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Review

Prof. George Whitesides' Contributions to Self-Assembled Monolayers (SAMs): Advancing Biointerface Science and Beyond

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Abstract: Prof. George Whitesides' pioneering contributions to the field of self-assembled monolayers (SAMs) have profoundly influenced biointerface science and beyond. This review explores the development of SAMs as highly organized molecular structures, focusing on their role in advancing surface science, biointerface research, and biomedical applications. Prof. Whitesides' systematic investigations into the effects of SAMs' terminal group chemistries on protein adsorption and cell behavior culminated in formulating "Whitesides' Rules", which provide essential guidelines for designing bioinert surfaces. These principles have driven innovations in anti-fouling coatings for medical devices, diagnostics, and other biotechnological applications. We also discuss the critical role of interfacial water in SAM bioinertness, with studies demonstrating its function as a physical barrier preventing protein and cell adhesion. Furthermore, this review highlights how data science and machine learning have expanded the scope of SAM research, enabling predictive models for bioinert surface design. Remarkably, Whitesides' Rules have proven applicable not only to SAMs but also to polymer-brush films, illustrating their broad relevance. Prof. Whitesides' work provides a framework for interdisciplinary advancements in material science, bioengineering, and beyond. The enduring legacy of his contributions continues to inspire innovative approaches to addressing challenges in biomedicine and biotechnology.

Keywords: self-assembled monolayers; adsorption state; biointerface; machine learning; materials informatics; biomaterials, protein adsorption; cell adhesion; anti-fouling

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1. History of Self-Assembled Monolayers (SAMs)

In the 1980s, groundbreaking research by Nuzzo and Allara introduced self-assembled monolayers (SAMs) as highly organized molecular structures, with a primary focus on alkanethiols adsorbed on gold surfaces [1–4]. Their work demonstrated the remarkable capability of organic molecules to spontaneously form densely packed, well-ordered monolayers on a substrate, initiated by substrate–molecule and intermolecular interactions (Figure 1). Sagiv demonstrated that SAMs can be formed on silicon substrates using silane molecules [5–7]. Thus far, various combinations of substrate and anchoring groups have been reported [8].

The structures of SAMs, especially gold–thiol systems, are well-defined compared to polymer and polymer-brush films. The stability of SAMs is greater than that of lipid bilayers, especially in air. The tunability of surface functional groups has enabled quantitative discussion of physicochemical surface and interface properties, such as macroscopic wettability and frictions. This discovery not only provided a versatile platform for modifying surface properties but also established a foundational framework for studying interfacial phenomena. The SAMs can be fabricated in vacuum and liquid, basically providing SAMs with equivalent molecular packing structures.

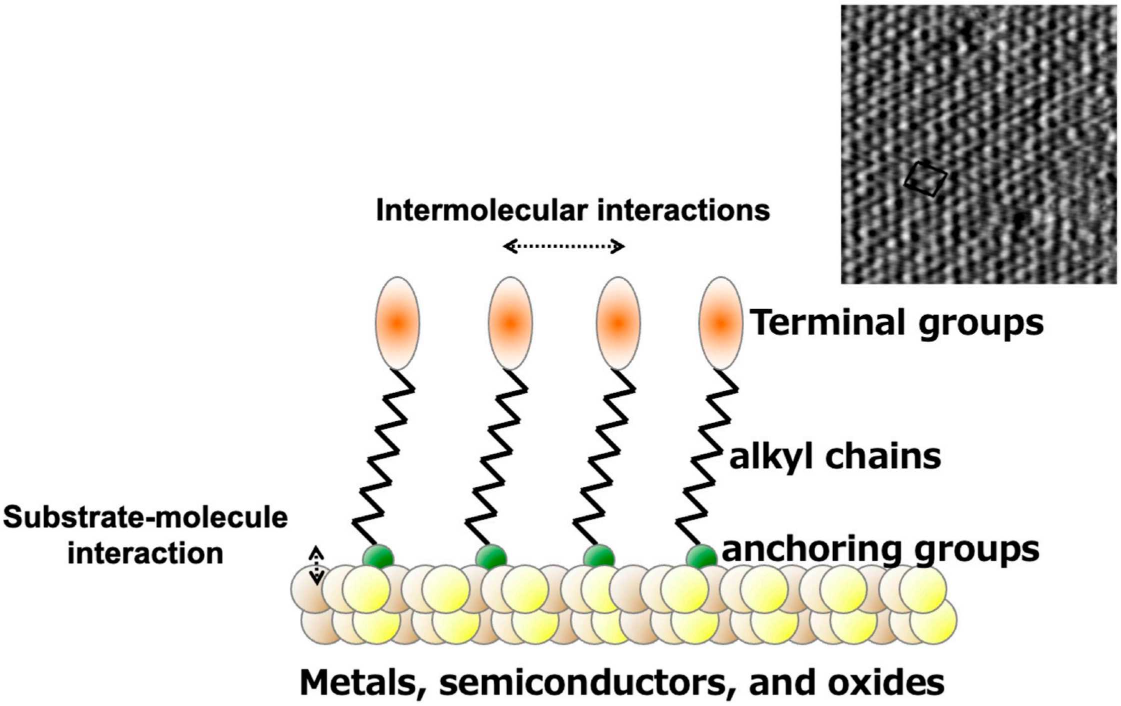

Figure 1. Schematic illustration of self-assembled monolayers (SAMs). The upper right figure is a scanning tunneling microscope image of *n*-butanethiol's SAM on Au(111) (image size: 20 × 20 nm^2). The unit cell is indicated by a rectangle.

The potential of SAMs is further expanded by fusion with printing. Moreover, they can be printed and patterned using the microcontact printing technique [4,5], inkjet printing, and irradiation with a laser, a UV, or an electron beam [9–13]. As a result, SAMs have become indispensable tools in various fields, including catalysis, electrochemistry, tribology, biosensing, and biology. Their utility stems from their molecular-level tunability, allowing researchers to precisely tailor surface chemistry for specific applications [8,14].

SAMs comprising mixtures of thiols enable fine-tuning of the physicochemical properties of the SAMs [15,16]. In particular, SAMs with a chemical gradient have provided combinatorial platforms to investigate the correlation between various physicochemical properties of SAMs and the composition of surface functional groups [17–22]. The SAMs with a chemical gradient can be fabricated through various methods, including UV and electron irradiation [23,24], electrochemical reaction [19], an addition of the second thiols [17], and exchange reactions of thiols [22]. SAMs play important roles to find optimal functions of SAMs with desired properties, such as work functions of substrates [18], protein adsorption, and cell adhesion [25,26].

In parallel with the exploration of SAM applications, substantial efforts have been directed toward unraveling the fundamental structural characteristics of these systems by using various experimental and theoretical techniques (Table 1). One key aspect of this research has been the investigation of the molecular packing patterns within SAMs. Using scanning tunneling microscopy (STM), Poirier et al. provided direct visual evidence of the packing arrangements of alkanethiols on Au(111) surfaces, which revealed a highly ordered hexagonal structure [27–30]. These findings were corroborated by other analytical techniques, including Fourier transform infrared absorption spectroscopy (FTIR) [31,32], helium scattering spectroscopy [33–35], thermal desorption [36], electron energy loss spectroscopy [37–40], and molecular dynamics simulations [41–43]. Collectively, these studies have highlighted the intricate interplay of van der Waals forces, molecule–substrate interactions, and intermolecular interactions that govern SAM formation and stability.

Table 1. Summary of analytical techniques to investigate the adsorption states of molecules constituting SAMs and representative articles.

Names of Techniques (Abbreviation)	Properties Investigated	References
X-ray photoelectron spectroscopy (XPS)	Molecular packing density on substrates. Adsorption states of head groups.	[44–49]
High-resolution electron energy loss spectroscopy (HREELS)	Molecular orientations on substrates. Adsorption states of head groups.	[38–40,50,51]
X-ray diffraction spectroscopy (XRD)	Periodic structure of molecules in the SAMs.	[52–54]
He-scattering spectroscopy	Periodic structure in SAMs (only terminal groups).	[35,55,56]
X-ray standing-wave spectroscopy	Positions of head groups	[57]
Fourier-transform infrared absorption spectroscopy, Raman scattering spectroscopy, and sum frequency generation (SFG)	Orientations and structures of alkyl chains and terminal groups.	[58–62]
Scanning probe microscopy (SPM), scanning tunneling microscopy (STM), and atomic force microscopy (AFM)	Molecular images of the molecules constituting SAMs.	[27,29,30,38,39,63,64]
Surface plasmon resonance (SPR), quartz crystal microbalance (QCM), and spectroscopic ellipsometry spectroscopy	Adsorption kinetics of molecules on solid substrates.	[65–69]
Water contact angle (WCA)	Wettability of SAMs to water.	Many of the works employed this method. Representative works [70–72].
Ab initio calculation and molecular dynamics and Monte Carlo simulations	Adsorption states of sulfur head groups. Molecular orientations and packing configurations of molecules.	[40,43,73–76]

Another critical focus of SAM research has been the adsorption mechanism of the sulfur head groups in alkanethiol molecules. This topic remained a contentious issue for decades, as researchers debated whether sulfur atoms in SAMs were bound directly to the gold surface or to gold ad-atoms. By the 2010s, a consensus emerged based on experimental and computational studies: alkanethiols adsorb as thiolate species on gold ad-atoms formed on the Au(111) surface during the adsorption process, which was elucidated through low-temperature STM. This adsorption involves the release of hydrogen atoms from the thiol groups, resulting in a robust sulfur–gold bond [77]. The formation of gold ad-atoms and their role in stabilizing the SAM structure have since been recognized as pivotal in understanding the molecular organization of these systems.

The insights gained from these fundamental studies have profoundly influenced the development and optimization of SAMs for practical applications. For instance, understanding the molecular packing and adsorption mechanisms has enabled researchers to fine-tune the stability and functionality of SAMs in environments ranging from biological systems to harsh industrial conditions. Today, SAMs are not only regarded as model systems for surface chemistry but also as essential components in the design of advanced materials and devices for sensing, catalysis, corrosion protection, and bioengineering [8].

2. Prof. George Whitesides' Contributions to Biointerface Studies

In the 1990s, Prof. George Whitesides and his collaborators significantly expanded the role of self-assembled monolayers (SAMs) in the study of biointerfaces, where organic molecules interact with biomolecules, cells, and tissues [78,79]. This research illuminated how the terminal groups of SAMs influence protein adsorption and cellular behavior, providing critical insights into the field of biomedical applications. Whitesides' work demonstrated that by modifying the chemical structure of SAM terminal groups, it is possible to precisely control biological responses. This approach laid the groundwork for applications in biosensors, tissue engineering, and biomaterials, where interactions between biological systems and synthetic surfaces are pivotal [80].

Their contributions went beyond observational studies, as they systematically investigated how functional groups, such as hydroxyl, methyl, and oligo(ethylene glycol) (OEG), affect surface properties. These systematic experiments enabled Prof. Whitesides' team to propose guiding principles for designing bioinert SAMs, commonly referred to as "Whitesides' Rules." These rules emphasize the importance of hydrophilicity, the presence of proton acceptors, the absence of proton donors, and charge neutrality in creating surfaces resistant to protein adsorption and cell adhesion. Prof. Whitesides' contributions not only advanced the field of non-fouling and anti-fouling surfaces but also provided a practical framework for researchers designing bioinert materials [81].

3. Significance of Anti-Biofouling SAMs

One of Prof. Whitesides' most notable achievements was the development of anti-biofouling SAMs, which resist the adsorption of biomolecules and the adhesion of cells. These surfaces are essential in medical devices, diagnostics, and implantable materials, where minimizing unwanted biological interactions is critical for functionality and biocompatibility. Whitesides' team demonstrated that OEG-SAMs exhibited exceptional resistance to protein adsorption, a property attributed to their ability to retain tightly bound water at the interface. This discovery sparked widespread interest and inspired decades of research into the design and optimization of anti-biofouling surfaces [78,82].

However, their studies also uncovered several unexpected challenges. For instance, Ostuni et al. and Harder et al. revealed that the bioinertness of OEG-terminated SAMs depends on the underlying substrate [83,84]. While SAMs on gold (Au) surfaces exhibited excellent protein resistance, those on silver (Ag) allowed protein adsorption despite identical terminal groups. This perplexing observation called into question the simplistic understanding of SAM bioinertness and highlighted the need for deeper investigation into the underlying mechanisms [85].

4. Bioinertness in SAMs vs. Polymers

The bioinertness of SAMs is fundamentally distinct from that of polymer and polymer-brush films. In polymers, bioinertness is often explained by steric repulsion or volume exclusion, where hydrated, flexible polymer chains resist protein and cell adsorption due to their high entropy state [86,87]. However, SAM molecules are densely packed and relatively rigid, rendering steric repulsion an insufficient explanation for their bioinert properties. This discrepancy led to the development of alternative models to explain SAM bioinertness [85,88–91]. To address the enigmatic nature of SAM bioinertness, several hypotheses have been proposed.

Electrostatic Repulsion Model

This model suggests that an electric double-layer repulsion between negatively charged proteins and hydroxyl ions accumulated at the SAM interface is responsible for protein resistance. Supporting evidence comes from streaming potential measurements and surface force analysis, which have confirmed the preferential adsorption of hydroxyl ions on bioinert SAMs [92–94]. However, this model fails to explain the bioinertness observed against positively charged proteins, leaving gaps in its applicability.

Tightly Bound Water Model

According to this hypothesis, water molecules strongly adsorbed to OEG-terminated SAMs form a hydration barrier that prevents protein adsorption [95]. This tightly bound water layer is thought to be energetically unfavorable for proteins to penetrate. Despite its intuitive appeal, this model struggles to explain why hydrophilic surfaces like hydroxyl-terminated SAMs and hydrophilic inorganic surfaces (e.g., titanium or silicon) often allow protein adsorption, challenging its universality.

Water Barrier Model

Computer simulations have proposed a water barrier model, where a thin layer of water, several molecules thick, forms between the SAM surface and the approaching protein [96]. This water barrier creates a repulsive force that inhibits protein adsorption. Although promising, experimental validation of this model remains elusive, and its generality across different SAM systems is uncertain.

Experimental evidence for the "water barrier model"

Interfacial water is hypothesized to act as a barrier preventing the adsorption of both positively and negatively charged proteins onto surfaces. The author's group conducted surface force measurements using an atomic force microscope (AFM) to test this hypothesis. During protein adsorption onto bioinert self-assembled monolayers (SAMs), repulsive forces are expected to operate between the SAM and protein molecules. Observing these repulsive forces under physiological conditions (e.g., in water) would help elucidate the underlying mechanism and the origin of these forces.

Hayashi et al. investigated the interactions between SAMs composed of OEG-SAMs in phosphate-buffered saline (PBS), mimicking human body fluid conditions (same salt concentration and pH) (Figure 2) [97]. Using an atomic- force microscope (AFM) equipped with a colloidal probe (Figure 2a), they detected water-induced repulsive forces operating between bioinert SAMs (EG3-OH, SB, and MC) (Figure 2d), whereas bio-adhering SAMs (C8, SA, and TMA) showed an attractive interaction. These forces exhibited a range of approximately 4–6 nm (Figure 2d). The nature (repulsive or attractive) and range of the surface forces correlated with the SAMs' protein resistance and blood compatibility. The findings suggest that water molecules within a 2–3 nm interfacial layer act as a physical barrier, preventing the adsorption of biomolecules and cells onto the SAMs [90,97–100]. It should be noted that their results also explained the substrate dependence (Au and Ag) of protein resistance of the OEG-SAMs, verifying that the interfacial water is responsible for the protein and cell resistance [99].

Interestingly, similar water-mediated barriers have been observed for other SAMs, such as those composed of zwitterionic peptides [90,101], mismatched deoxyribonucleic acid (DNA) at their termini [102,103], and saccharides. These observations imply that biomolecules leverage their surrounding water molecules to facilitate precise target-specific molecular interactions, a mechanism integral to biological processes.

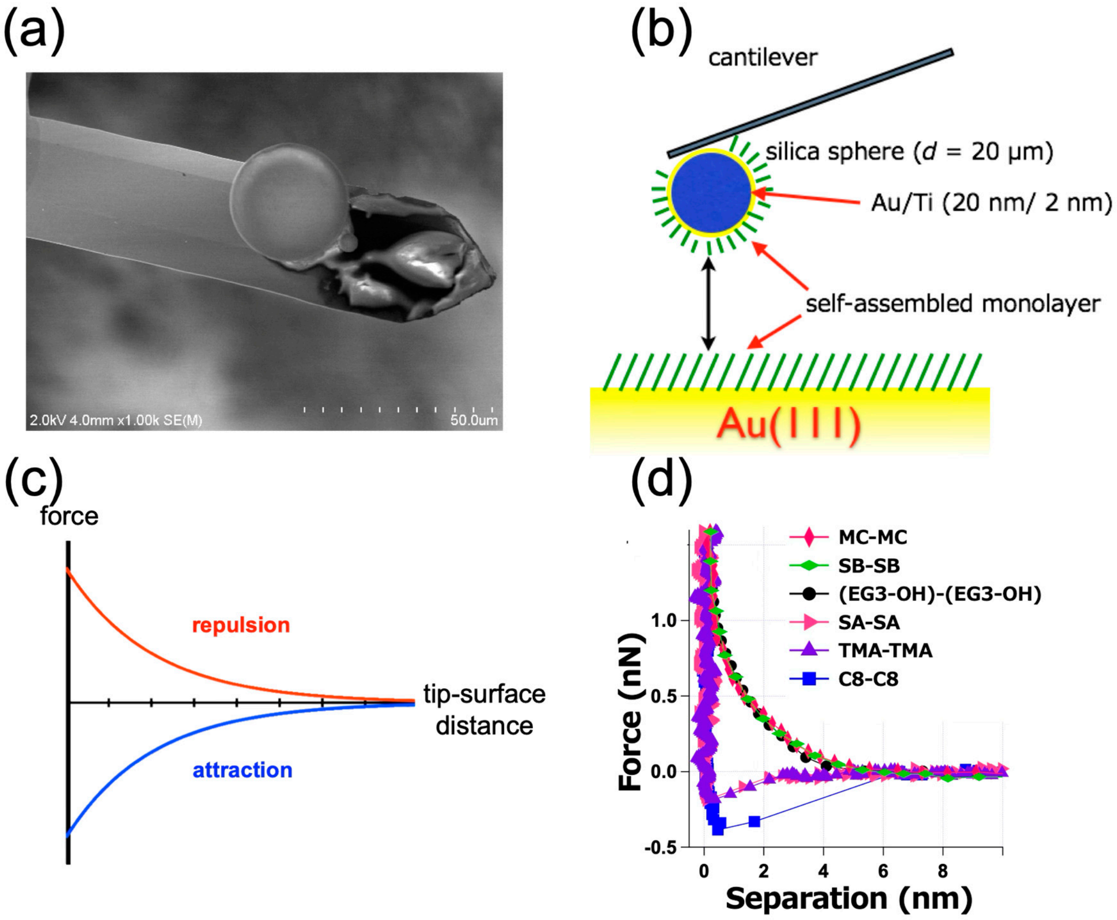

Figure 2. (**a**) Scanning electron microscope image of a colloidal probe (a silica bead with a diameter of 20 μm attached to a cantilever of AFM). (**b**) Experimental configuration of the surface force measurements. Identical SAMs were formed on both the probe and substrate. (**c**) Typical examples of a force–distance curve obtained through surface force measurement; the x and y axes are the surface–probe distance and the surface force, respectively. (**d**) Surface force–distance curves obtained with SAMs comprising C8: $HS\text{-}(CH_2)_7\text{-}CH_3$; SA: $HS\text{-}(CH_2)_{11}\text{-}SO_3^-$; TMA: $HS\text{-}(CH_2)_{11}\text{-}N^+(CH_3)_3$; EG3-OH: $HS\text{-}(CH_2)_{11}\text{-}(O\text{-}CH_2\text{-}CH_2)_3\text{-}OH$; SB: $HS\text{-}(CH_2)_{11}\text{-}N^+(CH_3)_3\text{-}(CH_2)_3\text{-}SO_3^-$; and MC: SA + TMA. EG3-OH, SB, and MC SAMs are protein- and cell-resistant.

5. Design of Bioinert Surfaces Using Information Technology

As mentioned above, the mechanism underlying the bioinertness of non-fouling SAMs has been unveiled, and the design of SAMs with the desired affinity with biomolecules involves difficulties. Although Whitesides' group introduced foundational principles, commonly referred to as "Whitesides' Rules [81]", the practical design of bioinert surfaces remains challenging due to the vast number of potential chemical structures for terminal groups. To address this, regression models that predict biomolecular affinity based on chemical structures are essential. Information technology, particularly data science techniques, offers a promising solution.

The application of materials informatics—leveraging information technology for material design—has shown success in areas like superconductivity, batteries, catalysis, and drug development [104,105]. Accurate prediction of material properties requires large, diverse datasets. For SAM-based surfaces, constructing such datasets involves theoretical calculations and molecular simulations, which systematically vary atomic compositions and chemical bonds. However, designing biomaterials that regulate biomolecular adsorption and cellular behavior has proven more difficult, as data on biomolecule, cell, and tissue responses must be experimentally derived.

Data collection from the published literature has proven useful. Given SAMs' widespread use as model systems to study protein and cell interactions, over a thousand articles exist on protein adsorption onto SAMs [106]. Several research groups have compiled data and developed regression models to predict protein adsorption based on the chemical structures of SAMs. However, inconsistencies in experimental conditions (e.g., protein concentration, solution flux, and measurement techniques) have resulted in significant prediction errors when using literature-based models.

The authors' group addressed these issues with a combinatorial approach, employing SAMs with chemical gradients [22,25]. These SAMs were composed of two distinct thiols, with their mixing ratios varying continuously across the surface. Regression models (an artificial neural network algorithm in this case) (Figure 3a) trained on these datasets enabled the prediction of water contact angles (WCA) (Figure 3b) and the amounts of the adsorbed fibrinogen on the SAMs (Figure 3c) and the quantitative evaluation of structural parameters influencing protein adsorption (Figure 3d). Notably, several groups have reported that the results from these quantitative models align with Whitesides' Rules [107,108]. This convergence suggests that empirical insights initially derived from systematic analyses by Whitesides' group have been transformed into quantitative frameworks for predicting the bioinertness of SAMs.

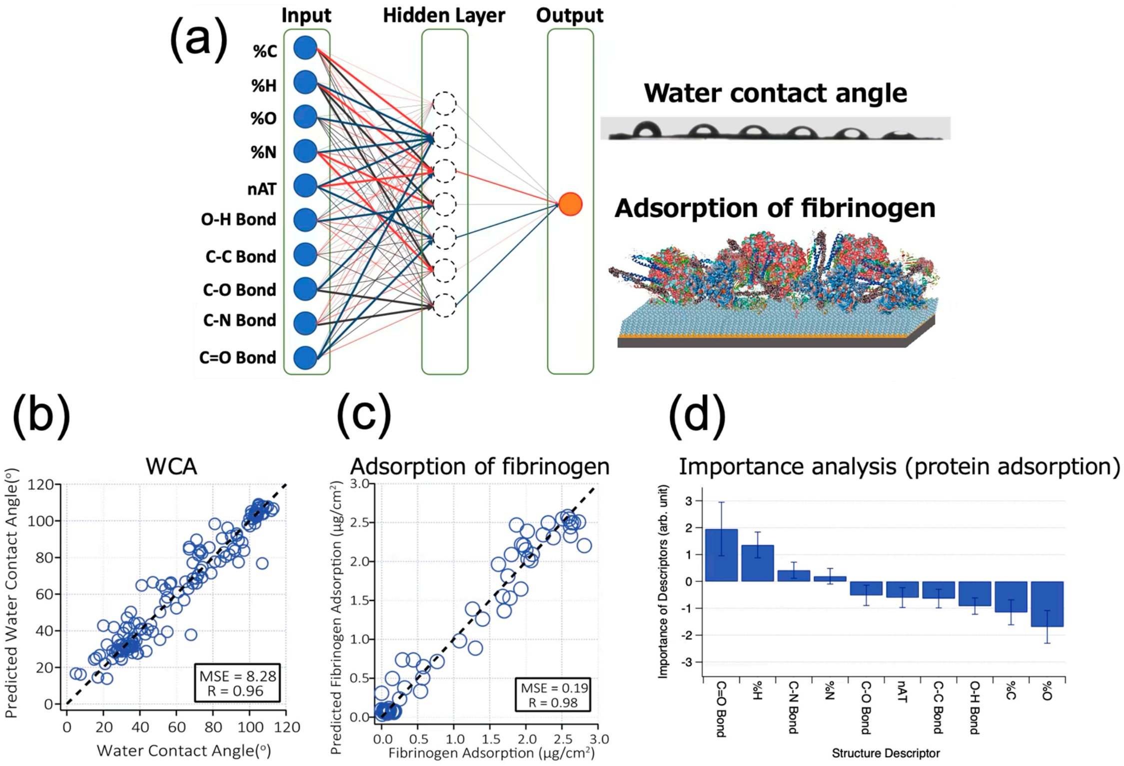

Figure 3. (**a**) Schematic illustration of the artificial neural network to predict water contact angles and amounts of adsorbed protein (fibrinogen) from the chemical structures of the molecules constituting SAMs. Plots of (**b**) predicted amounts of water contact angles and (**c**) amount of adsorbed fibrinogen on the SAMs as a function of their experimental results. The dotted lines denote plots of $y = x$ for eye guides. (**d**) Relative importance of chemical parameters contributing to the amount of the adsorbed fibrinogen.

Machine learning has also been utilized to design polymer-brush films (Figure 4a,b), which are more practical than SAMs due to their superior chemical stability and bioinert properties [109,110]. Remarkably, the machine learning analysis demonstrated that Whitesides' Rules remain valid even for polymer-brush films (Figure 4b). This finding highlights the broad applicability of Whitesides' Rules, extending their relevance beyond SAMs to polymeric biomaterials. These results emphasize the versatility of Whitesides' principles as a foundational framework for guiding the design of diverse bioinert surfaces.

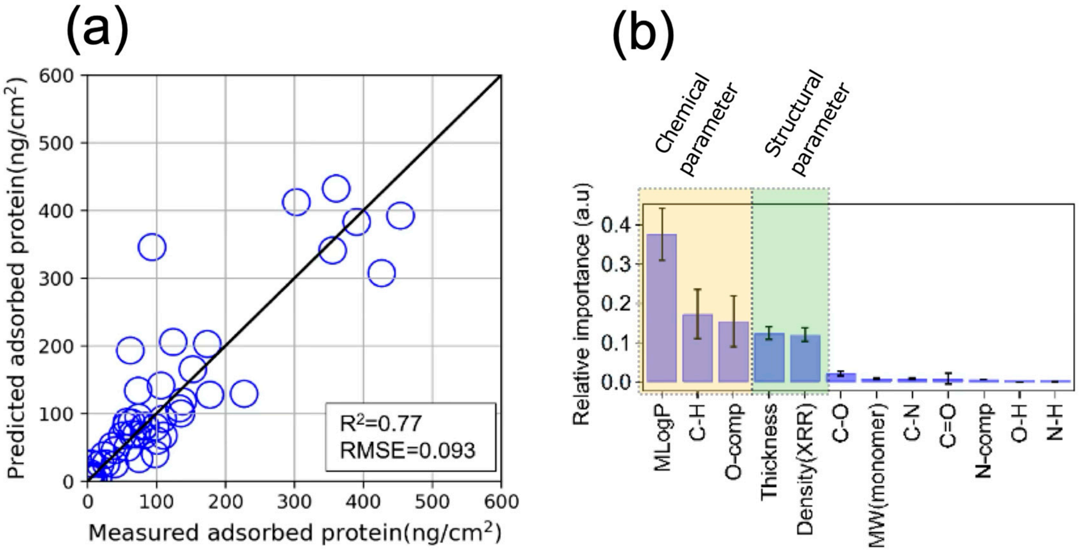

Figure 4. (**a**) Plots of predicted amounts of serum proteins on the SAMs as a function of their experimental results. The dotted line denotes a plot of $y = x$ for an eye guide. (**b**) Relative importance of polymer-brush films' physicochemical parameters contributing to the amount of the adsorbed serum proteins.

6. Concluding Remarks

In this review, the author highlights Prof. George Whitesides' pioneering contributions to the development of self-assembled monolayers (SAMs) and their applications in biointerface research. His groundbreaking studies established a new paradigm for surface coatings using organic molecules, characterized by high reproducibility and well-defined structures. These advancements not only laid the foundation for the field of biointerface science but also catalyzed significant progress in both fundamental and applied research, driving innovation across multiple disciplines in the fields of molecular electronics, biosensing, catalysis, tribology, etc.

Despite the many benefits of SAMs of alkanethiols on gold, there are several weak points of SAMs, including thermal and chemical stability [36,111]. The reinforcement of the intermolecular interaction is a useful approach to improve the thermal stability of SAMs [112]. In addition, appropriate choice of substrate–head group combinations and choice of terminal groups sometimes drastically improve the stability of SAMs [113,114].

The findings discussed in this review underscore the critical role of interfacial water in establishing bioinert properties on self-assembled monolayers (SAMs). Through meticulous surface force measurements [100,115,116] and the application of cutting-edge data science techniques [117], researchers have advanced our understanding of the molecular interactions at biointerfaces. The repulsive forces generated by water layers, spanning a few nanometers, have been identified as a key mechanism that prevents protein and cell adhesion. This interfacial water not only serves as a physical barrier but also exemplifies how biomolecules utilize their surrounding environment to achieve highly specific and functional interactions. Such insights are transformative for the design of bioinert surfaces, particularly in biomedical applications, such as implants, biosensors, and antifouling materials.

Integrating information technology into material design has further opened new avenues for innovation. Materials informatics, although still in its early stages for biointerface engineering, has demonstrated its potential in connecting chemical structures with biological responses. The development of combinatorial approaches and advanced regression models marks significant progress in predicting and tailoring surface properties for desired biological functions [118]. Importantly, the alignment of these data-driven methods with Whitesides' Rules offers a promising path for converting empirical guidelines into robust predictive tools.

Despite challenges, such as data inconsistency and the experimental effort required to study biomolecular and cellular behaviors, the future of biointerface design is exceptionally bright. The increasing availability of high-quality datasets, advances in machine learning algorithms, and interdisciplinary collaborations are poised to accelerate the pace of discovery in this field. Researchers are now better equipped than ever to create highly specific and tunable bioinert surfaces that meet the growing demands of biomedicine and biotechnology.

As we move forward, the implications of this work extend far beyond fundamental science. The principles elucidated here hold the potential to address pressing societal challenges, from improving the biocompatibility of medical devices to developing novel solutions for controlling biofouling and enhancing diagnostics. By bridging the gap between molecular-level understanding and practical applications, the design of bioinert surfaces is not only advancing our scientific knowledge but also inspiring a future where material science and biology work hand in hand to create transformative solutions.

This journey of exploration exemplifies how curiosity-driven science, coupled with technological innovation, can lead to breakthroughs with profound real-world impact. The strides made in this field should motivate researchers, engineers, and clinicians to continue pushing boundaries, ensuring that the next generation of materials serves humanity in increasingly meaningful ways. The progress so far is only the beginning of an exciting chapter in biointerface research—a field rich with opportunities and limitless potential.

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