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Review

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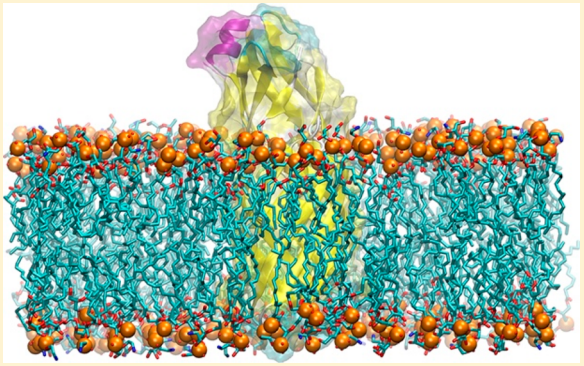
Molecular Dynamics Simulations of Membrane Proteins: An Overview

Kenneth Goossens and Hans De Winter*

Department of Pharmaceutical Sciences, Laboratory of Medicinal Chemistry, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

ABSTRACT: Simulations of membrane proteins have been rising in popularity in the past decade. Advancements in technology and force fields made it possible to simulate behavior of membrane proteins. Membrane protein simulations can now be used as supporting evidence for experimental findings, for elucidating protein mechanisms, and validating protein crystal structures. Unrelated to experimental data, these simulations can also serve to investigate larger scale processes like protein sorting, protein−membrane interactions, and more. In this review, the history as well as the state-of-the-art methodologies in membrane protein simulations will be summarized. An emphasis will be put on how to set up the system and on the current models for the different components of the simulation system. An overview of the available tools for membrane protein simulation will be given, and current limitations and prospects will also be discussed.



KEYWORDS: *protein−membrane molecular dynamics, phospholipid, atomistic scaling, coarse-grained scaling, multiscale modeling*

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1. INTRODUCTION

In the past decade, computational methods have become increasingly important in the study of proteins and ligand−protein interactions. The amount of structures that are deposited in the Protein Data Bank (PDB) has doubled in the last ten years.[1] However, while about 20% of our genes code for membrane proteins,[2] the amount of membrane protein crystal structures has consistently hovered around 1−2% of the total available structures. Obtaining crystals of membrane proteins is still a nontrivial process, hampered by the fact that membrane proteins are difficult to overexpress in bacteria, and due to the fact that their hydrophobic surface imposes the use of detergents to isolate and solubilize the protein. However, as about half of all available drugs target membrane proteins, it is imperative to gather more knowledge on these proteins. Molecular dynamics (MD) simulations offer a great and distinct approach to investigate the structure of membrane proteins in ways that are complementary to experimental procedures. Due to recent evolutions in computational efficiency and improvements in the force fields, MD simulations have become a valuable tool.

The first MD simulations of pure lipid bilayers date back to the 1980s.[3] Simulation of a membrane protein by using continuum electrostatics to mimic a bilayer followed not much later, while one of the first MD simulations utilizing an explicit phospholipid model happened over a decade later.[4] While the amount of appropriate force fields was very limited at the time, the molecular dynamics field has seen a lot of action since then. Today, a lot of different force fields are publicly available; many of them are compatible with lipids as well as proteins and are thus suited for simulation of membrane proteins. In this review, most of the currently relevant force fields will be discussed in combination with methods to set up the phospholipid bilayer system.

2. PREPARING THE MEMBRANE DOUBLE LAYER

2.1. Setting up the Double Layer. A considerable amount of thought has to be spent to consider the approach that will be taken for simulating the phospholipid bilayer. Several different options have been described, and most of them still see use today. There is no clearly superior method, and the trade-off is often the recurring one of an increase in reliability in exchange for an increased computational cost.

A first approach to represent a double layer system is to treat the membrane as an implicit hydrophobic slab.[5,6] Databases containing membrane protein orientations have been compiled to facilitate this method,[7−9] as well as methods to automate the prediction of protein orientation.[10] While this method is computationally efficient, it is unable to represent membrane fluctuations and lacks the specific lipid−protein interactions that coarse-grained (CG) or atomistic approaches offer. In another approach, a library of different phospholipid conformations was created based on the simulation of a pure lipid membrane simulation. The lipids were randomly positioned around the membrane protein, and clashes were

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removed followed by a constrained energy minimization step.[11]

With the exponential increase in computational resources, more recent approaches include the self-assembly of the bilayer on atomistic or CG scales. The atomistic approach is still quite computationally expensive to apply on a full-sized system,[12] but the coarse-grained bilayer assembly methods have seen widespread adoption. Examples of CG methods include the self-assembly from a randomly ordered system of phospholipids[13] or the insertion of the protein into a pre-equilibrated membrane followed by a new equilibration.[14] MemProtMD is a web server containing more than 3,000 membrane protein structures that have been identified in the PDB[1] and which have been inserted into simulated bilayers using CGMD simulations.[15]

2.2. Choice of Phospholipids. A lipid double layer consists of highly varying types of phospholipids depending on the organism. However, depending on current growth cycle and environmental factors, even within a species, drastic differences in lipid bilayer composition have been observed.

In Figure 1 the most important bilayer components are shown. The amphipathic phospholipids can be divided into zwitterionic, anionic, and cationic phospholipids. Most eukaryotic membranes mostly contain zwitterionic phosphatidylcholine (PC) and phosphoethanolamine (PE) lipids, with anionic lipids like phosphatidylserine (PS) being present in the inner layer in a lesser amount. Sterols also make up a significant portion of the eukaryotic membrane and are thought to have a stabilizing function. While often overlooked, various papers highlight the importance of sterol inclusion and the effect it can have on protein distribution within a lipid bilayer.[16,17] Generally, bacterial membranes consist of PE lipids, anionic phosphatidylglycerol (PG) lipids and the anionic cardiolipin, which substitutes sterols as a membrane stabilizing component. In bacteria, aminated PG head groups can sometimes occur and can also make up a major part of their membranes.

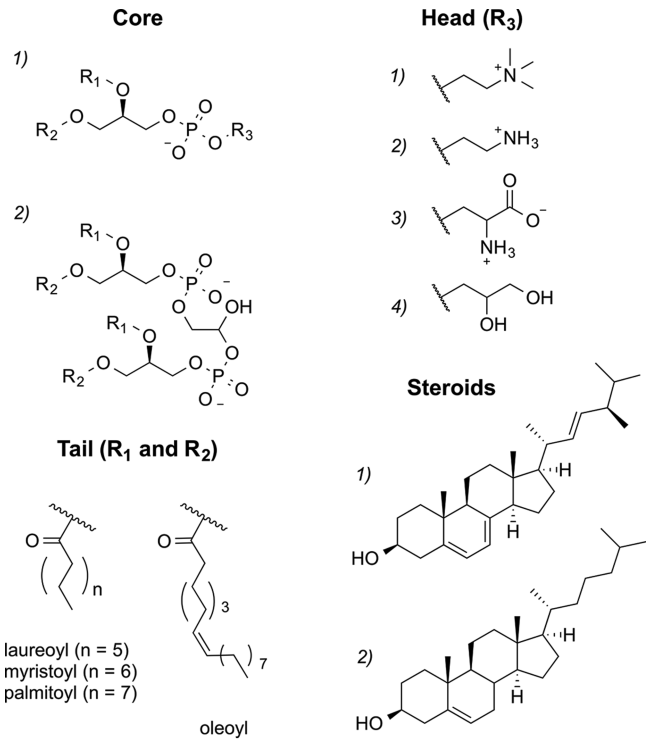

Figure 1. Phospholipid, which generally consists of a core element, combined with 2−4 fatty acid tails (R_1 and R_2) and an optional headgroup (R_3). (Core) A glycerol molecule attached to a phosphate group forms the core of a general lipid (1), or, in the case of cardiolipin (2), the core consists of a diphosphatidyl glycerol. R_1 and R_2 represent the hydrophobic tails, and R_3 represents the variable phospholipid headgroup. (Tail) Most common hydrophobic tails consist of laureoyl (C_{12} $H_{23}O$), myristeoyl ($C_{14}H_{27}O$), palmiteoyl ($C_{16}H_{31}O$), or oleoyl ($C_{18}H_{33}O$). (Head) Most common phospholipid head groups consist of choline (1), ethanolamine (2), serine (3), or glycerol (4). (Steroids) Ergosterol (1) and cholesterol (2), two frequently occurring membrane-stabilizing sterols in eukaryotes.

Accounting for the large variety of possible acyl chain types of phospholipids would result in very complex systems for simulation. Therefore, the usual approach is to use a palmitoyl and an oleyl chain in each phospholipid, as these are the most common acyl chains in many mammalian membranes. Phospholipids most frequently used in MD simulations include DLPC (1,2-dilaureoyl-*sn*-phosphatidylcholine), DMPC (1,2-dimyristoyl-*sn*-phosphatidylcholine), DPPC (1,2-dipalmitoyl-*sn*-phosphatidylcholine), DOPC (1,2-dioleoyl-*sn*-phosphatidylcholine), POPC (1-palmitoyl-2-oleoyl-*sn*-phosphatidylcholine), and POPE (1-palmitoyl-2-oleoyl-*sn*-phosphatidylethanolamine). When looking at other species, more attention should be paid to acyl chain composition. For some study cases, modifications to the acyl chain composition like addition of polyunsaturated acyl chains can be interesting as they can significantly affect membrane properties and molecular processes.[18]

Another important factor to consider is which force field parameters will be used for the phospholipids. The parameters should be fine-tuned depending on the properties that will be studied. The parametrization of these structures is not evident as experimental data on phospholipids is very scarce. Lipidbook is a public repository for force field parameters of lipids that are of interest when simulating biological membranes.[19]

3. SIMULATION SCALES AND CORRESPONDING FORCE FIELDS

A few decades ago, the utility of MD simulations was limited since only very short simulation lengths could be achieved due to limited computational resources. Since then, exponential growth in computational power, combined with improvements in parallelization and MD algorithms, have contributed to speeding up MD simulations. However, while these evolutions have led to significant increases in simulation lengths and system sizes, allowing for relevant simulations of systems containing over 150,000 atoms on microsecond time scales,[20,21] classical MD methods are generally still limited in regard to the study of membrane proteins. The systems used in these studies are frequently hundreds of thousands to millions of atoms in size, while the phenomena one wants to observe often happen on time scales up to several microseconds.[22] One study aimed at the crystal structure of a light-harvesting chromatophore involved a system with over 23 million atoms.[23] The simulation length was limited to 150 ns, even though the Titan cluster was used, which is currently ranked within the top 10 most powerful computing clusters in the world. Fortunately, simulation methods that reduce the complexity of the system have been developed. The concept of these methods is to group atoms into larger entities for

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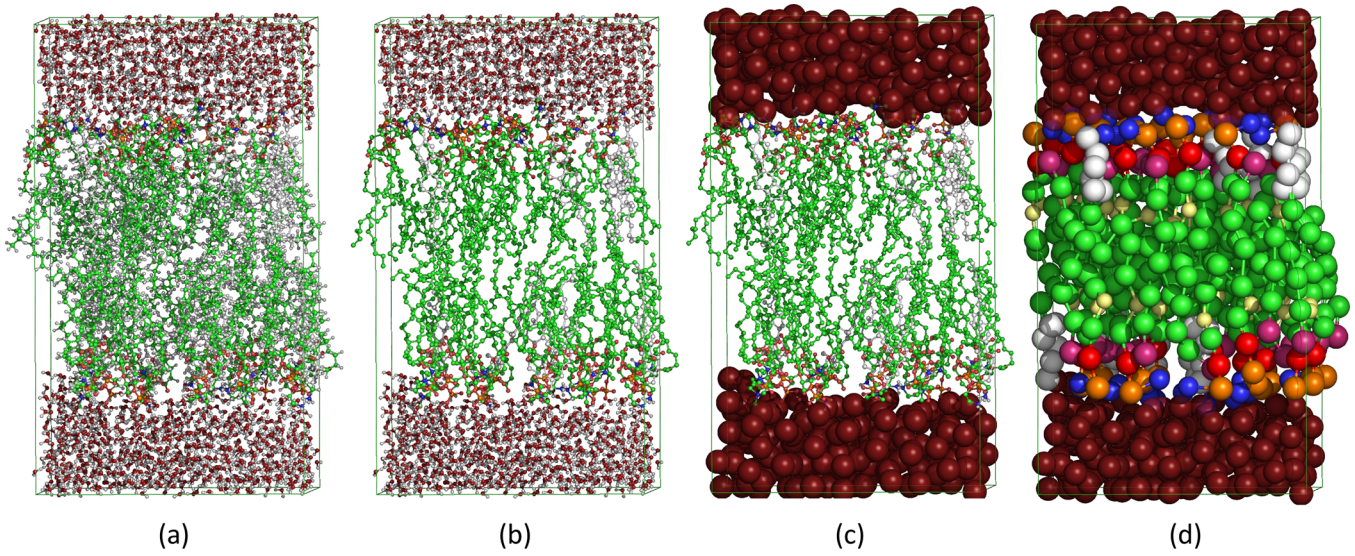

Figure 2. Four scales for MD simulations, illustrated by a double layer membrane surrounded by water. (a) Full atomistic scale in which all atoms are included (10,630 particles). (b) United-atom scale in which aliphatic carbons and their connected hydrogen atoms are treated as single beads (7,080 particles). (c) Hybrid model in which the phospholipids are represented on a united-atom scale and the water as coarse-grained beads (2,757 particles). (d) Coarse-grained representation of both solvent and phospholipids (947 particles).

which the equation of motion is calculated and derived, neglecting some of the atomistic degrees of freedom. This does not only significantly decrease the amount of interactions that have to be calculated, but due to the larger size of each particle, the potential energy surface is smoother, allowing for a larger time step between calculations. In this category, we can differentiate between approaches such as coarse-grained (CG) MD, Brownian dynamics (BD), dissipative particle dynamics (DPD), and molecular fragment dynamics (MFD). While the use of BD is largely outdated as it relies on the introduction of stochastic forces to replace solvent interactions, MFD and DPD, which also use stochastic forces, can sometimes prove useful for very large systems containing millions of atoms.[24,25] This review mainly focuses on atomistic and CGMD simulations (Figure 2).

3.1. Atomistic Scaling. Three atomistic scale force fields will be covered in this review in more detail. Charmm,[26] Gromos,[27] and Amber[28] force fields are used for the vast majority of membrane MD simulations. Although polarizable force fields are slowly gaining popularity, with examples including the Charmm Drude force field[29] and Atomic Multipole Optimized Energetics for Biomolecular Applications (AMOEBA) polarizable force fields,[30] these are not yet readily adopted for extensive MD simulations and will therefore not be covered here.

In most cases, parametrization of force fields for use with membrane proteins is focused on the optimization of a number of macroscopic properties, such as membrane thickness, curvature, and surface area per lipid (Figure 3). More advanced parameters include the angular distribution of the lipid tail vectors and the isothermal compressibility.

3.1.1. Amber. For several years, an Amber force field designated for the simulation of lipids was not available. In 2012 however, the GAFFlipid force field was released with reparametrized acyl chain carbons to allow for a more accurate simulation of phospholipids.[32] The force field was parametrized for DLPC, DMPC, DPPC, DOPC, POPC, and POPE phospholipids. It was noticed that the isothermal compressibility is highly sensitive to system size. Other properties were replicated relatively well, but the order parameters did not fully agree with experimental values.

Around the same time, Jämbeck and Lyubartsev introduced the Stockholm lipid parameters (Slipids).[33] Originally, DLPC, DMPC, and DPPC were extensively parametrized in order to reproduce the volume per lipid, bilayer thickness, and order parameters excellently. Later, the parameters were expanded to include unsaturated acyl chains and phosphoethanolamine head groups,[34] sphingomyelin, phosphatidylglycerol, phosphatidylserine, cholesterol,[35] and polyunsaturated lipids.[36]

In 2014, the LIPID14 force field was introduced,[37] with improved replication of phosphatidylcholine phospholipids and to be used without fixed surface tension. Later, the force field was expanded to include parameters for cholesterol.[38] The most recent Amber force field parametrized for simulation of lipids is the LIPID17 force field. It expands the LIPID14 force field by including parameters for anionic head groups and polyunsaturated acyl chains.[39] Although the specialized Amber force fields have improved parameters for lipids, they are scarcely used in reality. This is mostly because these force fields can only be used with the Amber MD package without using convoluted workarounds. Therefore, when Amber force fields are used in practice, it is most often one of the standard Amber force fields combined with Berger parameters for lipids.

3.1.2. Charmm. The Charmm96 parameter set was the first Charmm force field suitable for the simulation of lipids. However, this parameter set has not seen a lot of adoption, and comparisons have shown that it is inferior to the Charmm27 parameters for simulation of phospholipids.[40] The parameters of DPPC were revisited in a reparameterization of Charmm27, allowing for the simulation of bilayer systems in an NPT ensemble without the need of a fixed surface tension.[41] This Charmm36 lipid force field (C36 lipids) was later updated for bilayer simulations involving cholesterol (C36c)[42] and improved parameters for the simulation of polyunsaturated acyl chains (C36p).[43]

Finally, Charmm-GUI is a web-based service with a variety of tools, including a membrane builder which facilitates the

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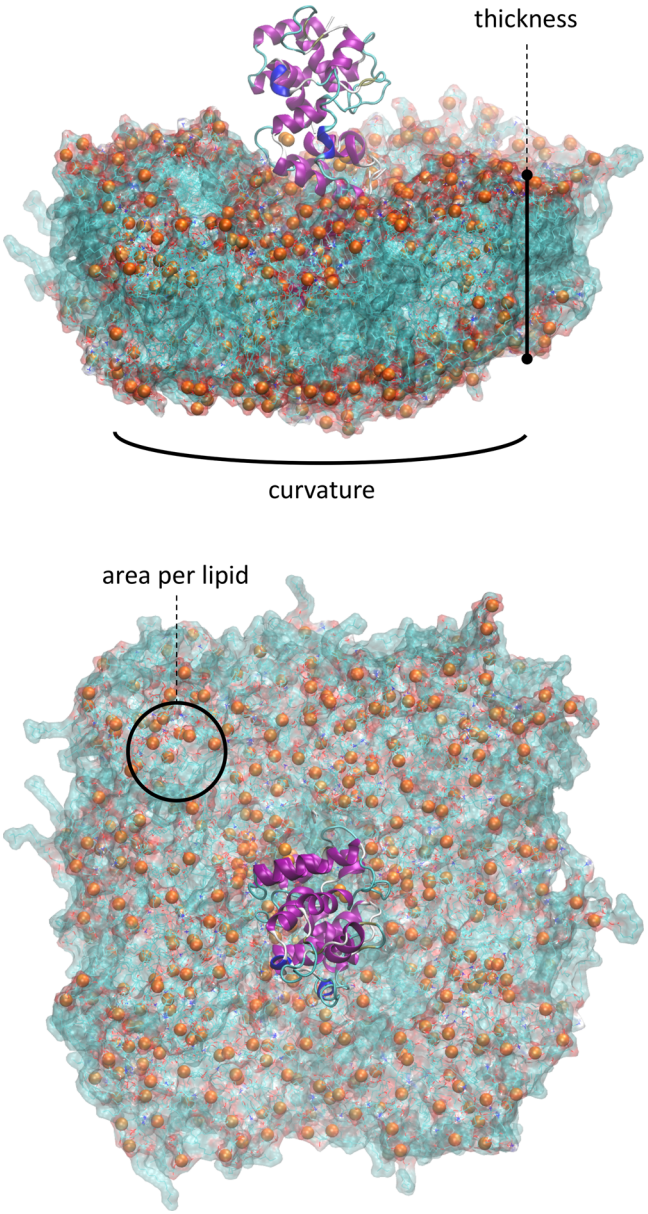

Figure 3. Side- and top view of an example protein/membrane complex to highlight some commonly used validation parameters. The thickness of the membrane is calculated as the mean distance between the phosphate groups of the outer and inner leaf of the double layer. The membrane curvature can be expressed as two principal curvature values C1 and C2, calculated from the corresponding principal radii of curvature.[31] Finally, the average area per lipid is calculated by dividing the area of the *XY* plane of a simulation box by the number of lipids in each leaflet.

generation of parameters for phospholipids, building of the bilayer, and insertion of proteins into the bilayer.[44]

3.1.3. Gromos. The initial Gromos force fields were not suited for the simulation of long alkane chains. Various reparameterizations ultimately gave birth to Gromos54A7/54B7 including improvements to the phosphatidylcholine parameters.[45] Since these recent versions of the Gromos force field utilize experimental solvation free energies for parametrization and are computationally efficient due to the united atom model, they have become a popular choice for simulation of membrane proteins. Several parameter sets compatible with the force field have been released over the years, with parameters that were designed for simulations of phospholipids. The Berger lipids parameter set is one of the older parameter sets and is actually not exclusively compatible with Gromos force fields, but was originally created for use with Gromos43A1.[46] While the original paper only discusses DPPC, various other lipids have been parametrized over the years. Berger lipid parameters are still a popular choice for simulations of phospholipids; however, it is not evident to use the Berger lipids in conjunction with more recent iterations of force fields as these often have been reparametrized for cutoff distances that vary from the original force field, resulting in incompatibilities.[47] The Berger parameters have been modified by Anézo and co-workers to be compatible with different nonbonded interaction cut-offs.[48]

The Gromos53A6 force field also received its own specialized phospholipid parameter sets: the Kukol parameters[49] and the parameters of Piggot, also known as the CKP parameter set,[50] that are derived from the Kukol parameters. The Kukol parameters are designed for simulation of saturated and unsaturated phosphatidylcholine and phosphatidylglycerol phospholipids, mainly focusing on replicating experimental area per lipid. Later on, Piggot adjusted the parameters to improve the results for phosphatidylglycerol, phosphoethanolamine, and cardiolipin phospholipids.[51] Although it is generally known that the Berger parameters are not the best choice for reproduction of experimental lipid properties, they are still found in many recent papers in conjunction with older versions of the Gromos force field or in conjunction with Amber force fields.

3.1.4. Which Atomistic Force Field to Choose? A multitude of appreciable force fields are available for simulations of membrane proteins in lipid bilayers. As every force field is consistent for at least some experimental property, it is not self-explanatory or trivial to decide which force field is the correct choice for a certain study. A number of papers compare the different force fields and can act as a starting point to evaluate the choice between force fields.[52−54]

As phosphatidylcholine phospholipids are the most prevalent type of phospholipids in mammals, a lot of experimental data is available on these lipids and most lipid force fields have focused on correctly representing these lipids in particular. However, for simulations involving more complex bilayers or bilayers containing more exotic phospholipids, the choice of parameters is narrowed down a lot, and in many cases, parametrization has to be done because no suitable force fields are available. As mentioned before, this is a time-consuming process and has been described in other papers.[38,45] It is recommended to use the newer versions of force fields, C36 and Gromos54A7 in particular, as these are currently the most popular choices for membrane protein simulations. However, in a recent comparative review, it was concluded that the Gromos54A7 force field performed worse than the Charmm36, Amber/Lipid14, and Amber/Slipids force fields when looking at the transmembrane helix tilt angle and hydrophobic and hydrophilic insertion behavior.[53]

3.2. Coarse-Grained Scaling. The development of reliable coarse-grained MD models has been relatively new for the simulation of biological systems, although the concept originated in the 1970s. In CG simulations, molecules are described by the interaction sites representing groups of atoms, providing a reduced resolution description of a given system. The CG representation of molecules was implemented to significantly reduce the amount of calculations of interactions

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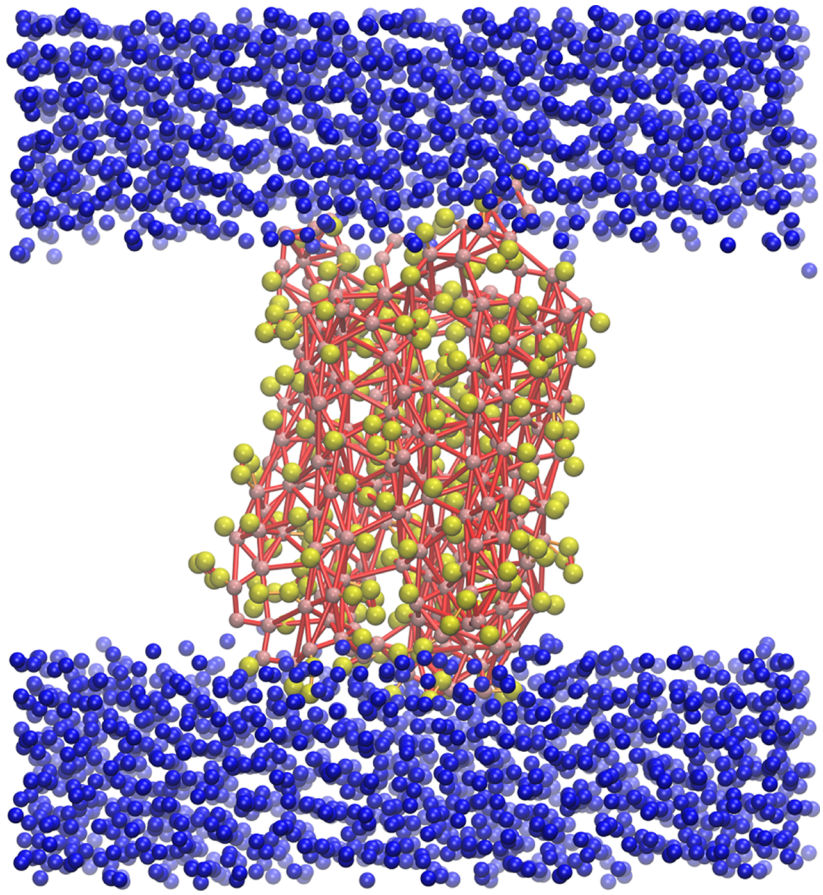

Figure 4. Illustration of the dummy bonds needed in the elastic network approach in order to retain the secondary structure of the protein using the MARTINI CG force field (colored in red). Coarse-grained beads of the protein are colored yellow, and the water solvent is shown as blue spheres. The double layer membrane is not shown for clarity.

involved in each time step, thus substantially decreasing the computational cost. This method makes it possible to simulate systems up to a millisecond time scale, while retaining an acceptable reliability. A computational speed-up of 2−3 orders of magnitude can be achieved when compared to an atomistic setup. While the reduced amount of interactions has a major contribution toward this increase in speed, causing a 10- to 100-fold speed-up, particle-mesh Ewald summation or other long-range electrostatics calculations are also irrelevant in current CG force fields, leading to another 10-fold speed-up.[55] Finally, the smoother energy surface that is achieved by using larger particles also makes it possible to increase the integration time step to 20 fs or in some cases even more, without repercussions. In addition to the increased time step, the effective time simulated is 3−8 times more than the time step suggests. Generally, parameters are assigned to beads consisting of 3−4 atoms when using CG models. While this decreases the complexity of the system by reducing the number of atoms and interactions, it also makes the process of assigning parameters to molecules easier when compared to parametrization of atomistic systems.

3.2.1. MARTINI. Among the coarse-grained force fields, the MARTINI force field[56] is the most popular one by far for simulations of biological systems. Being one of the first released CG force fields, it has seen various optimizations and modifications for use in simulations with varying molecule types.[57,58] The popularity of MARTINI can be explained by the fact that it is the only CG force field that is parametrized for lipids as well as proteins, and the INSANE protocol facilitates the creation of complex lipid systems.[59] Recent updates of the Charmm-GUI web service have seen the implementation of the Martini Maker module, allowing for the easy assembly of bilayer systems.[44] A library of 82 lipids is available and various flavors of the MARTINI force field are supported.

The parametrization of the MARTINI force field is top-down using the partition coefficient between octanol and water. The advantage of such top-down parametrized force fields is that parameters based on experimental values are more general, which means the force field can be more reliably applied to molecules which it has not been parametrized for, while bottom-up force field parameters are usually only accurate for specific molecule sets. The standard MARTINI force field utilizes 18 different bead types. They are separated into four categories: charged, polar, nonpolar, and apolar beads. The charged and polar groups are further divided into five categories based on the polarity, while the nonpolar and apolar categories are divided into four categories based on the presence or absence of hydrogen bond donating or accepting groups. Nonbonded interactions between the beads are defined as Lennard-Jones potentials that are based on the interacting bead types. Electrostatic interactions are usually represented by a method similar to a distance-dependent screening. Bonded interactions are treated in a similar fashion to atomistic force fields. The secondary structure of proteins is not always retained very well. Approaches like the elastic

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network approach (ElNeDyn) have been implemented to keep proteins in the appropriate conformation during simulations (Figure 4).[60] Recently, the open beta of the MARTINI 3 force field was released, containing topologies for over 120 lipids, new beads types, reparameterization of several existing bead types, and more.

One paper specifically aimed to test the reliability of the CGMD approach.[61] Ninety-one membrane proteins, for which structural data was available, were submitted to a virtual insertion in a DPPC lipid bilayer using the MARTINI force field. The elastic network model was used to retain the protein folding. From these 91 proteins, only five showed a Cα RMSD greater than 0.5 nm. Various other validation publications have been written, all showing how the MARTINI force field is able to replicate experimental data within an acceptable standard deviation.[62,63]

3.2.2. CGProt. A recent addition to the CG force fields is CGProt, which has been reparametrized to support simulation of membrane proteins.[64] Until now, only limited amount of validation and use cases for this force field is available, but the force field seems to be promising as it is able to replicate secondary protein structure without the need of using an elastic network to pertain secondary structure. Currently, this force field employs an implicit solvent model and the study of membrane proteins was tested using a pre-equilibrated lipid bilayer.

3.2.3. PRIMO. The PRIMO CG force field has recently been extended for membrane protein simulations as well.[65] It shows good conformational agreement compared to crystal structures of membrane proteins. By being able to replicate secondary protein structure, it holds the same advantage over the MARTINI force field that the CGProt force field does. This removes the requirement of a constraining network and makes it possible to sample conformational transitions.

3.3. Multiscale Modeling Approaches. Both atomistic and coarse-grained models have their own advantages and disadvantages. Researchers have attempted to combine both in order to get the best of both worlds: a model of high resolution to investigate microscopic interactions in a short time frame, combined with a coarser model which makes it possible to look at events on a larger scale within a larger time frame. Combining both models is called multiscale modeling. A further distinction is made between parallel and serial multiscale modeling, which will both be covered in their respective subsection. While this strategy shows a lot of promise, it is a relatively recent innovation in the field and there are still some issues that cannot be overcome easily, which prevent widespread use of these approaches.

3.3.1. Parallel Multiscale Modeling. In the parallel multiscale modeling approach, parts of the system are described by a coarse-grained model, while other parts are described by an atomistic model. The obvious advantage here is that this makes it possible to study a large system on larger time scale (μs), while at the same time making it possible to zoom in on the atomistic scale properties of desired parts of the system. Issues with this approach revolve around the interactions between the CG and atomistic parts of the system. Electrostatics are defined through a Coulomb potential in atomistic force fields, but the CG water models are often described by a Lennard-Jones potential; hence electrostatic coupling is not possible. This results in an acceptable accuracy for apolar particles, but for polar particles results can deviate significantly from experimental data. Various methods involving the mapping of one solvent molecule to one CG bead and inclusion of scaling factors have been tested to counteract this issue with relative success,[66,67] however, at the cost of losing most of the computational speed advantages of the CG method.

The interactions of polar protein residues with the surrounding water molecules may have important effects on protein conformation. The absence of an accurate representation of the interactions between protein and solvation layer is an issue that limits the static parallel multiscale method. One could include an atomistic solvation layer for the protein, but the water molecules would quickly diffuse into the CG solvent. However, the adaptive resolution (AdResS) method has been developed to address this problem.[68] In AdResS simulations, atoms get a resolution assigned which is automatically changed as a function of the position of the molecule in the simulation box. In general, the system is made up of a part in CG resolution, a fully atomistic part, and a hybrid area separating the two. In the hybrid layer, molecules can interchange between CG and atomistic resolutions. Molecules in the hybrid area are usually represented by a combination of AA and CG parameters. While the AdResS method appears to be the most promising among the parallel multiscale methods, no work has been released adopting this technique for simulations of membrane proteins. Simulations of simple systems have been reported, but even with the current state-of-the-art methods, simulation of bilayer-containing systems is still out of reach, with the largest limiting factor being an unsatisfactory representation of the phospholipids.

3.3.2. Serial Multiscale Modeling. The difficulties of parallel multiscale MD simulations can be avoided when both resolutions are applied sequentially. In serial multiscale modeling, the system is first evaluated at a CG resolution and subsequently converted to atomistic resolution and evaluated again. This approach takes two established methods and uses them separately, with the only catch being the conversion of a CG system to an atomistic system. This approach holds a lot of the advantages that the parallel multiscaling method does, but interactions at the atomistic resolution that are interesting to the user cannot be studied during an equally long time frame, as the entire system is converted into an atomistic resolution. The approach is often used for validation or refinement of CGMD simulations.

3.4. Conversion between the Atomistic and Coarse-Grained Scales. For the purpose of setting up a CG-represented system from crystal structures or from atomistic scale simulations, methods are necessary to convert a system from an atomistic representation to a CG representation. Likewise, methods are necessary to convert a system from a CG representation to an atomistic representation for performing serial multiscale modeling simulations.

3.4.1. From Atomic Scale to Coarse-Grained. The conversion of a protein from an atomistic model to a coarse-grained model can be done with various scripts. Methods like force matching were used to derive the potential of mean force (PMF) between beads from an atomistic model.[69] Similar methods, relying on calculations to derive parameters, are called "bottom-up" methods. While automated procedures to derive parameters are widely available for all-atom and united-atom modeling, such protocols are scarce for CG systems. Four different publicly available software packages have been reported using bottom-up methods. "VOTCA",[70] "IBIsCO",[71] "MagiC",[72] and, most recently, "PyCGTOOL".[73] These

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software packages derive a CG model based on an atomistic description of the system via inverse Monte Carlo or iterative Boltzmann inversion. "Top-down" approaches attempt to replicate experimental data by fine-tuning the parameter set. These can also be effective to obtain a CG model but are more laborious.[74] With these approaches, the CG model is tuned to the experimental properties of the molecule in a trial-and-error procedure.

3.4.2. From Coarse-Grained to Atomic Scale. Several methodologies have been created for the conversion of a CG system to an atomistic one that retains the correct conformation, and the most relevant ones will be discussed here. One approach is the use of molecular fragment libraries to retrieve stereochemical information for nonprotein and nonwater parts of the system.[75] Conversion happens by aligning the atomistic fragments to the CG lipids, followed by an energy minimization. A different approach for the back-mapping problem is the use of a three-step algorithm.[76] First, atoms are spatially positioned near their coarse-grained counterparts. A simulated annealing procedure is then used, constraining the atoms to the CG representation using harmonic restraints. Finally, the restraints are gradually removed and the system is allowed to relax. As the algorithm does not rely on the use of fragment databases, it is easily transferable between force fields and molecule types.

3.5. Use Cases of Each Force Field. When examining specific use cases, it becomes clear that various approaches are still commonly used and that there is no clear use-case per force field. While a clear preference can be seen toward use of the Charmm[20,77] and Gromos[78,79] suites of force fields, the less used Amber suite is still commonly applied.[80,81] In some papers, the availability of the different approaches is used to the authors' advantage. For example, in a paper of Aponte-Santamaría and co-workers,[82] the correlation between temperature and protein conformation of a yeast aquaporin is investigated in separate simulations with suites of the Amber, Charmm, and OPLS-AA force fields, aiming for a form of consensus between the methods. The MARTINI force field and other CG force fields can be applied in many cases. They are generally avoided whenever possible, but as soon as the system size grows too big, the MARTINI force field is used in part of or the entire simulations.[83,84]

Today, the use of MD in membrane protein studies can generally be divided into four categories: membrane−protein interactions, protein sorting in the lipid bilayer, protein-induced membrane remodeling, and membrane protein function. Serial multiscale approaches are very popular for investigating membrane−protein interactions. Most often, the MARTINI force field is combined with a version of the Gromos force field. As many dynamic processes in the lipid bilayer happen on the microsecond scale, CG simulations are used to simulate these events, followed by atomistic simulations which allow investigation of key interactions between protein and lipids.[85−87] When investigating protein sorting in bilayers, the choice toward CG methods is almost unanimous. Sorting events occur on the microsecond scale and the systems used are often large, which does not really leave any other options with the currently available resources.[88,89] When regarding membrane remodeling, the systems are even larger. Here, CG methods are commonly used, but some researchers also use mesoscale dynamics in combination with atomistic simulations.[90] Finally, function is the property of membrane proteins that is most frequently tackled with MD simulations. As these experiments put the emphasis on the protein, reproduction of lipid properties is valued less, and accuracy of the protein force field is valued more. For this reason, Charmm force fields are most common in these experiments,[91−94] although the other common force fields such as Amber also see a lot of use.[94] Moreover, since the release of Gromos54A7, the use of the Gromos suite has increased significantly.[95,96]

To summarize: when working in large systems containing many lipids, coarse-grained and united atom force fields are most commonly used. When working in smaller systems, where the focus is put on dynamics within the protein, a preference can be seen toward the Charmm suite of force fields. Nevertheless, force field choice often depends on the research group. Groups that have been working with a certain force field for years will often continue using this same force field due to convenience.

4. FUTURE PROSPECTIVE

As it stands today, MD simulations still have a lot of limitations. With the computational power we have at our disposal, simulations on a time scale of milliseconds and up are almost impossible for large systems. Highly specialized computers like Anton are a step in the right direction but can still be improved upon. Efficiency of integration steps in molecular dynamics software can also be improved upon. The advent of coarse-grained MD methods has made time scales less of an issue, but when attempting to look at microscopic interactions on a large time scale, there are still no clear-cut available methods. A lot of novel methods like parallel multiscale modeling and polarizable coarse-grained force fields are being developed but are currently not mature enough for simulation of large bilayer systems. In the future, time scale issues could be overcome by the development of sophisticated parallel multiscale methods, more reliable implicit solvent models, and the development of million-core specialized computing clusters resulting in a drastic increase in computational power. The effective size of the system is another hurdle. Ideally, molecular modeling would be possible on entire cells. This, however, still lies far out of reach. On one end, the experimental data that is necessary for construction of an MD system and for assignment of reasonable parameters is not yet available. On the other hand, simulating such a large system is simply not feasible with the current techniques. The gap toward full cell simulations could also be closed by an increase in computational power and, through the use of sampling tricks, decreasing the amount of necessary computations. In a full cell, a lot of degrees of freedom are unnecessary, and removing these irrelevant degrees of freedom can significantly speed up simulations.

When we focus more specifically on the simulation of bilayer systems, other issues arise. Curvature and rigidity of the lipid bilayer are still big issues in many force fields, and this can possibly be attributed to the cytoskeleton. We know that the cytoskeleton of the cell helps to maintain its shape and likely has a stabilizing effect on the lipid bilayer. As long as we do not have a clear idea of how the interactions between the cytoskeleton and the bilayer affect the bilayer properties, it is difficult to account for this shortcoming. A second limitation concerning bilayer simulations is the approximations that are made in force fields. As more experimental data becomes available for phospholipids and other membrane lipids, it will be possible to optimize force field parameters in a more

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thorough manner. Toward the future, it should also become a point of discussion which properties are suitable for validation. Right now, area per lipid is largely used[47] but might in fact not be the best property to rely on for validation. Other properties like order parameter, lateral diffusion, and membrane thickness should also be considered and evaluated.[50,51] The lack of knowledge on lipid behavior and lipid properties significantly holds back the development of such parameters, with experimental data being inconsistent for many properties of some phospholipids and completely absent for most phospholipids.

Finally, a consensus on simulation parameters should also be achieved in the future. Different papers discuss the advantages and disadvantages of methods, but ultimately it is unclear what method would be optimal for a specific system. Various discussions like the use of isotropic or semi-isotropic pressure coupling,[97] periodic boundary conditions and long-range interaction cut-offs,[98] system hydration,[99] and salt concentration[100] make it clear that we still have a long way to go toward a uniform simulation method that is suitable for general system conditions and for investigating a broader range of properties.

AUTHOR INFORMATION

Corresponding Author

*E-mail: hans.dewinter@uantwerpen.be.

ORCID

Hans De Winter: 0000-0002-4450-7677

Notes

The authors declare no competing financial interest.

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