipid force fields. Faster computers, improved sampling, free energy techniques, and coarse-grained models can overcome the first problem for simulations. The degree of the second problem is hard to ascertain. How much chemical detail is required to capture the important molecular driving forces for lipid domain formation? Much more simplified lattice simulations and continuum models have had success in understanding aspects of domain formation. Defining the boundaries for the use of different simulation methods will be important work in the next few years. Recently, the popular CHARMM, AMBER, and GROMOS force fields have had new lipid parameters published, indicating

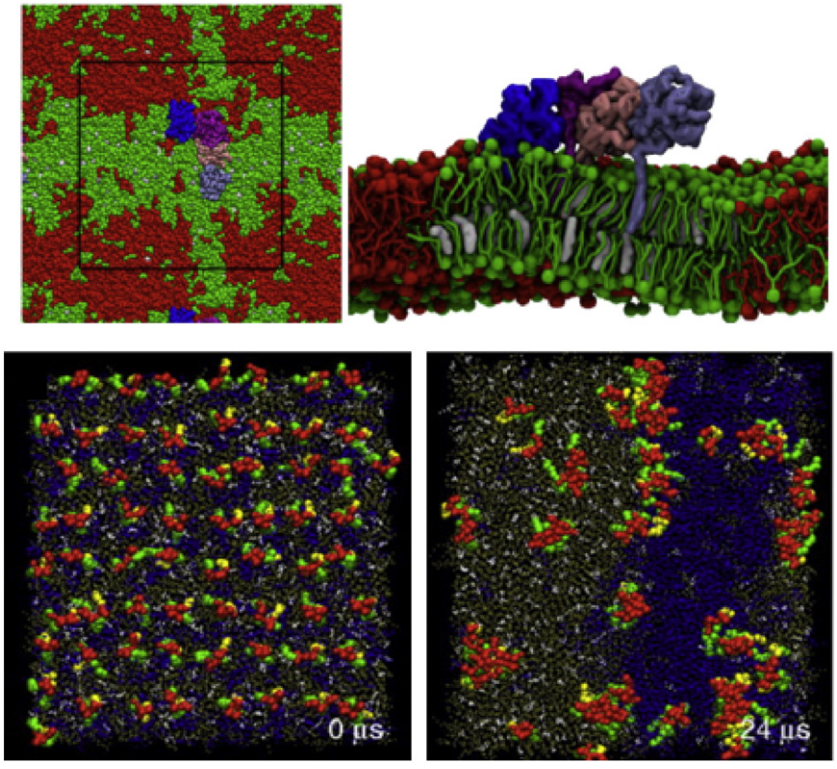

Fig. 5. Top: anchor driven partitioning of Hedgehog proteins into the Lo domain. Top and side views of a simulation of 4 Hedgehog peripheral proteins in a DPPC:DLiPC:cholesterol mixture after 12 μs. The different copies are colored pink, purple, blue and light blue, DPPC, DLiPC and cholesterol are red, green and white, respectively. Bottom: top view of the initial structure (left) and after 24 μs (right) of a system with 64 H-ras molecules bound to one side of the bilayer. The 64 H-ras molecules were initially distributed on a grid with random orientations but cluster with time. H-ras is shown in red with palmitoyl and farnesyl tails colored in green and yellow, respectively.
Reproduced from ref [133] and bottom from [130].

progress in the field. Other developments and testing of polarizable models on lipid problems will continue [138,139].

Collaborations between MD simulations and experiments illustrate the complimentary information that can be gained from simulations and experiments, and how they can be combined to solve important biophysical problems. Further collaboration between experiments and simulations will help to validate and parameterize future force fields. Increased resolution of experimental techniques, such as STED microscopy, and increased sampling of simulations will encourage exciting lipid domain research and collaboration. Lipid domain formation will be directly observed in the near future using atomistic simulations, while CG simulations will soon overlap the resolution of many experimental techniques. Mixed atomistic and CG methods, or other multiscale simulation techniques will allow mesoscale modeling of many interesting domain related problems.

For membrane proteins, there is huge potential for simulations of larger and longer simulations, with more complex lipid mixtures. The effect of membrane composition on the structure and stability of raft-associated proteins is one key area of interest. Increased free energy calculations for dimerization of helices and entire proteins will likely be undertaken. Relating the activity and localization of membrane-associated proteins to atomistic level details ascertained through simulations will be accomplished in the future. By having a better understanding of the relationship between lipids in the membrane and integral membrane protein structure, dynamics, and activity, we hope to better understand the function of lipid rafts.

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