Emerging Era of Biomolecular Membrane Simulations: Automated Physically-Justified Force Field Development and Quality-Evaluated Databanks

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Abstract

Molecular simulations of biological membranes and proxies thereof are entering a new era characterized by several key aspects. Progress starts with the realization that the outcome of the simulations can be only as good as the underlying force field and we actually need to know precisely how good or bad the results are. Therefore, standardized procedures for data quality evaluation are being established and will be applied to biomembrane simulations available in the literature. This provides the necessary basis and impetus for new force field development. Here, we propose to systematically build up physically well-justified models which effectively account for electronic polarization effects for all components of the biomembrane systems in aqueous environments. Such a massive task can only be achieved within a reasonable timescale by applying automated parameterization tools.

Introduction

Classical molecular dynamics (MD) simulations of biomembranes are nowadays increasingly used in various applications, ranging from molecular cell biology to lipid nanoparticle formulations for vaccines.[1–6] Such applications are expected to increase further because MD simulations are becoming more accessible to a wider audience thanks to tools streamlining the simulation workflow, such as CHARMM-GUI[7] and Schrödinger-Maestro combined with Desmond,[8] and impressive performance of widely available GPU-computing hardware. At the same time, software and hardware development enable experts in the field to push the limits of MD simulations towards increasingly complex and large systems, such as cell membrane mimics[9] and virus particles.[10]

In both of these lines of development, it is increasingly important to understand the consequences arising from the approximations in the classical potential functions, i.e., force field, and simulation algorithms used in MD simulations. The new wave of users, consisting of practitioners with varying experience on methodological details, are often unaware of these limitations. At the same time, increasing the size, time scale, and complexity of the simulated systems may lead to the multiplication or cancellation of errors in the physical description of the systems. Furthermore, with the growing impact of MD simulations in biomedical and other applications, the potentially incorrect or misleading results will have increasingly severe consequences. Therefore, improving the MD methodology and the protocols to evaluate the quality of MD simulations is becoming more and more important.

Contrary to ther fields, there are no currently generally accepted standards when it comes to MD. In the field of structural biology, the Protein Data Bank (PDB) defines the quality measures for protein structures determined with different experimental techniques and enables access to vast amount of data for experts to evaluate the quality of each structure by themselves.[11–14] For intrinsically disordered proteins, belonging to the same class of unstructured molecules as lipids, such a databank is emerging,[15] but universal quality measures for conformational ensembles determined with different methods, including MD simulations,[16,17] are yet to be defined. While importance of such databanks for MD simulations is widely recognized[18–25] and different kinds of approaches are emerging,[25–32] generally accepted protocols and best practices are still under active development.

At the same time, accumulating evidence on simulation artefacts arising from force fields (the sets of functions that approximate the physical interactions between atoms in MD simulations) raises the need for more accurate parameters and improved description of physics, particularly for lipids and disordered proteins.[16,33–38] Due to the semi-empirical nature of MD simulation force fields, a consistent parameterization represents a daunting task, often requiring simultaneous refinement of almost all interactions within a force field. To this end, several fully or semi-automatic approaches for force field parameterization are emerging.[39–43]

Here, we discuss current issues and ongoing activities in evaluating and improving biomolecular MD simulations with quality-evaluated databanks and automated force field development approaches. We focus on systems where atomic resolution description of lipid membranes, and lipid interactions with other molecules, play a major role. Coarse grained simulations and other biomolecular systems are left outside the scope of this perspective.

Current issues in lipid membrane MD simulation quality

Controversies in lipid membrane simulations

Dozens of force fields and combinations thereof are available for simulating lipid membranes and their interactions with other molecules, such as proteins, drugs, and ions.[9,44] Even though the quality of force fields has been widely evaluated against experimental data during parameterization and in separate comparison studies,[33–37,44] defining unambiguously their overall quality still remains unclear, and several controversial results are reported for each in the literature, as exemplified in Table 1. Because universal quality measures for membrane simulations are not available, it is difficult to estimate, even for an expert, the reliability of a certain MD simulation result or to select the best force field for a specific application. Therefore, lipid membrane MD simulations in their current state have to be used with great care to avoid misinterpreting experimental data or even launching questionable research directions inspired by artificial MD results.

As evident from Table 1, many controversies can be traced to interactions between lipids and other molecules including water. These disagreements are not surprising from the historical perspective, because early development of lipid bilayer simulations focused on correctly capturing membrane phase and area per lipid, which depend mainly on acyl chain properties,[56,69] while the glycerol backbone and headgroup and their interactions with ions and other molecules have gained attention only more recently.[33,34,38,45–48,70] Consequently, the hydrophobic acyl chain regions are commonly described quite well by MD simulations, while force fields struggle to correctly capture behaviour of the hydrophilic regions of membranes.[35]

In particular, the interactions between charged water-soluble species and membranes have been challenging for MD simulations. Canonical force fields tend to predict stronger binding of sodium and calcium to membranes than experiments,[34,48] yet this can be improved by including electronic polarization via the electronic continuum correction (ECC)[34,45–47] or by an ad hoc increase of the effective separation between specific atoms (NBFIX).[48–50] Also,

Table 1: Examples of controversial MD simulation results reported in the literature. PC = phosphatidylcholine. ECC = electronic continuum correction. NBFIX = increasing the effective separation between specific atoms.[48–50] PS = phosphatidylserine. JM-A = the N-terminal portion of the juxtamembrane segments. EGF = epidermal growth factor. MC3 = dilinoleylmethyl-4-dimethylaminobutyrate.

Issue	Controversy	Proposed solutions
Cation binding to zwitterionic membrane	Strong binding of Na^+ and Ca^{2+} ions to zwitterionic PC lipid headgroups observed in most force fields do not agree with NMR or other experimental data.[34]	Ion binding in force fields with ECC is more realistic.[45–47] NBFIX parameters between specific atoms have been introduced in CHARMM force field.[48–50]
Lipid-headgroup–cholesterol interactions	Direct interactions between cholesterol and lipid headgroups are observed in simulations with the Berger/Höltje force field combination,[51] while CHARMM36 predicts only weak preference for the nearest lipid headgroups to locate over cholesterol.[52]	NMR data agrees better with CHARMM36, suggesting that headgroups are rotating more freely in the cholesterol-containing membranes,[53] probably due to a less dense headgroup region.
Calcium binding position in PS lipid headgroup	CHARMM36 with NBFIX parameters[48,49] suggests that Ca^{2+} ions interact only with the carboxylate group of PS lipids.[54] Without NBFIX the same force field indicates a significant binding affinity also to the phosphate region.[55] Berger lipid force field[56,57] suggests substantial binding also to the carbonyls in the acyl chains.[58]	In Amber-based force field with ECC, which has the most realistic ion binding behaviour when compared with NMR experiments, Ca^{2+} binds approximately twice as likely to the carboxylate than to the phosphate moiety of PS, and binding only to acyl chain carbonyls is almost negligible.[46]
Langmuir monolayer simulations	Lipid monolayer can remain stable in a non-physical negative-surface-pressure state, and porates at too low area per lipid values.[59,60]	Water model with the correct surface tension and a sufficiently large periodic box are required to simulate lipid monolayers and quantitatively reproduce the surface pressure–area isotherms.[61,62]
Lipid–protein interactions	In simulations combining an Amber-based protein force field and CHARMM lipids, the kinase domain and JM-A fragments of EGF receptor interact only with the negatively charged PS headgroups,[63] while in simulations with an OPLS-based force field they interact also with neutral membranes.[64]	Unresolved
Melting temperature of single-component lipid bilayers	Overestimated melting temperatures for single-component lipid bilayers have been reported,[36] while good agreement with experiments are found in other studies.[65]	Unresolved
Serotonin binding in different membrane phases	Serotonin binds preferentially to disordered phase in simulations and acyl chain order parameters of ordered phase are not affected, while its signal originates mostly from ordered state in NMR experiments.[66,67]	Unresolved
Accumulation of the ionizable MC3-lipids	Ionizable MC3-lipids, used in lipid-nanoparticle formulations for vaccines, accumulate in the bilayer center when the CHARMM36 force field is used,[6] while Slipids shows almost no accumulation.[68]	Unresolved

lipid–protein interactions depend on force field parameters,[71–75] which is particularly evident for charged residues[37,76] and their interactions with lipid headgroups.[75,77] While sodium and calcium ion binding to membranes with various compositions have been quantitatively evaluated using lipid headgroup order parameter data,[34,38,47] such comparison is not available for proteins or amino acids interacting with membranes. The evaluation of lipid–protein interactions has focused on comparing hydrophobicity scales,[37,76,78] NMR data[71,79] or crystallized lipid–protein complexes.[80] While hydrophobicity scales are often qualitatively reproduced by MD simulations, and proteins are usually oriented reasonably in membranes in these studies, charged residues often appear as outliers or potential sources of discrepancies with experiments.[37,71,76,78,79] Also, the partitioning of small neutral molecules seems to agree with experiments qualitatively,[81] but experimental data is more scarce for charged molecules, and a systematic comparison of MD simulations with experiments is not available.[82]

In conclusion, we see that many controversial results from MD simulations originate from the description of polar and charged molecules or molecular groups, including water, and particularly their interactions with lipids. Therefore, we focus in the following on the effects of water models and electronic polarizability on interactions involving lipids. Other force field inaccuracies and issues related to simulation methodology, such as insufficient sampling or algorithms, are left for other accounts.

Water models

As water plays at least an indirect role in all biological processes, much effort has been put to describe water properties in atomistic MD simulations accurately, and available parameters to model water have improved significantly over the years.[83] However, using the most realistic water model in biomolecular MD simulations is often not straightforward due to the semi-empirical nature of force fields: The change of water model would, in principle, require reparameterization of the complete force field. The change of the water model without such reparameterization compromises the consistency of parameters. Therefore, early

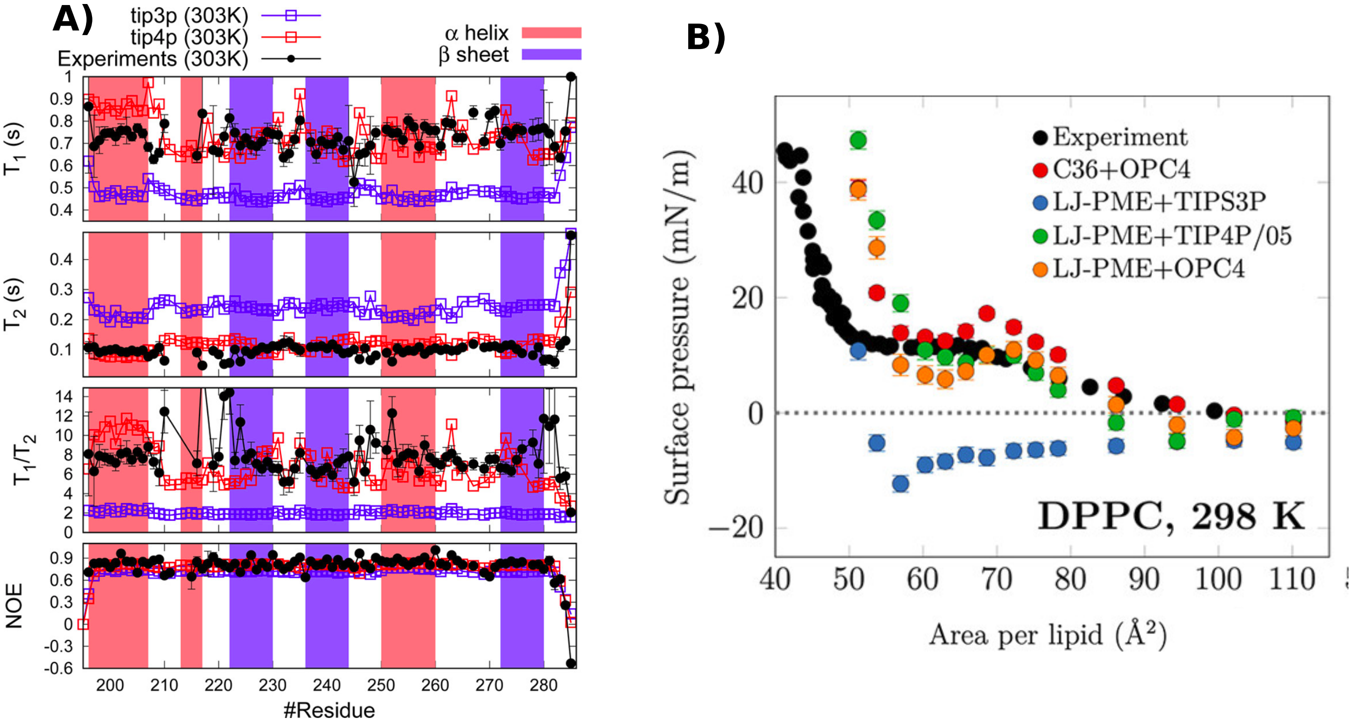

Figure 1: A) NMR spin relaxation times calculated from simulations of HpTonB-92 C-terminal domain using Amber ff99SB-ILDN force field with different water models compared with the experimental data. The results with TIP3P are off from experiments due to too fast rotational diffusion caused by the underestimated water viscosity, while results with TIP4P are close to experiments. Figure adapted from Ref. 85. B) Surface pressure-area isotherms of DPPC lipid monolayer from CHARMM36 simulations with different water models and long-range Lennard-Jones treatments compared with experimental data.[62] Simulations with TIP3P based water models suffer from artefacts arising from underestimated surface tension, such as negative surface pressures and pore formation at too low areas, while simulations with better water models give almost quantitative agreement with experiments.[60–62] Figure adapted from Ref. 62.

water models, such as TIP3P and its derivatives,[84] are still widely used in biomolecular MD simulations despite their known inaccuracies.

The most notable shortcomings of water models (leading to known artefacts in biomolecular MD simulations, demonstrated in Fig. 1) are the underestimated surface tension and viscosity, as well as the dielectric constant (see Fig. 1 and the next section for a detailed discussion on the proper treatment of the dielectric response). Underestimated surface tension leads to incorrect phase behaviour and opening of pores at too low areas per molecule in lipid monolayer simulations.[60–62] Too low viscosity leads to overestimated rotational dynamics of proteins as follows from comparison between simulations and experiments. The incorrect overall rotational diffusion can be corrected during analysis for folded proteins but not for disordered proteins or other biomolecules.[17,85] Furthermore, incorrect bulk water properties usually imply inaccuracies in interactions between water molecules, which are likely to cause other problems in biomolecular simulations. Indeed, the commonly observed over-compact ensembles of disordered proteins have been related to inaccuracies in water models.[86,87]

In applications where the water viscosity or surface tension are critical, the optimal solution is to use a more advanced water model,[17,61,62] which without careful reparameterization, however, could lead to inconsistencies with other parameters. In practise, such inconsistencies are observed to be less severe than issues arising from incorrect water properties.[61,62,85] In conclusion, we are convinced that using modern water models with correct surface tension, viscosity, dielectric response, and other physical properties is a must for future MD simulations of biomolecules.

Lack of electronic polarizability

A general problem pertinent to the vast majority of membrane simulations is the lack of electronic polarizability effects. Indeed, standard force fields employed in membrane simulations are non-polarizable, meaning that atomic charges are fixed. This does not reflect reality where charged, or polar objects (i.e., ions or polar molecules) can polarize neighbouring molecules and thus effectively change their charge distributions, which if not considered results in several artifacts listed in Table 1. Explicitly polarizable force fields[88–90] aim at fixing this problem. However, they have not been widely employed in biomembrane simulations yet. In general, the limited use of explicitly polarizable force fields may be traced back to several factors. They include issues concerning their accurate parameterization (potentially leading to failures in reproducing experimental data; see below for more discussion), instability of the iterative algorithm (the so-called polarization catastrophe[91]), the need for specialized, not always user friendly software, and significantly increased computational costs.

Recently, a simple approach for including electronic polarization in a mean-field way in classical non-polarizable force fields has been suggested.[80,92] Within this method, denoted as the electronic continuum correction (ECC), electronic polarization effects are accounted for by scaling the charged groups by the inverse square root of the high-frequency dielectric constant of the surrounding medium, i.e., by the inverse of its refractive index. Note that the high-frequency dielectric constants of the relevant biomembrane distinct environments—aqueous solutions, membranes, and protein interiors—have values around 2, being very similar to each other (unlike the total dielectric constants), which renders this essentially continuous approach applicable. In principle, charge scaling should be equivalent to immersing the whole system into a dielectric continuum with a dielectric constant of about 2. However, since our charge scaling is based on previously parameterized non-polarizable force fields, it has turned out to be prudent to scale only the charges of ions and ionic groups and not, e.g., of polar molecules like water. In other words, some degree of charge scaling may have been already included implicitly in the original force field when fitting it to experimental data. Note that partial charges are not experimental observables and, therefore, their values depend to some extent on the particular procedure adopted for their derivation. Also, the dielectric properties of common water models may not be entirely consistent with the ECC approach in the sense that their dielectric constants are larger than the experimental low-frequency value. Therefore, scaling factors lying anywhere between the inverse square root of the high-frequency dielectric constant and unity have been suggested.[80]

In the context of phospholipid membrane modelling, one of the key experimental manifestations of the deficiency of standard non-polarizable force fields is the grossly overestimated binding of biologically important cations such as sodium and calcium to lipid headgroups. This overbinding is true for membranes formed from both zwitterionic and anionic lipids, as exemplified by the a much larger effect of these cations on the lipid headgroup order parameters in the simulations than obtained from NMR measurements.[34,38] We have shown that charge scaling via the ECC approach fixes this problem in a physically well-justified way and brings the simulation results in a quantitative agreement with experiments. This grossly improved agreement is demonstrated for membranes containing PC, PS and PG lipids by plotting the dependence of the lipid headgroup order parameters on the aqueous salt concentration for sodium and calcium chloride.[45–47] The comparison to experiment of the results from ECC vs. standard non-polarizable force fields clearly shows the dramatic improvement charge scaling brings to the description of cation–headgroup interactions. The overestimated interaction between charged species within non-polarizable force fields has far-reaching consequences in biomembranes, since transmembrane proteins,[93] the glycocalyx,[94] and other species that interact with the membrane[95] are rich in charged groups. All these issues are due to by wrong electrostatics, and we showed that charge scaling can to a large extent fix that.[80]

In the future, we plan to revisit the ECC force field development for biomolecules, starting the work from scratch, i.e., building up *de novo* a charge-scaled force field for water, ions, amino acids (and the corresponding peptides and proteins), phospholipids, nucleic acids, sugars, and other biologically relevant molecules. In this way, we will no longer be subject to potential overscaling due to reliance on existing force fields and inconsistent dielectric responses of water models. The challenge of building, from scratch, a new force field for biomembranes that is ECC-compatible would have been unsurmountable just a few years back. Developing a new force field is still a monumental task involving several research groups and countless iteration rounds, where mistakes are corrected. In fact, there is still a lot of manual work involved that justifies why all well-known force fields used to simulate biomembranes started their development more than two decades ago. Nevertheless, the constant increase of available computational power and the surge of computational techniques that potentially allow considerable automatization of such tasks (e.g., machine learning,[96] see below) make present day the right moment to attempt such an endeavor. If successful in our goal, we will eventually provide to the community an accurate force field that accounts for electronic polarizability in a mean-field charge scaling way such that it is fully equivalent to immersing the system into a dielectric continuum with the high-frequency dielectric constant.

Current status of quality-evaluated databanks and automated force field development

Quality-evaluated databanks

The importance of sharing MD simulation data following the FAIR principles[97] has been widely recognized,[18–25] and databanks are emerging.[25–32] The relevance of quality evaluation of simulation trajectories in databanks regarding technical details of simulations and accuracy of the underlying physical description of the system (force field) has become evident[19,23,26] and such quality evaluation has in some cases also been implemented.[26,28] However, straightforward quality comparisons between individual simulations or force fields within these databanks remain challenging.

The quality of lipid bilayer simulations has been quite extensively evaluated under various conditions,[33–38,44,47,65,98–100] yet determining unambiguously the overall accuracies of different force fields remains still unclear, as exemplified in Table 1. Within the NMRlipids Project (`nmrlipids.blogspot.fi`), we have used the open collaboration approach, inspired by the Polymath Project[101] and open-source software development, to find lipid force fields that would correctly capture the lipid conformational ensembles and ion binding to membranes.[33–35,38,47] So far, we have used the data collected through the open collaboration to evaluate against NMR data the lipid headgroup conformational ensembles and ion binding affinities to membranes in the most commonly used force fields,[33,34,38,47] and to propose the *inverse conformational selection* model for lipid–protein interactions.[47] We are currently using the NMRlipids open collaboration approach and the data collected during the project to build an openly accessible databank of lipid bilayer simulations (`github.com/NMRlipids/Databank`). The NMRlipids Databank will conduct by default automatic evaluations of sim-

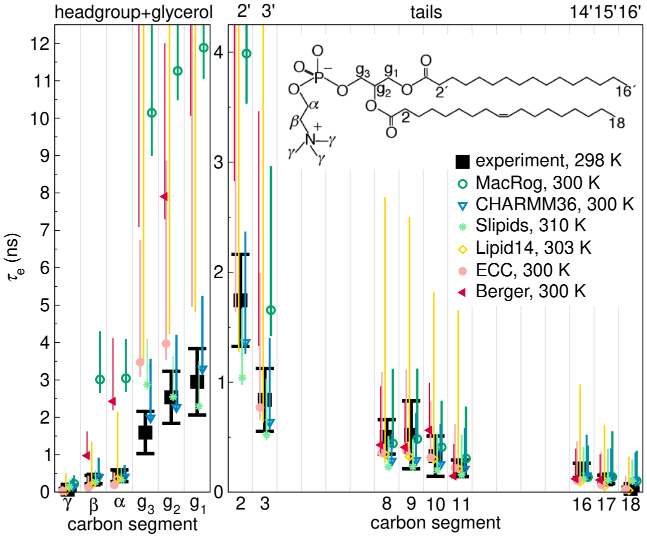

Figure 2: Evaluation of conformational dynamics of lipid from the preliminary NMRlipids Databank[102] against the effective correlation time of C–H bond rotation, τ_e, determined using spin-relaxation data.[103] Figure adapted from Ref. 102.

ulation trajectory qualities against NMR and X-ray scattering data, and enable arbitrary user-defined automatic analyses over the vast sets of MD simulation data.

As an example application of using the NMRlipids Databank to evaluate conformational dynamics of a large set of simulation data, Fig. 2 shows the effective rotational correlation times of lipid C–H bond vectors, τ_e, calculated from all simulations in a preliminary version of the databank:[102] Only Slipids and CHARMM36 force fields are in line with the experimental data, predicting conformational timescales below 5 ns for all lipid segments. Other tested force fields exhibit significantly slower dynamics in the glycerol backbone and headgroup regions, but such discrepancies are not observed in the acyl chain region. This provides further support for the results from the NMRlipids Project indicating that CHARMM36 gives the most realistic description for the lipid headgroup region, while all force fields capture acyl chain region properties with reasonable accuracy.[33,35,38,47]

Another application of the NMRlipids Databank is exemplified in Fig. 3, which shows the area per lipid calculated from all POPC:POPS mixture simulations currently available in the NMRlipids Databank. The area per lipid relates to the lateral density and is commonly used to characterize membrane properties. Most force fields predict a decreased area per lipid

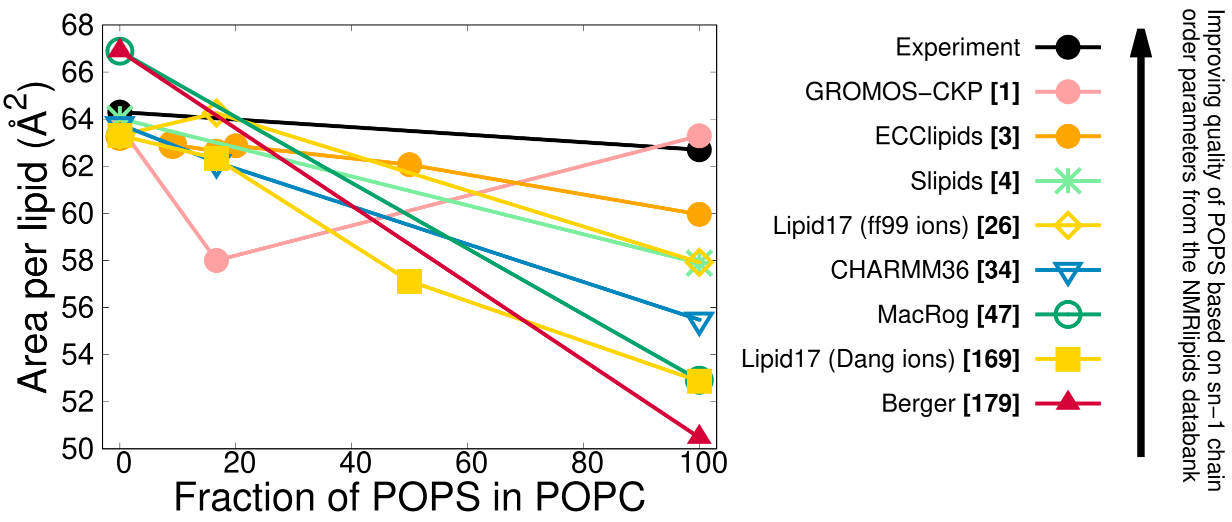

Figure 3: Area per lipid calculated from all simulations of POPC:POPS mixtures at 298 K currently available in the NMRlipids Databank (left) ordered according to the quality of the POPS *sn*-1 acyl chain (right). The number in parenthesis describes the negative 10-base logarithm of the average probability of the acyl chain CH_2-group order parameters to reside within experimental error in a simulation, thereby decreasing with increasing simulation quality. For reference, the values extracted from the experimental X-ray scattering data using the scattering density profile (SDP) model are shown in black.[104,105]

(i.e., tighter membrane packing) with an increasing amount of charged POPS lipids in the membrane, yet the slope of the decrease depends on the force field parameters (Fig. 3). Since the area per lipid is not a directly measurable quantity in experiments, we quality-evaluate the results using the acyl chain order parameters. These depend on the membrane order, thereby being a good proxy for the area per lipid.[35,106] As all force fields predict acyl chain order parameters of pure POPC bilayers with reasonable accuracy, we focused on evaluating the quality of POPS acyl chain order parameters. The qualities of POPS simulations are ranked on the right-hand side of Fig. 3 based on C–H bond order parameters of the CH_2 groups in the *sn*-1 acyl chain of POPS. The quality of POPS simulations systematically decreases with decreasing area per lipid—from the GROMOS-CKP simulation with the largest area per lipid to the Berger simulation with the smallest area per lipid and the worst agreement with experiment. The quality evaluation based on acyl chain order parameters agrees with the comparison of area per lipid values extracted from X-ray scattering experiments using the SDP model[104,105] (Fig. 3). The force field dependent counterion binding affinities can explain the differences in the simulated POPS lipid bilayer areas: The bound ions screen the electrostatic repulsion between charged PS headgroups, thus leading to decreasing area per lipid with increasing binding affinity.[38] In conclusion, all force fields seem to overestimate to varying extent the counter ion binding affinity to POPS lipids, except for the GROMOS-CKP simulations. However, GROMOS-CKP predicts an unexpected minimum of area per lipid for a mixed PC:PS system, which cannot be verified with the currently available experimental data.

These examples demonstrate the power of the NMRlipids Databank in navigating the complex landscape of current lipid MD simulation quality. Notably, none of the current force fields overpasses others in all aspects of quality. For example, CHARMM36 force field best captured the conformational dynamics of lipids (Fig. 2) and the main differences between PC, PE, PG, and PS lipid headgroups, although not all order parameters were within the experimental accuracy.[47] At the same time, CHARMM36 is not the best option for applications where the packing of membranes containing PS lipids is relevant (Fig. 3). Consequently, the most reliable force field for a specific research question must be separately selected. Without automatic quality evaluation enabled by the NMRlipids Databank or a similar resource, performing such evaluation separately for each application would become an overwhelming task.

As exemplified here and in previous studies, already the current version of the NMRlipids Databank helps to resolve issues with contradicting simulation results related, for example, to lipid conformational ensembles, dynamics, membrane packing and ion binding. However, more robust methods and experimental data are still needed for the evaluation of drug and amino acid binding to membranes, which is related to many known controversies listed in Table 1. Some NMR data from lipid headgroup order parameters are also available for such systems,[107] but quantitative comparison with simulations is more complicated for molecules with higher binding affinity. Furthermore, publicly available tools and quality measures enabling quantitative evaluation of MD simulations of other biomolecular systems than lipid bilayers, such as sugars or proteins, are not yet generally available—but there is certainly ongoing work towards providing them.[16,17,108,109] The flexible design of the NMRlipids Databank enables also inclusion of other systems than lipid bilayers in the future.

Automated force field development

As discussed in the above sections, several significant simulation artefacts arise from fundamental issues in force field parameters, such as the lack of electronic polarizability or inaccuracies in water models. Correcting such issues is highly non-trivial because it requires systematic force field reparameterization. Building a new force field or extensively re-calibrating an existing one, is a daunting task owing to its sheer size (thousands of parameters); complexity (non-linear parameter dependencies with significant cross-correlations); the lock-in effect arising from the requirement of consistency with the decades of effort already invested in a particular force field; and the fact that such parameterization work is traditionally done by hand. Consequently, advances are made slowly, with efforts geared towards small yet important parts of the force fields with fewer target parameters, such as water models.[87,110,111]

Recently, however, the rise of machine learning (ML) has made the automated building of predictive models with an extensive amount of parameters a common day practise. This widely lauded development—along with the ever-increasing computational resources and the growing availability of high-fidelity target data from experiments and from increasingly realistic ab initio calculations—seems to have significantly increased interest also in automated force field development. The promise is that high-throughput approaches would revolutionize force field development, making the currently unavoidable extensive human involvement and especially the incremental hand-tuning obsolete.

Automated force field development can be roughly divided into (1) approaches where a machine learning algorithm,[96,112] such as a neural network[113–116] or a kernel-based approach[117] acts as the force field, predicting the forces for a specific configuration of molecules (black-box potentials), and (2) approaches where automated optimization algorithms (including ML tools[118]) are used to find better parameters for existing force field functions[40–43,119] (gray-box potentials). Quality-evaluated open access databanks of MD trajectories can aid both of these approaches, as they guide the choice of optimization targets (by pinpointing the typical failures of existing MD force fields), establish quality standards, and can even provide training data for ML methods in force field parameterization.

(1) Black-box potentials. Typically these methods rely on the bottom-up approach, where a ML algorithm is trained with QM data of small molecules to extract a description of immediate environments of atoms, and to predict the atom-wise energies and forces. Such an algorithm is free from the shackles of the fixed functional forms of the classical force fields and is also intrinsically polarizable. However, it is somewhat limited in describing long-range interactions that cannot be cut off, such as electrostatics. Perhaps the most prominent examples have been those using neural networks, pioneered by Behler and Parrinello,[113] after which several architectures, such as ANI[114,115] and SchNet[116] have emerged.

Although such ML algorithms can be well-scalable to larger molecules[120] so far no truly large-scale or complex (involving many molecular species) simulation has been conducted. Therefore, it is difficult to assess whether black-box potentials can accurately produce complex biomolecular simulation data in line with experiments, even though they do predict the potential energy surfaces, forces, and vibrational spectra with precision comparable to their training data for small molecules. They might suffer from a similar drawback that the classical force fields optimized using similar QM-based bottom-up approaches seem to have, i.e., not correctly probing the intermolecular interactions. Although subject to the same limitations in the types of systems (transferability and generalizability) and the level of theory used in generating the QM data for the training,[121] black-box potentials do not have the same flexibility for empirical error correction (e.g., by partial re-calibration to new experimental data) as classical force fields.

The computational cost of black-box potentials currently lies between those of ab initio and classical force fields.[112,121,122] This does not include the computational cost of training the black box, or creating the QM training data set, the size of which depends on the ML approach of choice. The cost associated with training data can be alleviated by exploiting or creating curated, open-access databanks and by using strategies, such as active learning, to sample the training data efficiently.[115]

(2) Gray-box potentials. There are two standard strategies for parameterizing a classical force field functions for MD simulations, either by 1) computing the function parameters from highly accurate QM calculations for (as large as possible) molecules and molecular fragments and piecing the model together bottom-up; or 2) optimizing the function parameters for molecules or multi-molecule systems directly against target experimental data.

In most of the currently used force fields, these two strategies have been used in conjunction with one another, usually by obtaining the starting point from QM calculations and then re-adjusting some parameters targeting experimental data. While force fields calibrated with this approach during the last decades have reached impressive performance, they also have severe flaws, as outlined in the sections above. The ever growing need for more accurate force fields and more realistic description of the underlying physics such as electronic polarization is a strong incentive to speed up the parameterization process using automated approaches.

Note that the force field function parameters are traditionally thought to have a physical meaning, even when looked at individually (say, a dihedral stiffness or an atom size). When it comes to automated optimization of many parameters simultaneously, however, it can be argued that the physical meaning of individual parameters is blurred, and thus it make only limited sense to make such individual interpretations. Only the collection of parameters as a whole, to the extent they reproduce the targeted behaviour of the simulated system, has such a physical meaning.[123] To emphasize this point, we call such automatically optimized force fields here gray-box potentials.

Automated force field calibration has been done since the late 1990's[124] but has thus far mostly remained in the realm of small molecules; that said, also force fields for complex unstructured biomolecules, such as lipids, have been developed using automated approaches.[43,125,126] Gradient-based minimizations,[41,43,127,128] gradient-free methods such as Simplex[129–131] and evolutionary algorithms,[39,40,42,119,131] surrogate or metamodel strategies,[39,111,132,133] and their various combinations have been used for this purpose (Table 2). In addition to the extreme complexity of the underlying optimization problem, one of the main hurdles preventing such automated approaches seems to be the computational cost arising from the fact that the optimization loop requires running MD simulations on (possibly thousands) of force field candidates. This cost can be alleviated, for example, by thermodynamic reweighing of cached MD trajectories.[43,134] However, it appears that in some cases the gain from reweighing is smaller than the cost of trying the reweighing with insufficient data,[135] and that the reweighing only works reliably with minimal perturbations.

At the same time, the swarm of (possibly thousands) of force field candidates created as a side product of the optimisation loop is not just computational waste but high-quality raw material that can be upcycled to train machine learning algorithms (such as a neural network), to act as a surrogate for the costly MD simulation in probing the optimization landscape,[39,42,133] or to create an expert (machine learning) model that directly predicts force field parameters from experimental data. Additionally, the major speed up by the next generation supercomputing architectures[136] may accelerate further automated parameterization procedures.

The increased automatization of force field parameter development with reduced human involvement underscores the importance of the quality and proper interpretation of target data. Optimal experimental target data have high accuracy and direct connection with simulations. Instead, data requiring approximate models to connect to physical properties should be relegated to an inferior role despite being easier for humans to interpret. For example, for lipid bilayers, the intuitively intelligible area per lipid can be determined only

Table 2: Automated force field calibration studies. Complex biomolecular systems highlighted with light blue. ReaXFF = Reactive force field. EA = Evolutionary Algorithm. GM = Gradient-based Minimization. PSO = Particle Swarm Optimization. LS-SVR = Least-squares support-vector regression EXP = Experiments. QM = Quantum Mechanics. BI = Bayesian inference. SS = Systematic search. NN = Neural network. RW = Reweighting.

authors	year	system	method	target
		Gray-box potentials		
Hunger et al.[124]	1998	Mo(CO)$_3$ compounds	EA	EXP
Norrby and Liljefors[137]	1998	Ethane	GM	QM + EXP
Wang and Kollman[40]	2001	Small organic molecules	EA + SS	QM
Mostaghim et al.[138]	2004	Small organic molecules	EA + PSO	QM
Tafipolsky and Schmid[139]	2009	Metal organic frameworks	EA	QM
Liu et al.[140]	2011	Protein	LS-SVR	EXP
Handley and Deeth[141]	2011	Iron amide	EA	QM
Li and Hartke[142]	2013	ReaXFF for azobenzene	EA	QM
Dittner et al.[143]	2015	ReaXFF for SiOH	EA	EXP
Gao et al.[144]	2015	(CD)Benzene	EA	QM
Betz and Walker[145]	2015	Small organic molecules	EA	QM
McKiernan et al.[125]	2016	DPPC lipid	GM	EXP
Zahariev et al.[119]	2017	Phosphine oxides	EA + Simplex	QM
Wang et al.[146]	2017	Proteins	GM	QM
Dutta et al.[111]	2018	Water	BI	MD
Messerly et al.[134]	2018	Small hydrocarbons	Surrogate + RW	MD
Cesari et al.[128]	2019	RNA	GM + RW	EXP
Oliveira et al.[147]	2020	Haloalkanes	GM + RW	EXP
Krishnamoorthy et al.[148]	2020	2H-MoSe$_2$	EA	QM
Oliveira and Hünenberger[149]	2021	Organic molecules	GM + RW	EXP
Yu et al.[43,126]	2021	Lipids	GM + RW	EXP
Yang et al.[150]	2021	ZrS$_2$	EA	QM
Boothroyd et al.[135]	2021	Organic molecules	GM + RW	EXP
Wang et al.[118]	2021	Small organic molecules	NN + RW	QM
Befort et al.[133]	2021	Hydrofluorocarbons	Surrogate	QM + MD
		Black-box potentials		
Morawietz and Behler[151]	2013	Water	NN	QM
Smith et al.[152]	2017	Organic molecules	NN	QM
Thaler and Zvadlav[153]	2021	Diamond	NN+RW	EXP+QM

indirectly from experiments, and with relatively low accuracy. In contrast, the C–H bond order parameters from NMR have a more direct connection with experiments and higher accuracy, thereby being better quantities to evaluate MD simulation quality.[35] However, care must be taken also when using order parameters as target data. For example, the lack of information on their sign or forking (two C–H bonds at the same carbon having different order parameters) can misguide the fitting algorithm to incorrect values, leading to significant deviation of the conformational ensemble from experiment, see Fig. 4. A similar situation may also appear if interfaces with incorrect surface pressures are used as fitting targets.[62] Nevertheless, the game-changing advantage of automated parameter optimization in such cases is the ease of repeating the fitting procedure with better target parameters when they become available.

Notably, even after carefully considering the various aspects of target data and fitting algorithms, one should be aware that fitting may not lead to a unique solution and that overfitting, e.g., by ignoring the inherent data uncertainty, targeting only one type of data, or severely overweighting one measurable, may lead to an incorrect ensemble being produced by the gray-box force field. Nevertheless, a force field that reproduces the high-quality experimental data with a robust connection to simulations has a higher likelihood of representing the correct, underlying physical behaviour.

In conclusion, the black-box ML potentials and the automated parameterization of classical force fields to create gray-box potentials are promising tools for improving MD models, e.g., by introducing more accurate water models and including electronic polarization effects, improve thus their consistency with experiments, thus paving the way toward more realistic MD simulations of membranes and other biomolecular systems. However, although black-box ML potentials can reach QM-like precision, and methods like gradient-based optimization have consistently shown their advantages in improving the classical force fields, no single approach has yet emerged as clearly superior to tackle this task. For this to happen, practitioners need to keep pushing the applications towards larger and more complex sys-

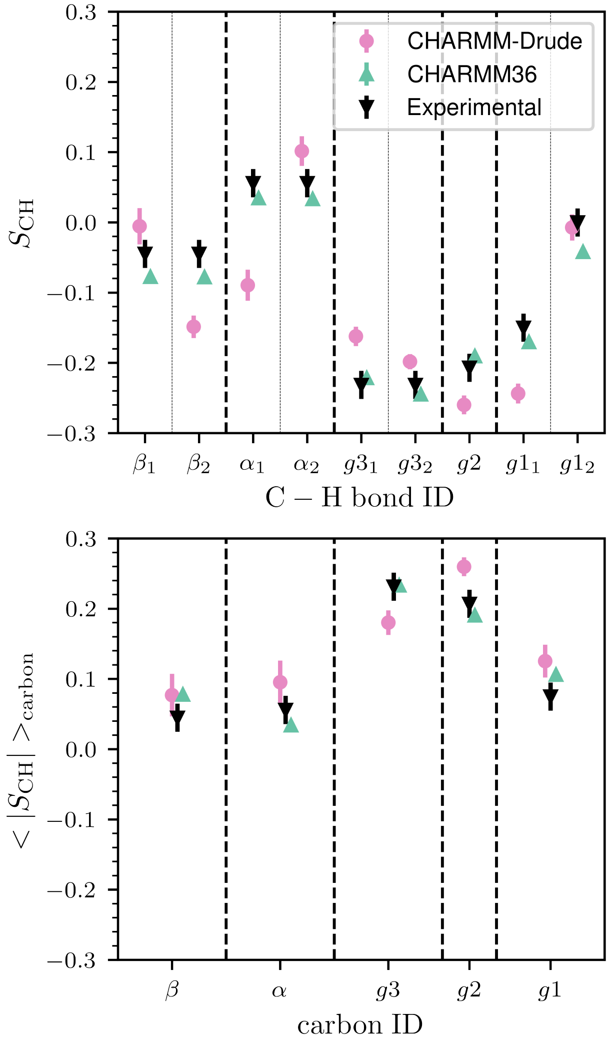

Figure 4: (*top*) Headgroup and glycerol backbone C–H bond order parameters from standard CHARMM36 parameters are close to experiments, while the polarizable Drude-CHARMM predicts forking (inequivalent order parameters S_{CH} for the two C–H bonds in the same carbon) for the headgroup α and β carbons. (*bottom*) Both force fields are close to experiments without the information on the signs and forking, probably because the average of absolute values over hydrogens attached to the same carbon were used as target parameters in the fitting procedure for the polarizable Drude-CHARMM.[88] C–H bonds are labelled as in Fig. 3. Data is taken from the NMRlipids VI project (`github.com/NMRlipids/NMRlipidsVIpolarizableFFs`).

tems. Considering this, we expect that the full potential of these approaches and the most successful methodologies of complex biomolecules will only be revealed in the coming years.

Future perspectives

We are confident that a new era of biological membrane simulations is just about to emerge. It will be characterized by computational data with quantitative relation to existing experiments and providing high fidelity predictions thanks to the following key features: (i) Force fields will be developed systematically based on physically well-justified models, including accurate representation of the aqueous solvent and an effective account for electronic polarization, (ii) Force field development will employ automated parameterization tools making the whole procedure much more efficient and thus feasible within a reasonable timescale, and (iii) A standard procedure for quality evaluation will be established and performed for published simulation data. All these features will benefit from the creation of databanks of MD simulations where quality control against experiments is enforced.

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