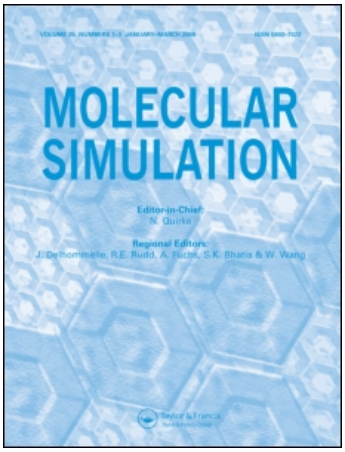

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Atomistic simulations of the interaction between lipid bilayers and substrates

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Atomistic simulations of the interaction between lipid bilayers and substrates

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Many modern biological applications involve the interaction of lipid bilayers with a substrate. Although free bilayers in solution have been studied extensively, the influence of a substrate on the complex dynamic behavior of a supported lipid bilayer (SLB) is not fully understood. We present fully atomistic molecular dynamics simulations of a lipid bilayer supported on α-quartz substrates with explicit water molecules. The results show an equilibrium separation distance of 33–35 Å between the lipid and substrate for both bare and hydroxylated quartz substrates, in excellent agreement with experimental measurements. The bilayer adhesion energy is found to be 30 mN/m on a hydroxylated α-quartz surface and 50 mN/m on a bare α-quartz surface, higher than experimental measurements of both free and fixed bilayers.

Keywords: Supported lipid bilayer; Lipid bilayer; Substrate; Surface; Interaction energy; Adhesion energy

1. Introduction

Supported lipid bilayers (SLBs) play an important role in many areas of biological and pharmaceutical research, such as signaling and transport across cell membranes, and high throughput screening for drug discovery [1–3]. Due to their technological importance, much research is aimed at understanding the structure and dynamics of these systems. Most work reported in the past has been experimental in nature [4–6]. Theoretical and computational research on these systems has been restricted to thermodynamic, continuum formulations of SLBs [7,8]. A perspective of these systems at the atomic level is crucial in the understanding of the nature of SLBs and the fundamental forces that govern the interaction between the lipid membrane and the substrate. In this paper, we describe explicit atom molecular dynamics (MD) simulations of a SLB composed of a common phospholipid, dipalmitoylphosphatidylcholine (DPPC).

Lipids are surfactant molecules which can be described in terms of a hydrophilic head group and a hydrophobic tail. Above the critical micellar concentration, lipids in aqueous solution spontaneously form vesicles and micellar structures [9]. Such vesicles can rupture upon contact with a surface, providing one pathway to the formation of supported bilayers [10,11]. These bilayers are immobilized on a solid substrate typically by weak adsorption, which involves electrostatic and van der Waals forces. Being flexible in nature, the bilayers also undergo thermal undulations that significantly affect their interaction with the substrate. The interaction energy between bilayers and substrates have neither been measured experimentally, nor computed numerically. Such measurements do exist for the forces between two free bilayers in solution. There is thus a gap in our knowledge of the forces that describe the bilayer-substrate interaction at the fundamental level.

SLBs are difficult to study from a modeling perspective for a number of reasons. The dynamical fluctuations of the SLBs cover a wide range of length and time scales, and require small time steps, long durations, and large system sizes to capture. The complex nature of the interactions of lipid molecules with one another and with the substrate and solvent molecules make it difficult to treat them with existing models of free lipid bilayers in solution. Specifically, the interaction forces between organic molecules and oxide surfaces are not well characterized in current force field models. It is also challenging to include soft matter systems like bilayers in the same framework as inorganic substrates, especially at the atomistic level. We have found no previous work modeling SLBs in atomistic or molecular detail.

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The closest approximations to SLBs reported in peer-reviewed literature include MD simulations of surfactant molecules interacting with surfaces [12], and of a DPPC monolayer on a self assembled alkane thiol monolayer [13]. These simulations did not have to deal with the development of force fields that govern the interaction of lipid bilayers with inorganic substrates like silica. In addition, neither study addresses the computation of an interaction energy between the macroscopic surfaces.

The aim of the work presented here is two-fold: (1) to develop a technique for performing explicit atom MD simulations of DPPC bilayers supported on an inorganic substrate, and (2) to compute the interaction energy between the lipid bilayer and substrate as a function of their separation, i.e. the force-distance curve between these surfaces. The simulation methodology is presented in Section 2 and the results for interaction energy are discussed in Section 3. In Section 4, we discuss the relevance of these results and their role in a larger computational framework, followed by our main conclusions.

2. Details of atomistic simulation

We use explicit atom MD in our study of supported bilayers. This technique has been successfully used in the past in studies of free lipid bilayers in aqueous solution [14,15]. With this approach, we capture the bonded and non-bonded interactions between atoms at a fundamental level. Although such simulations of biological systems are often computationally limited to small sizes, we can capture the dynamical behavior of these systems at the smallest end of the spectrum of length and time scales. Since macroscopic properties arise from the ensemble behavior of individual atoms, MD allows us to extract the macroscopic interaction energy between the bilayer and the substrate using an atomistic perspective.

When formulating an approach for simulating a SLB system, several challenges become apparent, the biggest of which are:

1. Development of self-consistent force fields for the lipid-substrate-water system.
2. Choice of the appropriate ensemble to correctly simulate soft biological matter with hard substrates.
3. Allowing the bilayer to approach its equilibrium separation from the substrate when lateral periodic boundary conditions are used.

We describe each of these points in detail below.

Very few simulations have been reported that study the interactions of biomolecules like proteins with inorganic oxide substrates such as silica glass [16]. A few models for the interatomic potentials of lipid molecules have been widely used in the literature. These are the CHARMM [17] model for fully atomistic representations and AMBER [18] or GROMOS [19] for united atom representations of the lipids. Their abilities to reproduce experimental measurements have been examined thoroughly, and some have been tuned to improve the agreement with experiment [20]. These models have been developed to work with either the SPC or TIP3P model for water. Several groups have studied the interaction of water at oxide surfaces and have developed potentials accordingly. For oxide-water potentials, many of the present-day models have been derived from Sanders' three-body potential [21], where the two-body short-range interaction is of the Buckingham form. In order to incorporate the Lennard-Jones (LJ) form of potentials for water molecules, these models either re-parameterize all of the two-body interactions into a LJ form [22], or treat water-oxide interactions with a Buckingham form and water-water interactions with a LJ form [23]. Others have developed potentials based on the Born-Mayer-Huggins (BMH) form [24] or a modified BMH potential with three-body terms [25]. Another option is the PN-TrAZ potential [26] which uses a modified exp-6 form for both the oxide and water phases. Although much effort has been invested in developing force fields for lipids in water, and separately for oxide surfaces in water, no force fields have been optimized to study the interaction of lipids with oxide surfaces.

It is relatively straightforward to describe the electrostatic interaction between the bilayer and substrate since all of the above atomic models account for electrostatic energies using the standard Coulomb expression for the energy between two point particles. Capturing the correct van der Waals interaction is more difficult because there is no single expression to describe this interaction in all cases. Although most force fields for oxide materials use an exponential-6 form, the ClayFF force field [27] utilizes the same 12–6 form for the van der Waals potential as the all-atom CHARMM [28,29] force field employed by us to simulate the lipid bilayer. The cross terms between lipid and substrate can then be obtained using the standard Berthelot mixing rules between the two force fields. This is not as accurate as calculating the cross terms from *ab initio* simulations of segments of the bilayer-substrate system. However, the zwitterionic nature of the head groups and the presence of a water layer between the bilayer and substrate suggest that the short-range van der Waals interactions between bilayer and substrate are secondary to the long-range electrostatic interactions. Thus, using mixing rules for the van der Waals cross terms is a reasonable approximation. For the simulations presented here, we use the all-atom CHARMM force field to describe the lipid bilayer, the ClayFF force field to describe the substrate, and Berthelot mixing rules to describe the interaction between the two. The water molecules are described using the flexible SPC model [30,31] to allow for variations in the bond angle due to the presence of the substrate [32]. No ions are present in the solution.

Simulations of lipid bilayers have typically been performed in either the constant pressure (NPT) or constant volume (NVT) ensembles. Simulating lipid bilayers in the NVT ensemble requires accurate parameters for certain bilayer properties such as the area per lipid,

but the range of these parameters in the literature is quite broad. It has been shown that such simulations can lead to a high positive or negative internal pressure or a large surface tension due to this uncertainty in the parameters describing the bilayer [33]. Although a constant pressure ensemble can be used to maintain zero tension on the bilayer in bulk water, this approach cannot be used here due to the overpowering cohesive energy of the silica substrate. The rigidity of the substrate causes the system energy to be very sensitive to volume changes that cause it to stretch or compress. The system would thus adopt the equilibrium areal density of the substrate regardless of the configuration of the bilayer. Instead of simulating the bilayer in the NPT ensemble, we fix the areal lipid density of the bilayer to match the value obtained from NPT simulations of the bilayer in bulk water [34]. We then perform our simulations in an NVT ensemble at a temperature of 323 K, which is above the chain melting temperature for DPPC. This approach offers a reasonable compromise despite the suppression of areal fluctuations of the bilayer.

Adding a substrate to a lipid bilayer simulation creates complications other than the pressure constraints mentioned above. It is difficult to exactly match an integer number of lipid molecules in the bilayer to the lattice spacing of the α-quartz substrate considered. The starting coordinates for the atomistic lipid bilayer are taken from the configuration provided by Feller [35], which contains 36 lipid molecules per monolayer equilibrated at zero surface tension in the NPT ensemble [34]. We impose periodic boundary conditions in the x and y directions to simulate an infinite bilayer (figure 1), and add a substrate at the lower x–y face of the simulation box. The substrate is modeled by cleaving the bulk α-quartz structure obtained from X-ray crystallography [36] along the [100] plane. This generates a slab that is six layers thick in the z direction, with the [100] surface facing the solvent. In the case of a hydroxylated substrate, hydroxyl ions are added to the [100] surface to produce a surface hydroxyl density of 7.9 OH/nm^2. The substrate has lateral dimensions of 49.2 × 48.6 Å, these values being the closest match to the bilayer's lateral dimensions for an integer number of substrate atoms. A slight difference in periodicities of the substrate and bilayer prevents us from exactly matching these simulation box dimensions to the equilibrated lateral dimensions of the bilayer. The resulting area per lipid is 0.66 nm^2, which is slightly less dense than the frequently quoted experimentally measured value for DPPC bilayers in the fluid-like L_α phase without a substrate (0.629 ± 0.013 nm^2/lipid [37]). Water molecules are added randomly in the remaining empty regions of the simulation box. The simulations contain 72 lipid molecules and 5985 water molecules, with a total of 29,745 atoms including the hydroxylated substrate and 29,475 for the bare substrate system. The SLB system is non-periodic in the z direction (perpendicular to the substrate), yet periodic boundary conditions generally must be used to efficiently calculate the long-range

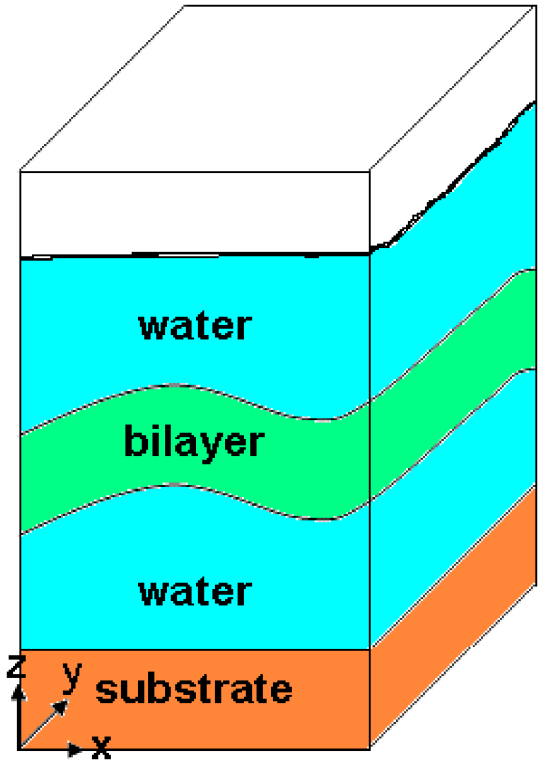

Figure 1. Schematic of supported lipid bilayer simulation cell.

contributions to the electrostatic interactions. Consequently, periodic images of the substrate must be prevented from interacting with either the bilayer or the substrate. To address this, a vacuum layer is added above the solvent to prevent van der Waals interactions between the solvent and the image of the substrate. Long-range electrostatic interactions are calculated using the PPPM algorithm [38]. Applying the slab geometry in the LAMMPS code [39], the system volume is extended by a factor of 3.0 in the z direction only for the electrostatic force calculation. This avoids interactions with the periodic images above and below the simulation box when calculating electrostatic interactions.

The third challenge listed above arises when we attempt to vary the distance between the bilayer and substrate. The use of periodic boundary conditions in the x and y directions allows us to simulate a bilayer of infinite extent, and has worked almost seamlessly when studying bilayers in bulk water [40–43]. These boundary conditions impose the restriction that water molecules can move from one side of the bilayer to the other only via permeation through the bilayer. The rate of water transport through a pure DPPC bilayer is essentially zero at the time scale of these simulations. In a real system, changes in the bilayer-substrate separation are accompanied by the movement of water molecules from one side of the bilayer to the other, which is made possible by the finite size of the bilayer. Since that option is unavailable in our computational system, our bilayer would essentially remain fixed at the initial separation. Moving the bilayer closer to the substrate by a specified distance would result in an

increased pressure in the sandwiched gap region and decreased pressure above the bilayer. Since these must be balanced, this would require a Grand Canonical approach to maintain the chemical potential in these regions by adding and removing water molecules [44]. However, such an approach would influence the dynamical behavior of the bilayer. It would also be computationally burdensome to simulate a sufficient number of molecule insertions into the dense liquid phase. Hybrid MD-Monte Carlo methods are an option that may be feasible in the future. We adopt a different approach in varying the bilayer-substrate separation. Instead of ensuring the correct distribution of water molecules for a specified separation, as is done in the Grand Canonical approach, we specify the number of water molecules above and below the bilayer. The resulting pressure differential allows the bilayer to adjust its separation from the substrate for the specified distribution of water molecules, typically within a few picoseconds. The bilayer-substrate separation is increased by taking water molecules from the bulk region above the bilayer and adding them to the gap region. Likewise, the separation is decreased by moving water molecules from the gap region to the bulk region. Using this approach, the separation is varied from 55.4 to 4.8 Å for a total of 11 simulations. The separation is defined as the distance between the average position of the nitrogen atoms on the lower leaflet and the first layer of silicon atoms on the substrate. This procedure for varying the separation distance ensures that the total number of water molecules in the simulations remains constant, and that any change in energy is due to the change in the bilayer-substrate interaction. The simulations are performed using the LAMMPS code [39]. The equations of motion are solved using a multiple time step second-order symplectic integrator (RESPA) [45] with time steps of 0.5, 1.0, 2.0 and 4.0 fs for bond, dihedral, pair, and k-space interactions, respectively. All interactions except the long-range Coulomb interactions are truncated at 12.0 Å with a potential shift function applied between 10.0 and 12.0 Å. During the simulations, the bottom three layers of the substrate are frozen while the top three layers along with the water and lipid molecules are maintained at 323 K using a Nose/Hoover thermostat with a temperature damping parameter of 100 fs. Each system was run for roughly one nanosecond of physical time, which required 80 h on eight 2.4 GHz AMD64 processors.

3. Results

A snapshot of a simulation showing an SLB with a gap spacing of 20 Å between bilayer and substrate is shown in figure 2. From this figure, one can see that the polar headgroups of the lipid molecules are completely solvated by the water molecules, but there is no water penetration into the hydrophobic tail groups. The average thickness of the bilayer, defined as the distance between the average positions of the nitrogen atoms in the lower and upper leaflets, is 39.4 Å and remains consistent as the distance between bilayer and substrate is varied. This is close to the value of 40.6 Å obtained from united atom simulations of a DPPC bilayer at the same temperature [46].

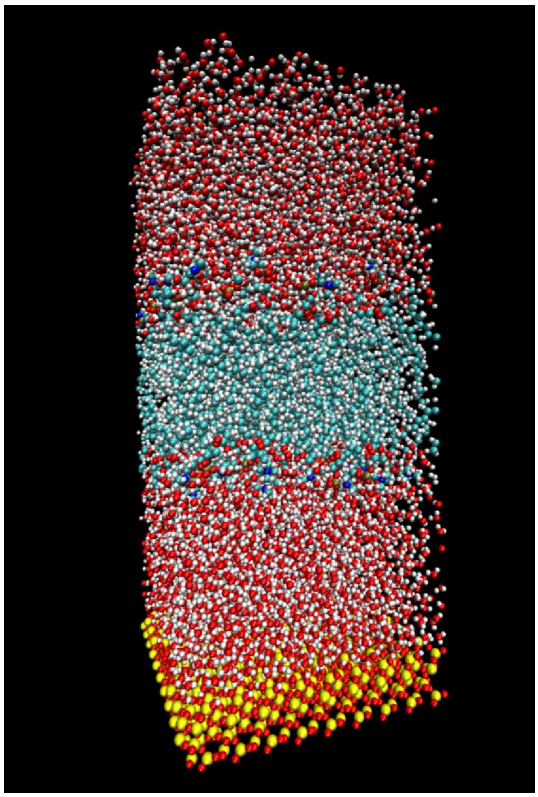

Figure 2. Simulation snapshot with a 35 Å gap separation between the lipid bilayer and quartz substrate. Nitrogen and phosphorus atoms of the head groups are shown as blue and gold spheres, respectively. The carbon and hydrogen atoms, mostly comprising the lipid tails, are cyan and white. Silicon and oxygen atoms in the substrate are yellow and red. For clarity, atoms are not to scale (colour in online version).

For each simulation, the total energy is recorded every 0.2 ps for a total simulation time of up to 1.2 ns. Roughly, a third of this time is required for the system to reach equilibrium. The remaining data is averaged to give the total system energy for a given gap separation. Using this approach, the total energy is extracted for several separations. Figure 3 shows the change in total energy for both the bare and hydroxylated surfaces as a function of separation distance as the bilayer is moved in from a maximum separation distance of 55.4 Å. The total energy gradually decreases as the bilayer approaches the substrate, eventually reaching the minimum. The minimum in the energy curve sets the equilibrium separation at 33–35 Å for this system. This is in excellent agreement with experimental measurements of SLBs [47]. A gradual increase in the total energy is observed as the separation distance decreases from 20 to about 5 Å. It is important to note that the interaction energy in this potential well is due to the electrostatic interaction between the bilayer and substrate, as the van der Waals interaction is truncated at a separation distance of 12 Å. The total energy then increases rapidly as the bilayer is brought closer than 5 Å to the substrate due to strong van der Waals repulsion.

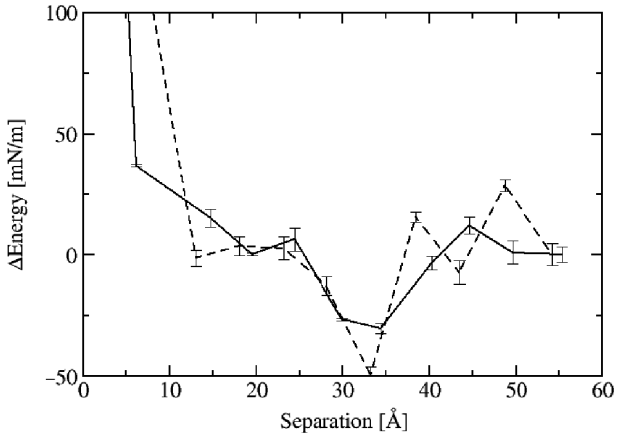

Figure 3. Total energy of the bilayer/substrate system as a function of separation distance for the bare (dashed) and hydroxylated (solid) substrate surfaces.

From this curve, the adhesion energy between bilayer and substrate is calculated as 50 and 30 mN/m for the bare and hydroxylated surfaces, respectively.

The experimentally measured adhesive energy between two bilayers ranges from 0.1 to 0.8 mN/m [48] and the value calculated here for the adhesion between bilayer and quartz is significantly higher. Surface forces apparatus measurements of supported DMPC lipid bilayers interacting with bare silica [47] show an adhesion energy of 0.8 mN/m, also well below the simulation value. For these measurements, the experimental substrate is silica glass as opposed to a quartz surface. Although silica glass is the substrate of practical interest in our applications, we simulate a crystalline quartz surface since the ClayFF force field does not provide an adequate model for amorphous materials. Still, the calculated interaction energy is not in quantitative agreement with the experimental values. We discuss the possible reasons in the next section.

4. Discussion

Earlier, we have described how to calculate the distance dependent energy of interaction between a bilayer and a substrate. The two critical parameters in this curve are the equilibrium separation distance and the adhesion energy between the bilayer and substrate. The system size plays a crucial role in the computation of adhesion energy. Since our approach involves a series of fully atomistic MD simulations, the spatial extent of the bilayer is computationally limited to an area of roughly 5×5 nm. This poses a limitation regarding the accurate determination of the interaction energy since a lipid bilayer undergoes undulations with wavelengths up to sub-micron scales [9,49]. At separations around the equilibrium value mentioned earlier, the undulations give rise to a repulsive interaction which can dominate the van der Waals and double layer forces [49]. Since DMPC bilayers are thinner than DPPC bilayers, we expect greater undulations for the DMPC bilayers. Dampening the undulatory modes of the bilayer reduces the repulsive interaction between the bilayer and the substrate. Given that the size of our simulation box eliminates essentially all undulatory fluctuation modes, we capture very little of this repulsive interaction. This may result in a higher computed adhesion energy than that measured experimentally. It has also been shown that variations in the separation at the level of a few Angstroms can significantly affect the interaction energy [49]. Since the computations of bilayer interaction were carried out on a molecularly smooth a-quartz surface and the experiments by Israelachvili *et al.* were performed on a silica surface, this difference in separations can also contribute to a large difference between computed and measured adhesion energies. We will be exploring these aspects of the bilayer-substrate interaction in a future publication that resolves the experimental and computational studies.

Simulations at a larger length scale that are capable of addressing the role of bilayer undulations on the bilayer-substrate interaction energy curve would be very valuable. One possible approach to address this issue is a coarse grained representation of the supported bilayer system, much along the lines of the united atom simulations of free bilayers [50]. However, this would require extensive matching of thermodynamic and structural parameters of the SLB system, which are both difficult to measure and time consuming in nature. Besides, the increase in the spatial size of the system is unlikely to exceed an order of magnitude—still inadequate in capturing the necessary undulatory modes. We are exploring the possibility of large scale parallel simulations of this system using explicit atom MD. This could increase the spatial scale of the system by more than an order of magnitude, while requiring little to no change in our approach.

Along with the possible effects of suppressed bilayer undulations on the computed interaction energy, we do expect some error to be present due to the approximations made in formulating the parameters for the lipid-substrate cross terms. A more rigorous force field development effort would certainly be useful as interest in the interaction of biological and inorganic material grows. This would have to include an accurate treatment of the polarizability of water as it influences the electrostatic interactions at these short separation distances.

The simulations presented here are performed in the canonical ensemble which prevents us from maintaining equilibrium between the bulk water and confined water regions while moving the bilayer. This approach is effective in computing different points on the interaction potential curve. However, it requires repeated manual fine tuning, especially in the region of the minimum. We are currently improving the resolution of the curve in this region, moving fewer water molecules at a time to either side of the bilayer. It is preferable to employ a more precise method of computing this curve in the future, some options being mentioned earlier. Although approaches like grand-canonical MD and hybrid Monte Carlo-MD are available for exchanging water molecules between regions, these approaches lead to a loss of dynamical information about the system. Other possible approaches include adding pores to the bilayer to allow water

permeation across the membrane [51]. The presence of pores in the bilayer would certainly influence the interaction energy and to a larger degree the lipid dynamics, but this would allow for the bilayer to continuously approach the substrate. These approaches could form the basis for future research on atomistic simulations of SLBs.

A successful atomistic simulation of SLBs offers a perspective of these systems at the molecular length and time scales. The range of phenomena occurring in this system involves length and time scales separated by many orders of magnitude. A comprehensive understanding of such systems requires an analysis of this system at atomistic and macroscopic levels with an effective bridge between these formulations. To this end, we have developed a continuum, dynamical model of the SLB system, where the interaction between the lipid bilayer and the substrate is governed by the interaction potential computed in this paper. This work will be described in a future publication.

5. Conclusions

The simulations presented here are, to our knowledge, the first atomistic simulation of SLBs. The methods detailed in Section 2 provide a framework for combining the soft matter of a bilayer with the hard matter of an oxide substrate while accounting for the system periodicity, varying distance of the gap region, and the long-range nature of the electrostatic interactions. Although some approximations were made, this does provide a starting point that can be refined in future efforts.

The atomistic simulations provide a detailed view of the interaction between the bilayer and substrate allowing us to extract both the equilibrium separation distance and adhesion energy. The equilibrium separation distance matches very well with experimental measurements. The adhesion energy calculated from the simulation is higher than the experimental values for SLBs and published measurements for two free bilayers, probably due to the damping of undulations of the bilayer due to the small simulation size. Analytical calculations of the repulsive interactions and large scale atomistic computations offer a means to resolve the effect of large length scale phenomena on the bilayer-substrate interaction energy.

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