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Molecular dynamics simulations as support for experimental studies on surfactant interfacial layers

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Abstract

Surfactants play an increasingly important role across diverse scientific and industrial domains. Gaining a deeper understanding of their molecular behavior at various interfaces is thus becoming ever more essential. Despite considerable advances in experimental techniques, challenges in capturing the detailed molecular-level behavior of surfactants at interfaces persist. In this work, we discuss the potential of combining various experimental methods with atomistic molecular dynamics (MD) simulations in studies of surfactant interfacial layers. MD simulations have emerged as a powerful tool that provides detailed insights into molecular structures and dynamic properties, some of which are inaccessible through experimental means alone. By re-examining existing MD simulation data and directly comparing them with experiments, we illustrate how MD simulations can be used to validate and support thermodynamic models and interpret spectroscopy and scattering data. While combining scattering experiments on Langmuir layers of insoluble surfactants with simulations seems to be well-established by now, we emphasize the growing capability of scattering techniques to also investigate the more disordered Gibbs layers of soluble surfactants. Here, MD simulations can now connect the pressure and adsorption isotherms with the equation of state. In light of the ongoing parallel developments of computational and experimental methods, their synergistic use can be expected to drive future progress in surfactant research.

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Introduction

Surfactants, molecules possessing both hydrophilic and hydrophobic entities, are critical players in various biological and environmental processes and indispensable in numerous industries. Owing to their amphiphilic nature, they have the unique ability to adsorb to various interfaces, where they form distinct layers [1]. There is considerable interest in understanding the fundamental properties of these layers, elucidating mechanisms governing adsorption, formation, and surface relaxations, and linking these findings to practical applications. Investigations involve relating molecular structures to thermodynamic parameters, understanding the area requirements of adsorbed molecules, characterizing interactions between adsorbed molecules, and discerning the composition of interfacial layers formed by various surfactants. Current activities are centered around surface-sensitive experiments alongside thermodynamic and molecular modeling approaches [2].

Studies of surfactants are probably one of the oldest forms of scientific exploration, with early observations on the cleaning properties of plant extracts, and the formation of foams in certain mixtures. The oldest documented evidence of soap-like substance production dates back to around 2800 BC in ancient Babylon [3]. In the modern day, far more advanced experimental techniques offer deep insights into the properties of surfactant assemblies and their organization at the molecular scale. However, despite their advanced capabilities, experimental techniques face challenges in capturing the molecular-level details of surfactant behavior at interfaces. These challenges necessitate complementary approaches to gain further understanding.

To this purpose, numerous thermodynamic models have been developed over the recent decades to link the experimentally most accessible quantities of surfactant layers, such as the surface tension γ, the surface pressure $\Pi = \gamma_0 - \gamma$ (where γ_0 is the tension of the surfactant-free surface), the surface coverage Γ (i.e., the number of adsorbed surfactants per surface area), and the viscoelastic moduli G, which all vary with the surfactant bulk concentration c below the critical micelle concentration (CMC) [4,5]. These models aim to describe the *adsorption isotherm* $\Gamma(c)$, *pressure isotherm* $\Pi(c)$, and the *equation of state* (EoS) $\Pi(\Gamma)$ based on several underlying assumptions. Such descriptions can become complex, especially for ionic surfactants. As pointed out by Peng and Nguyen in their historical perspective article [6], thermodynamic models easily fall short in capturing the more intricate features of adsorption layers, as they cannot take into account the atom-scale molecular structure.

In this regard, classical atomistic molecular dynamics (MD) simulations have emerged as a powerful tool, as they can capture molecular structure and offer a complementary perspective to experimental studies. In MD simulations, the behavior of atoms and molecules is modeled computationally, allowing for detailed exploration of interfacial structures and dynamics at the molecular level [7,8]. By simulating the interactions between surfactant molecules and their surrounding environment, MD simulations provide insights into phenomena that may be challenging to access experimentally. Recent advancements in computational power and simulation techniques have made MD simulations increasingly feasible and accessible. Moreover, enhanced algorithms, improved force fields, and parallel computing have significantly expanded their scope and accuracy.

In this work, we discuss the potential of MD simulations in supporting experimental studies on surfactant interfacial layers. We delve into the motivations behind combining experimental and computational approaches and discuss the challenges and blind spots of experimental investigations in characterizing interfacial layers, and how MD simulations can complement and enhance these efforts. Although various experimental techniques are utilized in the analysis of surfactant layers [9], our discussion will primarily focus on tensiometry in terms of thermodynamic models and surface-sensitive experiments, with a particular emphasis on scattering techniques.

State of the art in computer modeling

Atomistic MD simulations have been extensively used for a while to study the structure and behavior of adsorbed surfactant layers at predefined surface coverage Γ [10–13]. These simulations enable the direct determination of the EoS in terms of $\Pi(\Gamma)$, with the surface tension being readily calculated from the diagonal pressure tensor components [14]. Such calculated EoS can be directly compared with experimental EoS for *insoluble* surfactants [15], typically obtained with a Langmuir–Blodgett trough. When it comes to soluble surfactants, $\Pi(\Gamma)$ is not as easily accessible anymore experimentally, and current all-atom simulations struggle to capture the timescales of surfactant exchange between the interface and bulk phases. For typical soluble surfactants (with chain lengths above 10 carbon atoms), these timescales easily exceed milliseconds, whereas atomistic simulations can nowadays capture timescales only up to microseconds [16,17]. Recent, more advanced MD modeling studies have therefore started to tackle this challenge by examining the transfer free energies to the interface and micelles, and combining them with a self-consistent theoretical framework to obtain a full thermodynamic description of micellization and interface adsorption [17–19].

Apart from atomistic force-field simulations, modeling techniques extend toward both more coarse-grained approaches and methods based on first principles (i.e., *ab initio*). As reviewed by Taddese et al. [16], recent progress in surfactant research has focused on developing, improving, and refining coarse-grained (CG) models in particular. These models are especially useful for studying larger-scale phenomena, such as surfactant self-assembly, micelle formation, and micelle kinetics [20,21]. Yet, as these models oversimplify certain molecular details, they sometimes fall short in accurately capturing the organization of surfactants at the molecular scale [22].

On the *ab initio* side, quantum chemical calculations offer another avenue to analyze adsorbed monolayers and estimate intermolecular interaction parameters [23]. However, full *ab initio* simulations are computationally intensive, leading to the wider use of semi-empirical methods for calculating the thermodynamic characteristics of surfactant layers. These methods have been successful in analyzing small clusters and large aggregate formation in adsorption layers. Additionally, recent studies have combined quantum chemical calculations with thermodynamic models to examine mixed systems of surfactant solutions and the molecular patterns formed at the interfaces [24]. However, *ab initio* methods, while accurate for capturing the effects at the atomic scale, often do not scale well to molecular and supramolecular dimensions. A notable limitation is also their restriction to a relatively small number of molecules due to computational limitations, often excluding simulating the solvent explicitly and relying on approximate approaches. Given these limitations of *ab initio* and CG approaches, atomistic force-field simulations currently seem to represent the best compromise for studying surfactant layers, offering a balanced approach between accuracy and efficiency.

Combining experimental techniques with computer simulations is motivated by several factors. Firstly, experimental results serve to validate simulations or to fine-tune simulation parameters, such as inter-particle potentials or conformational flexibility. Secondly, experiments can provide starting configurations for simulations that might not be reached in simulations (e.g., because of the slow dynamics or considerable free energy barriers). Moreover, simulations can help in understanding experimental results, by clarifying ambiguous data. Lastly, simulations can be used to plan experiments and optimize beam-time usage at large-scale facilities. By simulating the impact of varying parameters, one can predict whether a particular effect is expected to be observed with a given experiment design [25].

MD as a parallel method

The simplest, arguably most common strategy in combined experimental/simulation studies is the use of MD simulations as an independent parallel method, which does not engage in direct quantitative comparisons but rather explores distinct and independent aspects. By simulating the experimental system, MD offers insights into the molecular-level picture, which typically cannot be achieved through experimental efforts alone. These include surfactant conformations, distribution patterns, hydrogen bonding networks, and dynamic behaviors. This approach enables the construction of a more nuanced and comprehensive picture of surfactant layers, their characteristics, and the underlying mechanisms.

For instance, a recent study demonstrated the superiority of the surfactant cocamidopropyl betaine (CAB) over coconut oil diethanolamide in reducing surface tension on low-rank coal [26]. Here, MD simulations unraveled the adsorption mechanisms at a molecular level, pointing to the important role of hydrogen bonds behind the stronger adsorption of CAB. In another recent study, tensiometry measurements demonstrated that a surfactant mixture is much more efficient in reducing oil/water interfacial tensions compared to single surfactant solutions, underscoring the synergistic effects between surfactants [27]. MD simulations corroborated these findings by revealing distinct molecular arrangements of the surfactants at the oil/water interface. The structural analysis emphasized the role of aromatic cation components and $\pi-\pi$ stacking in enhancing synergistic effects and promoting compactness of the surfactant monolayer.

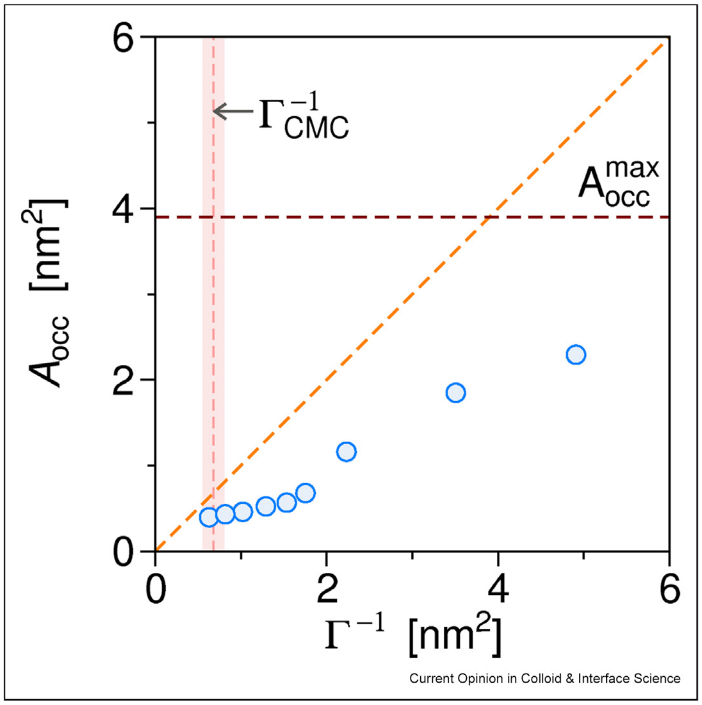
MD as a tool to aid thermodynamic models

Our understanding of surfactant adsorption layers at fluid interfaces has significantly advanced through the analysis of tensiometric, $\gamma(c)$, data and interface-rheological data, supported by thermodynamic models [28–31]. These models have helped in interpreting experimental results by incorporating several molecular parameters, such as interaction parameters and the effective areas per molecule. Within the range of their applicability, they successfully reproduce the concentration-dependent behaviors of interfacial tension and viscoelastic modulus. Yet, as the model parameters are typically fitted to experimental data, ambiguities and redundancy may arise. In this regard, the MD framework can serve to validate and guide these models.

Specifically, multistate models account for the conformational changes of surfactants by assigning s distinct states (indexed $i = 1, \ldots, s$), each with a unique occupied area per molecule, ω_i. These areas range from the minimum area ω_1 (reached at the CMC) to the maximum area ω_s (at infinite dilution) [32]. The mean occupied area, ω, at a given surface coverage is associated with different molecular states as $\omega\Gamma = \sum_i \omega_i \Gamma_i$, where Γ_i is the partial adsorption of state i. With that, ω can be compared with the one determined from a simulation, denoted as A_{occ}; however, there are multiple ways to define A_{occ}. For the sake of illustration, we propose calculating it as $A_{\text{occ}} = \pi r_{\text{exc}}^2$, where r_{exc} is the radius of the exclusion zone (identified as the smallest distance at which the two-dimensional radial distribution function reaches 1/2, thus $g_{2\text{D}}(r_{\text{exc}}) = 1/2$). We demonstrate this principle in Figure 1, where we plot the occupied area against the inverse coverage, Γ^{-1} (corresponding to the mean available area per molecule), extracted from the data of our recent MD study on the nonionic surfactants $C_{12}EO_6$ (hexaethylene glycol monododecyl ether) at an *n*-decane/water interface [17]. At infinite dilution, the occupied area reaches $A_{\text{occ}}^{\max} = 3.9\ \text{nm}^2$, marked by a horizontal dashed line. As adsorption increases (reflected by a decrease in Γ^{-1}), the surfactants progressively occupy smaller areas, resulting in a systematic decrease in A_{occ}, whereby the surfactants also become more perpendicularly oriented. At the CMC, the effective occupied area reaches the minimum value of $A_{\text{occ}}^{\min} = 0.4\ \text{nm}^2$. From the perspective of a multistate model, this trend suggests that states characterized by smaller molecular areas, ω_i, become more prevalently populated at higher adsorption. A diagonal line, $A_{\text{occ}} = \Gamma^{-1}$, is plotted for reference.

Furthermore, the interactions between surfactants at the interface in these models are quantified by the Frumkin constant a (an interaction parameter), where positive and negative values indicate intermolecular attraction and repulsion, respectively [28,29]. Here, too, MD simulations can provide insights into this parameter for a specific system. Namely, a is closely related to the two-dimensional second virial coefficient, $B_2^{2\text{D}}$, which can be extracted from MD simulations of two surfactants at an interface, as described in Appendix A. From the data on $C_{12}EO_6$ surfactants, we estimated the

Figure 1



Occupied area, $A_{occ} = \pi r^2_{exc}$ (computed from the exclusion radius defined as $g_{2D}(r_{exc}) = 1/2$) plotted against the inverse coverage for $C_{12}EO_6$ surfactants simulated at an *n*-decane/water interface. The data were extracted from published MD trajectories in Ref. [17]. The red-shaded region is the predicted value of Γ^{-1} at the CMC. The horizontal dashed line denotes the occupied area at infinite dilution, A^{max}_{occ}, whereas the diagonal dashed line denotes $A_{occ} = \Gamma^{-1}$ for orientation.

interaction parameter to be $a = 0.44$. The positive value indicates effectively attractive interactions between surfactants of this type.

MD and sum frequency generation spectroscopy

In studies of molecular interfaces, sum frequency generation (SFG) spectroscopy has established itself as another indispensable analytical tool. In this nonlinear optical process, two laser beams are combined and generate a new beam at the sum of their frequencies. What makes SFG unique is its ability to exclude signals from the centrosymmetric bulk material, which does not contribute to the second-order nonlinear response, making it highly surface-sensitive. The technique thus provides detailed insights into the vibrational and electronic properties of molecules adsorbed or bound to an interface.

Recently, Khan et al. [33] used SFG spectroscopy to study the spontaneous adsorption of cationic surfactants onto gold surfaces from aqueous solutions. They found that the longer alkyl tail surfactant (C_{12}) forms an ordered monolayer due to strong tail–tail interactions, while the shorter alkyl tail surfactant (C_4) forms a less-ordered monolayer. They additionally conducted MD simulations to provide further support to experimental observations, emphasizing the role of tail length and conformation in monolayer formation. In another recent study [34], MD simulations were combined with SFG and quartz crystal microbalance for the first time to investigate nonionic surfactants at the silica–solution interface. Experimental findings revealed disorder among surfactant molecules, with higher concentrations leading to increased adsorption and ordering of interfacial water molecules. MD simulations were subsequently used to explore potential scenarios of the interaction between water, silica, and surfactants that were compatible with the enhanced water SFG signal. Model calculations highlighted the preference of surfactants for adsorption onto silanol and Si–O–Si bridge sites on silica.

MD simulations can also be used to directly reproduce SFG spectra associated with stretching and bending modes of particular bonds. However, such predictions are only possible by applying specialized force fields that account for anharmonicities in bonded interactions and modeling of induced dipole moments and polarizabilities [35]. Early on, disagreement between simulation-based predictions and SFG measurements was not uncommon. An example includes a challenging interpretation of experimental SFG data, which suggested that interfacial water molecules at charged lipid monolayers were oriented opposite to that predicted by electrostatics (i.e., corresponding to a negative O—H stretch peak) [36], while simulations predicted the orientation consistent with electrostatics (a positive peak) [37]. This contradiction urged more detailed analysis, which ultimately confirmed that the initial simulation predictions were accurate [38,39]. Another case involves the bare air/water interface, where early interpretations of SFG spectra indicated a positive peak at 3200 cm^{-1} for the O—H stretch [40,41], contradicting simulation predictions that no such peak exists [42,43]. Subsequently, more precise SFG measurements validated the simulation-based predictions [44,45].

These examples demonstrate the challenges involved in interpreting SFG measurements and emphasize the critical role of combining SFG spectra with simulations. Looking forward, *ab initio* MD simulations, supported by machine learning techniques, hold promise for refining predictions and understanding of molecular interactions at interfaces [46,47].

MD interpretation of scattering data

Methodological background

Scattering techniques using X-rays or neutrons are among the most powerful methods for the characterization of interfacial adsorption layers because they are sensitive to the molecular composition and capable of probing the atomic, molecular, and supramolecular length scales [48—50].

Small-angle X-ray scattering (SAXS), small-angle neutron scattering (SANS), and wide-angle X-ray scattering are applied to isotropic bulk samples, like vesicle suspensions or oil/water emulsions, where they reveal the sizes, shapes, and interface structures of the dispersed objects, within certain limitations [50,51]. Greater detail with regard to the interface structure is achieved with experiments on oriented single interfaces, where the incident beam with wavelength λ hits the interface at a defined relative angle α, and the reflected or diffracted intensity is measured as a function of the perpendicular component $Q_z = (4\pi/\lambda)\sin\alpha$ of the scattering vector $\boldsymbol{Q} = (Q_{xy}, Q_z)^{\mathrm{T}}$. X-ray reflectometry (XRR) and the closely related grazing-incidence X-ray off specular scattering (GIXOS) technique have a high depth resolution and allow reconstructing surface-transverse electron density profiles, which contain information on the thicknesses of the tail and headgroup regions of the adsorbed surfactants [52]. Neutron reflectometry (NR) is non-destructive and reveals transverse profiles of the scattering length density (SLD), a quantity that is governed by the nuclear composition of the constituent atoms. The depth resolution is lower; however, NR is extremely good at quantifying the surfactant surface coverage Γ when suitable SLD contrast conditions are generated through selective deuteration [53—55]. Another variant of X-ray diffraction from oriented interfaces is grazing-incidence X-ray diffraction (GIXD) [48,52], in which the analysis focuses on the parallel component of the scattered beam (Q_{xy}), offering precise information on the 2D arrangement of molecules and their tilt angles relative to the surface normal.

All these scattering techniques provide intensity distributions $I(\boldsymbol{Q})$ in reciprocal space. Within the kinematic approximation (which applies to reciprocal space regions with not-too-high intensity), such a distribution corresponds to a Fourier transform of the sample structure in terms of its spatial electron density or SLD distribution. In certain cases, $I(\boldsymbol{Q})$ can be decomposed into the product of a form factor $F(\boldsymbol{Q})$, characterizing the shape and internal structure of a scattering object (e.g., an atom), and a structure factor $S(\boldsymbol{Q})$, characterizing the spatial arrangement of these objects. For samples containing multiple types of objects, the intensity can be expressed in terms of the partial structure factors $S_{ij}(\boldsymbol{Q})$ associated with objects of types i and j [56]. Any back conversion of $I(\boldsymbol{Q})$ into real-space structures has to deal with the phase problem and, consequently, a single experimental dataset $I(\boldsymbol{Q})$ can correspond to several real-space structures. Although adjusting the scattering contrast of different constituents (e.g., combining light and heavy water in neutron scattering) can help reduce ambiguity to some extent, the problem is not completely resolved.

Instead of tackling this inverse problem, an alternative approach is thus to focus on the forward problem. Indeed, the analysis of scattering data typically involves parameterized layer models (NR/XRR/GIXOS), particle models (SANS/SAXS), or rod models (GIXD/WAXS). However, the interpretation of the obtained model parameters in terms of molecular configurations and structures remains challenging, especially when the structures exhibit significant disorder, which is the rule rather than an exception in soft matter systems. Particle-based computer simulations, such as MD simulations, are well-suited for a more rigorous approach to this problem. In simulations where all particle positions are known, it is relatively straightforward to calculate the scattering pattern corresponding to an MD-simulated structure and to compare it with experimental data. If the computed and experimental patterns match, this serves as validation for the molecular model. Once validated, the trajectories can be analyzed in detail to uncover in-depth insights into molecular mechanisms, dynamics, and interactions. Post-processing also allows for the extraction of a broad range of quantities of interest from the trajectories, some of which may be challenging to characterize through experimental methods [25].

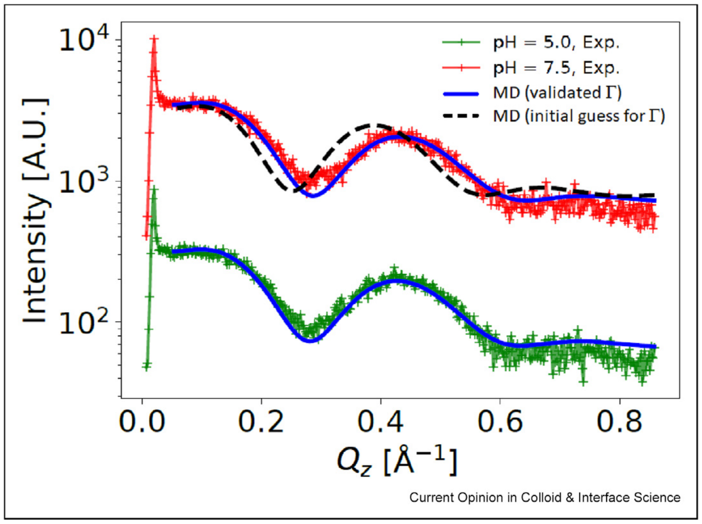
While the concept of combining simulations with scattering experiments is commonplace, it faces its own challenges. A study from 2005 [57] compared MD simulations with X-ray and neutron reflectivity data and found that neither the GROMOS nor the CHARMM22/27 force fields—two very general and widely used force fields at the time—accurately matched experimental results for lipid bilayers. Similarly, McCluskey et al. [22] observed issues with the coarse-grained MARTINI force field in reproducing NR data of lipid monolayers. They suggested that the likely cause is that with one bead representing four carbon atoms, this force field struggles to accurately represent tails containing 18 carbon atoms. In contrast, the united-atom Berger and all-atom Slipid force fields demonstrated better agreement with the measurements. These findings stress the limitations of coarse-grained models in capturing molecular structure and the importance of continuous refinement and validation of all-atom simulation models to improve their reliability in complementing experiments.

Transverse profile from scattering

MD simulation trajectories allow for a simple reconstruction of transverse electron density and SLD profiles of the layers, as was done by Pan et al. in their study on phosphatidylglycerol (PG) lipid bilayers in the form of unilamellar vesicles [58]. They directly compared the form factors from SANS and SAXS to simulated data and employed their developed model for a concurrent analysis of the scattering data with input from MD simulations and volume measurements. They found that PG lipids have larger areas but smaller volumes than phosphatidylcholine (PC) lipids, likely due to electrostatic headgroup interactions. Additionally, while PG and PC bilayers respond similarly to variations in temperature and chain length, they differ in their response to chain unsaturation. Likewise, electron density profiles extracted from MD simulations of lipid monolayers at the air/water interface have been used to model the associated GIXOS curves [59]. These models were then compared with experimental data collected under various pH conditions to fine-tune lipid packing in simulations, as shown in Figure 2, where the agreement served as validation of the simulation model.

Deducing the surface coverage Γ from the electron density profiles in this way is straightforward only for densely-packed layers of lipids or long-chain surfactants, where the layer thickness and Γ are highly coupled. By contrast, extracting Γ of water-soluble surfactants solely from XRR or GIXOS measurements is challenging because of the difficulty in interpreting electron density profiles of sparse, laterally heterogeneous layers. In such cases, MD-based interpretation is particularly useful, as all these effects are captured in the computed electron density profiles (provided that the force fields are accurate). Comparisons between experimentally obtained and simulation-based electron density profiles in the real-space domain enable validating Γ in simulations. Such a validation in simulations of water-soluble surfactants enabled the exploration of other crucial, yet experimentally inaccessible aspects, such as inter-surfactant hydrogen bonding [60]. To the best of our knowledge, the only scattering technique that directly

Figure 2



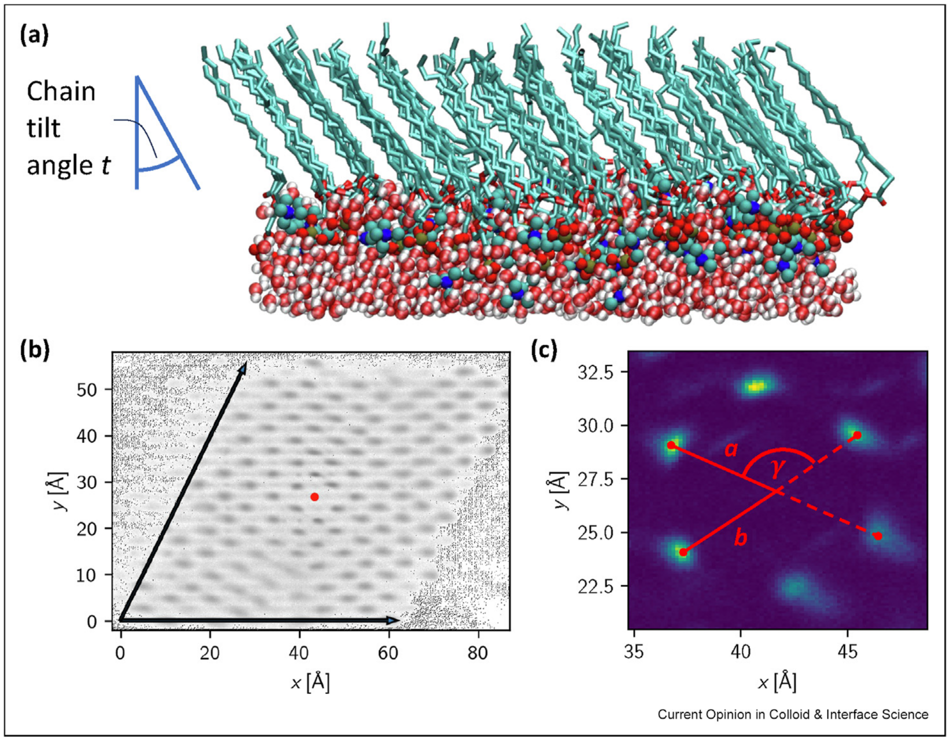
Comparison between experimental GIXOS intensity (data points) and simulations (solid lines) using optimized values of Γ. The dashed black line indicates a simulation result based on an initially presumed value of Γ. The system comprises 20 mol% protonable transfection lipid and 80 mol% zwitterionic phospholipid. Figure adapted from Ref. [59].

yields Γ in an unambiguous manner is NR in combination with air-contrast-matched water [53–55], a poorly accessible and clearly non-standard technique.

Modeling diffraction data from ordered surfactant monolayers

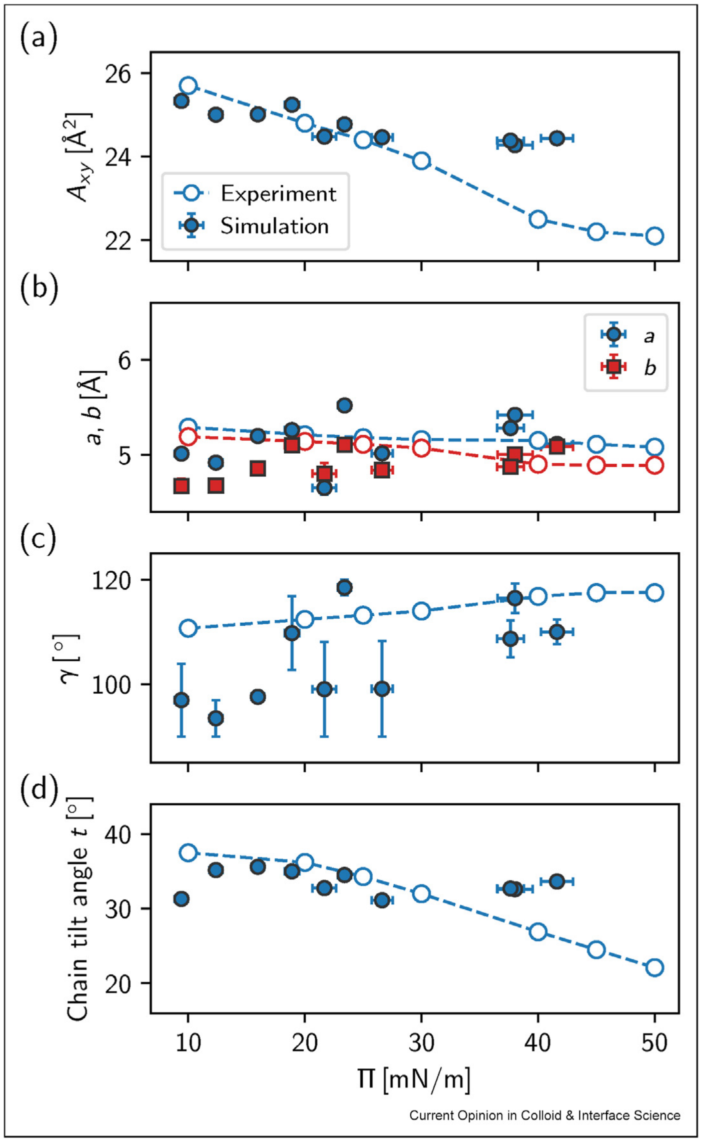
Water-insoluble lipids with saturated alkyl chains tend to form *liquid-condensed* (LC) monolayers with considerable in-plane crystalline ordering that gives rise to sharp and distinct diffraction peaks [52]. Although the two-dimensional crystal lattice is often limited to the alkyl chains and characterized by the unit cell vectors and the chain tilt, sometimes the unit cells can accommodate several whole molecules [61]. Interestingly, diffraction peaks due to in-plane crystalline structures also occasionally occur for Gibbs-type monolayers of water-soluble surfactants [62]. These peaks offer a way for high-precision structural investigations that can benefit from complementary MD simulations. The capability of MD to predict crystalline monolayer structures is shown here for a Langmuir-type monolayer of the well-studied lipid dipalmitoylphosphatidylcholine (DPPC). A simulation snapshot in Figure 3a shows a DPPC monolayer after equilibration at a surface pressure of $\Pi = 10$ mN/m. The simulations were conducted using the force fields and parameters specified in Ref. [63]. The surface pressure, as determined from the pressure tensor [14], was controlled using anisotropic pressure coupling with free lattice angle in the monolayer plane, corresponding to variations in the area per molecule, $A_{\mathrm{mol}} = \Gamma^{-1}$. Like in the experiments, the monolayer forms a chain-crystalline LC arrangement with a considerable chain tilt relative to the surface normal. The parameters of the two-dimensional lattice, as illustrated in Figure 3 and obtained from the chains' centers of mass and average end-to-end vectors, generally depend on Π and are presented in Figure 4. It is seen that the area per chain ($A_{xy} = A_{\mathrm{mol}}/2 = ab\sin\gamma$; panel a), the lattice vector lengths (a and b; panel b), their relative angle (γ; panel c), and the chain tilt angle (t; panel d) are in good agreement with the experimental data obtained as a function of Π [64], although not all trends are fully reproduced with the employed force field. This is not surprising since the used force field was merely optimized to reproduce the density of alkanes and their heat of vaporization [65]. Nonetheless, the qualitative agreement demonstrates the transferability of thermodynamic optimization approaches. Once simulations are experimentally validated in such a way, the trajectories can be used to elucidate atomic-scale phenomena at the

Figure 3



(a) Snapshot of a DPPC monolayer simulation at $\Pi = 10$ mN/m. **(b)** Corresponding histogram of the tail center of mass positions. In the course of the simulations, the position of the box center marked in red is kept fixed, arrows show the corresponding box vectors. **(c)** Extraction of the lattice parameters a, b, and γ.

Figure 4



Parameters of the two-dimensional chain lattice of DPPC versus surface pressure as obtained in MD simulations (present study) and in earlier GIXD experiments [64]: **(a)** area per chain A_{xy}, **(b)** lattice vector lengths a and b, **(c)** their relative angle γ, and **(d)** chain tilt angle t (see Figure 3 for definitions).

headgroups that contribute to the observed lattice, such as hydrogen bond formation [60], headgroup conformations, or ion interaction sites in charged surfactants [66].

Another noteworthy example of how MD simulations can be useful in interpreting scattering data were provided by Zec et al., who emphasized the need for caution with D_2O contamination by hydrogenated molecules in neutron scattering experiments [25]. Using MD simulations of a stack of phospholipid bilayers, they showed how to effectively model the impact of contamination on NR data by rescaling specific SLD components. They demonstrated the ability to discriminate between two types of D_2O contamination: one arising from infiltration of light water (H_2O), and the other from the detachment of phospholipids with hydrogenated tails that form a bilayer, migrating into the surrounding D_2O. Nonetheless, they also noted a certain redundancy, such as the similarity in reflectivity effects observed from adjusting the water SLD and reducing the number of bilayers in the stack.

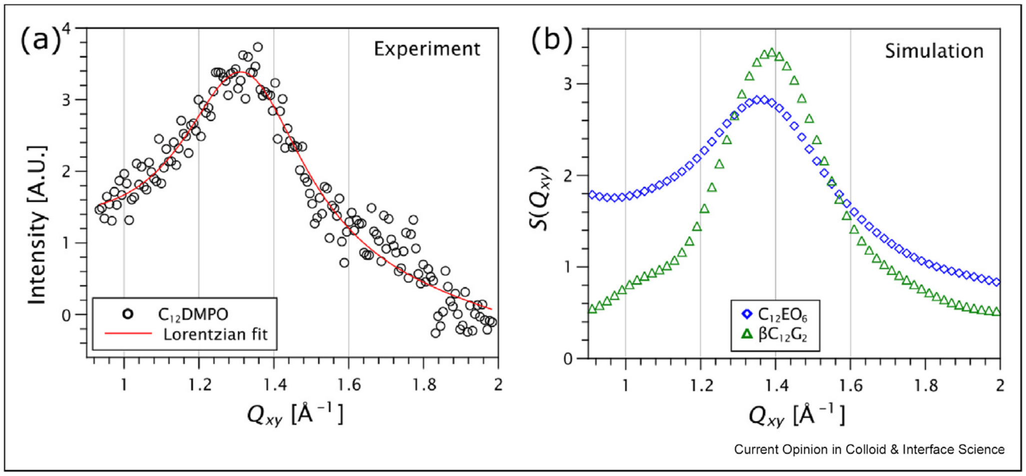
Modeling scattering data from loosely organized surfactant monolayers

GIXD on surfactant monolayers has so far been applied almost exclusively to the 2D-crystalline LC phases of (typically water-insoluble) surfactants with long saturated alkyl chains, which produce sharp diffraction peaks [52,61,62] (see previous section). However, the method has now evolved to the point where it can sufficiently characterize the weaker and much broader correlation maxima associated with the molecular organization in the disordered *liquid-expanded* states, commonly found in Gibbs-type surfactant monolayers (manuscript in preparation by some of the authors).

Figure 5a shows such a correlation peak for the surfactant dodecyldimethyl phosphineoxide (C_{12}DMPO) at the air/water interface at a bulk concentration of 0.5 mM (above the CMC of 0.25 mM, where the surface pressure is $\Pi \approx 43$ mN/m [67]), recently measured at the beamline P08 of storage ring PetraIII at DESY (Hamburg, Germany) with a setup described in Ref. [66]. The data are corrected for the background intensity measured with a bare water surface and integrated over the interval $0 < Q_z < 0.25$ Å^{-1}. The solid line is an empirical Lorentzian fit on a linear baseline, intended to guide the eye. Both the position and width of the correlation maximum represent key layer characteristics related to molecular packing and correlation range, respectively, which lend themselves toward an interpretation with MD simulations. Figure 5b demonstrates that such correlation peaks can indeed be reconstructed from MD simulations. The plot shows the theoretical scattering intensity $S(Q_{xy})$ (diamonds) for $C_{12}EO_6$ at an *n*-decane/water interface at the CMC (where $\Gamma = 1.63$ nm^{-2}), derived from previously published simulation trajectories [17]. Given that the water contribution has been subtracted and C_{12}DMPO has a small headgroup, the measured peak stems primarily from the chains. Therefore, we used the in-plane radial distribution function of all alkyl-chain carbon atoms only for this analysis to ensure maximal comparability between the simulated $C_{12}EO_6$ and the experiments on C_{12}DMPO. Finally, assuming not-too-high Q, the form factor is approximately a constant, $f(Q) \approx$ const, such that $S(Q_{xy})$ can be directly compared to the measured intensity $I(Q_{xy})$. For details on deriving the simulated $S(Q_{xy})$ from the RDF through a 2D Fourier transform, see Appendix B. The resemblance between the experimental and simulation-based scattering intensities in peak positions, widths, and shapes, is striking. However, a direct comparison cannot be made because these are different surfactant types adsorbed to different fluid interfaces. Nevertheless, the power of MD simulations in providing clear interpretations is undeniable, and the prospect of having more relevant experimental data available in the near future is highly anticipated.

The triangles in Figure 5b indicate the MD-derived $S(Q_{xy})$ of the sugar-based surfactant *n*-dodecyl-β-D-maltoside ($\beta C_{12}G_2$) at an air/water interface, measured at the CMC (where $\Gamma = 2.8$ nm^{-2}), based on trajectories from Ref. [60]. The peak is similar to that of $C_{12}EO_6$ at an *n*-decane/water interface, yet it exhibits distinct differences in position, width, and shape. Importantly, the simulations clearly resolve the influence of the surfactant chemical structure and of the nature of the interface on the peak characteristics, which is a prerequisite for a meaningful comparative interpretation of experimental data from different samples.

Figure 5



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(a) Q_z-integrated experimental GIXD intensity of C_{12}DMPO at the air/water interface at 0.5 mM total bulk concentration. Solid line: Empirical Lorentzian fit to the data points. **(b)** Simulation-based structure factor $S(Q_{xy})$ for $C_{12}EO_6$ at an *n*-decane/water interface (diamonds) and for $\beta C_{12}G_2$ at the air/water interface (triangles), both at the CMC as obtained from the in-plane radial distribution function of all alkyl chain carbon atoms (see Appendix B).

In the future, when experimental and simulation data become available for the same systems, it will be beneficial to include all surfactant atoms in the analysis. Alternatively, by examining only distinct subgroups of atoms, MD simulations may enable pinpointing the molecular regions responsible for specific features observed in the experimental peaks. This approach will further strengthen the synergy between experimental and simulation studies, offering deeper insights into the underlying molecular characteristics.

Challenges and limitations in simulations and experiments

It is important to recognize that the rather simple means of comparing simulated and measured scattering curves can sometimes lead to overconfidence. Recently, Zec et al. have reviewed how both experimental and simulation techniques can be prone to various artifacts and misinterpretations [25]. Simulations and experiments face intrinsic limitations, which can sometimes be difficult to identify. One primary concern in simulations is the accuracy and applicability of classical, predefined force fields. This framework often struggles with transferability across different systems or conditions. For example, a force field parameterized for reproducing the density and heat of vaporization of alkanes [65] may not accurately capture the structural behavior of the modeled surfactants, as already seen above. Additionally, computational limitations of feasible time scales and system sizes prevent observing processes with slower dynamics caused by, for instance, high free energy barriers (e.g., slow surfactant exchange between the layer and the bulk) or small driving forces (e.g., slow lipid-phase separation within a mixed monolayer).

On the experimental side, contamination remains a significant challenge. An instructive example concerns surfactant impurities in lab water, which can introduce artifacts, such as the Jones—Ray effect, where the surface tension of water unexpectedly decreases with the addition of tiny amounts of salt [68,69]. Accumulation of impurities at nominally bare liquid interfaces has also been identified with X-ray and neutron reflectometry [70]. These phenomena play less of a role in the presence of sufficiently high concentrations of purposefully added, highly surface-active surfactants or amphiphiles because these dominate the competition for the interface. Nevertheless, rigorous validation of experimental results is important and, here again, simulations can be of great value [69]. Speaking more generally, being aware of these limitations and challenges is crucial for achieving meaningful synergy between the two approaches.

Conclusions

The synergy between experimental techniques and MD simulations has begun to advance our understanding of surfactant interfacial structures substantially. This synergy involves reciprocal exchange where experiments help validate and refine simulations, while simulations provide a microscopic perspective, which is beyond the reach of experiments alone. MD simulations have thus become a powerful tool in complementing traditional experimental techniques.

In this opinion article, we have not aimed for an exhaustive literature review but have illustrated this synergy through selected examples from the more recent literature in this field. Our approach involved re-examining existing MD simulation data with an emphasis on direct comparison with experimental results. We demonstrated how molecular simulations effectively act as virtual experiments that can be used to validate and tune parameters in thermodynamic models and help interpret X-ray and neutron scattering experiments. We argue that scattering experiments, in particular, can benefit from suitably set up complementary MD simulations because the experimental data typically have to be interpreted through forward modeling to reconstruct molecular structures.

While the complementarity between simulations and experimental data has so far mainly been exploited for Langmuir layers of insoluble surfactants, we point out the evolving capability of scattering techniques to also characterize the less ordered Gibbs adsorption layers of soluble surfactants, where we anticipate more research in the future. However, simulation-based improvements in the analysis of experiments can serve also for the refined interpretation of the large body of tensiometry data (in terms of $\gamma(c)$ or $\Pi(c)$) from experiments in the past.

Looking ahead, the continued development of computational techniques, alongside advances in experimental methods, leaves no doubt that the synergy between MD simulations and experiments will continue to drive progress in surfactant research.

Declaration of competing interest

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Data availability

Data will be made available on request.

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Appendix A. Relation between interaction parameter and virial coefficient

The expression for the second-order virial expansion of the surface pressure is given by

$$\Pi = k_{\mathrm{B}}T\Gamma + k_{\mathrm{B}}TB_2^{\mathrm{2D}}\Gamma^2 \tag{A.1}$$

where B_2^{2D} is the two-dimensional second virial coefficient. The virial expansion is applicable in the regime of low adsorption, characterized by low values of Γ.

At the same time, the multistate adsorption model [32] gives the expression for the surface pressure as

$$\Pi = -\frac{k_{\mathrm{B}}T}{\omega_1}\left[\ln(1-\omega\Gamma) + \Gamma(\omega-\omega_1) + a(\omega\Gamma)^2\right] \tag{A.2}$$

where ω is the mean molecular area, ω_1 the minimum molecular area, and a the interaction parameter. This model is applicable across the entire range of adsorption levels. The expansion of the above expression to the second order in Γ gives

$$\Pi = k_{\mathrm{B}}T\Gamma + k_{\mathrm{B}}T\Gamma^2\,\frac{\omega^2}{\omega_1}\left(\frac{1}{2}-a\right) \tag{A.3}$$

Furthermore, in the low adsorption regime, where surfactants minimally interact with one another, each surfactant occupies its maximum possible area, thus $\omega \approx \omega_s$.

Comparing Eq. (A.1) with Eq. (A.3) gives the relation between B_2^{2D} and a,

$$a = \frac{1}{2} - \frac{B_2^{\mathrm{2D}}\omega_1}{\omega_s^2} \tag{A.4}$$

From the results in Figure 1, we assign $\omega_1 = A_{\mathrm{occ}}^{\mathrm{min}} = 0.4$ nm^2 and $\omega_s = A_{\mathrm{occ}}^{\mathrm{max}} = 3.9$ nm^2. Incorporating the two-dimensional virial coefficient from Ref. [17], $B_2^{\mathrm{2D}} = 2.2$ nm^2, our estimate based on Eq. (A.4) yields $a = 0.44$.

Appendix B. Structure factor from MD

Here, we briefly summarize the main steps involved in deriving the structure factor from simulations. The shifted structure factor, $S(\boldsymbol{Q})-1$, and RDF, $g(\boldsymbol{r})-1$, are a Fourier transform pair, following the relation

$$S(\boldsymbol{Q}) - 1 = \rho\int[g(\boldsymbol{r})-1]\mathrm{e}^{\mathrm{i}\boldsymbol{Q}\cdot\boldsymbol{r}}\mathrm{d}\boldsymbol{r} \tag{B.1}$$

where ρ is the average number density of atoms. In our case, where the atoms are arranged in the x—y plane in a laterally isotropic manner, the 3D RDF, $g(\boldsymbol{r})$, becomes a 2D RDF, $g_{\mathrm{2D}}(r)$, which only depends on the radial distance in the x—y plane. The density is then expressed as $\rho(z) = n_{\mathrm{C}}\Gamma\delta(z)$, where n_{C} is the number of C atoms in a tail and Γ is the surface coverage of surfactants. The delta function $\delta(z)$ positions the layer at $z = 0$. Performing the integration over the perpendicular and angular directions, yields

$$S(Q_{xy}) = 1 + 2\pi n_{\mathrm{C}}\Gamma\int_0^\infty[g_{\mathrm{2D}}(r)-1]J_0(Q_{xy}r)r\mathrm{d}r \tag{B.2}$$

where J_0 denotes the zeroth Bessel function of the first kind.

The results presented in Figure 5b were achieved in two steps. Initially, we calculated $g_{\mathrm{2D}}(r)$ (i.e., the RDF with distances projected onto the x—y plane) for carbon atoms within the alkyl tails of adsorbed surfactants. Subsequently, we used Eq. (B.2) to compute $S(Q_{xy})$.

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