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# Simulations of interfacial processes: recent advances in force field development

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Interfacial systems are ubiquitous and important to myriad processes of interest such as protein-protein interactions and catalysis of reactions. Investigating interfacial systems at the molecular level presents unique challenges to both experiments and molecular simulations. The challenges in molecular simulations of interfacial systems range from scalability of quantum simulations to transferability of empirical force fields in classical simulations. In this article, we focus on the advances in force field development to study interfacial systems using protein-surface interactions and heterogeneous catalysis as case studies. We also discuss the emerging role of machine learning in force field development. We conclude by providing our perspective on accelerating the progress in force field development through concerted efforts for data collection and standardization of parameter fitting protocols for extending the force fields to new interfacial systems.

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#### Current Opinion in Chemical Engineering 2018, 23:138-145

This review comes from a themed issue on Frontiers of Chemical Engineering

# Edited by Jim Pfaendtner, Randall Q Snurr and Veronique Van Speybroeck

For a complete overview see the Issue and the Editorial

Available online 11th May 2019

#### https://doi.org/10.1016/j.coche.2019.04.003

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# Introduction

Interfacial systems are ubiquitous and play an important role in every aspect of life — from governing the interactions between proteins to formation of clouds. Behavior of molecules near interfaces is different than in bulk due to the asymmetry of interactions, and can be manipulated to govern various processes. For example, through tuning the interactions between a solid surface, water, and proteins, the surface can be made toxic or non-toxic to living organisms. However, the complexity of water-protein, protein-surface, and surface-water interactions makes it challenging to elucidate the exact knobs that need to be turned to make a toxic or nontoxic surface [1]. This thus, requires detailed molecular level understanding of the processes governing the interfacial behavior. However, interfacial systems present a challenge to both experiments and simulations. In experiments it is particularly challenging to image entities such as proteins, small molecules, and water at interfaces [2]. Often, computer simulations are used in synergy with experiments to fill this gap and elucidate the interfacial behavior of molecules. Most widely used computational techniques include quantum simulations, and *ab initio* and classical molecular dynamics. Computational studies are a powerful tool that have the potential of unlocking the mysteries of interfacial systems; however, there are some key limitations that need to be addressed.

One of the most prominent and recurrent questions relates to the development of the potential energy functions (i.e. force fields (FFs)) used in the simulations to capture the various phenomena relevant to interfacial processes (see Figure 1). Phenomena such as adsorption of molecules to the surfaces, surface rearrangements upon adsorption, effects of surface defects, and chemical reactions on the surfaces need to be captured effectively while keeping the simulations computationally viable to access relevant length and timescales. In this perspective, we highlight some recent advances in FFs addressing these challenges using two interfacial phenomena as examples - protein interaction with surfaces and heterogeneous catalysis. We also discuss the recent efforts using machine learning for FF development. We provide our perspective on the potential role of these advances in furthering the studies of interfacial systems and processes. We note that this is not intended to be an exhaustive review, and thus few selected examples are presented to illustrate the breadth of approaches.

# Adsorption of proteins to surfaces

Carbon nanomaterials, molybdenum disulfide ( $MoS_2$ ), metallic nanoparticles, and polymers are some of the material surfaces that are of both biological and industrial interest in protein–surface adsorption studies [3]. Molecular simulations play a critical role in elucidating the adsorption mechanisms of proteins and in complementing experiments by providing a detailed picture of the adsorbed structures [4,5]. Studies report that the results of protein adsorption behavior can be sensitive to the details



Interfacial systems involve a broad range of processes from the rearrangements of the surface to chemical reactions that all need to be captured in the FFs for simulations of interfacial phenomena.

of the FFs, especially when considering the adsorbed structure [6–8]. For example, Gu et al. [7] observed lesser changes in the secondary structure of proteins (polyalanine, YAP65 WW-domain, and HP35) on a MoS<sub>2</sub> surface when the nonbonded parameters of MoS<sub>2</sub> were tuned to capture the experimentally observed contact angle of water on MoS<sub>2</sub>. Consequently, they concluded that the potential toxic effects of MoS<sub>2</sub> were lower than those predicted using the unmodified FF parameters.

The most common approach to study protein-surface interactions has been to use the available FFs to describe the proteins and surfaces. Most of these available FFs have been parameterized based on bulk properties [9,10]. The usage of general FFs based on chemical equivalency for material surfaces seems reasonable because of the fragment-based approach used in developing such FFs. Nevertheless, the accuracy of the FF in describing the interfacial phenomena needs to be verified [11]. Latour's group investigated this aspect by determining the free energy of adsorption of peptides on self-assembled monolayers (SAM) functionalized with different chemical groups [12]. They obtained experimental values using surface plasmon resonance spectroscopy and simulations results were obtained using non-polarizable CHARMM FF (CHARMM22/CMAP) [13,14]). They found that the simulation values did not match well with experimental results. They thus implemented Dual FF parameters to represent the bulk and interfacial regions separately, which gave better agreement with experimental results. This type of validation and tuning with adsorption free energies can improve the reliability of FFs for interfacial phenomena. We recently assessed the sensitivity of amino acid-graphene interactions to the choice of FF [8]. The graphene carbon atoms were represented by aromatic carbon type of protein FF. We observed that the relative free energies of adsorption of amino acids on graphene were qualitatively similar across different non-polarizable protein FFs, and the trends were consistent with available experimental data. On the other hand, the structures of amino acids in the graphene adsorbed state were more FF dependent. The reliability of the FF used for protein–surface systems will become clearer when more relevant experimental data becomes available. However, access to such experimental data is limited. Thus, currently most studies rely on *ab initio* calculations and physiochemical knowledge of surfaces to parameterize the FFs [3].

It has been contended that polarizability can play a significant role in protein adsorption on surfaces like graphene. This is usually not captured through classical FFs. Thus, various approaches have been proposed to capture these effects while balancing the computational cost of such simulations [15,16]. An example of incorporating polarizability while balancing transferability and computational cost is the polarizable FF, GRAPPA. Developed by Hughes and Walsh [17], GRAPPA captures the potential disruption of the electron densities of carbons in graphene in the presence of ions and other molecules. In GRAPPA, only the graphene atoms are polarizable. The interactions between amino acids (or analogs) and graphene are described using the standard combination rules, where the amino acids (or analogs) are represented by CHARMM22\* [13,18] non-polarizable FF. The cross interaction terms are derived if the adsorption energies and the position of the analog molecules with graphene in vacuum thus obtained are not consistent with revPBE-vdW-DF based density functional theory (DFT) calculations. In a later study [19], Comer's group compared the binding constants of small organic molecules on graphene obtained from simulations using GRAPPA with experimental values. The agreement was moderate. In contrast, better agreement was observed with experiments when the non-polarizable CHARMM36 FF [20] and standard combination rules were used for the same system [19]. This highlights the difficulty in obtaining an accurate description of interfacial phenomena while retaining transferability.

For metallic nanoparticles, the treatment of electrostatic interactions with fixed point charges may not always be valid because of their free valence electrons [3]. Similar to GRAPPA, several polarizable FFs were developed to represent metallic nanoparticles that work in conjunction with non-polarizable protein FFs for protein-metallic nanoparticle systems [21]. An additional challenge with metallic nanoparticles and also mineral surfaces is in developing FF parameters that can also differentiate the selectivity of proteins to the various facets of a given surface. Interfacial force field (IFF) developed by Heinz's group attempts to address this and also improves upon the FF accuracy for numerous metals and mineral surfaces with or without defects [22<sup>•</sup>]. IFF parameters were recently extended to graphene and graphite systems to improve the accuracy of the possible weak  $\pi$ -related interactions of graphene when represented by uncharged Lennard-Jones carbon atoms. IFF is designed to be transferable and compatible with common protein FFs and uses the standard combination rules. Parameters from IFF have been validated against a variety of experimentally available structural and thermodynamic properties of surfaces such as lattice parameters, surface energy, and hydration energy. IFF addresses several challenges but its validation for protein-surface systems require extensive experimental data similar to other FFs.

In addition to the ongoing efforts to improve all-atom force fields for protein–surface systems, coarse-grained (CG) models are in development. Wei and Knotts [23] used Karanicolas and Brooks  $G\overline{o}$ -like protein model and benchmark experimental data of peptide–SAM surfaces reported by Latour's group [12] to develop CG models for protein–surface systems. The resulting CG model that can describe surfaces with tunable hydrophobicity gave reasonable agreement when validated against free energy of adsorption of globular proteins (lysozyme, myoglobin, cytochrome C) on hydrophobic surfaces such as hydroxypatite, and butyl and octyl sepharoses. Brooks's group used a similar CG model and knowledge of the binding affinity of various amino acids estimated from all-atom simulations to develop CG model for protein–graphene [24<sup>•</sup>] and protein– $MoS_2$  [25] systems. The resulting CG model was used for explaining experimental observations and to determine residue level structure of adsorbed peptides.

Modeling protein-surface interactions also requires the ability to differentiate the affinity of a protein for different facets of the solid. In a recent study, Pacella and Gray [26] tested the ability of RosettaSurface to predict selectivity of peptides to various facets and their binding affinity on four mineral surfaces (calcite, brushite, calcium oxalate monohydrate, and mica). RosettaSurface uses a combination of Monte Carlo simulations and energy minimization techniques to determine low energy adsorbed structures of peptides on a surface using implicit solvent [27]. Pacella and Gray used IFF and CHARMM22/CMAP FF [13,14] to describe the mineral surfaces, and the peptide was described by Rosetta parameters. Indirect inferences from experiments were made to rank the preference of peptides to various facets and binding affinity of the peptides for a given facet. While the algorithm made reasonable predictions on the selectivity of peptides to various facets, it had problems with predicting the order of peptide binding preferences for a given facet.

From polarizability to coarse-graining — several approaches have been proposed to capture the details of molecular interactions at play in protein-surface systems. These approaches are indeed applicable to a broad range of interfacial systems beyond protein–surface interactions. One aspect that can play an important role but has not been integrated much into these studies pertains to reactions. These are important when considering reactions mediated by proteins (e.g. enzymatic reactions) and also in cases where proteins might react with the surface (e.g. functionalization of surfaces with peptides). The field where bond breaking and forming has been pivotal and the focus in FF development is heterogeneous catalysis.

## Heterogeneous catalysis of reactions

In heterogeneous catalysis, the catalyst is a solid while the reaction environment is a fluid. Force fields are needed when the fluid environment is a liquid, and thus interacts with the catalyst surface and catalytic species. In this regard, most attention has been focused on aqueous reaction conditions and metal nanoparticle catalysts. Since catalysis involves bond breaking and forming, quantum chemistry must be used to some extent. However, since quantum simulations are more computationally demanding than atomistic simulations, balance is needed. To address this, Getman and co-workers developed a "multiscale sampling" method [28]. This approach uses classical MD simulations to generate configurations of liquid  $H_2O$  molecules at the water/metal catalyst interface and DFT to calculate the system energies [29–31]. In the

MD simulations, interactions between the H<sub>2</sub>O molecules and the metal surfaces/catalytic species are modeled using Lennard-Jones + Coulomb potentials with parameters from standard FFs such as TIP3P [32], UFF [33], and OPLS-AA [34]. Indeed, approaches such as GRAPPA or IFF can be used in these MD simulations. However, as pointed out by Steinmann et al., interactions between water and metal catalyst surfaces can also be chemical in nature and thus atomistic simulations can be incomplete for modeling the interfacial H<sub>2</sub>O structure. To address this, they developed the GAL17 FF, a DFT-based FF designed to improve the solvation free energy at Pt interfaces [35]. GAL17 FF describes chemical interactions between H<sub>2</sub>O/Pt(111), by means of an anisotropic potential, which describes molecule-surface interactions as a function of the xyzcoordinates of the molecule in relation to the surface capturing the "surface corrugation" effects that influence the interaction. GAL17 can be combined with other wellestablished FFs for H<sub>2</sub>O, such as TIP3P and TIP4P, in the MD simulations in order to model H<sub>2</sub>O/Pt interfacial phenomena. Such an approach could be beneficial in describing facet dependence of protein-surface interactions. The main challenge in developing such anisotropic potentials is the parameterization, since a general approach for developing FFs at interfaces has not been established.

Even with improved FFs, modeling bond breaking and forming in catalysis still requires quantum methods. unless reactive FFs can be developed. Theoretically, if a reactive FF could be developed that could accurately model the bond breaking and forming processes that occur on the catalyst surface, then the entire system could be simulated in MD. Reactive FFs such as ReaxFF [36] could serve this purpose. ReaxFF parameters are obtained based on training sets generated from quantum calculations and have been applied to a variety of gas and liquid interfaces at solid catalyst surfaces [37<sup>•</sup>]. However, challenges associated with accuracy and parameterization have hindered the wider adoption of reactive potentials for modeling catalytic phenomena at fluid/solid interfaces. For one, producing the training set of DFT data is time- and cost-intensive. For example, to study the Pd/ O<sub>2</sub> interface with ReaxFF, Senftle et al. developed a training set comprising bulk Pd metal as well as Pd oxides [38]. The Pd metal included three different surface facets at various coverages of atomic oxygen — coverage is equal to the number of species chemisorbed to the surface divided by the number of surface metal atoms. Kinetics of O<sub>2</sub> dissociation were computed on the various facets and coverages. Computing kinetic quantities on metal catalyst surfaces is cost intensive in itself, having inspired a subfield of "computational catalyst screening and design," which aims to reduce the cost of studying catalytic reactions by estimating kinetic quantities based on thermodynamic quantities [39]. Incorporating an interacting fluid phase would certainly add to the computational expense [81]. For two, since ReaxFFs are parameterized from DFT data, they could potentially inherit the limitations of DFT. For instance, the ability of DFT to accurately capture non-covalent interactionssuch as dispersion— [40,41], and its ability to calculate the electronic structures of fluid phase molecules is debated [42]. To address issues with the DFT description of dispersion, approaches such as the D2 [43] and D3 [44] methods of Grimme have been developed. The DFT-D3 method has been shown to quantify dispersion effects at metal surfaces efficiently and accurately [45-48]. However, even with improved descriptions of dispersion, parameterization of FFs from DFT data may miss key phenomena such as polarization. We have recently demonstrated that polarization effects at metal/H2O interfaces can significantly influence the free energies of adsorbed species [49]. Force fields including such interactions might thus be needed. For example, the multipole expansion method breaks an interaction energy down a priori into contributions from dispersion, electrostatics, and polarization, allowing each one to be fit individually [41,50]. Further, charge equilibration methods, which alter the partial charges on atoms based on their interaction environments [51,52], could improve the ability of FFs to capture non-covalent interactions (e.g. polarization or induction) in interfacial phenomena. Such methods can be applied to reactive FFs as well [53,54,55<sup>•</sup>].

### **Conclusions and outlook**

The examples discussed illustrate the broad range of phenomena that need to be captured in the FFs to study interfacial processes in molecular simulations. It is desirable to have FFs that can describe structure and dynamics of both molecules adsorbed to the surfaces as well as the surfaces themselves in various environments. Furthermore, the FFs need to be transferable and computationally feasible. This is clearly a rather challenging goal to achieve. There has been commendable progress in developing such FFs; however, the efforts involved in parameterizing FF are rather resource consuming. Furthermore, the limited experimental results of molecular structures near surfaces makes it challenging to validate the results from simulations. Thus, for further progress in FF development it is desirable to have approaches that can enable fast reparameterization of FFs or development of new ones driven by availability of additional experimental data and extension of interfacial studies to new systems.

Machine learning (ML) has found a valuable place in FF development [56]. The attraction to these is primarily grounded in the fact that they do not need to be limited to standard functional forms of potential energy functions. This is particularly attractive for reactive systems, which can be difficult to represent with simple equations, since in essence, representing a chemical reaction with a force field is attempting to represent a non-continuous phenomenon with a continuous functional form. They also provide potentially quick pathways to go from detailed





Illustration of customizable FF for interfacial systems using databases containing experimental and *ab initio* data, and code repositories with standard protocols to generate FF parameters. q,  $\alpha$ , and  $\mu$  refer to point charge, polarizability, and dipole moment, respectively.  $\sigma$  and  $\varepsilon$  are Lennard-Jones parameters.

(and expensive) quantum calculations to more atomistic (classical) potential energy functions. Given the challenges of constructing potential energy surfaces with quantum-level accuracy, several studies have focused on the composition and morphology of the interfaces themselves [57,58,59°,60-62]. However, Hakouri et al. [63] and Ulissi and co-workers have begun to use ML to determine binding sites and geometries of catalytic species [64,65,66]. Many-body interactions can also be incorporated to improve accuracy of FFs (which are traditionally focused on pair interactions) through ML methods. This has been demonstrated for developing water models [67]. Theoretically such ML approaches could be coupled with FFs such as GAL17 and approaches such as multiscale sampling to model phenomena at liquid/solid interfaces.

While the current approaches provide a strong platform for simulations of interfacial systems, the key bottlenecks are in validating the results and extending the FFs to novel systems. The validation limitation can be addressed as more experimental data becomes available. For the rapid extension and updating of FFs, it is desirable to streamline the data acquisition and parameter fitting protocols for generating FFs (see Figure 2). We can imagine constructing databases of experimental properties for various materials and detailed quantum calculations that can be used for validation as well as development of FF parameters. In synergy, we can build repositories of codes that provide standard protocols for obtaining FF parameters from the input data. These protocols would include both ML and non-ML based methods. This would be followed with simulations, validation and refinement of the FFs parameters, if needed. Access to such streamlined approaches and databases can greatly reduce the time and cost of FF development and result in rapid community-based growth of FFs for interfacial systems. Furthermore, it can assist in developing approaches for quantifying systematic errors that are typically difficult to identify. These systematic errors can arise from approximations in the highest resolution data (e.g., approximations made in DFT calculations) as well as from errors in the experimental data that is used to validate the FF. Recent efforts to overcome this have utilized Bayesian approach to identify the FF parameters while accounting for the errors in the reference data. [68,69] Additionally,

the errors from overfitting, which arise from excessively complex FF functional forms, can be addressed by using regularization-based techniques [70,71,72°].

Foundations for platforms as envisioned in Figure 2 are already in place through the various efforts for materials databases [73,74] and code sharing [75–78,72<sup>•</sup>] that have come online in recent years. A recent effort towards such a platform for biomolecular systems with a focus currently on small molecules is the Open Force Field (OpenFF) [79]. OpenFF provides an open source and open data framework for sustainable and extensible automated force field improvements. It combines several approaches to make this process efficient and robust — Bayesian framework for optimization of the functional form of a potential, regularization-based techniques to address overfitting and avoiding atom type proliferation for increased efficiency [80]. Furthermore, integration of the new FFs with existing simulation software will facilitate the widespread use of the FFs. Indeed, with such databases and information sharing questions related to data curation, data quality and reproducibility will have to be tackled. Combining such rapid FF development with advanced sampling techniques, and greater computational resources have the potential of accelerating simulation-enabled discoveries in interfacial systems.

#### Conflict of interest statement

Nothing declared.

#### Acknowledgment

SD and SS acknowledge the financial support, in part, by the Defense Threat Reduction Agency (HDTRA-1-16-1-0023). PJMM, RBG, and SS acknowledge financial support from Clemson University's R-Initiative Program under the CU FELLOWS program. The content is solely the responsibility of the authors and does not necessarily represent the official views of Clemson University.

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