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Machine Learning Aided Design and Optimization of Antifouling Surfaces

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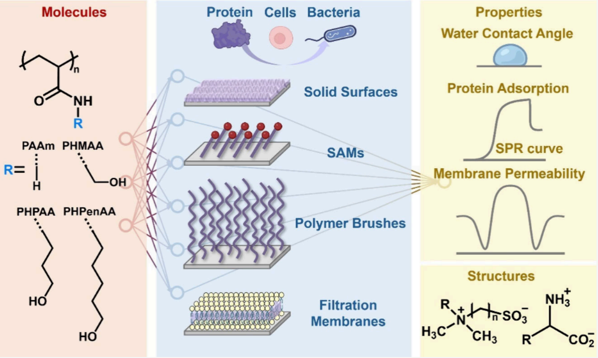

ABSTRACT: Antifouling surfaces, renowned for their strong surface resistance to proteins, cells, or tissues in various biological and environmental conditions, have broad applications in implanted devices, antibacterial coatings, biosensors, responsive materials, water treatment, and lab-on-a-chip. While extensive experimental research exists on antifouling surfaces, machine learning studies on this topic are relatively few. This perspective specifically focuses on exploring the complex relationships between the composition, structure, and properties of antifouling surfaces, examining how these factors correlate with surface hydration and protein adsorption. Different machine learning models have been developed to analyze and predict single and multiple protein adsorptions on various types of surfaces, ranging from structureless surfaces to well-ordered and rigid self-assembled monolayers, dynamically ordered polymer brushes, and complex filtration membranes. These models not only identify key descriptors or functional groups critical for antifouling performance (surface hydration, protein adsorption) but also predict the antifouling properties for a specific surface. Recognizing current challenges, this perspective delineates future research directions in the antifouling field. By leveraging and comparing current machine learning approaches, it aims to advance both the design and fundamental understanding of antifouling surfaces, thereby pushing the boundaries of innovation in this critical field.

1. INTRODUCTION

Antifouling surfaces are engineered by coating materials like self-assembled monolayers, polymer brushes, and membranes onto substrates to prevent the nonspecific adsorption of biomolecules and organisms such as proteins, cells, and bacteria.[1−4] A fundamental principle guiding the design of antifouling surfaces is to minimize the interactions and adhesion of biomolecules and organisms with the coated materials, tailored for specific applications across various environments.[5] This principle is particularly effective, as most antifouling surfaces are inherently hydrophilic. Surface hydrophilicity promotes strong hydration, which serves as both energetic and physical barriers for preventing other molecules from displacing water molecules bound to the surface and subsequently adhering to it, thereby enhancing the antifouling properties.[6−8] Two polymer types contribute to the formation of a stable hydration layer on surfaces: hydrophilic polymers, such as poly(ethylene glycol) (PEG),[9,10] poly(acrylamide),[11] poly(saccharides),[12] polypeptoids,[13] and poly(hydroxyethyl methacrylate),[14] establish this layer through hydrogen bonding, while zwitterionic polymers like poly(sulfobetaine methacrylate) (pSBMA),[15−21] poly(carboxybetaine methacrylate) (pCBMA),[21,22] poly(carboxybetaine acrylamide),[23,24] and poly(3-(1-(4-vinylbenzyl)-1H-imidazol-3-ium-3-yl)propane-1-sulfonate) (pVBIPS)[25,26] predominantly use ionic solvation, supplemented by hydrogen bonding, to achieve hydration.[27] The relationship between surface hydration and the antifouling properties of polymers has been assessed through water contact angle measurements, which give a macroscopic view of surface hydration. Additionally, sum frequency generation (SFG) vibrational spectroscopy provides a deeper analysis into water structures at the polymer−water interface. SFG characterizes surface hydration by studying the vibrational properties of interfacial water molecules on various surfaces, including polymers, lipids, and proteins, with a focus on the O−H stretching modes indicative of hydrogen bonding and

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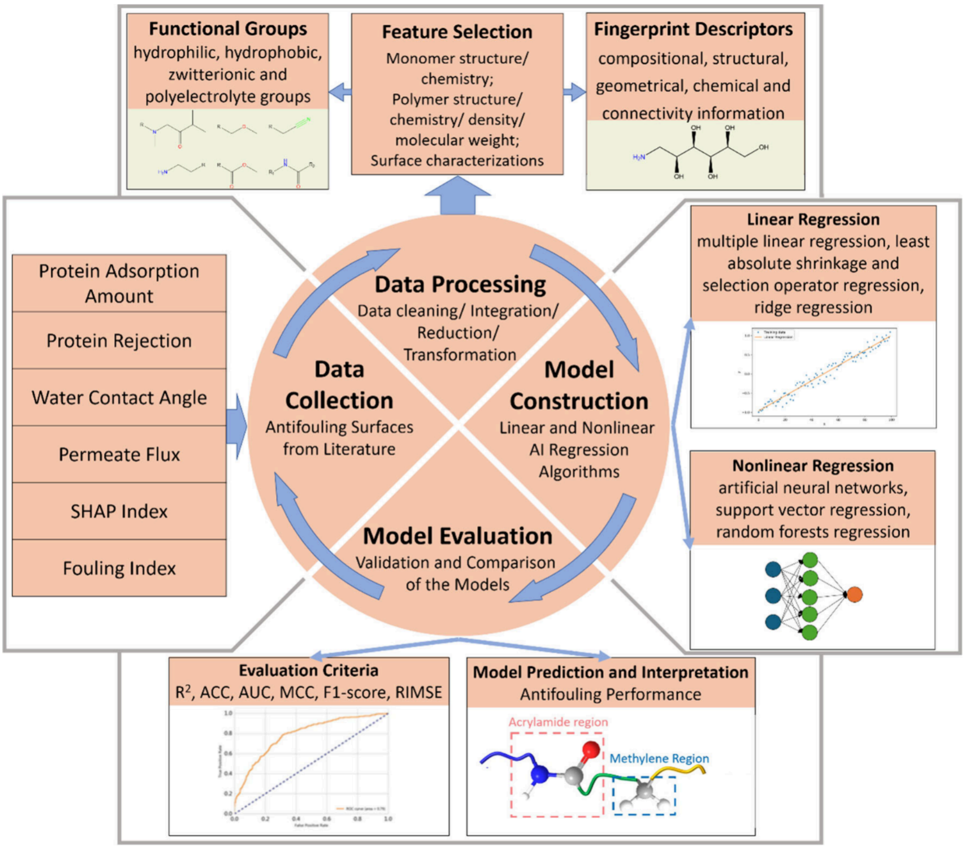

Figure 1. A general workflow in machine learning protocol of antifouling surfaces.

hydration.[28−31] By analyzing the SFG spectra, especially the O−H stretch region, it is possible to determine the presence, orientation, and bonding state (free OH groups vs hydrogen-bonded OH groups) of water molecules at the interface, a molecular indicative of surface hydration. Furthermore, the effectiveness of surface hydration is determined by the materials intrinsic properties including chemical composition, hydrophobicity, charge distribution, and molecular weight, as well as by surface characteristics like packing density, film thickness, roughness, and polymer chain conformation. Many antifouling polymers, used for coating surfaces, are applied via graft-to or graft-from techniques. These advanced surface modification methods, incorporating controlled polymerization technologies, enable precise manipulation of surface properties at the nanoscale to enhance antifouling effectiveness.

In parallel, advanced molecular dynamics (MD) simulations have provided critical insights into the role of surface hydration in conferring antifouling properties on surfaces. These MD simulations assess antifouling efficacy by examining the structure, dynamics, and interactions of water molecules at the interfaces of coatings, illustrating how behaviors of interfacial water contribute significantly to the antifouling efficacy of these surfaces. These simulations also measure repulsive forces between foulants and antifouling surfaces.[32−38] Furthermore, MD simulations explore how various factors such as carbon spacer lengths,[32] surface terminal groups,[33] surface dipole orientations,[39] surface hydrophilicity,[40] and surface grafting density[34] influence the antifouling capabilities of these surfaces. For instance, MD simulations of different self-assembled monolayers (SAMs),[41−43] poly(*N*-hydroxyalkyl acrylamides) (PAMs) brushes,[32] and zwitterionic brushes[44] have revealed that (1) PEG-, PC-, and OH-terminated SAMs strongly interact with interfacial water, indicating that surface hydration is crucial for antifouling, (2) pHMAA and pHEAA with shorter side chains (CSLs = 1−2) establish more robust hydration layers than those with longer chains (pHPAA, pHPenAA with CSLs = 3,5), and (3) pCBMA, pSBMA, and pMPC displayed stronger water interactions than PEG, with pCBMA showing the highest protein resistance and hydration strength.

While extensive experiments and MD simulations have deepened our understanding of antifouling surfaces,[44,45] they often rely on empirical, trial-and-error methods focused on specific materials, which lack the extraction of systematic insights from large-scale data. The advent of big data, artificial intelligence, and high-performance computing has facilitated data-driven, machine learning approaches to design new antifouling materials and surfaces. While there have been only a limited number of machine learning studies specifically targeting antifouling surfaces, the past five years have witnessed a significant expansion in data-driven computational research in polymer area.[46−48] While machine learning strategies generally follow a set process for designing and optimizing antifouling coatings (Figure 1), they also encounter some challenges in collecting and translating complex, heterogeneous data into effective, actionable design strategies. A major challenge in the antifouling research field (data scarcity issue) is the absence of standardized antifouling databases, requiring researchers to manually compile experimental data from scattered studies to construct databases for modeling. This challenge is further complicated by inconsistencies in antifouling performance across different laboratories (data quality issue), even when the same materials are used. Variations in synthesis conditions and characterization methods contribute to these discrepancies, adding layers of complexity to efforts in data training and analysis.

While still in early stages, this perspective on machine learning approaches for antifouling surfaces presents recent advancements in the field. It explores the molecular basis of antifouling surfaces and compares various machine learning methods applied to solid surfaces, self-assembled monolayers, polymer brushes, and membranes. Special attention is given to how machine learning predicts the physical and chemical properties of these surfaces and identifies key descriptors for improving antifouling effectiveness. The perspective concludes with insights into how these methods can guide the design of new antifouling polymers from the molecular to the macroscale.

2. APPLICATION OF MACHINE LEARNING IN ANTIFOULING SURFACES

While machine learning is an emerging technique primarily applied to the design of inorganic solid materials such as metal,[49−51] ceramics,[52] zeolites,[53,54] and metal−organic frameworks (MOFs),[55,56] which benefit from extensive data sets, well-characterized molecular structures, and consistent chemical/physical/biological properties, its application to antifouling surfaces remains underexplored. These studies are largely summarized in Table 1 and Figure 2. This section explores how machine learning can optimize the formulation and performance of antifouling coatings, including solid surfaces, SAMs, polymer brushes, and filtration membranes, with specific focuses on predicting and analyzing the interactions between various materials and environmental factors. The four surfaces were selected based on the availability of machine learning models that have been used to analyze specific antifouling characteristics of these surfaces. These studies not only demonstrate the applicability of machine learning but also underscore the relevance of common surface hydration mechanisms in antifouling across diverse surfaces. It further discusses the potential for machine learning algorithms to revolutionize the design process by identifying novel materials and surface structures that enhance antifouling efficacy.

Solid Surfaces. The Biomolecular Adsorption Database (BAD 2.0),[57] accessible at https://www.bionanoinfo.com/bad/, features a comprehensive collection of 865 protein adsorption records. These records support the construction of three types of descriptors: proteins from the Protein Data Bank (PDB), surfaces (hydrophobicity, water contact angle, or surface tension), and biological media solution (pH, ionic strength, and protein concentration). Three machine learning models of linear regression, ridge regression, and random forest regression, along with BAD 2.0, were developed to identify and quantify the physical and chemical properties of three types of descriptors, as well as to establish semiempirical relationships for predicting protein adsorption on both hydrophobic and hydrophilic surfaces based on operational, structural, and molecular properties of proteins, surfaces, and fluid media. The importance analysis in Figure 2a indicates that operational parameters influence protein adsorption differently on hydrophobic and hydrophilic surfaces. For both types of surfaces, protein concentration in the solution and fluid temperature significantly affect adsorption, particularly on hydrophilic surfaces. Ionic strength shows minimal impact overall. Interestingly, the contact angle's relevance is minimal

Table 1. A Survey of Machine Learning Studies on Antifouling Surfaces over the Past Five Years

System	Machine Learning Models	Data set	Key Descriptors	Ref
solid surfaces	linear regression, ridge regression, and random forest regression	111 for hydrophobic surfaces, 71 for hydrophilic surfaces	global protein properties for hydrophilic surfaces, specific protein properties for hydrophobic surfaces	57
SAMs	artificial neural network, supporting vector regression	48	Group 1, 4, 9, 10	62
SAMs	artificial neural network	145	O% (representing hydrogen bond acceptors), O−H (representing hydroxyl terminal groups)	61
zwitterionic polymer brushes	random forest regression	123	polymer density, molecular weight,	65
polymer brushes	artificial neural network, supporting vector regression	91 for SVR model, 94 for ANN model	charge−charge energy, Mi, C-005, and C-007 in ANN model; groups 2 (amino acid-based), 3 (sulfobetaine), 4 (secondary amide), 7 (carboxybetaine), and 8 (isopropanol alcohol-like) in SVR model	63
polymer brushes	random forest regression	51	hydrophobicity index, the thickness and density of polymer brush films, the number of C−H bonds, the net charge of the monomer, and film density	64
membranes	random forest regression, artificial neural network	692 for permeate flux, 505 for random forest model	membrane pore size, transmembrane pressure	70

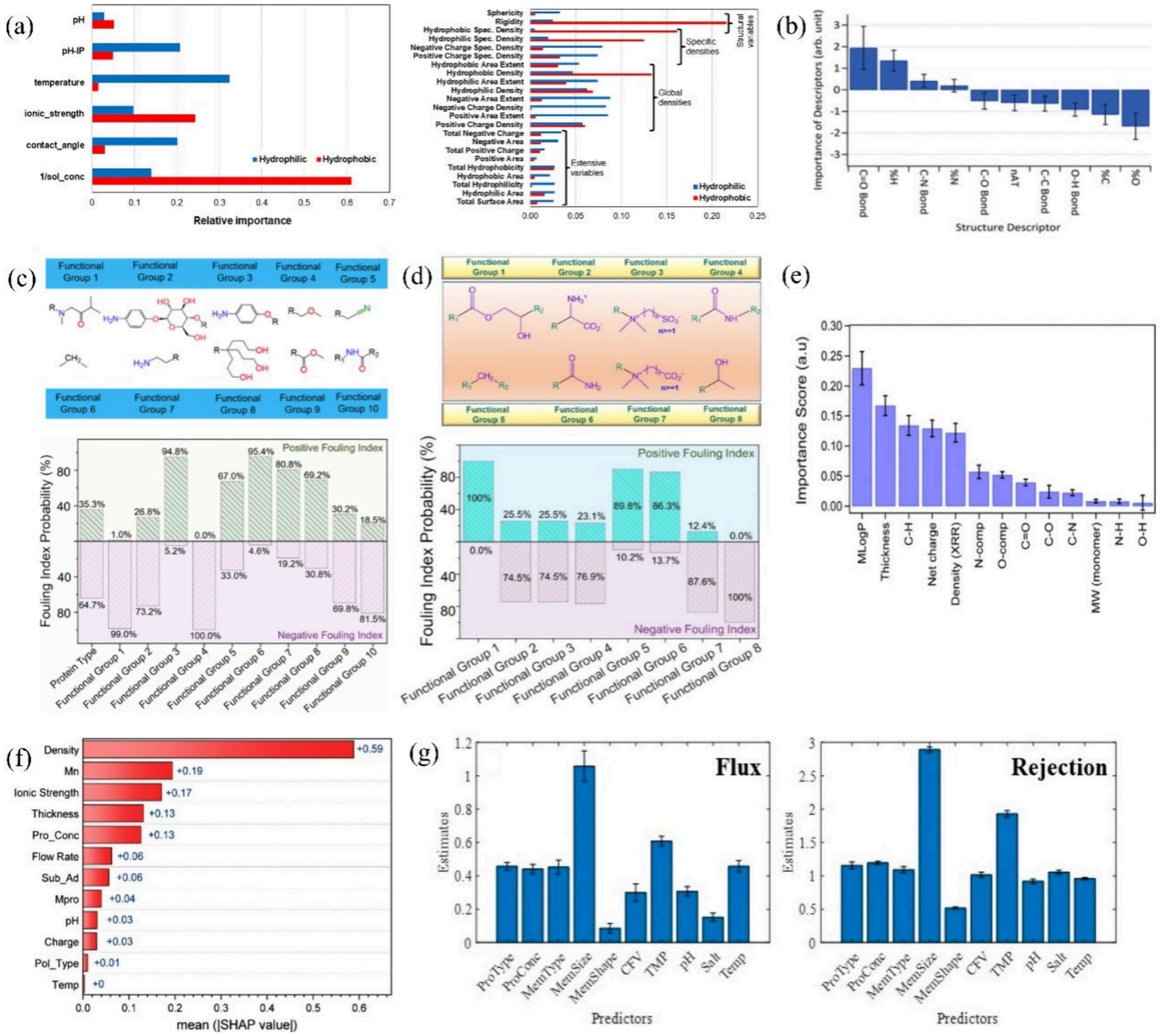

Figure 2. Comparative importance of various descriptors in machine learning models for antifouling surfaces. (a) Importance analysis of the operational and protein-derived descriptors for protein adsorption on hydrophobic and hydrophilic surfaces.[57] Reproduced with permission. Copyright 2024, American Chemical Society. (b) Importance analysis of 10 structural descriptors in determining fibrinogen adsorption on SAMs.[61] Reproduced with permission. Copyright 2020, American Chemical Society. (c) Fouling index probability (%) of 10 different functional groups in relation to protein adsorption on SAMs by a four-layer artificial neural network.[62] Reproduced with permission. Copyright 2021, American Chemical Society. (d) Fouling index probability (%) of 8 different functional groups in relation to protein adsorption on polymer brushes by a supporting vector regression (SVR) model.[63] Reproduced with permission. Copyright 2021, Elsevier. A positive fouling index in (c) and (d) indicates that the functional group promotes protein adsorption on SAMs, while a negative index indicates an antifouling property. (e) Importance analysis of 13 descriptors in determining serum protein adsorption on polymer brushes.[64] Reproduced with permission. Copyright 2022, American Chemical Society. (f) The mean Shapley additive explanations (SHAP) values for 12 crucial descriptors of zwitterionic polymer brushes, where a higher SHAP value corresponds to lower protein adsorption, indicating enhanced antifouling properties.[65] Reproduced with permission. Copyright 2024, American Chemical Society. (g) Importance analysis of 10 parameters in determining permeate flux and protein rejection.[70] Reproduced with permission. Copyright 2023, American Chemical Society.

for adsorption on hydrophobic surfaces, but for hydrophilic surfaces, pH, pH-IP, and contact angle are crucial factors. The analysis of protein-derived descriptors reveals that protein adsorption on hydrophilic surfaces largely depends on global protein properties, including total positive, total negative charges, and their ratio, total hydrophilic, total hydrophobic, and their ratio characteristics. Conversely, on hydrophobic surfaces, protein adsorption is more influenced by specific protein properties, which are the global properties normalized by the protein surface area. This study highlights how solution conditions and protein characteristics differently affect protein adsorption on hydrophobic versus hydrophilic surfaces. Given the simplification of solid surfaces in the models, future research should enhance these predictive semiempirical relationships by incorporating detailed structural and physicochemical surface parameters. This will provide a more accurate understanding of how these factors interact and influence protein adsorption across different surface types.

Self-Assembled Monolayers (SAMs). Self-assembled monolayers (SAMs), first developed in 1946,[58] are renowned for their molecular-level surface uniformity, high packing density, diverse structures, and minimal surface defects. These features make SAMs as ideal surface-active materials for studying protein adsorption, enabling early and extensive use in such research around the 2000s.[59] A notable study by Whitesides et al. surveyed protein adsorption on various SAMs with different functional groups using Surface Plasmon Resonance (SPR).[60] Unexpectedly, this research, after 20 years, provided a valuable data set (referred to the Whitesides Data set) that is now essential for developing machine learning models to understand the composition-property relationships in antifouling SAMs.

A artificial neural networks (ANN) model was developed using data from 145 SAMs to predict both the water contact angle and fibrinogen adsorption on SAMs.[61] This model identified ten structural descriptors and evaluated their importance for both water contact angle and fibrinogen adsorption. Among these descriptors in Figure 2b, only two—O% (representing hydrogen bond acceptors) and O−H (representing hydroxyl terminal groups)—contribute to both low water contact angles (high surface wettability) and low fibrinogen adsorption (high antifouling property). The other eight descriptors do not show a consistent correlation between water contact angle and fibrinogen adsorption, indicating that water contact angle is not a perfect indicator of protein resistance, aligning with our general perception.[1,6,7] The ANN model also indicates that alkyl chains longer than six units are not sensitive to protein adsorption on SAMs. Instead, the terminal groups are critical properties in determining both water contact angle and protein adsorption. Additionally, the ANN trained with the single-lab data set (the Whitesides Data set) provided more accurate predictions than the ANN trained with the multilab data set, indicating that the model accuracy critically depends on the consistency and quality of the data set used for training.

The above-discussed machine learning studies on antifouling SAMs primarily focus on analyzing the relationship between the structural composition and antifouling properties of existing SAMs, rather than developing new ones. These studies utilize descriptors such as N-066, N-067, C-002, C-006, and AlogP, which do not have a clear physical or chemical rationale, complicating the direct design of innovative antifouling SAMs. Recently, a machine learning model was developed using the Whiteside Data set to computationally analyze the structure, chemical, and surface features of SAMs in relation to antifouling activity.[62] This model utilizes a combination of factor analysis of functional groups (FAFG), Pearson analysis, random forest (RF), ANN, and Bayesian statistics. Unlike traditional models that use basic descriptors, this approach uses FAFG to encode comprehensive data of 43 descriptors into 10 functional groups (Figure 2c), which are then analyzed to determine their contribution to protein adsorption capacity, quantified through ANN and Bayesian statistics. It was observed that functional groups 1, 4, and 10, possessing a high negative fouling index between 81.5% and 100%, are highly hydrophilic and include hydrogen bond acceptors and donors such as O−, OH−, NH−, COO−, and $-NR_3$. This composition endows SAMs with these groups exceptional surface resistance to proteins, attributed to their ability to establish a robust hydration layer through hydrogen bonding. Leveraging the established relationship between functional groups and protein resistance in SAMs, new SAMs were developed combining a common methylene backbone (group 6) and acrylamide (group 10) with various terminal groups (1−9). This innovation led to the synthesis of two SAMs that exhibited exceptional resistance to protein adsorption, achieving levels as low as ~3/ ~ 2 and ~7/ ~ 4 ng/cm^2 from undiluted blood serum/plasma by SPR. These results were attributed to the effective use of an amide group as an anchor and a functional terminal group in the designs.

Hydrophilic Polymer Brushes. Polymer brushes represent another class of surface-active materials, which attain high packing densities and exhibit well-defined surface structures at the nanoscale,[59] similar to SAMs, but through a more dedicated and controlled radical polymerization. These brushes offer flexible modification of (i) pendant and terminal chemistries across various properties such as chemical structure, hydrophobicity, charge distribution, and molecular weight; (ii) surface characteristics like grafting density, thickness, roughness, and conformation, providing a versatile toolkit for specific applications.[5] Building on the versatile and highly customizable nature of polymer brushes, the progression into machine learning approaches represents a significant advance.

To develop machine learning models for the characterization and design of polymer brushes, data sets comprising 14 zwitterionic and 14 hydrophilic polymer brushes, each with unique spatial, compositional, and interaction properties, were utilized to construct two machine learning models:[63] (i) an ANN model with 94 data sets using gross-level, property-based descriptors aimed at either repurposing or discovering existing antifouling polymer brushes, and (ii) an SVR model with 91 data set employing fragmental-level, group-based descriptors aiming to design new antifouling polymer brushes. In the ANN model for repurposing or discovering antifouling polymer brushes, four out of seven descriptors—charge−charge energy, Mi, C-005, and C-007—demonstrated potent protein resistance, evidenced by very high negative fouling indexes between 98% and 100%. Conversely, the remaining three descriptors, RBF (78.7%), O% (73.6%), and ALOGP (97.9%) contributed significantly to high protein adsorption. Differently, in the SVR model, assisted by factor analysis and Bayesian statistics, eight functional groups critical for influencing protein adsorption and resistance were identified. As shown in Figure 2d, groups 2 (amino acid-based), 3 (sulfobetaine), 4 (secondary amide), 7 (carboxybetaine), and 8 (isopropanol alcohol-like) showed high probabilities (74.5−100%) of negative fouling indexes, indicating strong protein resistance. Conversely, group 5 (methylene), group 1 (high oxygen content), and group 6 ($-NH_2$ terminal) displayed high positive fouling indexes (86−100%), categorizing them as fouling-induced groups. Leveraging the predictive relationship between descriptors/groups and protein resistance, the ANN and SVR models successfully guided the development of six polymer brushes—three repurposed and three newly designed, all of which exhibited exceptional surface resistance to protein adsorption, ranging from 0.0 to 9.0 ng/cm^2 when tested with undiluted human blood serum and plasma, consistent with the model predictions.

In a recent study, a consistent data set comprising 51 polymer brushes using five different monomers—HPMA, DMAEMA, HEMA, CBMA, and EG—was established. Each brush was analyzed for their film thickness, grafting density, and serum protein adsorption by Surface Plasmon Resonance (SPR). This study, the first to synthesize, characterize, and compile a data set within the same laboratory, provided a reliable foundation for constructing a descriptor-based Random Forest (RF) regression machine learning model,[64] aiming to establish a correlation between serum protein adsorption on polymer brushes and the physicochemical and structural properties of the monomers and brushes. In Figure 2e, the importance analysis of 13 descriptors demonstrates that with a threshold value of 0.12, factors like the hydrophobicity index (MLogP), the thickness and density of polymer brush films, the number of C−H bonds, the net charge of the monomer, and film density play a crucial role (0.22−0.12). In contrast, other descriptors such as N-comp, O-comp, C−O, C═O, C−N, MW, N−H, and O−H are of less importance (<0.06), particularly monomer molecular weight and the number of O−H bonds, which can be disregarded. Pearson correlation analysis shows that film thickness and grafting density exhibit a complex correlation with protein adsorption, depending on the structure and physiochemistry of the grafted polymers. For instance, while thicker polyDMAEMA and polyHEMA brushes promote protein adsorption, thicker polyHPMA, PEG, and polyCBMA brushes reduce protein adsorption. Additionally, except for polyDMAEMA brushes, other hydrophilic and zwitterionic brushes with higher grafting density reduce protein adsorption. These contrasting antifouling effects stem from the strength of hydration layers and the steric repulsion induced by polymer chains with varying degrees of flexibility.

Zwitterionic Polymer Brushes. Compared to nonionic hydrophilic polymer brushes that adopt diverse chemical structures and achieve surface hydration via hydrogen bonding, zwitterionic polymer brushes exhibit limited chemical diversity. These brushes typically consist of a few types of anionic groups, such as phosphorylcholine, sulphobetaine, and carboxybetaine, combined with predominantly ammonium cations, all tethered to the polymer backbone. Their zwitterionic nature enables superior antifouling properties by forming strong electrostatic interactions with water molecules, enhancing stability and effectiveness compared to hydrophilic brushes that rely on hydrogen bonding for hydration.

In a recent study applying machine learning to analyze protein adsorption on zwitterionic polymer brushes, Random Forest Regression was utilized to process data from 123 zwitterionic brushes.[65] This data, gathered from various studies, included 12 descriptors split into three categories: five brush properties (density, molecular weight, thickness, polymer type), six solution properties (pH, temperature, concentration, protein characteristics, ionic strength), and one operational parameter (flow rate). Upon analyzing the Shapley additive explanations (SHAP) values for various descriptors (Figure 2f), polymer density (+0.59) emerged as the most influential parameter, suggesting that higher polymer density effectively inhibits protein adsorption by promoting osmotic pressure against protein insertion into the polymer layer. Polymer molecular weight (+0.19) also significantly impacts protein adsorption by increasing the distance between the substrate surface and the solution. While polymer density more significantly influences protein adsorption than its molecular weight, both higher polymer density and molecular weight contribute to the steric repulsion effect observed in experiments with graft polymers.[27,66] This effect creates a physical separation that impedes proteins from approaching and adhering to the surface. Other factors (0.06−0.13) such as ionic strength, protein concentration, and flow velocity showed intermediate importance, whereas solution temperature, pH, protein properties, and polymer type exhibited negligible effects on protein adsorption (<0.05). Similar to another study using an ANN model,[63] zwitterionic polymer brushes characterized by descriptors such as charge−charge energy, molecular interactions (Mi), and the methyl groups of betaine (C-005) achieved exceptionally low protein adsorption levels, approximately 5 ng/cm^2.

It should be noted that both SAMs and polymer brushes share common antifouling mechanisms, such as strong surface hydration and high grafting density. However, SAMs, characterized by their rigid and short chains, and polymer brushes, with their longer chains, exhibit significant differences in their mechanisms of steric repulsion, which is a critical factor in their antifouling performance. Polymer brushes, with their long chains, provide sufficient elasticity to effectively repel proteins through steric hindrance as proteins approach and compress these chains. This results in superior antifouling properties. Therefore, the optimal antifouling performance for polymer brushes is achieved through a combination of maximal surface hydration and effective steric repulsion to resist protein adsorption.

Filtration Membranes. Building on the foundation set by SAMs and polymer brushes as ideal surface-active materials, the design of antifouling microfiltration (MF) and ultrafiltration (UF) membranes is progressing toward practical applications. These advancements are characterized by the deployment of MF membranes for efficient protein retention and UF membranes for the removal of bacteria, particulates, and cell debris from various feeds.[67−69] In a machine learning study aimed at addressing protein fouling in MF and UF membranes,[70] two models were applied: Random Forest (RF) and Neural Network (NN) to analyze how ten input parameters (protein and membrane characteristics, and operating conditions) impact protein rejection and permeate flux. The RF model focused on determining the influence of these variables on fouling, while the NN model was used to predict their effects on membrane performance. This approach enhances the understanding and predictive capability regarding fouling mechanisms in MF and UF membranes. In Figure 2g, the analysis of ten input parameters on protein fouling indicators—steady state flux and protein rejection—highlights membrane pore size and transmembrane pressure as the most influential factors. Given the sieving mechanism of MF and UF, optimizing size ratio between protein and membrane pore size and adjusting transmembrane pressure are crucial in microfiltration and ultrafiltration processes to enhance resistance to protein fouling. Conversely, salt concentration and the type of membrane configuration, such as flat sheet, tubular, or hollow fiber, are identified as the least impactful parameters on protein fouling. However, existing models fail to consider the significant impact of surface interactions between proteins and the membrane, which experiments have yet to thoroughly document, potentially influencing protein fouling on membranes.

3. COMPARATIVE MACHINE LEARNING APPROACHES IN ANTIFOULING SURFACES

Machine learning approaches in antifouling research are transitioning from traditional Quantitative-structure−prop-

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erty/activity-relationship (QSPR/QSAR) models to more complex algorithms. Despite limited studies, various machine learning methods—categorized into nonlinear regression algorithms including ANN, Support Vector Regression (SVR), Random Forests Regression (RFR) and linear regression algorithms including Multiple Linear Regression (MLR), Least Absolute Shrinkage and Selection Operator Regression (LASSO), Ridge Regression—have been applied to identify critical descriptors of surfaces, proteins, and operating conditions.[57,61−64,70] These methods aid in designing, optimizing, and predicting the effectiveness of antifouling surfaces, leveraging complex data analyses to enhance material performance in preventing biofouling.

When comparing different machine learning approaches for antifouling surfaces, each has distinct advantages and drawbacks. A study of protein adsorption on zwitterionic polymer brushes[65] revealed that nonlinear regression models such as RFR, Gradient-Boosted Regression (GBR), and Extra-Tree Regression (ETR) significantly outperform linear models like MLR, LASSO, and Ridge Regression, as evidenced by higher R^2 scores and lower Root Mean Square Error (RMSE), indicating that the protein adsorption process is too complex to be adequately described by simply summing up each descriptor linearly. Furthermore, additional machine learning studies on antifouling surfaces have predominantly utilized ANN, SVR, and RFR, consistently highlighting the efficacy of nonlinear models in accurately predicting protein adsorption on these surfaces compared to traditional linear models in addressing the complexities of antifouling phenomena.

Table 2 provides a comparative view of the three nonlinear regression techniques, highlighting their learning mechanisms, structural complexities, methods for handling nonlinearity, interpretability, and scalability. Specifically, among ANN, SVR, and RFR, ANNs are particularly adept at modeling nonlinear relationships and managing large, complex data sets for antifouling SAMs,[61,62] polymer brushes,[63] and membranes.[70] This capability stems from their design, which mimics the human brain's neuronal structure. ANNs correlate inputs and outputs through interconnected neurons in hidden layers, using transfer functions to capture complex data patterns. This makes them highly effective for predicting antifouling surface performance under varying conditions. However, ANNs require substantial, high-quality training data to function optimally, heavily relying on the consistency and quality of the data set provided. SVR provides a robust alternative for smaller data sets, excelling in constructing predictive models by determining the optimal hyperplane that minimizes prediction errors while maximizing the margin between data points. This technique effectively identifies crucial factors influencing antifouling performance of SAMs[62] and polymer brushes.[63] However, the SVR model's complexity can make it challenging to interpret, which may obscure the understanding of intricate relationships between variables. RFR, a decision tree-based approach, offers robust applications for machine learning in antifouling surfaces including solid surfaces,[37] polymer brushes,[64,65] and membranes.[70] Decision Trees are straightforward and interpretable, employing numerous independent decision processes with outcomes derived from a majority vote or mean prediction, enhancing accuracy and robustness. However, they are susceptible to overfitting, especially with noisy data sets. It is important to recognize that, unlike SVR which employs kernel functions to analyze and interpret complex data relationships, both ANN and RF models are

Table 2. Key Differences among Nonlinear Regression Algorithms of Artificial Neural Networks (ANN), Support Vector Regression (SVR), and Random Forests Regression (RFR) Commonly Used in Machine learning Models for Antifouling Surfaces

	ANN	SVR	RFR
Learning Mechanism	Utilizes a back-propagation process, cycling back from output to hidden layers for weight updates.	Employs an optimization process focused on margin maximization with kernel transformation.	Uses an ensemble learning method where multiple decision trees contribute to the final output.
Structural Complexity	Composed of multiple layers (input, hidden, output) with interconnected nodes.	Features a simpler, linear-like structure until transformed by the kernel trick.	Consists of numerous decision trees, each representing a subset of features and data points.
Handling Nonlinearity	Uses activation functions (e.g., ReLU, sigmoid) at nodes to handle nonlinearity.	Applies a kernel trick to project data into a higher-dimensional space, revealing hidden patterns.	Manages nonlinearity by averaging multiple decision trees, each fitted on different parts of the data.
Interpretability	Often considered a "black box" due to its complex network structure and internal transformations.	Relatively more interpretable because the role of the support vectors and the kernel function is clearer.	Highly interpretable as individual decisions and the importance of features can be examined in each tree.
Scalability	Highly scalable with increasing data and complexity but requires significant computational power.	Scalable to high-dimensional data but may become computationally intensive with large data sets.	Very scalable, especially with large data sets, and can handle high feature dimensions efficiently.
Specific Antifouling Surface Properties	SAMs and associated descriptors and chemical groups; polymer brushes and associated descriptors; filtration membranes and membrane properties	SAMs and associated chemical groups; polymer brushes and associated descriptors	zwitterionic polymer brushes and associated polymer properties; polymer brushes and associated descriptors; filtration membranes and membrane properties

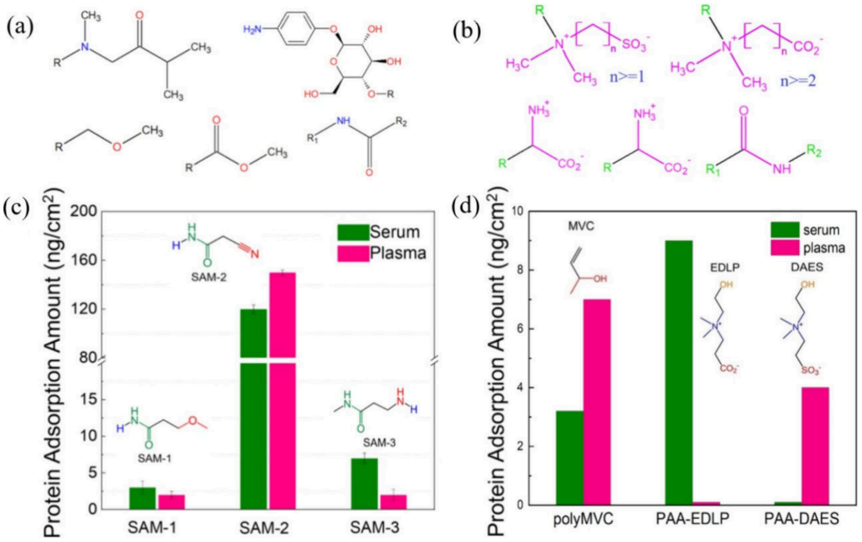

Figure 3. Machine learning-enabled inverse molecular design of new antifouling surfaces. Functional groups critical for (a) antifouling SAMs[62] (Reproduced with permission. Copyright 2021, American Chemical Society) and (b) antifouling polymer brushes[63] (Reproduced with permission. Copyright 2021, Elsevier). Design, synthesis, and evaluation of protein resistance in (c) three newly SAMs and (d) three newly synthesized polymer brushes—polyMVC, PAA-EDLP, and PAA-DAES—tested against undiluted human serum and plasma, demonstrating the effectiveness of functional group-based design in reducing protein adsorption.[63]

considered “black box” models. These models do not require explicit governing equations to handle antifouling phenomena in both classification and regression tasks, allowing for flexible applications without detailed understanding of the underlying mechanisms.

Each machine learning model brings specific advantages and challenges to antifouling research. ANNs are highly accurate but require extensive data and computational power. SVR models are robust and efficient even with smaller data sets but are complex to optimize. RFR excel in accuracy and provide insights into feature importance but perform best with large data sets. The choice of model often depends on the data set nature, availability of inputs, desired properties, and the trade-off between model interpretability and predictive performance. Selecting the right model can significantly enhance the development of innovative antifouling materials, leading to more effective solutions across various applications.

4. DESIGN PARAMETERS FOR ANTIFOULING SURFACE VIA MACHINE LEARNING PREDICTIONS

Upon identifying key descriptors and functional groups as major contributors to antifouling materials, inverse molecular design is often employed to design new antifouling materials and identify optimal experimental conditions. From a descriptor-based design perspective, four key descriptors—charge−charge energy, Mi, CH_3X, and CH_2X_2 —demonstrate significant protein resistance,[63] achieving fouling indexes as high as 98−100%. The zwitterionic groups encoded by charge−charge energy and CH_3X create ionic hydration barriers that effectively hinder protein adsorption. This aligns with the empirical understanding that charge neutrality is a crucial condition for ensuring surface resistance to protein adsorption.[66] The Mi descriptor, indicating the scaled first ionization potential, is typically found in polar or hydrophilic groups containing nitrogen and oxygen atoms that facilitate hydrogen bonding with water. Meanwhile, CH_2X_2 relates more to the structural integrity of the polymer backbone, providing mechanical support that enhances the stability and protein resistance of the polymer brushes. Conversely, hydrophobic index, the number of C−H bonds (representing methylene groups), a higher ratio of oxygen atoms (O%), charged -NH_2 group are identified as critical factors that enhance protein adsorption.[63,64] Due to the use of different data sets, descriptors, and training algorithms, some machine learning studies have yielded contradictory results. For instance, hydrophilic descriptors such as N−H and O−H bonds, crucial for forming hydrogen bonds with water, show minimal impact on protein adsorption or desorption in one study[64] but are significant factors in another.[61] The former finding contradicts surface hydration theory, which emphasizes groups like amide, hydroxyl, and ethylene glycol as essential for antifouling materials due to their hydrogen bonding capabilities. These discrepancies may arise because structure−property relationships are based on monomer structures rather than polymer conformations.

Unlike more abstract descriptors, functional groups provide straightforward chemical structures essential for material design and discovery. This direct representation facilitates easier application in developing and repurposing antifouling materials. Functional groups in Figure 3a,b, including amino acid-based group, sulfobetaine group, secondary amide group, carboxybetaine group, and isopropanol-like group with high negative fouling indexes, are strongly associated with protein resistance. These groups, containing either zwitterionic or hydrogen-bonding moieties, effectively interact with water molecules to establish a strong hydration layer that prevents protein adsorption.[63] Guided by the established relationship between functional groups and protein resistance, an SVR models facilitated the design and synthesis of three new SAMs (Figure 3c) and three new polymer brushes (Figure 3d). The three SAMs are based on a common backbone of methylene linked with hydrophilic acrylamide groups, terminated with hydrophilic NH−, N═, and −O− groups. Among these in Figure 3c, SAM-1 and SAM-3, featuring hydrogen bonding groups, demonstrated excellent resistance to protein adsorption, achieving levels of approximately 3/2 and 7/4 ng/cm^2, respectively, from undiluted blood serum/plasma. Conversely, SAM-2, which incorporates charged groups, exhibited significantly higher protein adsorption levels, at around 120/150 ng/cm^2. Three new polymer brushes include poly(methyl vinylcarbinol) (polyMVC), composed of isopropanol-like and vinyl groups; poly(hydroxyethyl)dimethylammonio)-propanoate (polyEDLP), consisting of sulfobetaine, methylene, and hydroxyl groups; and poly(hydroxyethyl)-dimethylammonio)ethane-1-sulfonate (polyDAES), made from carboxybetaine, methylene, and hydroxyl groups. Using Surface-Initiated Atom Transfer Radical Polymerization (SI-ATRP) to create polymer brushes on gold substrates, SPR spectra in Figure 3d indicated very low protein adsorption from undiluted blood serum/plasma: 3.2/7.0 ng/cm^2 on polyMVC, 9.0/0.0 ng/cm^2 on polyEDLP, and 0.0/4.0 ng/cm^2 on polyDAES. These results validate the SVR model's accuracy in designing these surfaces as highly effective antifouling materials.

Apart from either descriptors or functional groups, some physical parameters are identified by machine learning as major contributors to antifouling performance. Examples include membrane pore size and transmembrane pressures, which effectively prevent protein adsorption on MF and UF membranes.[70] For polymer brushes, the brush thickness is a critical factor for significantly influencing protein adsorption, with a specific optimal thickness identified that minimizes such adsorption.[63,64] Deviations from this optimal thickness, either too low or too high, have been shown to increase protein adsorption to some extent. Various theories and experimental findings have highlighted the crucial roles of grafting density, chain length, and end-group hydrophobicity in determining antifouling performance. However, grafting density has emerged as more influential than chain length in enhancing antifouling efficacy.[71−73] This influence is attributed to steric repulsion where compressed polymer chains in a thermodynamically unfavorable state repel water molecules bound to the layer, suggesting that antifouling efficacy should improve with increased chain length and grafting density of polymer chains.

5. CONCLUSION

While antifouling surfaces continue to evolve with effective, robust, and straightforward designs, the complexity of fouling processes implies that no single solution will suffice. Instead, diverse material design strategies are required for the rapid development of next-generation antifouling materials and surfaces, aimed at bridging fundamental research with practical applications. Despite advancements, there remains a pressing need for more effective designs at the molecular level. In this regard, the development of data-driven, machine learning approaches is crucial for designing, engineering, characterizing, and predicting antifouling surfaces. These approaches are employed to extract, learn, evaluate, and manipulate data, revealing intricate relationships that govern antifouling mechanisms. This drives the continuous exploration and rational design of innovative antifouling solutions.

While machine learning approaches for antifouling surfaces are still emerging, they have demonstrated significant potential in designing and predicting new materials from limited data sets. However, the field faces substantial challenges. First, the complexity of antifouling surfaces arises from the need to molecularly characterize coating materials, surface attributes, and proteins as primary foulants, along with the intricate interactions among these components. Systematically exploring the extensive variety of factors necessary to interpret the compositional, structural, geometrical, and connectivity information related to antifouling surfaces, coating materials, and processing conditions presents a formidable task. This complexity introduces significant obstacles in analyzing and optimizing antifouling surfaces effectively. To address this issue, the acquisition and expansion of high-quality data, which can capture both the structural and property domains of soft materials, are essential for developing advanced machine learning algorithms that can effectively design and evaluate soft materials beyond just antifouling materials and surfaces. Second, the lack of high-quality, consistent experimental data poses considerable obstacles in modeling the complexities of antifouling surfaces. Moreover, a limited pool of molecular descriptors from small data sets hinders effective characterization of material properties and their protein interactions. This requires the necessity for better data encoding methods to effectively capture the complex interplay between material structure and function. On the other hand, massive data mining from open sources is not always necessary; the innovative extraction of all possible information from limited data to perform advanced material design also proves a more challenging but rewarding strategy, emphasizing the efficient use of available data.

Current machine learning models for antifouling surfaces primarily use intrinsic material properties such as chemical structure, hydrophobicity, charge distribution, and molecular weight to predict antifouling performance based on metrics like water contact angle for surface hydration and protein adsorption for surface resistance. However, these models often overlook other critical surface attributes such as packing density, layer thickness, surface roughness, and chain conformation, which also significantly impact antifouling effectiveness. For instance, incorporating factors like polymer chain length, flexibility, and packing density could enhance the understanding of "steric repulsion" mechanisms, further elucidating how these factors combine with surface hydration to influence antifouling performance. Moreover, relying solely on structure−property relationships derived from monomers may neglect the conformational characteristics of polymers, rendering it insufficient for accurately describing the properties of materials coated on surfaces. Finally, incorporating molecular descriptors derived from molecular simulations—such as atom types, functional groups, fragment counts, and topological and geometrical features—can significantly refine the structural information essential for material design, enhancing its relevance and applicability. Future research should focus on integrating comprehensive data sets and refining ML models to better capture the intricate relationships between surface properties and antifouling performance. By leveraging these advanced computational approaches, researchers can further optimize antifouling surfaces, ultimately enhancing their efficacy and broadening their application scope.

In a broader perspective, the integration of artificial intelligence (AI) into materials science, chemistry, and physics offers grand opportunities yet challenges for polymer design beyond antifouling materials. This includes merging (i) physics-based and data-driven computational methods (e.g., combining theoretical frameworks with machine learning or integrating molecular simulations with AI) and (ii) computational and experimental approaches to drive the design, synthesis, and characterization of new polymers through machine learning. To address these challenges in polymer design, a key priority is to develop extensive, uniform polymer platforms that aggregate a wide range of polymer informatics—covering molecular, structural, physical, chemical, and spectral data, as well as synthetic routes and reaction conditions. This initiative would involve collaborative efforts from industries, universities, national laboratories, and federal agencies. These platforms would integrate and standardize various existing polymer data sets, such as SMILES and BigSMILES, to ensure consistency in data formats, quality, and standards. This standardization would allow users to effectively select, extract, and analyze data on specific polymer families using machine learning algorithms. Second, complementing extensive experimental data, the enhancement of data through various computational methods offers significant value. Techniques such as quantum mechanics, molecular dynamics, Monte Carlo, and coarse-grained simulations can provide atomic-level information on polymers, which is often unobtainable through experimental methods alone. This approach not only fills gaps in experimental data but also enriches the understanding of polymer behaviors and properties. Additionally, the ongoing development of machine learning algorithms, including transfer learning, deep learning with regularization algorithms, and Bayesian methods, that do not necessarily depend on large data sets is essential for advancing our understanding of polymers. These algorithms are particularly valuable because they allow researchers to extract meaningful insights from limited data, which is often the case in specialized fields like polymer science where extensive data sets may not be readily available. These advancements in machine learning are expected to accurately identify structural features that influence protein adsorption, facilitating rapid discovery and better understanding of functional antifouling materials and coatings.

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Notes

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