# Simulations of water at the interface with hydrophilic self-assembled monolayers (Review)

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Simulations of water at hydrophilic self-assembled monolayer (SAM) surfaces are especially relevant for biological interfaces. Well-defined, atomically smooth surfaces that can be continuously varied are possible with SAMs. These characteristics enable more accurate measurements than many other surfaces with the added advantage of tailoring the surface to treat specific chemical groups. A fundamental question is how solid surfaces affect the structure and dynamics of water. Measurements of the structure and dynamics of water at solid surfaces have improved significantly, but there remain differences among the experiments. In this article, the authors review simulations of water at the interface with hydrophilic SAMs. These simulations find that while the interfacial water molecules are slower than the bulk water molecules, the interfacial dynamics remains that of a liquid. A major biological application of SAMs is for making coatings resistant to protein adsorption. SAMs terminated with ethylene glycol monomers have proven to be excellent at resisting protein adsorption. Understanding the mechanisms behind this resistance remains an unresolved issue. Recent simulations suggest a new perspective of the role of interfacial water and the inseparable interplay between the SAM and the water. © *2008 American Vacuum Society.*
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## I. INTRODUCTION

The structure and dynamics of water at interfaces are fundamental to a broad range of biophysical phenomena. This can be either at the interface between biomolecules or at the interface of a biomolecule and synthetic material.[1–6] A basic example is the interactions of two proteins as they approach each other and bind.[7] Water influences the approach especially at separations of only a few water layers. In some case, there are strongly bound water molecules, whose release involves large entropic as well as energetic contributions to the binding. Coatings resistant to protein adsorption are critical for devices ranging from implants to biomolecular diagnostic devices. The aqueous interface at such coated surfaces is thought to be a key aspect of protein adsorption.[8,9] Determining the interfacial structure and dynamics of any system tends to be difficult, not least because separating the bulk and interfacial signals is nontrivial. Significant developments in experimental techniques have recently advanced the ability to measure interfacial structure and dynamics.[10–15] Simulations of water interfaces, which can easily separate the interface from the bulk, have also provided new insight.[3,16–20]

Self-assembled monolayers (SAMs) are an important means of altering surfaces in a highly controllable fashion. By varying the termination of the SAM molecules, the surface properties can be fundamentally altered. For example, changing the termination of the SAM molecule from $CH_3$ to OH or COOH alters the surface from hydrophobic to hydrophilic. By mixing SAM molecules with hydrophobic and hydrophilic terminal groups, the wetting angle can be varied over the range from 0° to 120°.[21] The SAM surface can be atomically smooth, which greatly simplifies experiments. In general, SAMs are one of the better means to perform controlled studies of water interacting with hydrophilic surfaces. A major motivation for interest in SAMs as a biologically relevant surface is that terminating alkanethiols with ethylene glycol groups produces the archtypical protein resistant coating.[8]

Computationally, SAMs are well suited to be studied by atomistic simulations. For the typical SAM molecules there are well developed force fields. Molecular dynamics simulations can provide information on structure and dynamics that is not easily attainable experimentally. At the same time, the simulations can connect the calculated structural data with experimentally measured quantities. This article reviews simulations on hydrophilic SAMs, which are particularly pertinent for biointerphases. In the following paragraphs, we briefly introduce the experimental data relevant for water at hydrophilic surfaces. We will next present and discuss the simulation work on water at hydrophilic SAMs.

Two major issues have arisen from the studies of water on hydrophilic surfaces. At a solid surface, there have been experiments that suggest that water is icelike and has a high viscosity.[12,22–24] However, there are also experiments that claim the opposite.[25–30] Thus, the basic structure of water on hydrophilic surfaces remains a major issue. The nature of the water interface at protein resistant SAM coatings is connected to the above differing claims. Claims have been made of "tightly bound" water preventing proteins from adsorbing.[31] While there is much experimental data on this interface, deciphering the source of the resistance to protein adsorption remains an open issue.

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### A. Water structure and dynamics

Direct measurements of the structure of water at a solid interface have been difficult. The first x-ray structure of water under ambient conditions was measured by Cheng *et al.*[32] Their measurements of the structure of water on a mica substrate found density oscillations in the surface-normal direction with spacing of 2.6 Å, which extend to about 10 Å from the mica surface. Schwendel *et al.*[33] measured the interfacial structure of water on $S(CH_2)_{11}(OCH_2CH_2)_nOH$ SAMs for $n=3$ and 6 on $SiO_2$ using neutron reflectivity. They found that the water density at the interface was within a few percent of the bulk water density. They also did reflectivity measurements on OH terminated SAMs with no ethylene glycol monomers ($S(CH_2)_{11}OH$). However, their reflectivity data were inconclusive concerning whether the water density at the interface increases or not.

Nonlinear spectroscopic techniques can probe the interface, because the spectral mode is excited preferentially by molecules at the interface.[4,6] Recently new advances have improved the data that can be obtained by vibrational sum frequency generation (SFG).[12,13,25] Using this technique for water at quartz surfaces, both liquidlike and icelike spectra have been indentified.[12,22] These experiments varied the bulk *p*H, which changes the protonation of the quartz surface. At high *p*H the spectra resembles the quartz-ice spectra and at all *p*H one peaks corresponds to a bulk ice peak. The peak at the frequency corresponding to bulk ice has been observed at other water interfaces, including the water-vapor interface.[6] The interpretation has been that the surface induces an icelike structure on the interfacial water. However, Sovago *et al.*[25] recently re-examined the identification of the spectral peaks. Using deuterated water, the different possible sources of the peaks could be distinguished. From this analysis, the interfacial water SFG spectra orginate, not from distinct water structures (liquidlike and icelike), but from intramolecular coupling of the vibrational modes split by the Fermi resonance. This analysis shows that interpretation of structure from the spectra is nontrivial and requires a separate confirmation.

Mechanical measurements such as the surface force apparatus (SFA) and the interfacial force microscope (IFM) are another valuable source of experimental data on liquids at interfaces. The behavior of simple nonpolar organic liquids at interfaces is largely understood.[26,34–36] These liquids exhibit two main interfacial characteristics. The molecules pack at the interface with flat surfaces yielding oscillations in the density profile perpendicular to the surface. When confined to separations less than their chain length, their rotational motion is curtailed, which reduces the rotational diffusion. The combination of the packing and restricted rotational dynamics leads to much higher viscosities at separations of a few atomic layers. At confinement of a few atomic diameters, the viscosity reaches glass values or the layers solidify.

The situation for water is much less conclusive. Some works find that water dynamics is weakly perturbed,[27] while others find that it is strongly perturbed.[23] One complicating issue is that many of the experiments are actually for saltwater, which brings in an extra component. Horn *et al.*[37] measured the separation forces and the viscosity of water at different NaCl concentrations between silica sheets. While they found a short-ranged repulsion in the force measurements, the viscosity did not differ from the bulk value. Klein and co-workers[26–29] measured the viscosity of interfacial water using SFA and find that it remains close to bulk values even when confined to one or two monolayers. In Ref. 29, salt-free water is specifically studied and the viscosities are fluidlike, within a factor of 3 over the bulk. Raviv *et al.*[27] argue that water behavior is different from the nonpolar liquids due to the difference in the nature of solidification. For nonpolar liquids confinement suppresses translational (and rotational) motion, which promotes solidification. However, for water confinement suppresses highly directional hydrogen bonding associated with freezing. Zhu and Granick[30] measured shear response of nanoconfined water (with salt) and found that the viscosity increased orders of magnitude, but water remains liquid. Using the IFM, Kim *et al.*[23] measured the normal and lateral forces between a coated tip and coated surface for alkanethiol SAMs with OH and ethylene glycol terminations. From the velocity dependence of the normal force measurement, the viscosity was calculated to increase by a factor of $10^6$ over the bulk value. Major *et al.*[24] studied COOH terminated SAMs and calculated from a hydrodynamic model of Feibelman[38] that the viscosity was $10^7$ times larger for the confined water than bulk.

### B. Protein resistant surface

Obtaining surfaces resistant to protein adsoprtion is a major challenge. Because proteins contain monomers that are hydrophobic, hydrophilic, and charged (both positively and negatively), they can achieve strong favorable interactions with most surfaces. Proteins can change their conformation so that the monomers exposed to the surface preferentially bind to the given surface. For these reasons, proteins typically adsorb to most surfaces and finding surfaces resistant to protein adsorption is difficult. Polymer brushes of poly(ethylene glycol) are resistant to protein adsorption. The basic mechanism is understood in terms of the entropic cost of protein penetration in the brush.[39,40] SAMs terminated with oligo ethylene glycol (OEG) groups are also a standard for surfaces that resists protein adsorption.[8] However, for SAMs the entropy is not dominant in determining protein adsorption as it is for polymer brushes. Molecular theory methods have been able to accurately calculate the amount of protein adsorption on mixed SAMs without treating the details of the hydrogen bonding interactions of water.[41] Almost a decade ago Morra asked the simple question, "is it polyethylene oxide or water that imparts and controls fouling resistance?"[9] The basic two interactions are the protein-SAM and protein-water interactions. In the context of the SAM-water interface, there is the issue of the effect of the SAM on the water at the interface and whether this effect (if any) alters the protein-water interaction at the interface. Many experiments have shown that the nature of the water interface with an OEG SAM is involved in determining the protein resistance

and may give insight into the general nature of water interfaces. An intriguing experimental result is that methyl terminated OEG SAMs on Ag are not protein resistant, even though they have the same wetting angles as the SAMs on Au, which are protein resistant.[42] Ag has a smaller lattice spacing resulting in the area per chain for the OEG chains being smaller than on Au. This tight packing forces the OEG chains to be in all-trans conformations. How the difference in packing results in different protein resistances is still not fully clear, but there is clearly a difference in the interface. At a more fundamental level scanning force microscopy experiments with functionalized tips have found repulsive interactions for OEG SAMs on Au, but attractive interactions on Ag.[43] Similar experiments on the *p*H dependence confirm an effective negative charge at the OEG SAM interface[44] and density functional calculations indicate $OH^-$ molecules preferentially adsorb to the interface.[45] More recently, Vanderah *et al.*[46] and Zheng and co-workers[31,47] showed that the protein resistance on Au is maximal not at full coverage, but at about two-third coverage. Herrweth *et al.*[48] previously noted a dependence of protein resistance on packing density. These results imply that there is something significant about area per molecule and its effect on the interfacial structure and dynamics.

Atomistic simulations of the water interface can provide direct characterization of key quantities such as the water diffusion and the hydrogen bonding configurations. In conjunction with the experimental data, such simulation data can reveal insights into the major issues concerning interfacial water at hydrophilic SAMs. We now describe the simulation methods for modeling for water on hydrophilic SAMs. We then describe the simulations results on hydrophilic SAMs. First, we will discuss the simulation data and its implications on the structure and dynamics of interfacial water. Second, we will discuss the simulations results that pertain to resistance to protein adsorption. We end with some comments on future directions.

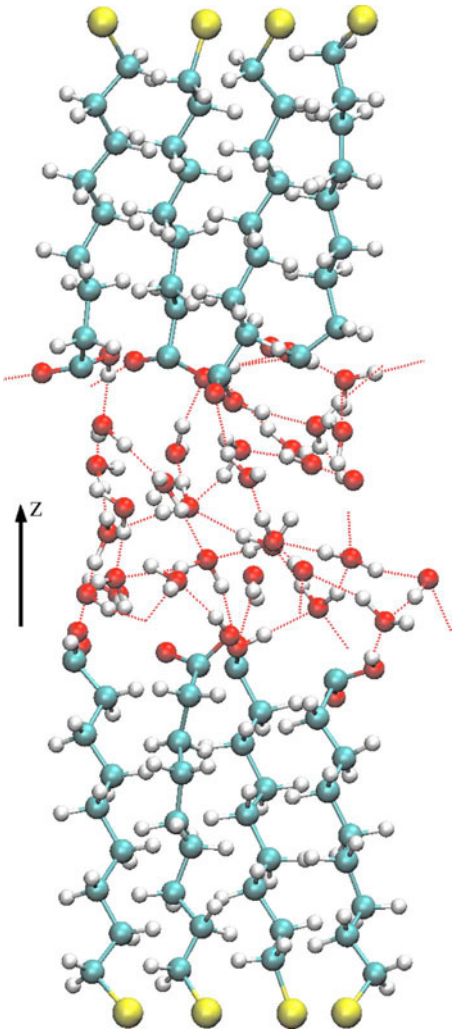


FIG. 1. Image of a section a system with water between two $S(CH_2)_8COOH$ SAMs. The atom colors are S (yellow), C (blue), H (white), and O (red). The dotted lines represent hydrogen bonds.

## II. SIMULATION METHODS AND SETUP

The two most widely studied SAMs are alkanethiols on gold and alkylsilanes on silicon oxide. Figure 1 shows an image of water between two alkanethiol SAMs on gold (not shown). In this article, the $z$ direction will be taken as normal to the substrate. The basic structural motif of a full-coverage alkanethiol monolayer on Au(111) is a $(\sqrt{3}\times\sqrt{3})R30°$ lattice.[49] This comes from simple packing arguments, which involve a tilt angle of the hydrocarbon backbone of about 30° with respect to the surface normal. Closer analysis has revealed that the chains tend to form a $(2\sqrt{3}\times 3)R30°$ lattice (typically denoted as $c(4\times 2)$),[49] which has a herringbone arrangement that maximizes the packing of the chains especially with respect to the position of the H atoms. For details see two recent reviews on the subject.[49,50] At full coverage the spacing between molecules in the SAM on gold is $a$ =4.97 Å with the area per chains about 21.4 $Å^2$.[50] Some interesting effects have been observed on the Ag substrate, which has a smaller spacing (4.77 Å) and commensurate smaller area per molecule (18.4 $Å^2$). These spacings are for small terminal groups such as methyl or hydroxyl. For larger groups such as ethylene glycol oligomers, the area per molecule is larger.

On $SiO_2$, the SAMs are typically not as well ordered as alkanethiols on gold, in part, because the silicon oxide surface tends to be less ordered. Originally, it was believed that the alkylsilane formed a two-dimensional (2D) polymerized layer at the substrate.[51] Certainly, cross-linking can occur between silanes, but a 2D polymerized structure is not possible.[52] A 2D polymerization would have a density much greater than crystal alkanes (i.e., the chains would overlap). Cross polymerization is inconsistent with Si–O bonding and the underlying substrate structure. Crystalline $SiO_2$ surfaces, cristoballite, and tridymite, have hexagonal arrays of $Si–O_4$ tetrahedra. One triangle of alternating sites on the hexagon has tetrahedra pointing up and the other has them pointing down. Only the O sites on the tetrahedra pointing up can be hydroxylated. If all the upward pointing sites are hydroxylated, the area per OH is 25 $Å^2$, which is consistent with

measurements.[53,54] The lattice constant of bulk tridymite is $a=5.03$ Å which gives an area per chain of 21.9 Å. For the SAMs at full coverage, the measured area per chain $A$ is in the range 22–25 Å$^2$.[53,54] In a similar fashion, the silane chemistry cannot cross polymerize without chains pointing up and down, which would require a bilayer. The main lesson is that to produce well ordered silane SAMs requires that cross-linking between the silanes be avoided as they produce defects.[52,55]

Most simulations of SAMs on a silicon oxide substrate treat the $SiO_2$ as a crystal. However, oxide surfaces are often amorphous, especially in applications. Treatment of simulations of SAMs on amorphous $SiO_2$ has been described by Chandross *et al.*[56] The amorphous $SiO_2$ is constructed using a procedure in which an $SiO_2$ liquid is quenched followed by removal of the periodic boundary conditions in one direction.[57] One surface is then held fixed while the other is annealed and subsequently requenched. Random surface positions were chosen at which a Si–O bond was broken to create two reaction sites. Chemisorbed SAMs can be formed by attaching chains to each reaction site to reach the desired coverage with excess sites capped with OH groups.

The simulations to date use standard classical force fields. For water the corresponding standard three point models (TIP3P, SPC/E) has usually been used.[31,58–63] The four point water model TIP4P has been used in the OEG SAM simulations,[64–66] since the force field optimized for ethylene glycol was developed to work with TIP4P.[67] While the various force fields will sometimes yield quantitatively different properties, major issues such as the whether the water is liquid or solid at the interface should not depend on the details of the force field. Some works have used united atom representation for $CH_n$ groups, in which the H atoms are combined with the C backbone atoms to form a single unit.[58,62,68,69] However, most of the works use the all atom model, which explicitly treat the H atoms. For closely packed hydrocarbons, the explicit presence of the H atoms impacts the rotational dynamics of the chain.[70] Most of the studies performed molecular dynamics simulations, using standard integration and ensembles.

The diffusion constant is a standard quantity for characterizing the dynamics. In order to determine the dynamics at an interface as a function of the distance from the substrate $z$, one would ideally calculate the diffusion constant for water in a slab volume parallel to the substrate at selected $z$ positions and compare to bulk water diffusion. However, since individual water molecules might (and actually do) diffuse from one slab to another, significant care is required in interpreting results using this approach. The diffusion constant can only be calculated for the time within a slab, which might be insufficient. In addition, the result would be a two-dimensional diffusion constant that cannot be compared to the standard bulk, three-dimensional constant. This difficulty has been addressed in two ways. The mean squared displacement for water molecules can be calculated as a function of their initial position.[64] A main consideration is whether the waters near or within SAMs are mobile and this mean squared displacement can determine that unequivocally. A direct way to study the water mobility is to calculate the residence time for water to move from one slab to another.[61,64] Results from both methods will be discussed in Sec. III. We also note that diffusion and viscosity are related in that an increase in one quantity implies an decrease in the other.

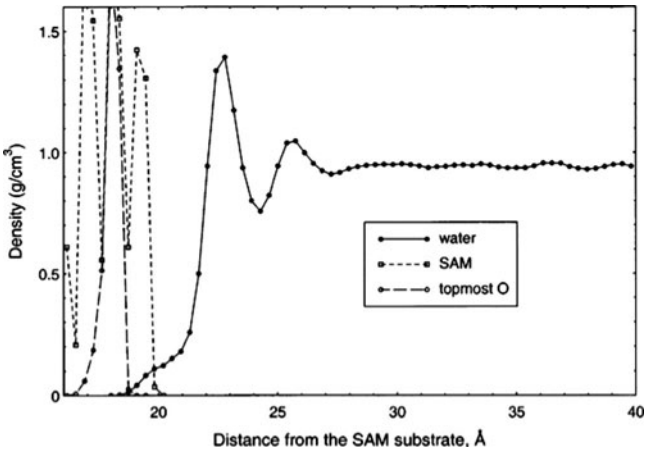


FIG. 2. Density profiles of water, SAM, and topmost oxygen atoms of the methoxy groups near the interface formed by the Ag-supported SAM and water. This figure is reproduced with permission from Ref. 66.

## III. RESULTS AND DISCUSSION

### A. Structure and dynamics at interface

Pertsin and co-workers[65,66] performed some of the earliest simulation studies of water at the interface with a SAM. The motivation was the difference in protein adsorption for OEG $(S(CH_2)_3-(OCH_2CH_2)_3-OCH_3)$ SAMs on Au and Ag substrates. They used Monte Carlo simulations to examine the interfacial structure for water on OEG SAMs on both Au and Ag substrates. In an idealized, densely packed, alkanethiol SAM with 100% coverage, the area per molecule is 21.4 Å$^2$ on Au(111) and 19.1 Å$^2$ on Ag(111).[42] On the Au substrate the spacing of the OEG SAM molecules is such that a helical conformation of the OEG group is possible. However, on the Ag substrate the reduced area per molecule results in an all-trans configuration of the OEG group. Pertsin and Grunze found that the water density next to the SAM has oscillations for both cases, with the first peaks about 15% higher for the Ag substrate than the Au substrate. The density of water for the Ag substrate shows two clear peaks near the SAM (see Fig. 2), while for the Au substrate there is one distinguishable peak in the density next to the SAM. There probably is a second peak, but the height is unclear due to the noise in the data. Water was found to penetrate into the SAM on the Au substrate, as there are small peaks in the water density at 7 and 12 Å from the Au surface. For this chain length, the SAM density extended to 20 Å from the Au surface. Examination of the water structure through the number of hydrogen bonds per water molecule and orientational order parameters shows that the water structure becomes bulklike by about 5 Å above the SAM surface. In the 5 Å region that includes

overlap of the water and the SAMs, the water structure deviates substantially from the bulk structure. In this region most of the interfacial water molecules have three hydrogen bonds compared to four in bulk. For both substrates, the water molecules at the interface have a preferred orientation with the dipole moment pointing toward the substrate. For the Ag substrate, the average water dipole is parallel to the normal, while for the Au substrate the angle with respect to the normal is about 70°. Overall, the authors found that the OEG SAM on Au alters the water structure only slightly.

Vieceli and Benjamin[68,69] studied the interfacial structure for varying roughness and polarity of water-SAM interfaces. The roughness is varied by studying SAMs with mixed chains of different lengths. The polarity is varied by substituting Cl for the methyl. Specifically, $(CH_2)_{17}Cl$ and $(CH_2)_{22}Cl$ are the Cl terminated chains in the simulations and corresponding neutral molecules are methyl terminated. They studied the single component SAMs and binary mixtures at 50:50 concentrations for each possible combination. The systems consist of 100 chains on a square lattice with spacing 4.3 Å or $A=18.5$ Å$^2$. This is a much smaller spacing and different geometries than $SiO_2$ surfaces, which is the system being modeled. In addition, a united atom model is used, which is surprising since at such dense packing the lack of explicit H atoms on the methylene groups can affect the chain dynamics.[70]

A model chromophore was included in two studies.[68,69] Vieceli and Benjamin studied the electronic adsorption spectra of an adsorbed chromophore,[68] and its solvation dynamics.[69] The orientation of waters in the first layer at the smooth, single chain length SAM interface is preferentially with the water dipole moment at 60° with respect to the surface normal. For the mixed SAMs yielding atomically rough surfaces, the orientation distribution of the dipole moment changes. With the Cl on the longer molecule, the orientation is peaked at 90°, which is similar to the water-carbon tetrachloride interface. The water molecules in the second layer at the interface in the mixed, rough surfaces is more uniform and bulklike. While there is a decrease in the water polarization at the interface. the polarity at the interface is greater than in the bulk, due to the polar terminal group in SAM molecule contributing a net larger polarization. The relaxation times for chromophore at the interface are slower than bulk. For the smooth, single component SAMs the difference is almost a factor of 2, while for the mixed monolayers, the increase is a factor of about 6.

In a related work, the hydrogen bond structure and dynamics at the interface with a carboxyl terminated SAM have been studied by Winter *et al.*[58] The same setup as described above is used except the SAM molecules are $(CH_2)_{18}COOH$. They find that the water molecules immediately next to the SAM have their dipole moment parallel to the surface with one of the OH bonds pointing at the surface. There is a hierarchy of relaxation times for hydrogen bonds that depends on the bond partners. Between interfacial water molecules the relaxation time for hydrogen bonds is 7.9 ps, which is about twice as slow as in bulk (4.6 ps). The relaxation time for hydrogen bonds between water and SAM molecules are a few tens of picoseconds. The hydrogen bonds between the terminal groups of the SAM molecule are much slower, estimated to be in the hundreds of picoseconds.

Jiang and co-workers[31,60,61,63] studied OEG terminated SAMs. The area per OEG SAM was varied by studying mixed monolayers of $S(CH_2)_4(OCH_2CH_2)_4OH$ and $S(CH_2)_4OH$. The area per chain at full coverage for the OEG SAMS was set to the experimental value of 27 Å$^2$. They calculated density profiles and examined the hydrogen bonding of the waters and the OEG molecules. As the OEG SAM coverage decreases, they found the mobility of the SAM molecules increases and water penetrates deep into the SAM. From calculations of the radial distribution function of the O atoms, Zheng *et al.*[31] claim that a "tightly bound" water layer occurs just above the interface. The distribution functions have multiple peaks and decay to 1 at large distances from the substrate. The initial studies did not present direct calculations of the water dynamics. In a related work on mannitol and sorbitol terminated SAMs, the residence time for water in the layer of thickness 4 Å next to the SAM was calculated.[61] For mannitol, the residence time is 10.5 ps and for sorbitol, it is 13.5 ps. These values are about 2.5–3 times larger than the bulk water value.

Ismail *et al.*[64] also performed simulations of OEG SAMs. They were motivated by the experiments of Vanderah *et al.*,[46] who studied the protein resistance as a function of SAM coverage. Following these experiments, Ismail *et al.* performed simulations of the SAMs with the molecule $SCH_2(CH_2CH_2O)_6CH_3$ varying the coverage ranging from $A=21$ Å$^2$ (corresponding to maximum packing) to $A=54$ Å$^2$ (50% coverage on Au). At the densest coverage ($A=21$ Å), the interfacial region is very narrow. There is very little penetration of water into the SAM as in earlier simulations,[65] and the mixing of water and SAM is confined to the terminal region of the SAM. As $A$ increases the overlap between the water and SAM profiles increases. The hydrophilic character of SAM results in a mixing of the water and the SAM. Calculations of the number of hydrogen bonds as a function of $z$ show that the number of hydrogen bonds increases within the SAM as the water mixes with the SAM at the lower coverages. As noted in Sec. II, the dynamics can be characterized by calculating the mean squared displacement as a function of $z$ and the residence times for water remaining in a slab as a function of $z$. Their calculations show that the water is mobile in all cases (see Fig. 3). For coverages such as $A=36$ Å$^2$, which have substantial overlap between the SAM and water, the water molecules closest to the substrate have the longest residence time and the times get shorter for larger $z$. For this coverage, the increase in residence times for interfacial water molecules is only a factor of 4 greater than in the bulk. Not only is water within the SAMs mobile but also the chain mobility increases as $A$ increases as can be seen in the chain torsional mobility.

While the simulations of the different water-SAM interfaces have differences in the details, the basic features are the same. There is an increase in water density at the hydro-

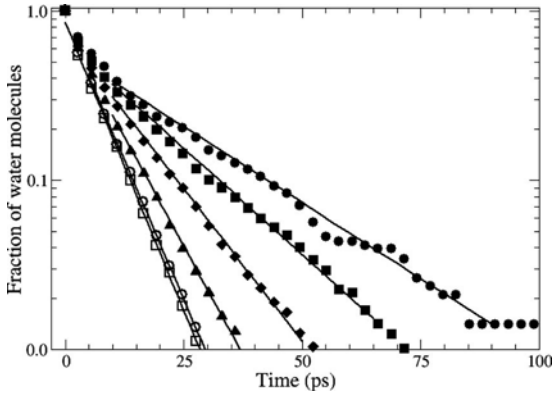


FIG. 3. Residence fraction of water molecules within slabs parallel to the substrate as a function of time in the $A=36$ Å$^2$ system of $SCH_2(CH_2CH_2O)_6CH_3$ SAMs on gold. The plot is semilog and the lines are least-squares fits to the data. From right to left, the profiles are shown for water molecules as a function of the water's initial position $z_{init}$: 5 Å $\leq z_{init} < 10$ Å (filled circles), 10 Å $\leq z_{init} < 15$ Å (filled squares), 15 Å $\leq z_{init} < 20$ Å (diamonds), and 20 Å $\leq z_{init} < 25$ Å (triangles). 25 Å $\leq z_{init} < 30$ Å (open circles) and 30 Å $\leq z_{init} < 35$ Å (open squares). This figure is reproduced with permission from Ref. 64.

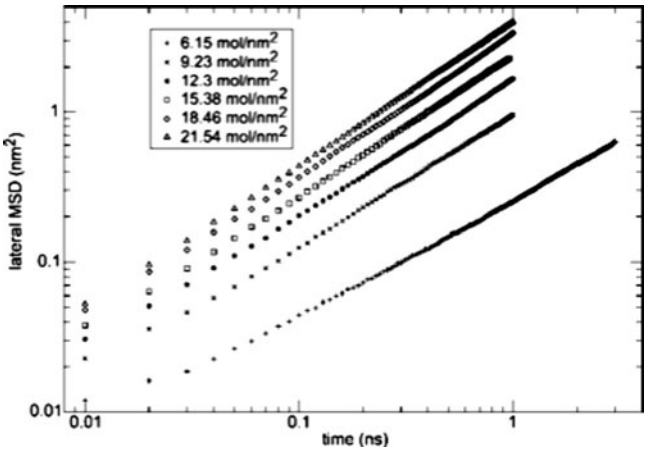


FIG. 4. Two-dimensional mean squared displacements for $P=10$ MPa show liquid, linear increases with time for the given water areal densities, which correspond from submonolayer to bilayer. This figure is reproduced with permission from Ref. 59.

philic surface of SAM at full coverage. The number of hydrogen bonds per water molecule at the interface tends to be reduced from the bulk value. If the interface is flexible, due to partial coverage, for example, then the interface may not be a sharp. In general, the dynamics of the water molecules next to the SAM is reduced by at most only a factor of 6. That is, the interfacial water has liquid dynamics and is not icelike in this sense. At full coverage, the liquid near the SAM will be more dense and diffuse more slowly than in bulk, but the structure and dynamics are far from solid.

All of the previously discussed simulations have focused on a single interface between water and a SAM. As discussed in Sec. I, many of the experiments, particularly atomic force microscopy and IFM, study water confined between two SAM surfaces. Especially at separations of just a few layers of water, confinement has the potential to exert more constraints on water dynamics than a single interface. If water were to behave like nonpolar liquids, it would solidify. However, as noted above, there is disagreement concerning what happens for water. Recently, to investigate water between two surfaces coated with SAMs at nanometer separations, Lane *et al.*[59] performed molecular dynamics (MD) simulations of water confined between two $S(CH_2)_8COOH$ SAMs on Au. The amount of water was varied to from submonolayer to two layers. In order to obtain good statistics for the small amount of water between the SAMs, the area of the systems was much than previously discussed simulations. Each surface had 3000 SAM molecules and was about 250 Å on a side. The spacing of the monolayers was determined by applying a constant normal pressure. Simulations were performed for pressures between −25 and 70 MPa. The lowest diffusion constant was about 0.01 times to bulk diffusion for submonolayer coverages and highest pressure, which are well above 1 atm. Figure 4 shows the mean squared displacement as a function of time. Thus, even under such confinement, the dynamics of the water molecules was liquid.

Simulations of water between $S(CH_2)_{15}COOH$ terminated SAMs were presented in the work of Major *et al.*[24] The water confined between the two SAMs was studied at a low relative humidity of 10% using grand canonical Monte Carlo simulations. They determined the number of water molecules, the number of hydrogen bonds, and the value of a tetrahedral order parameter at separations from 3.0 down to 0.3 nm. At the largest separation only about 10 water molecules are in the system compared to 56 SAM molecules per surface. Near a separation of 1–2 nm the number of water molecules increases to about 60–80 depending on whether the simulation is treating approach or retraction of the two surfaces. The number of hydrogen bonds increases with the number of water molecules. Major *et al.* observed that the increase in the measured friction corresponds to the increase in hydrogen bonding in the simulations and claim that the cooperative effect of hydrogen bonding by the water molecules between the two SAMs is responsible for the high viscosity calculated from the experimental data. Since the simulations are Monte Carlo simulations, no diffusion or viscosity was directly calculated.

Most simulations of water either at other single solid, hydrophilic surfaces,[71,72] or confined between such surfaces[73–76] have found that water has liquid dynamics at the interface. A few simulations have found ordered states of water layers at solid substrates.[77,78] Zangi and Mark treat a substrate that is a triangular lattice (of unspecified spacing) with substrate van der Waals parameters derived from $SiO_2$ as a single material. However, the model for the substrate contains no charges, and therefore is hydrophobic. They find a solid structure for separations between 5.1 and 5.5 Å. At shorter or longer separations, the water is liquid. Wissner-Gross and Kaxiras studied the (111) surface of diamond with a Na termination. They find the thickness of the frozen water to be seven layers at room temperature on this surface. The

spacing on the (111) surface of diamond is much smaller than the O spacing on most oxide. Presumably this difference is crucial in producing solid water layers. This work appears to indicate the type of substrate necessary to solidify water at the interface in ambient conditions. The fact that the substrate is quite different from hydrophilic SAM interfaces or even oxide surfaces is indicative of the strength and geometry of the interactions necessary to perturb water from its liquid state.

### B. Protein-SAM interactions

Raut *et al.*[62] studied the interactions between a peptide and SAMs with different termination. The peptide was $G_4XG_4$, where $G$ is glycine and $X$ is either lysine ($K$) or glycine. The SAM molecules were $S(CH_2)_nY$ with $Y$=OH, COOH and $(O-CH_2-CH_2)_2-OH$. A united atom model was used for the $CH_2$ groups. However, all the atoms in the SAM except the terminal groups were constrained, because they found the chain mobility too high producing incorrect tilt angles and SAM height. For the COOH SAM 5% of the chains were protonated. Three independent sets of simulations of 10 ns were performed for each peptide-SAM pair. Raut *et al.* calculated probability distributions of the surface separation distance between the peptide and the SAM. The probability distributions for the OH-SAM showed that both peptides do not occupy the space within 5 Å of the SAM. In contrast, for the COOH-SAM, both peptide distributions had a sharp peak at 3.5 Å indicating that the peptide adsorbs. They also found the peptides adsorb to the OEG SAM, although the peaks are smaller than the COOH-SAM implying a weaker adsorption.

Jiang and co-workers performed calculations of the force on the lysozyme protein near SAM with $CH_3$, OH and OEG(Ref. 60) and mannitol and sorbitol[61] termination. The force on the protein was determined for separations of 5, 10, and 20 Å for a single, fixed orientation of the protein. The MD simulation run time was 1.5 ns. In all cases, the force increased as the separation decreased. Decomposition of the force into terms due to water-protein and SAM-protein interactions showed that the water-protein interaction became increasingly repulsive for shorter separations. On the other hand the SAM-protein interactions become attractive at 5 Å.

The recent experiments of Vanderah *et al.*[46] and Li *et al.*,[47] which showed the protein resistance of OEG SAMs on Au is better at a partial coverage instead of full coverage, indicate that the SAM plays an important role in the protein resistance in these systems. We can view the protein as a probe of the interface: whether a protein absorbs or not gives information about the interface. As noted in Sec. I, the question of whether the water or the surface molecule plays the important role in protein resistance has remained unanswered for quite a while. The simulations of these OEG SAMs reveal fundamental aspects of the SAM-water interphase.[31,60,61,64] The data now suggest that both play important, nonseparable roles.

A suggested source of protein resistance is that the water layer directly above the interface has unusual physical properties, leading to enhanced resistance.[31,60,79] While there is no disagreement among the different simulations that the water dynamics at the interface with a SAM (at full coverage) is slower than the bulk, there is disagreement concerning the interpretation of the results with respect to protein adsorption. Jiang and co-workers claim that the slow water dynamics implies that the interfacial water molecules are "tightly bound," which presents a barrier preventing proteins contacting the SAM. They consider their simulation results, which found a repulsive interaction as a function of protein separation from the SAM surface, as further confirmation of the effects of water. While Ismail *et al.* did not model proteins interacting with the SAMS, they argue the opposite, that proteins will not adsorb when the interface is sufficiently close to bulk that the protein can reside equally well at the surface or in the bulk. For this reason, the optimal coverage in the Vanderah *et al.*[46] experiments is less than full, where the interface is most like bulk water.

Direct simulation of protein adsorption is beyond the present capability of computer resources. There are several difficulties for such simulations. Treating all the possible orientations of the protein with respect to the surface requires multiple simulations, which increases the cost by at least an order of magnitude. Furthermore, the conformation of the protein interacting with a surface is not fixed. Simulations need to be able to at least treat the change in conformation of the surface residues in response to the presence of the surface. The time scales for such rearrangement are not completely known. From general protein simulations, one expects the time scales for just the surface groups to rearrange to be greater than 1 ns. In addition, the tertiary structure of the protein may change upon interacting with a surface and the time scales for such interactions are very long compared to typical simulation time scales ($>100$ ns). With respect to hydrophobic surfaces, even larger conformational changes are expected to occur since the protein may partially unfold. The time scale to treat such unfolding is outside the realm of atomistic simulations. In addition to all these issues, calculating the free energy of a protein as a function of separation from the surface requires using sophisticated and expensive simulations methods.[80] Such methods are required in order to obtain well sampled distributions that are necessary for calculating the free energy. Thus, atomistic simulation of protein adsorption is a daunting task to attempt at the present time.

Simulations of proteins adsorbing to SAMs have either treated only the interaction between a soluble, folded protein, and the OEG SAM (Refs. 31 and 60) or between a peptide and the SAM.[62] The simulations of Jiang and co-workers can only obtain the "colloidal" interaction between a folded protein and the surface at a few selected separation distances and for only a single orientation of the protein. Simplified models are used to obtain a preferred protein orientation. However, given the fact that the water at the interface is different from the bulk and that such details are not treatable in the simplified models, the calculations for a single separation are questionable especially at short separations from

the surface. Moreover, the simulations do not determine whether a protein will adsorb, because the essential dynamics of the protein responding structurally to the surface requires much longer simulation times as noted above. The need for the longer simulations is confirmed by the work of Raut *et al.* on peptides that has a different conclusion (attraction).[62] Furthermore, a repulsive interaction does not necessarily imply resistance to adsorption. Consider, for example, the case of two lipid bilayers coming in contact. Their interaction is repulsive, yet vesicles will fuse spontaneously (on time scales long for simulation) as the fused structure has a lower free energy.[81,82] The repulsion presents a kinetic barrier for fusion, but does not prevent fusion. Similarly, repulsive protein-surface interactions are not conclusive of protein resistance to adsorption. There can be an adsorbed state of the protein with a minimum free energy, while the soluble protein conformation has a repulsive interaction. In other words, at zero separation the free energy has a minimum with a repulsive barrier at short separations. Sampling at zero or small separations can be very expensive, especially in the presence of a repulsive barrier and especially if conformational changes occur on long time scales.[80]

Ismail *et al.*[64] discussed the different free energy terms of protein adsorption on the OEG SAM surface[46] at $\frac{2}{3}$ coverage, which is maximally resistant. As the protein diffuses to contact, it sees a hydrophilic surface. There is no gain in free energy from the protein unfolding to expose its hydrophobic core to the surface. The protein as a whole is limited to diffusing into the SAM-water interface, due to the lack of available free volume. The individual side chains of a protein can penetrate the interfacial region, as the region is flexible, but there are no specific sites to which the protein can strongly bind. The flexibility of the interface is a key factor in protein resistance, because the interfacial region of mixed SAM and water has a hydrogen bonding network similar to bulk water. Consequently, the protein cannot distinguish being at the interface from being in the bulk, and the protein moves on and does not adsorb.

## IV. CONCLUSIONS

One of the fundamental questions is how solid surfaces affect the structure and dynamics of water. Simulations of water on hydrophilic SAMs find that the water dynamics is slower than the bulk, but the water diffusion remain liquid. This is true even for water confined between two SAMs at submonolayer levels. A major biological application of SAMs is for making coatings resistant to protein adsorption. Understanding the mechanisms behind this resistance has been an unresolved issue. Recent simulations suggest a new perspective of the role of interfacial water and the interplay between the SAM and the water. Instead of the water being different from bulk, the suggestion has been that the more the interfacial region including the SAM is like bulk water, the protein cannot distinguish interfacial from bulk locations and does not adhere. The interface is more bulklike when the SAM termination is a hydrophilic oligomer (not just a single unit) and the SAM coverage is high, but not full in order that the interface be fluid.

There are several clear directions that the simulation will take in the future. Biological systems are almost always in salt solution, not salt-free water. Studying interfacial salt solution is straightforward within the realm of classical force-field simulations, although low concentrations can pose difficulties in obtaining sufficient statistics.[3] There has been recent exciting simulation work on ions at the water-vapor interface.[83,84] A related factor is the *p*H of the solution. Many hydrophilic terminal groups in a SAM become protonated at the appropriate *p*H. Moreover, the effect of $OH^-$ groups and hydronium ions has been claimed as source for some of the phenomena of interfacial water.[43–45] Treating *p*H poses various challenges. At *p*H=7, the number of $OH^-$ or hydronium molecules contained in the volume of a typical simulation is less than one, which makes such simulation not viable. To have sufficient ions in solution, high concentrations are required, which may not be the system of interest. The dynamics of hydroxide and hydronium ions involves the motion of single H atoms, which has a significant quantum character. Thus classical force-field simulations are not applicable for some aspects of such systems. Molecular dynamics simulations with quantum interactions are being performed and producing interesting results (e.g. Ref. 85), but they also have strong time scale limitations. Polarizable force fields are obviously relevant at surfaces and the first generation are available.[86–89] Using such force fields interesting simulation results on the water-vapor interface have been published recently.[90–92]

One of the advantages of SAMs is the ability to change the terminal group. To date the terminal group has been rather simple in simulations (e.g., –OH, –COOH), while there has been a wide range in experimental studies. Future simulations will explore more complex terminal groups, exploring the interfacial structure and interactions with biomolecules. While SAMs offer a controllable interface and the possibility to study water between two different hydrophilic surfaces, direct studies of the interface between proteins are being performed.[7] With the knowledge gained from studies of simpler SAM systems, the more complex interactions between proteins and other biomolecules can be deciphered.

Performing a simulation on system with a biomolecule that changes conformation while interacting with a SAM is typically a challenge. The time scale associated with the biomolecular conformation change are often outside the range of present computational resources. A protein (partially) unfolding to adsorb to a surface is one example. Simulations of polypeptides are possible as shown by Raut *et al.*,[62] although treating a polypeptide with secondary structure has yet to be done. The interaction of carbohydrates with SAM surfaces, especially terminated with sugar groups, involve slow polymerlike dynamics that are presently outside the range of atomistic simulations except for short carbohydrates. These examples are sufficiently challenging that the development of new simulation techniques may be required.

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