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Review

Advances in Antibacterial Polymer Coatings Synthesized via Chemical Vapor Deposition

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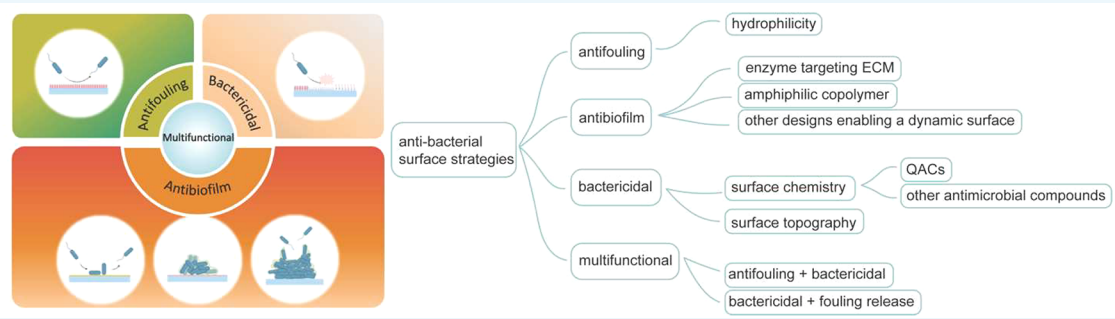

ABSTRACT: Biofouling is a major issue across various industries ranging from healthcare to the production of food and water and transportation. Biofouling is often induced or mediated by environmental microbes, such as bacteria. Therefore, developing antibacterial coatings has been an essential focus of recent research on functional polymer thin films. To achieve high film quality, vapor-phase techniques represent promising alternatives to traditional solution-based methods, especially for the design and synthesis of antibacterial polymer coatings, as they enable highly uniform, chemically precise, and substrate-independent coatings. This Perspective examines the potential of vapor-phase polymerization techniques to create novel antibacterial polymer coatings. Current advancements in the design of antifouling, bactericidal, antibiofilm, and multifunctional coatings via vapor-phase techniques are organized based on their action mechanisms and design principles. The opportunities and challenges associated with implementing vapor-phase polymerization for developing antibacterial coatings are highlighted.

KEYWORDS: *antibacterial, biofouling, chemical vapor deposition, polymer thin film, functional coating, biomaterials*

1. INTRODUCTION

Biofilms are ubiquitous in nature. These surface-attached bacterial communities form quickly on virtually any submerged surfaces, causing biofouling that challenges a broad cross-section of applications, such as implants or chronic infections in healthcare,[1] contaminations in food manufacturing,[2] efficiency reduction in water purification,[3] and increased fuel consumption for maritime transportation.[4] Taking healthcare as an example, the growing number of bacterial infections caused by fomite transmission (e.g., via surfaces of public facilities or medical devices) and contamination of implants or other devices have posed significant challenges to public health and safety.[5] Traditional approaches, such as chemical disinfection, have been plagued by issues related to bacterial resistance and environmental pollution, necessitating the development of strategies that do not rely on toxic chemicals to combat biofouling caused or mediated by bacteria.[6] One promising approach is the use of polymer coatings to prevent bacterial adhesion and proliferation on surfaces. In this Perspective, we aim to provide an overview of the recent progress in the design and synthesis of such polymer coatings, which we termed "antibacterial polymer coatings" to capture relevant functions, including prevention of bacterial adhesion, inhibition of growth or biofilm formation, or combinations of both. We focus on the coatings synthesized using chemical vapor deposition (CVD) techniques for their distinct advantages, as detailed below.

Key considerations in choosing an appropriate synthesis or coating technique for a particular antibacterial application include the compatibility with the substrate to be coated (e.g., reverse osmosis membranes are incompatible with organic solvents) and the coating conformality (e.g., ventricular catheters have 3D structures that need to be preserved). CVD-based techniques show distinct advantages over solution-based approaches in both regards.[7] The substrate-independ-

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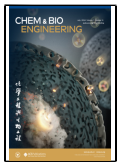

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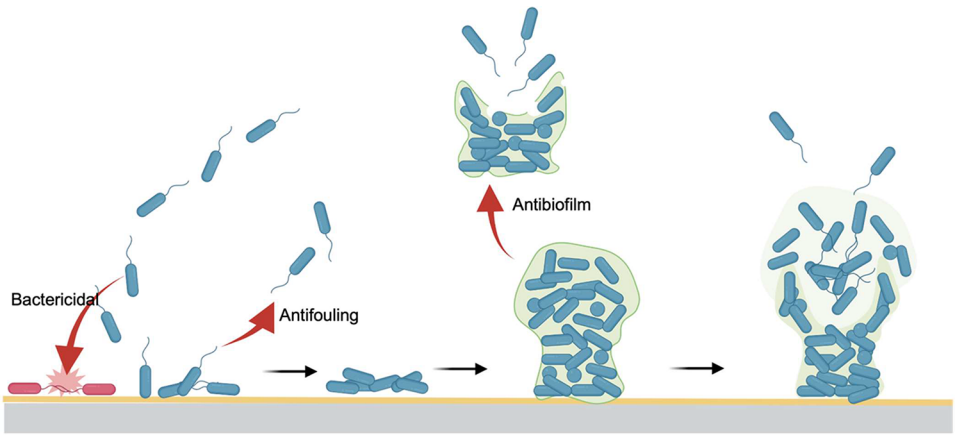

Figure 1. Antibacterial mechanisms considered in this Perspective include antifouling, bactericidal, antibiofilm, and combinations of two or three of these mechanisms.

ence of CVD processes partially arises from their all-dry nature, where delicate substrates like textiles are coated by simple exposure to a reactive vapor free from the potential damage caused by organic solvents. The van der Waals interactions between the as-deposited coating and a solid substrate, enabled by the physisorption of gaseous monomers on a substrate during CVD, are sufficient in most cases for preventing coating delamination. This intrinsic quality ensures precise control over coating chemistry and thickness regardless of the substrate characteristics. This versatile characteristic of CVD techniques enables the individual optimization of surface and bulk properties, allowing for the transfer of antibacterial surface chemistries to virtually any substrate.[8] Demonstrated through techniques like initiated chemical vapor deposition (iCVD), this feature allows for successful coating application across scales from centimeters to nanometers, including high-aspect-ratio structures.[9,10]

CVD polymer synthesis techniques have been of particular interest to researchers in the field of antibacterial coatings. Their substrate independence and conformal coverage are critical for rendering the large surface area of porous materials antifouling, thus addressing a bottleneck issue in membrane separation and purification/MEMS processes.[11] They excel in retaining intricate surface morphology, thus ensuring conformal coverage, by avoiding surface tension and delivering reactants in a non-line-of-sight fashion due to Knudsen diffusion into micro- and nanoscale features.[11] In addition, conformal CVD polymer thin films at the nanoscale have proven valuable in diverse applications, including the application of conformal iCVD fluoropolymer nanocoatings on single-wall carbon nanotubes (SWCNTs) for high-speed flexographic printing of transistors,[12] as well as the surface modification of membranes used in water purification processes.[13] In antibacterial research, this unique advantage of CVD-based techniques allows for the surface modification of various natural and nature-inspired micro/nanostructures, such as those mimicking cicada wings[14] or shark skin,[15] while retaining their surface topography. CVD polymer coatings on such surfaces have demonstrated the ability to maintain the bactericidal effect induced by the surface topography while introducing antibacterial chemical functionalities to further enhance the overall antibacterial effectiveness.[16,17]

Over the past decade, vapor deposition methods have enabled the synthesis of a wide variety of functional polymers for antibacterial purposes, most notably zwitterionic polymers, which have become the gold standard in antibiofouling research, and ultrastable antifouling coatings, which leverage the tunable cross-linking density that is unique to CVD polymerization techniques, especially to iCVD. Among the CVD polymerization techniques, we chose to focus on iCVD, plasma-enhanced chemical vapor deposition (PECVD), and paracyclophane-based CVD, as these techniques take precedence in the creation of antibacterial surfaces via vapor-based techniques. Within this scope, we further chose to emphasize innovations in materials design or modes of action that enable antibacterial performance.

Compared to previous reviews on the topic of CVD-synthesized antifouling coatings,[18−20] which predominantly focus on the physicochemical interactions at the bacteria−material interface, we aim to provide a more comprehensive discussion by including the dynamic and intricate biological processes at play during biofouling. Take bacterial biofilm formation as an example (Figure 1), which presents a significant challenge to global health by causing drug-resistant and/or chronic infections, as well as device contamination and performance degradation in bioimplants, water purification, food production, and marine transportation.[21] It occurs over a four-stage process, including (1) reversible attachment, where bacteria attach to the substratum, e.g., via the cell pole or via the flagellum,[22] (2) irreversible attachment, where bacterial cells commit to a more stable surface existence, e.g., by forming attachment along their longitudinal axis, which is often associated with the production of extracellular matrix (ECM) components and reduced flagella reversal rate and flagella gene expression; (3) maturation, where cell clusters (often several cell layers thick) appear within the ECM, forming microcolonies with stable 3D structures, and (4) dispersion, where ECM components decrease and degrade, dispersing motile cells.[23,24]

Within the scope of the design and synthesis of CVD polymer coatings for dynamic antibacterial functions, we first briefly review several frequently used CVD techniques and the types of antibacterial polymer coatings that can be synthesized using these methods. The bulk of this review comprises a discussion on the design of antibacterial materials (Figure 1), which are categorized into antifouling (i.e., prevention of microbial adhesion and accumulation), bactericidal (i.e., eradication of microbes upon contact), antibiofilm (i.e.,

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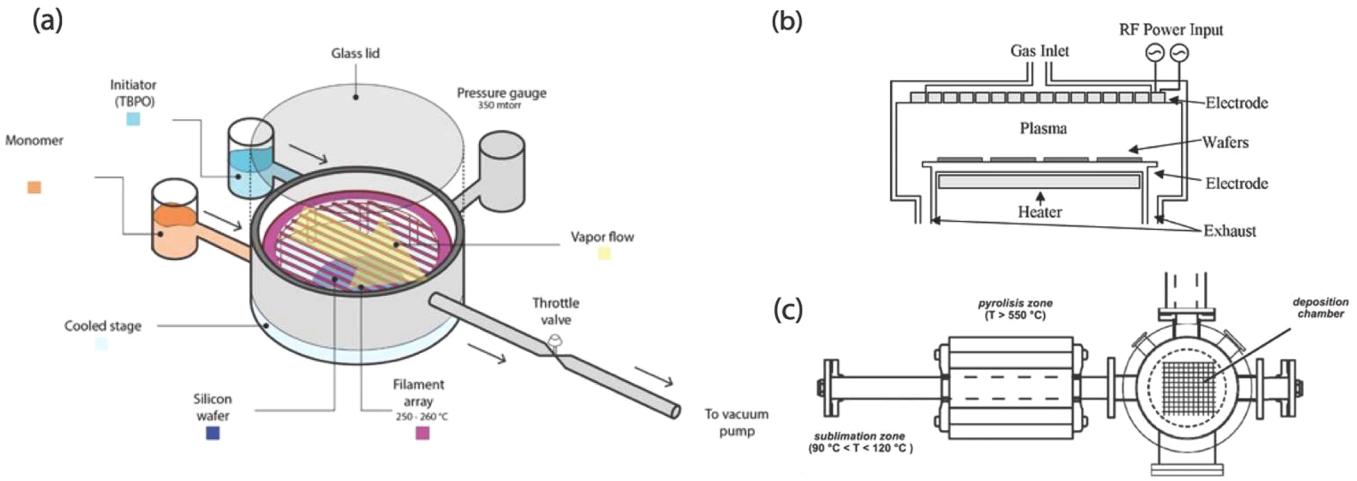

Figure 2. Schematic of CVD polymerization techniques. (a) iCVD. Reproduced with permission from ref 36. Copyright 2021, The Authors, under the terms of the Creative Commons (CC BY 4.0) License https://creativecommons.org/licenses/by/4.0/. (b) PECVD. Reproduced with permission from ref 37. Copyright 2011, Springer Science Business Media, LLC. (c) Paracyclophane-based CVD. Reproduced with permission from ref 32. Copyright 2022, The Authors. Published by Wiley-VCH GmbH.

inhibition of the formation or disruption of a surface-attached microbial community with 3D structures), and multifunctional coatings (i.e., a combination of the aforementioned three categories, mostly antifouling and bactericidal properties). Furthermore, we will address the challenges and opportunities associated with the development and implementation of CVD polymer coatings for antibacterial applications. By providing a thorough understanding of the current state of the art and potential future directions, we hope to inspire further research and innovation in this critical area of materials science and public health.

2. CVD POLYMERIZATION TECHNIQUES

CVD, a mature technology in the semiconductor industry, is a powerful tool for creating and processing inorganic and organic surfaces. When it comes to organic material synthesis, it is key to maintain a low process temperature to avoid damaging the material. Various CVD-based polymerization processes are classified based on their mechanism for activating the reactive precursors to enable the polymerization reaction. Activation can occur through thermal means (iCVD and hot wire CVD), UV exposure (photo-iCVD), or plasma excitation (initiated PECVD). While most CVD polymerization techniques rely on step growth polymerization, including oxidative CVD (oCVD), vapor-phase polymerization, molecular layer deposition, and oxidative molecular layer deposition,[18] chain growth polymerization has been achieved using iCVD, where a volatile initiator enables free-radical polymerization.

The iCVD technique has played a pivotal role in enabling numerous antifouling coatings owing to its distinctive advantages. Indeed, the fields of iCVD polymer coatings[1] and antibacterial polymer coatings both emerged in the past few decades[2] and have been interacting synergistically. While early iCVD research drew inspiration from solution-synthesized antibacterial polymers, it is advancing the field of antibacterial polymers through the development of new chemistries, reactions, and previously unknown biological effects of insoluble polymer coatings. Several discoveries that originated in iCVD have been adopted by antimicrobial material researchers in general.[25] The iCVD process scheme is depicted in Figure 2a. Activation of the initiator occurs thermally as it passes through a heating zone, leading to the generation of radicals. Subsequently, these radicals collide with the monomers adsorbed on the actively cooled substrate, initiating polymerization in a chain growth fashion. Notably, the deposition kinetics of iCVD have been extensively investigated, particularly in nanoconfined areas challenging for conventional coating techniques to access.[26,27] Compared to other CVD polymerization techniques, iCVD avoids the use of high-energy activation methods, such as plasma in PECVD or high temperatures in paracyclophane-based CVD, mitigating potential material degradation and ensuring maximum retention of organic functional moieties.[25] Importantly for the development of antibacterial materials, iCVD demonstrates chemical versatility, enabling CVD polymer chemistries unique to iCVD, such as zwitterionic polymers, a subject that will be elaborated upon in detail in section 3.

In PECVD, polymerization is activated by low-temperature inductively/capacitively-coupled plasma generated by direct current or radio frequency (RF) power (Figure 2b).[28,29] The properties of thin films produced by PECVD are influenced by parameters such as RF power, plasma temperature, reactor pressure, gas-phase diffusion, and gas flow rate, as well as the types of carriers and reacting gases. Due to the presence of plasma, material etching and film deposition occur simultaneously during PECVD, which may produce coatings that are less conformal over micro- and nanostructures. Moreover, the high-energy plasma in PECVD limits its applicability to fragile substrates such as soft tissue scaffolds.

Paracyclophane-based CVD, also known as parylene CVD or chemical vapor polymerization (CVP), has been instrumental for interface engineering in biological applications, such as implantable electronic devices.[30] Various substituted [2,2]paracyclophanes (PCPs) have been developed as precursors, showcasing diverse functional groups. The preservation of these functional groups during the CVD process enabled the deposition of functionalized parylene films with tailored chemical, mechanical, and electrical properties. In the polymerization of parylene-C, the precursor undergoes sublimation under a vacuum and heat. The sublimed precursor is then transported into the heated reactor for pyrolysis, producing two 1,4-quinodimethane radicals (*p*-xylylene) that

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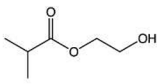
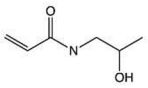
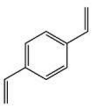
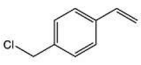
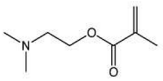
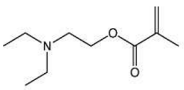
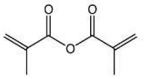
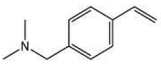
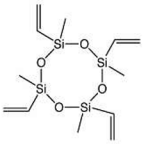
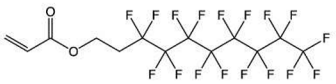
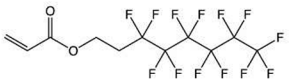
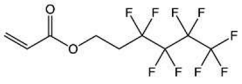
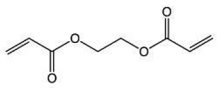
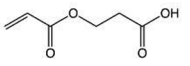
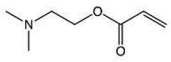
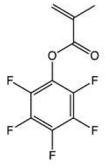
Table 1. Monomers Discussed in Sections 3−7 of This Review Are Listed in the Order That They Are Mentioned[a]

Molecular Structure	Acronym	Monomer	Features
	HEMA	2-hydroxyethyl methacrylate	●
	VP	vinyl pyrrolidone	●
	HPMA	hydroxypropyl methacrylate	●
	MAA	methacrylic acid	● ●
	AA	acrylic acid	● ●
	VI	vinyl imidazole	● ●
	DVB	divinylbenzene	● ●
	VBC	vinylbenzyl chloride	●
	DMAEMA	2-(dimethylamino)ethyl methacrylate	● ●
	DEAEMA	laminoethy 2-diethylaminoethyl methacrylate	● ●

Molecular Structure	Acronym	Monomer	Features
	MAH	methacrylic anhydride	●
	DMAMS	dimethylamino methyl styrene	● ●
	V4D4	1, 3, 5, 7-tetramethyl-1, 3, 5, 7-tetravinyl cyclotetrasiloxane	● ●
	PFDA	1H, 1H, 2H, 2H-perfluorodecyl acrylate	●
	PFOA	1H, 1H, 2H, 2H-perfluorooctyl acrylate	●
	HFBA	2, 2, 3, 4, 4, 4-hexafluorobutyl acrylate	●
	EGDA	Ethylene glycol diacrylate	●
	CA	2-carboxyethyl acrylate	● ●
	DMAEA	2-(dimethylamino)ethyl acrylate	● ●
	PFPMA	pentafluorophenyl methacrylate	●

● positively charged ● negatively charged ● hydrophilic ● hydrophobic ● crosslinker ● precursor for zwitterionic polymer ● precursor for anchoring enzyme

[a]The colored dots identify the key antibacterial attributes.

polymerize into parylene via step growth (Figure 2c).[31] This technique has seen an expansion of the library of compatible functional moieties through precursor decoration and post-CVD fabrication strategies, as comprehensively reviewed elsewhere.[32] Moreover, these strategies have been applied to develop antibacterial surfaces via topographical[33] and chemical designs.[34,35]

3. ANTIFOULING SURFACES

Antifouling surfaces are designed with features that prevent biological matter (e.g., protein, bacteria, marine organisms, etc.) from attaching. The surface features that have been engineered to deliver antifouling properties include surface energy, surface chain mobility, local and overall charge, surface morphology, and stimuli responsiveness.[38,39] Despite this large variety, most extant antifouling coatings rely on strong hydration or chemical ambiguity to achieve fouling resistance. The hydration-driven antifouling mechanisms rely on the formation of a strongly bonded hydration layer, leading to a large enthalpic penalty for the displacement of surface-bonded water molecules by fouling organisms.[40] Zwitterionic polymers bearing covalently linked cationic and anionic groups represent best-in-class hydration-based antifouling materials. Their antifouling performance is often attributed to the electrostatically induced strong hydration.[41] This class of materials has demonstrated broad-spectrum fouling resistance against proteins, polysaccharides, marine bacteria, barnacle cyprids, and mussel larvae.[42,43] Over the past two decades, zwitterionic materials have become some of the most reported antifouling polymers discovered to date.[43] The ambiguity-driven antifouling mechanisms are often at play for amphiphilic antifouling copolymers, i.e., copolymers that simultaneously contain hydrophilic and hydrophobic moieties. Their fouling resistance is considered a result of the intrinsic high density of phase

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boundaries (e.g., between a hydrophilic and a hydrophobic domain),[44] creating an "ambiguous" surface for foulants.[42,45] Notably, amphiphilic coatings made of oligopeptides or oligopeptoids have been shown to reduce settlement of *Ulva linza*, a model organism commonly used in marine fouling studies.[42,46,47] In general, these materials, especially the hydration-based antifouling polymers, embody the widely accepted design rules reported by Whitesides et al., which specify that a good antifouling surface should exhibit (1) polar functional groups to ensure hydrophilicity, (2) a hydrogen bond acceptor (e.g., oxygen- and nitrogen-containing groups) but not a hydrogen bond donor and 3) charge-neutrality.

A sizable library of antifouling polymer coatings has been developed using iCVD over the past decade, including poly(2-hydroxyethyl methacrylate) (HEMA),[48] poly(vinylpyrrolidone) (VP),[49−51] poly(hydroxypropyl methacrylate) (HPMA),[52] poly(methacrylic acid) (MAA),[53−55] zwitterionic polymers,[56,57] and amphiphilic polymers.[58] For instance, a heparin-like coating consisting of PMAA grafted on PMAA-*co*-ethylene glycol dimethacrylate (PMAA-*co*-EGDMA) on a polylactide (PLA) dialysis membrane was synthesized using iCVD.[54] The resulting membrane retained its hydrophilicity with a static water contact angle of 33° and less than 10% reduction in water flux, indicating reasonable retention of permeability. The copolymer-grafted membrane showed a higher clearance rate for urea (147.5 mL/min) and lysozyme (103.5 mL/min) compared to the pristine membrane (89.1 mL/min for urea and 62.4 mL/min for lysozyme), yet its clearance rate for bovine serum albumin (BSA) was reduced compared to that of the pristine membrane. Its antifouling performance was measured via a protein (BSA) adsorption test by exposing membranes to BSA solutions with different concentrations and volumes before and after 4 h of adsorption at 37 °C using the Bradford assay. The grafted membrane showed BSA adsorption of ∼0.6 $\mu g/cm^2$ in a 50 $\mu g/mL$ BSA solution, which was about a 97% reduction compared with the pristine PLA membrane.

PECVD has also contributed to the development of antifouling coatings. One recent example involves the deposition of a hydrophilic 1-vinyl-2-pyrrolidinone (NVP) and poly(ethylene glycol)methacrylate (PEGMA) coating onto orthokeratology lenses as an antifouling measure.[59] Given the delicate nature of orthokeratology lenses and the necessity to retain their optical properties postmodification, the conformal coating capability of PECVD proved advantageous. Following NVP and PEGMA deposition, the convex surface roughness of the lenses was reduced, while the light transmittance remained unaffected. The water contact angle of the lenses significantly decreased from 84.7° to 27.6°. Reportedly, to evaluate the antibacterial efficacy, the coated lenses were incubated with *Escherichia coli* and *Staphylococcus aureus* cultures at 37 °C for 8 h in a 1 mL bacterial culture, with the optical density at 600 nm serving as a measure of the antifouling performance. Results indicated a reduction in OD600 values for *E. coli* from 0.8 to 0.7 and that for *S. aureus* from 0.47 to 0.37 on the coated surfaces.

In the library of antifouling polymer coatings, zwitterionic polymers are among the most fouling-resistant reported to date. While zwitterionic polymers are seemingly incompatible with CVD techniques due to the low volatility of existing zwitterionic precursors (e.g., [2-(methacryloyloxy)ethyl]-dimethyl-(3-sulfopropyl)ammonium hydroxide), a two-step synthesis scheme has been developed to enable their synthesis using iCVD.[60] The synthesis scheme comprises (1) iCVD polymerization, where a tertiary nitrogen-bearing polymer thin film is synthesized from volatile precursors (e.g., 2-(dimethylamino)ethyl methacrylate (DMAEMA)[61] or 4-vinylpyridine (4VP)[62]), and (2) vapor-phase derivatization,[63] where exposure to a reactive vapor, e.g., that of 1,3-propane sultone (PS)[64] or β-propiolactone,[65] gives rise to sulfobetaine or carboxybetaine functional moieties via a ring-opening reaction. This derivatization reaction has been widely adopted in recent years by researchers within and beyond the CVD polymerization community to obtain zwitterionic polymers.[66] Using the iCVD zwitterionic polymer coatings, delicate substrates, such as ultrafiltration,[67] nanofiltration,[49] and reverse osmosis (RO) membranes,[68,69] can be rendered antifouling without compromising their performance. Since its invention, the two-step synthesis scheme has been further leveraged to obtain a broader palette of zwitterionic polymer chemistries with different biological functions.[70] In 2022, an imidazolium-based zwitterionic polymer was designed and synthesized by iCVD poly(1-vinyl imidazole) (1VI), lightly cross-linked by divinylbenzene (DVB), and then derivatized using PS.[71] The coating demonstrated excellent antifouling performance, reducing *Pseudomonas aeruginosa* biofilm formation by 85% compared to a polyvinyl chloride (PVC) surface after 24 h of incubation. In addition, it also exhibited contact-enabled deactivation of a human coronavirus, HCoV-OC43, by 86.6%.

Zwitterionic polymer coatings have also been obtained using a graft-from method, starting with a CVP-synthesized surface bearing initiators followed by solution-based atom transfer radical polymerization (ATRP).[72] Specifically, bromoisobutyrate-functionalized parylene (Parylene-Br) films were deposited via CVP. The bromoisobutyrate groups subsequently initiated the ATRP of methacryloyloxyethyl phosphorylcholine (MPC) monomers, resulting in grafted poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) chains on the Parylene-Br film. Upon continuous exposure to 30 $\mu L/min$ BSA, fibrinogen, and fetal bovine serum (FBS) for over 1 h, the modified surface showed strong resistance to the adsorption of these biomolecules, as assessed by quartz crystal microbalance (QCM). This resistance was further enhanced by extending the ATRP reaction time. Furthermore, the modified surface exhibited strong resistance to cell attachment, which was evaluated by seeding NIH3T3 cells and HAPI cells at densities of 2×10^4 and 6×10^4 cm^{-2}, respectively, onto both parylene and zwitterionic parylene films in their corresponding media and incubating the samples at 37 °C with 5% CO_2. After 60 days of immersion, the cell density on the zwitterionic parylene film was significantly reduced by more than 90%. This system was also utilized to encapsulate and fabricate flexible organic electrochemical transistor (OECT) arrays, demonstrating its compatibility with UV lithography and its ability to maintain antifouling properties and conform complex surfaces. Additionally, this system facilitated the development of a fabrication platform with high yield and uniformity to prepare biomimetic OECT arrays with strong antifouling properties.[73]

While zwitterionic polymers have exhibited exceptional antifouling performance and rapid adoption and development in recent years,[74] a broad range of CVD techniques, such as PECVD, have enabled a selection of other hydrophilic antifouling polymers, such as poly(acrylic acid) (AA),[75] HEMA,[76] etc., that perform well in their respective applications. We refer the readers to the existing excellent

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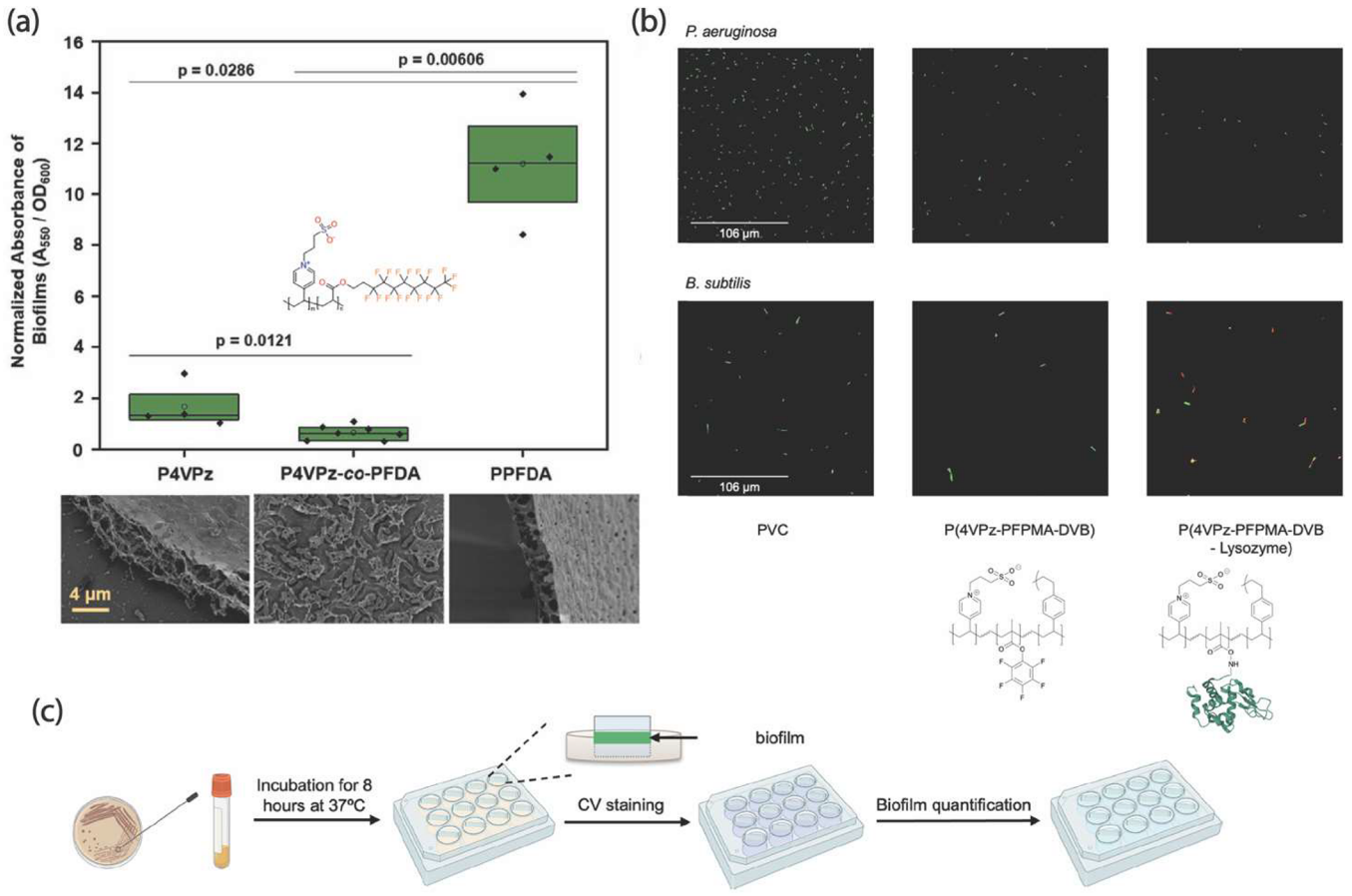

Figure 3. Antibacterial properties tests and results. (a) Biofilm reduction quantification via absorbance measurements of CV-stained *P. aeruginosa* biofilms after 8 h of growth on amphiphilic P4VP*z*-*co*-PFDA-coated samples, quantifying biofilm growth. Scanning electron microscope (SEM) images of biofilms grown on P4VP*z*-, P4VP*z*-*co*-PFDA-, and PPFDA-coated surfaces illustrate the biofilm morphology. Reproduced with permission from ref 86. Copyright 2021, Wiley-VCH GmbH. (b) Surface fouling reduction quantification. Confocal microscope images of *P. aeruginosa* and *B. subtilis* after 2 h of incubation at 37 °C with PVC, P(4VP*z*-PFPMA-DVB), and P(4VP*z*-PFPMA-DVB-lysozyme), followed by staining using the LIVE/DEAD BacLight Bacterial Viability Kit. Reproduced with permission from ref 88. Copyright 2022, Royal Society of Chemistry. (c) Schematic of a typical experimental procedure using CV staining for *P. aeruginosa* biofilm quantification at the three-phase interphase. Reproduced with permission from ref 83. Copyright 2022, American Chemical Society.

reviews[8,11] for a comprehensive discussion on those CVD-enabled antifouling polymer chemistries.

4. ANTIBIOFILM SURFACES

Biofilms, the surface-attached multicellular bacterial communities, exhibit distinct features compared to planktonic biofoulants, such as the presence of a self-secreted ECM, an impermeable polymeric matrix that protects the encapsulated bacteria from environmental attacks like those from antimicrobials. The ECM is composed of proteins, polysaccharides, nucleic acids, lipids, dissolved nutrients, and phage.[77] Immobilization of enzymes such as amylase, cellobiohydrolase, pectinase, subtilisin A, and β-*N*-acetyl-glucosaminidas (DspB) has been demonstrated to degrade the ECM, inhibiting biofilm formation and facilitating detachment of the mature biofilm.[21] Physical and chemical immobilization of these enzymes on CVD surfaces has been demonstrated to enhance their thermostability[78] and reusability,[79] resulting in improved antibiofilm efficiency. The CVD antibiofilm coatings that leverage this strategy are summarized in section 4.1 below.[80]

In addition to the ECM, biofilms also differ from planktonic foulants in that motile bacteria preferentially form biofilms at the solid−liquid−gas three-phase interface. This interface has been understudied in the development of antibiofouling coatings, as existing antifouling coating designs have primarily focused on submerged surfaces, i.e., the solid−liquid interface.[81] Indeed, even the state-of-the-art zwitterionic polymer coatings have been demonstrated to be ineffective at resisting biofilm formation at the three-phase interface.[82] Addressing this challenge requires that the interfacial energy is simultaneously minimized at the air−solid and liquid−solid interfaces, the former requiring a hydrophobic surface and the latter requiring a hydrophilic one, thus creating a dilemma in antifouling materials design. An emerging class of antibiofilm coatings that target the three-phase interface has been uniquely synthesized using iCVD, namely, statistical amphiphilic copolymers. The amphiphilic copolymers enable rapid and dynamic side chain reorientation, thus allowing the surface to exhibit different surface energies in response to the wetting state.[83] Section 4.2 introduces CVD antibiofilm coatings employing this strategy.

4.1. Strategies Targeting the ECM. The antibiofilm enzyme DspB degrades the ECM components and thus inhibits biofilm formation and facilitates detachment of the mature biofilm.[84] To achieve antibiofilm properties, a catechol- and quinone-bearing surface was synthesized by atmospheric-

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pressure PECVD to immobilize DspB.[85] While the antibiofilm properties of the DspB-immobilized surface were not directly evaluated in this study, the immobilized DspB was shown to enhance the antimicrobial efficacy of silver nanoparticles. The PECVD film enabled sequential immobilization of Ag^+ and DspB via the catechol and quinone groups through dip-coating. The surface's antibacterial performance was evaluated by culturing the surface with a *Bacillus subtilis* solution for up to 120 h and measuring the bacterial population in suspension by CFU. Compared to bare stainless steel, the surface exhibited a 62% reduction in bacterial population after 120 h of incubation. Additionally, other known antibiofilm enzymes, such as those mentioned previously, could potentially be immobilized using the same approach, potentially enhancing antibiofilm properties.[80]

4.2. Amphiphilic Copolymer with Dynamic Chain Reorientation. Leveraging the design principles of amphiphilic copolymers to enable rapid and dynamic side chain reorientation, a suite of amphiphilic copolymer coatings capable of dynamic chain reorientation has been developed by using iCVD, fostering antibiofilm performance. The solvent-free synthesis uniquely enables molecular-scale heterogeneities without microphase separation by eliminating the need for a common solvent for the hydrophilic and hydrophobic constituents, which represents a major challenge for conventional solution-phase synthesis. For example, hydrophilic zwitterionic and hydrophobic fluorinated components have been copolymerized with statistical mixing, giving rise to molecular-scale heterogeneities with the largest contrast in surface energy reported to date. This amphiphilic copolymer was synthesized by copolymerizing 4VP and 1*H*,1*H*,2*H*,2*H*-perfluorodecyl acrylate (PFDA) using iCVD, followed by vapor-based PS derivatization to convert the pyridine into a pyridinium-based sulfobetaine, with *z* representing the zwitterionic polymer.[86] The copolymer P4VP*z*-*co*-PFDA exhibited an advancing contact angle of 96.9 ± 1.5° and a receding contact angle of close to zero. This significant hysteresis and low receding angle in the copolymer were evidence of its amphiphilic nature, where the hydrophilic and hydrophobic side chains reoriented in response to the surface wetting conditions. The conflicting needs to simultaneously minimize surface energy under both dry and wet conditions were thus satisfied by presenting zwitterionic groups at the water−solid interface and fluorinated side chains at the air−solid interface. As shown in Figure 3a, the amphiphilic copolymer reduced the *P. aeruginosa* biofilm at the three-phase interface by 94% compared to PPFDA and by 61% compared to P4VP*z*-*co*-DVB after an 8 h incubation according to absorbance measurements at 550 nm of crystal violet (CV)-stained biofilms.

Concerns regarding the hydrolysis of the PFDA (with eight fluorocarbons) repeating unit, which can produce harmful C8 perfluoroalkyl substances (PFAS), prompted systematic investigations on the effects of varying the length of fluorocarbon side chains on amphiphilic polymers on the antifouling performance. Specifically, the antifouling effects of less toxic 1*H*,1*H*,2*H*,2*H*-perfluorooctyl acrylate (PFOA, six fluorocarbons) and 2,2,3,4,4,4-hexafluorobutyl acrylate (HFBA, three fluorocarbons) based amphiphilic copolymers were evaluated.[83] P4VP*z*-*co*-PFOA and P4VP*z*-*co*-HFBA were synthesized by iCVD and PS derivatization. After 8 h of incubation with *P. aeruginosa*, all three amphiphilic copolymers outperformed the zwitterionic P4VP*z*-*co*-DVB coating by around 45% (measurement method as shown in Figure 3c), yet there was no statistically significant difference in their antibiofilm performances, suggesting that the length of the fluorinated chain in amphiphilic copolymers did not affect their antibiofilm effectiveness in the range of 0.5-1.1 nm.

The vast chemistry composition design space associated with amphiphilic copolymers makes the screening and performance optimization process laborious. The incomplete fundamental understanding of the acting mechanisms of amphiphilic copolymers makes it rational to turn to machine learning (ML) aided approaches for screening optimal amphiphilic copolymer compositions and gaining deeper insight into their fouling resistance mechanisms.[87] A general support vector regression (SVR) was developed that captured the fundamental quantitative structure−activity relationship underlying both vapor and solution-synthesized copolymers. Comonomer pairs with drastically different surface energies were selected to form an amphiphilic copolymer, which created a high energy mismatch. 137 monomers were converted to simplified molecular-input line-entry (SMILE) strings and linearly combined pairwise to derive features for all polymers to predict their antibiofilm performance against *P. aeruginosa* for incubation of 72 h. The model predicted the quantity of *P. aeruginosa* solid-liquid biofilms reasonably well (R^2 = 0.60, RMSE = 0.38log(F_{PA})) and how the antibiofilm performance varied with the polymer composition, which was validated with experimental results from PHEMA-*co*-HFBA.

4.3. Other Polymer Coating Designs Enabling a Dynamic Interface. A dynamic interface design was demonstrated using small-molecule surfactants adsorbed on the solid surface. Anionic surfactants, exemplified by SDS, and cationic surfactants, exemplified by DTAC, led to reduced levels of biofilm formation by *P. aeruginosa* (64% and 70%, respectively, on PVC) when added in trace amounts (0.1 mM, far below their minimum inhibitory concentrations). That antibiofilm effect was attributed to the facile reorientation of these small-molecule amphiphiles at the three-phase interface in response to the surface wetting state. This strategy effectively reduced *P. aeruginosa* biofilms on various surfaces with diverse hydrophilicities and polarities, including a zwitterionic polymer, PHEMA, PVC, and PPFDA.[89]

An iCVD coating grafted with polysulfide surface chains also demonstrated an antibiofilm property, which was attributed to the dynamic nature of the polysulfide chains, undergoing reversible S−S bond exchange at room temperature (the cleavage/dissociation energy of which was 2/3 that of a C−C bond).[90] The grafting was enabled by a UV-activated thiol−ene reaction between the vinyl groups formed by PV4D4 and sulfur vapor. Antibiofilm performance, calculated using fouling area observed in microscopic images, demonstrated that after 24 h of incubation with *E. coli* the polysulfide-grafted surfaces reduced the biofilm by 41.1%, 90.3%, and 94.9% compared to polyethylene glycol (PEG), PDMS, and tissue culture polystyrene (TCPS), respectively. The incubation with *S. aureus* revealed that the adherent area on the polysulfide-grafted surface was 47.4%, 86.3% smaller than that of PDMS and TCPS and comparable to that of PEG. The antibiofilm performance was retained after 7 days of incubation.

5. BACTERICIDAL SURFACES

Bactericidal surfaces refer to surfaces that kill bacteria they come into contact with. Traditional strategies involve the release of biocidal compounds such as antibiotics and copper-

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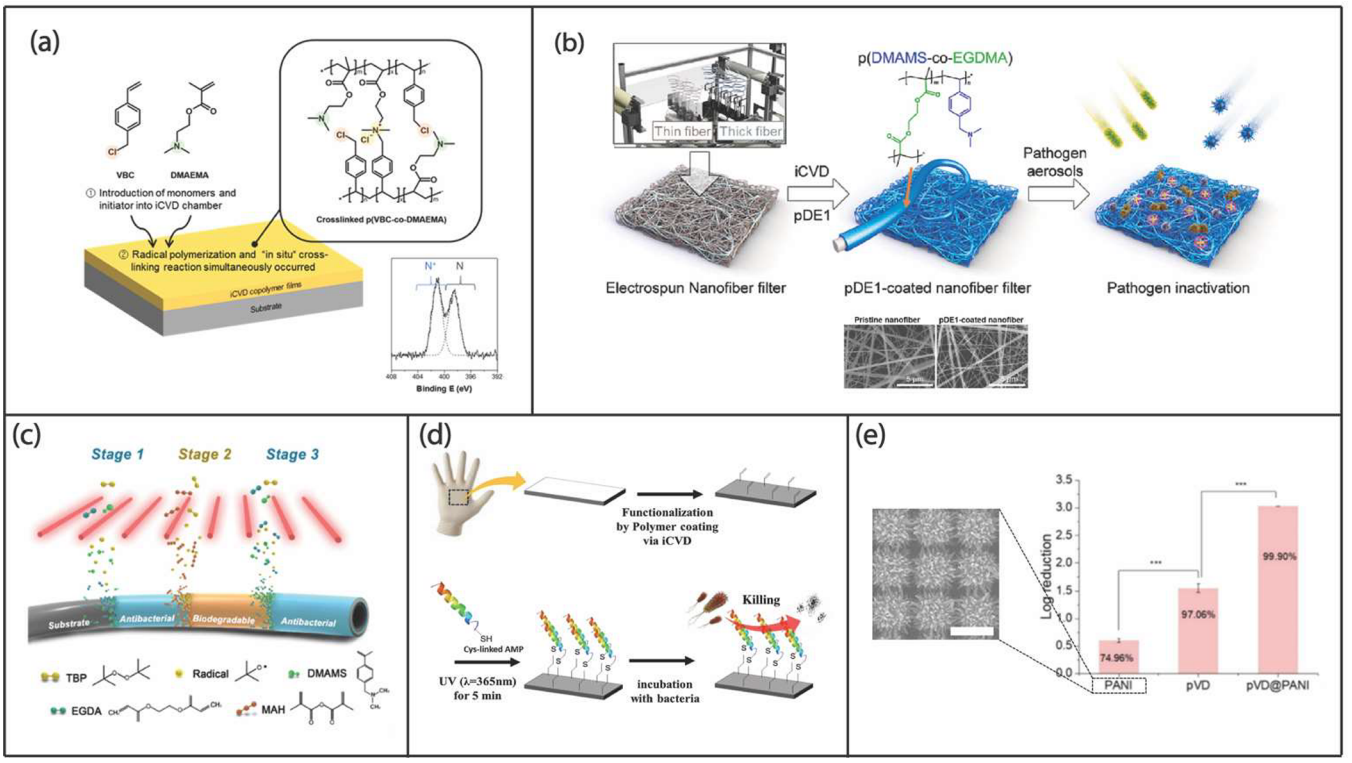

Figure 4. Design of bactericidal surfaces. (a) Schematic of bactericidal surface modification via cross-linked ionic polymer coating and structure, the PVBC-*co*-DMAEMA copolymer, and XPS high-resolution scan of N 1s of the copolymer. Reproduced with permission from ref 101. Copyright 2018, American Chemical Society. (b) Schematic of the fabrication process and SEM images of the PDMAMS-*co*-EGDMA-coated nanofiber filter. Reproduced with permission from ref 103. Copyright 2023, Elsevier B.V. (c) Schematic of a three-staged deposition process of the layered degradable coating using iCVD. PDMAMS-*co*-EGDA as the bactericidal layer, PMAH as the biodegradable layer, and another PDMAMS-*co*-EGDA layer were deposited sequentially. Reproduced with permission from ref 106. Copyright 2021, American Chemical Society. (d) Scheme for PV4D4 coating and SHAP1 peptide immobilization on the surface of a substrate. Reproduced with permission from ref 107. Copyright 2017, The Korean Society of Industrial and Engineering Chemistry. Published by Elsevier B.V. (e) SEM image of PANI NPA. The scale bar is 1 μm. On the right is the log reduction of bacteria of an uncoated PANI NPA, a flat PVBC-*co*-DMAEMA thin film, and a PVBC-*co*-DMAEMA-coated PANI NPA. Reproduced with permission from ref 108. Copyright 2021, The Authors, under the terms of the Creative Commons (CC BY 4.0) License https://creativecommons.org/licenses/by/4.0/.

and silver-containing compounds. A number of polymers have been utilized to stabilize and release metal/metal oxide particles (e.g., Ag,[91] CuO,[92] ZnO,[93] TiO_2,[94] etc.) for obtaining antimicrobial nanocomposites.[95] However, their broad-spectrum toxicity has led to serious ecological concerns.[7] For example, despite copper replacing tributyltin in ship hull paints as the antimicrobial active ingredient, its environmental impact, including toxicity to marine life[96] and water quality challenges,[97] led to its recommendation to be phased out, as suggested by the U.S. Environmental Protection Agency (EPA) and European Environment Agency (EEA). For instance, the California Regional Water Quality Control Board has mandated that the copper loading in the Shelter Island Yacht Basin will need to be reduced by 76% by 2028. As such, recent advances in bactericidal strategies focus on designing green, non-toxic coatings. The vapor-synthesized bactericidal surfaces reviewed in this section are categorized into surface chemistry and surface topography based on their underlying mechanisms of action.

5.1. Surface Chemistry. *5.1.1. Quaternary Ammonium Compounds.* Quaternary ammonium compounds (QACs) have been generally regarded as bactericidal and broadly used as the active ingredients in over 200 disinfectants.[98] The cationic quaternary nitrogen interacts strongly with the anionic head groups of phospholipids and negatively charged structural proteins in the bacterial cell wall, resulting in rapid cell lysis.[99] CVD polymer coatings with QACs have been discussed in detail in previous reviews;[100] here, we aim to provide an updated perspective by focusing on the latest efforts in this direction.

Poly(4-vinylbenzyl chloride-*co*-DMAEMA) (PVBC-*co*-DMAEMA) has been synthesized using iCVD for infection-resistant medical applications.[101] VBC and DMAEMA were chosen to induce a reaction between the benzyl chloride and the tertiary amine, giving rise to a quaternary ammonium while introducing cross-linking to improve film stability (Figure 4a). The observed increase in positive surface charge with increasing DMAEMA content, measured by zeta potential measurements and confirmed through high-resolution X-ray photoelectron spectroscopy (XPS) analysis, demonstrated the successful incorporation of the quaternary ammonium group.[17] The conversion rate was calculated from XPS data of the contents of N^+ and Cl^-. Flow cytometry analysis and a colony-forming unit (CFU) counting assay revealed over 99.5% contact-killing of *E. coli* and *Corynebacterium glutamicum* after 168 h of incubation with the copolymer, with no detectable leaching of film components. A follow-up study examined the bactericidal effect of a similar copolymer, made of VBC and 2-diethylaminoethyl methacrylate (DEAEMA), and reported a 3−6 order of magnitude reduction in the CFU after the

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copolymer was incubated with *E. coli* and *S. aureus* for 16 h, highlighting the potential of VBC to react with other tertiary-nitrogen-bearing monomers.[102]

Another example of a QAC-embedded bactericidal coating was demonstrated through iCVD of a QAC-bearing dimethylamino methylstyrene (DMAMS) monomer and a biocompatible cross-linker EGDMA, resulting in a PDMAMS-*co*-EGDMA copolymer, onto an electrospun nanofiber filter designed for use as a face mask with bactericidal properties (Figure 4b).[103] iCVD enabled the conformal deposition of 10 nm functional copolymers films over the polyacrylonitrile (PAN) nanofiber filter comprising a mixture of 150 and 300 nm diameter fibers. This process demonstrated a coating mass of 35 $\mu g/cm^2$ while preserving the nanoporous nature of the filter (with over 90% filtration efficiency). To assess the bactericidal efficacy of the coated nanofiber filter, it was incubated with *E. coli* and *S. aureus* for 2 h at 25 °C, followed by CFU counting of the recovered bacteria suspension. The results revealed that over 99.98% of both *E. coli* and *S. aureus* was eradicated from the initially inoculated 1 mL bacteria suspension containing 10^5 cells/mL.

Note that QAC-based bactericidal coatings are prone to biofouling due to the accumulation of deactivated cells and debris,[104] which interact strongly with the QACs to form a conditioning layer and trigger the biofouling cascade.[105] To address that challenge, a self-regenerating coating was made by sequentially depositing a layer of 800 nm bactericidal poly(DMAMS-*co*-ethylene glycol diacrylate) (PDMAMS-*co*-EGDA), a layer of 600 nm biodegradable poly(methacrylic anhydride) (PMAH), and another layer of 800 nm PDMAMS on urinary catheters, as shown in Figure 4c, by changing precursor feeds during iCVD.[106] As the top bactericidal layer gradually lost its killing ability due to biofouling, self-regeneration of the bactericidal property was triggered by the hydrolysis of PMAH, degrading the intermediate layer and revealing the underlying PDMAMS. The degradation time of the PMAH layer spanned from 30 min to 72 h while maintaining most of the bactericidal properties of the underlying layer (95% of *E. coli* and *S. aureus* was killed after 1 h incubation according to CFU counting compared to 99% with the initial coating).

5.1.2. Immobilization of Other Antimicrobial Compounds. Macromolecular compounds, such as peptides or enzymes, have also demonstrated bactericidal properties. Their incorporation into a coating often requires immobilization via functionalizable polymer chemistry. Such immobilization can be achieved by maleimide−thiol,[109] thiol−ene,[110] or carboxylic acid−amine reactions.[111] While similar reactions could be performed on a solution-processed polymer coating, some CVD techniques produce functional coatings with higher purity and retention of the functionalizable moieties and more conformal coverage.[112]

The cecropin−melittin hybrid peptide, derived from natural insect peptides, showcases potent bactericidal properties by disrupting bacterial cell membranes.[113] A cecropin−melittin hybrid peptide has been immobilized on surfaces coated by CVP of 4-(3,4-debromomaleimid) [2.2]paracyclophane.[114] The coating afforded dibromomaleimide (DBM) groups that reportedly reacted with the cysteine groups on the peptide. The immobilized peptides were demonstrated to effectively kill *E. coli* after 1 h of contact, as further investigated by sum frequency generation (SFG) vibrational spectroscopy, which revealed that the α-helical hybrid peptide adopted a lying-down orientation on the surface, potentially suggesting a charge-based mechanism of bacterial killing rather than membrane disruption.

SHAP1 is a synthetic peptide designed for infected wound treatment that is characterized by potent antimicrobial activity against various bacteria and fungi. Synthetic SHAP1 peptides were immobilized on in a poly(1, 3,5,7-tetramethyl-1,3,5,7-tetravinyl cyclotetrasiloxane) (PV4D4) coating synthesized using iCVD via thiol−ene click chemistry (activated by UV irradiation, Figure 4d).[107] The bactericidal property was demonstrated via a 2 h incubation with *E. coli* and *S. aureus*, achieving killing efficiencies of 96.4% and 96.3%, respectively, compared to pristine polymer surfaces without the immobilized SHAP1. Another study integrated lysosome, an antimicrobial enzyme, into an inherent antifouling surface,[88] which will be further discussed in section 6 due to its multifunctional mode of action.

In addition to antimicrobial peptides, small-molecule membrane-active agents also offer promising antimicrobial activity against a wide range of pathogens; around 90% of drugs on the market are small molecules, highlighting their significant role in pharmaceutical research.

Plasma polymers from oregano secondary metabolites (OSMs) potentially possess bactericidal activities, which are attributed to their rich composition of phenolic monoterpene carvacrol. They have been made into bactericidal polymer coatings using radiofrequency PECVD (RF-PECVD) in continuous or pulsed plasma modes at room temperature.[115] The bactericidal properties of the coatings were evaluated by fluorescence imaging with a LIVE/DEAD bacterial viability kit. After 18 h of incubation, the coating synthesized using pulsed plasma with power of 50 W eliminated >99% of *P. aeruginosa* and ∼20% of *S. aureus* in contact.

Due to its lipophilic nature, terpinen-4-ol, an essential oil precursor, is considered bactericidal as it can penetrate the cell wall and cytoplasmic membrane of bacteria, compromising their structural integrity. It has been polymerized by PECVD via a two-step process to achieve a dissolvable and self-polishing outer layer.[116] The applied power was set at 100 W in the first step to yield a base film and 10 or 25 W in the second step to deliberately achieve incomplete polymerization and thus contact killing by monomer elution and film renewal via outer layer dissolution. The fouling test was performed by immersing the samples in Curralea Lake, Townsville, Australia. The treated surface showed an 83% reduction in fouling (defined as surface coverage by foulants) after 7 days and a 47% reduction after 28 days compared to untreated glass coverslips. In a follow-up study, the bactericidal efficacy was correlated with the retention of terpinene-4-ol during synthesis, which was increased by using pulsed (instead of continuous) plasma.[117] The surface coated with pulsed plasma exhibited a greater bactericidal effect, achieving a log(0.90) reduction of *P. aeruginosa* viability after 24 h of incubation compared to a log(0.20) reduction for the unmodified glass coverslips. The bactericidal effects can be further increased by incorporating other antimicrobial agents, like ZnO nanoparticles.[118]

CVD polymer coatings have also been used to modify inherently bactericidal materials. In one application, titania nanotubes (TNTs) were coated with HEMA and MAA as modified nanofillers in thin film nanocomposite membrane fabrication by PECVD.[119] Due to the hydrophilic nature of TNTs, achieving homogeneous dispersion in organic solvents

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during interfacial polymerization is challenging. PECVD modification with a thin MAA coating improved the stability and dispersion quality of TNTs in solvents. The conformal coating thickness could be adjusted from 2 to 7 nm by varying the deposition time from 5 to 10 min. The antibacterial properties of the membranes were evaluated by soaking the membranes in 30 mL of an *E. coli* and *S. aureus* suspension with bacterial concentrations of 4×10^7 and 4×10^4 CFU/mL, respectively, at 37 °C for 24 h, followed by CFU counting of the bacteria suspension. The MAA-modified thin film nanocomposite membrane showed a slight improvement in bactericidal activity, killing 17.89% of *E. coli* and 18.37% of *S. aureus* compared to 15.56% and 16.33% for cultures without a membrane, respectively. However, the unmodified thin film nanocomposite membrane exhibited higher bactericidal activity, killing 20.94% of *E. coli* and 44.90% of *S. aureus*, indicating that the presence of the MAA coating layer limited the bactericidal efficacy of the TNTs.

5.2. Surface Topography. Nature represents an inexhaustible source of inspiration for the design of bactericidal materials. The low-adhesion, superhydrophobic, and self-cleaning surfaces found in nature, including insect wings, shark skins, and lotus leaves, have led to numerous biomimetic bactericidal surface designs.[120] More recently, cicada (*Psaltoda claripennis*) wings have been identified to have bactericidal properties against Gram-negative bacteria, which has inspired the development of biocompatible and bacteria-inhibiting implant materials.[121,122] The bactericidal effect has been attributed to bacterial cell rupture upon contacting the nanopillars lining a cicada wing.[123,124] While inorganic materials have led to rapid sterilization of bacteria, we do not include those materials in our discussion below to maintain a focus on polymer coatings.[100]

The CVD polymer coating techniques have a distinct advantage to be combined with the aforementioned biomimetic surface topographies due to the conformal coating coverage,[125] which is challenging to obtain using common solution-phase coating approaches. In the few emerging examples discussed below, the bactericidal topographies are often coated with a bactericidal polymer coating to explore the potential for synergistic bactericidal effects. In one example, the aforementioned PVBC-*co*-DMAEMA coating was applied using iCVD onto a nanopillar array (NPA), which was prepared by stamping polyurethane acrylate and Norland Optical Adhesive 63 on a prepatterned NPA mold with a diameter of 500 nm and a spacing of 1 μm.[126] The design rationale is that the QAC-containing polymer coating could increase the electrostatic interaction between the bacteria and nanopillars and thus enhance the bactericidal activity of NPA. After 2 h of incubation with *S. aureus*, the coated NPA reportedly killed 99.6% of bacteria, according to CFU counting of the culture suspension before and after the incubation, a considerable improvement compared to uncoated NPA, which eradicated 51% of surface-attached bacteria from the topological bacteria-killing effect.

The same copolymer coating was applied to a 3D polyaniline–gold (PANI/Au) hierarchical nanostructure (Figure 4e), where PANI spikes were grown on NPAs as secondary structures.[108] The bactericidal efficacy of the surface against *E. coli* was evaluated by CFU counting of bacteria suspensions extracted from surfaces after 2 h of incubation. The copolymer-modified PANI reportedly achieved a reduction of log(3.0) CFU, while the copolymer-coated flat surface and the PANI hierarchical structure showed a reduction of log(1.6) CFU and log(0.6) CFU, respectively.

A similar copolymer PVBC-*co*-DEAEMA was applied onto rough microstructures transferred from sandpaper to a polydimethylsiloxane (PDMS) replica surface.[127] The optimized surface exhibited a log(7.0) reduction against *E. coli* and a log(3.0) reduction against *S. aureus* in the CFU counting of bacteria suspensions on the surfaces after incubation of 16 h. The reduced effectiveness against *S. aureus* was attributed to the thicker cell wall of *S. aureus* containing many layers of peptidoglycans due to its Gram-positive nature.

6. MULTIFUNCTIONAL SURFACES: INTEGRATING ANTIFOULING, BACTERICIDAL, AND FOULING RELEASE MECHANISMS

Bactericidal surfaces, when used alone, are often prone to fouling due to the accumulation of bacterial cell debris, which can bury surface functionalities and halt the antimicrobial effect. While antifouling surfaces can significantly reduce fouling, they are unable to eradicate bacteria that continue to circulate, potentially leading to infections and contamination. As a result, researchers have sought to combine different antibacterial mechanisms via an innovative material design and synthesis. These multifunctional surfaces have enabled simultaneous functions, such as antifouling and bactericidal activities[88] or bactericidal and fouling release activities.[128]

To simultaneously achieve antifouling and bactericidal effects, QAC-bearing monomers and hydrophilic monomers have been copolymerized using iCVD.[129] For example, a coating was designed with a compositional gradient in the *z*-direction, with a bottom layer consisting of bactericidal QAC-bearing PDMAMS and a surface layer comprising both DMAMS and hydrophilic VP moieties.[130] The resulting coating exhibited a killing rate of more than 99.9% against both Gram-negative *E. coli* and Gram-positive *B. subtilis* compared to uncoated TCPS after 1 h of incubation, according to CFU counting of the bacterial suspension, despite the incorporation of VP on the surface, which potentially dilutes the presence of DMAMS. The performance was attributed to a high surface zeta potential of 16 mV of the graded coating, comparable to that of 19 mV of the bottom PDMAMS layer, which was argued to result from the combinatorial effect from positive charges both on the top surface and embedded underneath. By increasing the solution pH to 10, the surface-attached bacterial debris was released upon rinsing due to the weakened electrostatic attraction between the coating surface, bacterial cells and hydrophilic lactam groups of the VP-enriched surface.

Another illustration of integrating bactericidal and antifouling mechanisms involved an iCVD-based gradient polymer coating comprising a bottom layer of PV4D4 and a top layer of P(2-carboxyethyl acrylate-*co*-2-(dimethylamino)ethyl acrylate) (PCA-*co*-DMAEA).[131] The antifouling performance against protein was assessed using surface plasmon resonance (SPR) spectroscopy, renowned for its ultrasensitive quantification of molecular interactions with surfaces. Results from SPR demonstrated the coating's ability to resist protein fouling, with a protein surface concentration of 20.3 ng/cm^2 after 500 s of exposure to undiluted human serum. Furthermore, the antibiofilm property of the coating was evaluated following 24 h of incubation with *E. coli* and *S. aureus*. Subsequently, the biofilm was detached from the surface using the bead vortex method, involving vortexing with sterile glass beads for 3 min,

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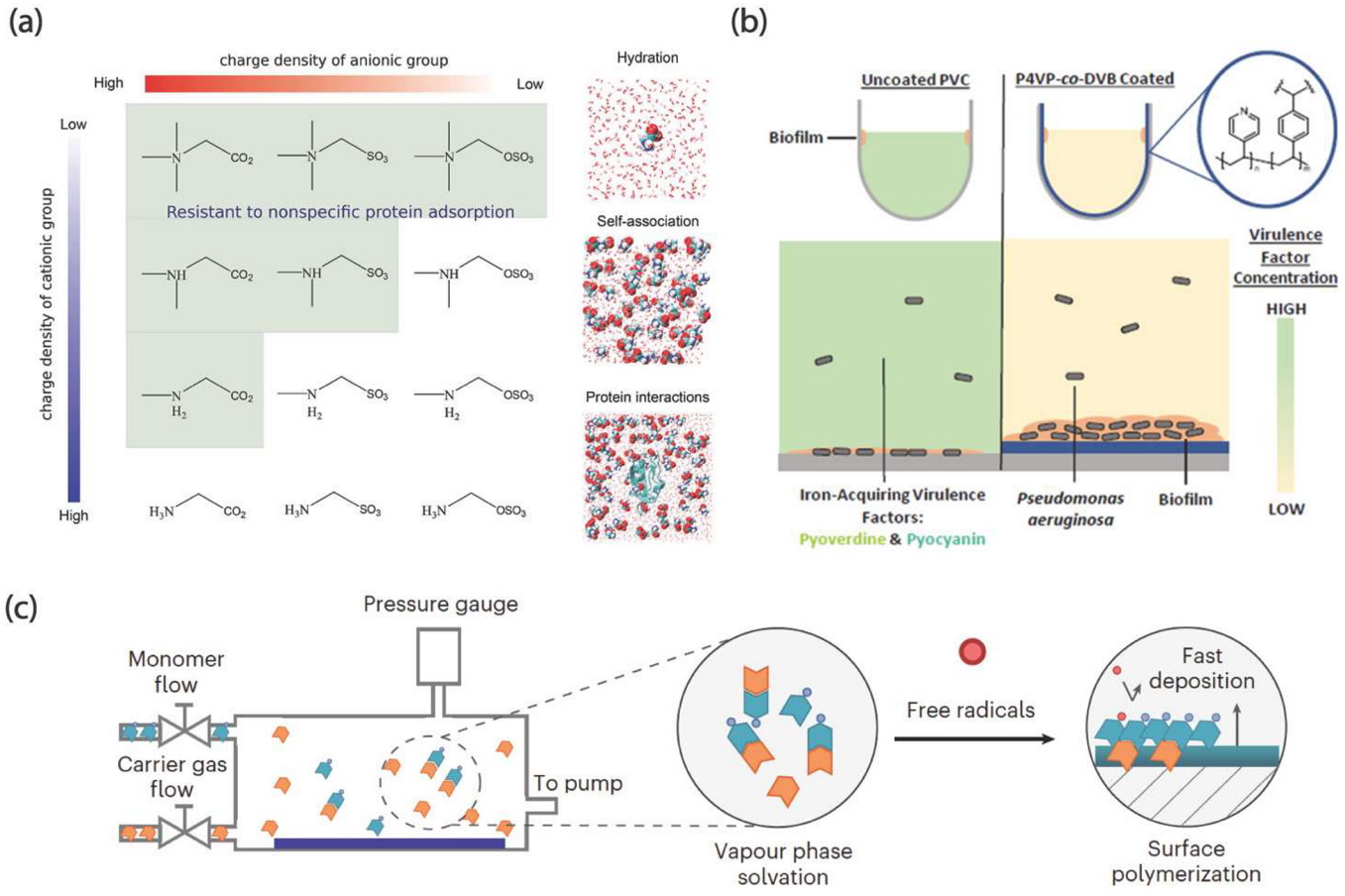

Figure 5. Challenges and opportunities in CVD techniques. (a) Molecular structures of 12 zwitterionic moieties. Half the moieties (highlighted in green) show resistance to nonspecific protein adhesion, pointing to the design criteria for antifouling materials of maximizing hydration, minimizing self-association, and reducing protein interaction. Reproduced with permission from ref 135. Copyright 2014, Wiley-VCH Verlag GmbH & Co. (b) Schematic of bio-informed material design: By securing iron ions onto the surface with a P4VP-*co*-DVB coating, the growth of the biofilm is promoted with reduced virulence, leveraging siderophore-mediated iron acquisition. Reproduced with permission from ref 136. Copyright 2021, American Chemical Society. (c) Schematic of the mechanism of the solvation-enhanced polymerization strategy in iCVD. Orange dots refer to HFIP molecules, while blue dots denote 4VP molecules. The two molecules form hydrogen bonds, leading to in situ complexation that enhances the surface adsorption of 4VP and increases its film growth speed and molecular weight. Reproduced with permission from ref 137. Copyright 2023, The Authors, under exclusive license to Springer Nature Limited.

and CFU counting was performed on the suspension to quantify the bacterial population within the biofilm. The coating exhibited more than 10-fold reduction against both *E. coli* and *S. aureus* biofilms compared with TCPS. PV4D4, with superior mechanical properties, acted as a grafting layer that could be applied conformally to various substrates to improve the adhesion of the coating to the substrate.

One example of integrating bactericidal and fouling release functions involved synthesizing a fluorinated polycationic coating of PDMAMS-*co*-PFDA on a hydrophilic and negatively charged polyester textile via iCVD.[132] The copolymer coating demonstrated a contact-killing efficiency of approximately 99.9% against both *E. coli* and *S. aureus* after 1 h of contact according to resuspension of surface-attached bacteria through sonication for 3 min, followed by CFU counting.

In addition to QACs directly integrated into polymer coatings, antimicrobial biomolecules have been immobilized onto functionalizable coatings to achieve antifouling−bactericidal dual functions. One such example is the immobilization of lysozyme, an effective antimicrobial enzyme that acts against Gram-positive bacteria by hydrolyzing the glycosidic ß-linkages in the cell wall, onto an iCVD zwitterionic coating (Figure 3b).[88] Specifically, lysozyme was immobilized on the surface of a pyridinium-based zwitterionic copolymer, poly(4VP*z*-*co*-pentafluorophenyl methacrylate) (PFPMA), via nucleophilic substitution of the pentafluorophenyl group. This approach resulted in a reduction in surface adhesion of 87% for *P. aeruginosa* and that of 71% for *B. subtilis* after 2 h of incubation compared to PVC based on fluorescence imaging of the post-incubation surface. Moreover, 67% of the Gram-positive *B. subtilis* was eradicated after 2 h of incubation based on LIVE/DEAD BacLight staining and fluorescence imaging.

7. CHALLENGES AND OPPORTUNITIES IN THE DEVELOPMENT OF VAPOR-DEPOSITED ANTIBACTERIAL MATERIALS

CVD-synthesized antibacterial polymer coatings serve as attractive alternatives to their solution-synthesized counterparts. Moreover, CVD polymerization techniques have enabled polymer chemistries and thin film attributes that challenge traditional solvent-based methods such as amphiphilic copolymers and conformal coating coverage over internal surfaces. The amphiphilic copolymers are uniquely positioned to address biofouling issues at the air−liquid−solid three-phase

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interface[133] in applications ranging from ship hull fouling deterrence to underwater operations (e.g., underwater oxygen generation for divers or hydrogen generation for submarines). The ultraconformal antifouling thin films have been applied to a variety of off-the-shelf membranes to render their external and internal surfaces antifouling thanks to the conformal nature of the CVD polymerization techniques. Example applications include those with intricate surface topographies like anodic aluminum oxide (AAO) membranes in nanofiltration and ultrafiltration, delicate reverse osmosis (RO) membranes that cannot withstand solution-synthesis methods without performance deterioration,[134] and nanopillar arrays[108] that act in synergy with the polymer coating to enhance their antimicrobial activities.[8]

Despite these advantages, the library of CVD polymer chemistry and organic functionalities represents a subset of those that can be attained using solution-based synthesis techniques. There is thus a need for new strategies to chemically diversify accessible chemistries via vapor deposition techniques. In section 7.1, we propose three potential strategies to achieve that goal. Furthermore, we have identified a critical need for standardization in the methodology employed to assess antibacterial efficacy. Section 7.2 contains a collated set of common practices for the assessment of protein adhesion, bacteria adhesion, and biofilm formation, which may help researchers in the field quickly identify a method that allows for benchmarking of the performance of the antibacterial material being developed. Finally, despite the success of existing antibacterial materials, the discovery of new antibacterial chemistries and strategies has slowed down in recent years. We believe a deeper understanding of fouling microbiology is needed to power continued innovation in antibacterial materials design, as discussed in section 7.3 below.

7.1. The Need to Develop New Material Chemistries. While the palette of polymer chemistries achieved by CVD polymerization may seem limited, especially compared with solution-based synthesis techniques, CVD has reasonably covered the key classes of antibacterial polymers. These include hydrophilic polymers (e.g., zwitterionic and PEG-like polymers), amphiphilic copolymers, positively charged polymers, and functionalizable polymers for the tethering of biomolecules or otherwise antibacterial molecules and materials (Table 1). Building upon the advancements made possible by CVD, particularly in synthesizing zwitterionic polymers and cross-linking-density-tunable antifouling coatings, we propose several strategies to develop next-generation antibacterial coatings using iCVD. Nevertheless, we recognize that the collection of functional polymers accessible to CVD techniques represents only a fraction of the existing polymer library. We attribute that narrow palette to the emerging nature of the CVD polymerization technologies, which likely leaves much of the design space largely unexplored, as well as the requirement for monomers to be sufficiently volatile and reactive. As such, we also include a discussion on potential strategies to diversify the CVD polymer library, using iCVD as an example, which may inspire sustained growth of iCVD polymer chemistries for antibacterial applications and beyond.

7.1.1. Future Design of Zwitterionic Materials. While hydration has been the predominant consideration in the design of CVD-based zwitterionic coatings, additional design considerations could further improve the antifouling performance through molecular design.[135,138] For example, strong self-associations among zwitterionic moieties have been observed in solution-synthesized sulfobetaine moieties, rendering them hydrophobic with reduced antifouling performance.[139] While such self-association and reduction in antifouling performance have not been observed in CVD-synthesized zwitterionic coatings, a systematic study of the structure-property relationship, like that shown in Figure 5a,[140] for vapor-deposited coatings could lead to unprecedented antibacterial performance. Vapor-phase synthesized polymers could behave drastically differently from solution-synthesized polymers. As such, systematically investigating the antifouling effectiveness of different CVD-enabled zwitterionic polymer structures would also advance our understanding of the antibacterial mechanism of vapor-synthesized polymers and the design of next-generation vapor-deposited zwitterionic structures.

7.1.2. Functional Crosslinkers. The all-dry nature of iCVD polymerization allows facile incorporation of cross-linkers into the polymer coating without any limit posed by polymer solubility or the need for subsequent curing steps. The chemical and mechanical stabilities of the iCVD coatings thus tend to compare favorably to those of their solution-processed counterparts. Future designs using iCVD polymerization may consider leveraging this unique advantage to achieve unprecedented antibacterial effects. For example, coating stiffness has been demonstrated to affect the motility of near-surface bacteria.[39] As such, iCVD polymer coatings with systematically tuned stiffness, which can be achieved by simply varying the cross-linking density of iCVD polymer coatings, may lead to new design strategies for antibacterial materials. Furthermore, while most extant iCVD research treats the cross-linker as a component that serves the sole purpose of improving coating stability, cross-linkers, in fact, can be designed to bear functional moieties, which presents an opportunity to enhance the functional properties of polymer films.

7.1.3. Broaden the Collection of Polymers Accessible to CVD Techniques. CVD techniques require that a precursor be volatile enough to be delivered in the vapor phase, placing a considerable constraint on the feasible precursors. For example, zwitterionic monomers are commercially available but almost never used directly in CVD polymerization because the ionic nature of the monomers renders them insufficiently volatile. To address that bottleneck, a two-step synthesis scheme (as described in section 3) has been developed.[71] Expanding the CVD monomer library could lead to improved antibacterial performance and beyond. For example, the incorporation of amino groups and thiol groups could open a path toward several classes of facile functionalization reactions (e.g., the click reaction).

While the low volatility of a precursor may render it incompatible with CVD technologies, excessive volatility results in inadequate adsorption of a precursor onto the substrate, which in turn would require laborious optimization of the experimental conditions to overcome. The development of the vapor-phase solvation strategy in iCVD has shown promise in addressing this limitation.[137] As shown in Figure 5c, by using hexafluoroisopropyl alcohol (HFIP) as a carrier gas instead of traditionally used argon, the solvation of 4VP by HFIP in the vapor phase formed vapor complexes, which greatly accelerated P4VP's deposition rate, increased its molecular weight, and enabled facile film morphology control, all without any HFIP incorporation. This vapor solvation mechanism introduces a new dimension of control in iCVD. Applying these strategies to other polar monomers and volatile

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solvents could expand the available monomer library for iCVD, opening up new possibilities for all-dry synthesis.

The potential solutions that we discussed to expand the accessible chemistries in iCVD, such as the incorporation of vapor solvents, or the in situ synthesis of heavier monomers during deposition, may not be applicable to other CVD polymerization techniques like PECVD or CVP. Instead, to expand the library of precursors for those technologies, less-volatile monomers can be and have been introduced through techniques like a precursor bubbler[141] or ultrasonication bath to facilitate the evaporation of monomers. In addition, it is key to achieve high retention rates of the functional moieties (e.g., zwitterionic side groups) to maximize antibacterial effectiveness. This may prove challenging for techniques such as PECVD that leverage high-energy reaction zones to enable polymer growth. Several reports cleverly leveraged these techniques to immobilize precursors and enabled subsequent controlled polymerization under more benign conditions (e.g., CVP-immobilized initiator for subsequent solution-base ATRP[73]), capitalizing on the benefits of both solution- and vapor-based synthesis techniques. With the prevalence of thermal electric cooling devices, it is also possible that active cooling can be introduced retroactively, with a reactor layout that does not interfere with the activation step, to increase the retention of the antibacterial functional moieties.

7.2. A Call for Standardization in Antibacterial Assays. There is a critical need for standardization in the assessment methodology employed to compare antibacterial materials. While commercial LIVE/DEAD® staining kits are available for bacteria, they are not necessary for most genetically modified strains or could be replaced by other staining procedures such as CV staining. Different studies focus on a vast diversity of foulants, different flavors of proteins, strains of bacteria, growth modes of planktonic bacteria versus biofilms, or even domains of life, the selection criteria of which are not always obvious. Furthermore, the disparities in testing procedures and data presentation hinder accurate and consistent comparisons across coatings bearing different functional moieties or synthesized using different techniques. In addition, CVD-synthesized polymers can differ from solution-synthesized polymers on the molecular level. CVD-synthesized polymers tend to be cross-linked solid thin films instead of polymer brushes (which are common among solution-synthesized antifouling coatings). While the tunable cross-linking density affords control over film stability, it limits access to an antifouling mechanism, i.e., entropy-driven antifouling by densely packed polymer brushes. Nonetheless, CVD delivers control over film architecture to enhance the antibacterial performance, e.g., placing antifouling moieties at the topmost surface by leveraging diffusion-limited derivatization reactions, which may be challenging for solution synthesis methods. Systematic studies to compare vapor- versus solution-synthesized polymer surfaces would offer immense value to the advancement of the structure−property relationships that will guide the design of next-generation antibacterial coatings. In an effort to move toward standardized comparison, we summarize a few observations below based on the current trends in the literature; this is by no means a set of recommendations but rather a collection of common practices. We organize the summary below based on the intended function into antifouling, bactericidal, and antibiofilm categories and provide an overview of the common assessment methods for each.

7.2.1. Antifouling Assays. Benchmarking antifouling materials commonly involves using materials such as bare glass, polypropylene (PP), polystyrene, TCPS, PDMS, PVC, and others as controls. Antifouling performance is commonly assessed against proteins and bacteria serving as model biofoulants. The evaluation process typically involves incubating the sample with a suspension containing a known concentration of protein (50−70 mg/mL) or bacteria (10^5−10^8 cells/mL) for a certain duration (1−6 h) to allow their attachment.

Numerous methods exist for quantifying surface-adsorbed proteins, each with their own advantages and limitations. Quantifying protein adsorption is an intricate subject, as different methods may exhibit incompatibilities. Interested readers can refer to other comprehensive reviews for an in-depth understanding.[142] However, as the scope of this Perspective is focused on evaluating the antifouling performance of materials, and only the methods commonly used for this purpose are introduced here. Common techniques for protein adsorption assessment include colorimetric protein assay (e.g., bicinchoninic acid (BCA) assay), enzyme-linked immunosorbent assay (ELISA), and SPR measurement.

The BCA assay offers stable and sensitive quantification of protein concentration by measuring a color change from green to purple, indicating the protein presence. This change occurs due to the reduction of Cu^{2+} ions by peptide bonds in proteins, forming a purple-colored complex with bicinchoninic acid at 562 nm. The assay can be conducted with a commercially available BCA protein assay kit. It is commonly employed to assess the adsorption behaviors of proteins, such as BSA, human fibrinogen, and human serum albumin, on surfaces. Despite its advantages, BCA may face interference from reducing agents, metal chelators, and common membrane lipids and phospholipids.

ELISA is also a potent tool to quantitate protein (e.g., fibrinogen) fouling on surfaces, with a detection limit much lower than that of the BCA method (0.5 μg/mL). ELISA is a highly sensitive technique used to detect antigens in biological samples through specific antibody−antigen interactions. It involves immobilizing antigens to a solid surface and complexing them with detection antibodies conjugated to molecules for detection. ELISA is typically performed in multi-well plates, allowing for high throughput and simultaneous handling of multiple samples. Compared to BCA, ELISA offers the advantage of targeting specific proteins, providing valuable insights beyond total protein concentration. While ELISA offers advantages such as high sensitivity, specificity, and quantitative analysis of antigen concentration, it has limitations, including temporary readouts based on enzyme/substrate reactions.

SPR is a phenomenon that occurs when incident light excites electrons in a metal surface, leading to plasmon oscillations that propagate parallel to the surface. By measuring changes in reflected light intensity or resonance angle shifts, SPR biosensors can detect biomolecular interactions with high sensitivity, quantifying the analyte concentration and binding kinetics. SPR is often used for analyzing protein (e.g., fibrinogen) and enzyme (e.g., lysozyme) adsorption behaviors on surfaces. It enables real-time monitoring of adsorption interactions, allowing for a kinetic analysis of adsorption events.

To quantitate surface-fouled bacteria, the prevalent method is fluorescent staining (with fluorescent dyes such as SYTO 9)

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of the postfouling surface, followed by imaging under confocal microscopy or fluorescent microscopy. By counting the bacteria adhered to the surface and comparing across different surfaces, antifouling performance is assessed. Commonly used bacteria strains include Gram-positive bacteria such as *S. aureus* and *B. subtilis* and Gram-negative bacteria such as *E. coli*, *P. aeruginosa*, and *Cellulophaga lytica*.

7.2.2. Bactericidal Assays. The primary method for assessing the surface bactericidal property involves LIVE/DEAD staining, where bacteria are cultured to a specific concentration (10^3–10^5 cells/mL) and then incubated with surfaces of interest and uncoated control surfaces for 1–2 h. After incubation, the surfaces are removed and gently rinsed to remove loosely attached bacteria. Subsequently, LIVE/DEAD staining, which differentiates live and dead cells via double staining (for instance, the LIVE/DEAD BacLight assay with the fluorescent nucleic acid dyes SYTO 9 and propidium iodide),[143] is performed on the removed surfaces. The stained surfaces are then imaged under confocal or fluorescent microscopy, enabling the enumeration of live and dead bacteria. This allows for the calculation of a bacteria-reduction ratio of a specific surface as an indicator of the surface's bactericidal effectiveness. Commonly used bacteria strains include Gram-positive bacteria such as *S. aureus* and *B. subtilis* and Gram-negative bacteria such as *E. coli* and *P. aeruginosa*.

Another experimental approach to quantitate live and dead bacteria on surfaces involves CFU counting. Similar to LIVE/DEAD staining, bacteria are cultured to a specific concentration (10^3–10^5 cells/mL) as a working bacteria suspension. Subsequently, a certain volume of bacteria suspension (100 μL to 1 mL) is transferred to the surfaces of interest for 1–2 h. After incubation, the bacteria are collected from the surfaces, either directly or by techniques such as vortexing or sonicating. The bacteria suspensions then undergo serial dilution, as described in ASTM E2149, for CFU counting to derive the bacterial killing rate (e.g., in terms of log reduction) resulting from the bactericidal surface.

The LIVE/DEAD staining method gives direct information about the ratio of live and dead bacteria on the surface. On the other hand, the CFU method is easier to operate and does not require fluorescence imaging techniques. However, it may not collect all the surface bacteria, and the collection process could lead to bacterial death, potentially affecting the accuracy of the surface's bactericidal property assessment.

7.2.3. Antibiofilm Assays. One of the most commonly used protocols to assess antibiofilm properties is the O'Toole protocol, which stains the total biomass with positively charged CV, as introduced previously in section 4.4.2.[144] Bacterial biofilms comprise the ECM, live cells, and dead cells. While the quantification of the overall biomass using stains like CV, Congo red, or dimethylmethylene blue (DMMB) serves as a good indicator of the antibiofilm performance, detailed information on the fractions of cells within a biofilm and their viability could inform us on the biological effects of synthetic materials. The biomass could be quantified using nucleic acid stains, such as 4′,6-diamidino-2-phenylindole (DAPI) or the LIVE/DEAD BacLight assay. Notwithstanding the availability of standardized staining methods, large disparities exist in biofilm culture methods. Without listing all the strains and culture conditions employed to date, we highlight the prevalence of *P. aeruginosa* (e.g., PAO1) as a model bacterium in antibiofilm studies, partially due to its natural tendency to form biofilms on virtually any synthetic surface. It is worth noting that most *P. aeruginosa* strains favor the air–liquid–solid interface for biofilm formation, a preference largely neglected in the existing antibiofilm literature. While most extant studies evaluate the biofilm formed from *P. aeruginosa* at the liquid–solid interface (i.e., under submerged conditions), the O'Toole protocol does offer an effective way to culture and quantify the biofilm at the three-phase interface. As such, one strategy toward standardization is the adoption of similar protocols in the antibiofilm literature, combined with the aforementioned standardized strains and assays, for a comprehensive assessment of the amount and bioactivity of bacterial biofilms in response to synthetic materials.

7.3. The Need to Develop New Antibacterial Strategies. Despite the plethora of research on the design of antifouling and bactericidal materials, the biotic–abiotic interface residing between living organisms and solid polymers remains largely understudied in the context of the molecular biology of bacterial fouling, especially on the cellular level. For example, fouling species like bacteria are often treated as passive colloidal particles and engineered surfaces as substrates for colloidal adsorption,[145] eliding the rich environmental adaptability of the fouling organisms.[146] Future anti-biofouling strategies likely require microbes to be recognized as complex systems with dynamic structures/metabolisms and sophisticated chemical communication mechanisms, all of which are potentially controllable via engineered surfaces. New knowledge of the molecular interactions and cellular activities that drive bacterial sensing and adhesion to a surface could become a powerhouse of innovation in antibacterial research.

One potential strategy is to integrate bacterial biofilm into the functional material, rendering it a living coating that combats subsequent biofouling while offering properties that currently do not exist in synthetic coatings, such as self-replication, adaptability, and the capability for chemical synthesis and biotechnological production.[147,148] Research on biofilm-based systems has the potential to uncover new ways of using these properties to our advantage. While most extant research in engineered living materials focuses on microbes that are genetically engineered to gain control over the properties of their ECM (i.e., the "material" produced by living organisms), such strains pose potential concerns around contamination and foreign species invasion once deployed. Instead, material-centric strategies for recruiting indigenous microbial species and controlling their phenotypes represent promising alternatives to living coatings. For example, a *P. aeruginosa* biofilm cultured on a coating composed of lightly cross-linked P4VP-*co*-DVB exhibited reduced virulence by 68% (Figure 5b) despite a greater quantity of biofilm that was nearly twofold that of the biofilm grown on uncoated culture plate (made of PVC).[136] This pyridine-rich surface was able to enrich dissolved iron on the coating surface. The abundance of surface iron led to reduced production and release of siderophores, phenazines, and rhamnolipids by the *P. aeruginosa* biofilm, which in turn decreased virulence. Investigating the relationships between microbial behavior/phenotype and material properties could provide valuable insight into design principles for new antibacterial materials that go beyond merely repelling or killing bacteria.

8. CONCLUSION

Antibacterial polymer coatings synthesized via chemical vapor deposition techniques, such as iCVD, PECVD, and CVP,

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present a promising approach to combat bacterial fouling, contamination, and biofilm formation on various surfaces. These vapor-phase techniques enable the fabrication of highly uniform, composition-controllable, substrate-independent coatings with superior antibacterial properties. This Perspective organizes recent advances in antibacterial coatings based on their functioning mechanisms and design principles. Antifouling surfaces primarily prevent adhesion by using hydrophilic polymers like zwitterionic polymers to create a hydration barrier, gaining non-specific adhesion resistance. Bactericidal surfaces involve contact-killing bacteria by incorporating QAC-based groups, modifying the surface topography, and immobilizing other bactericidal moieties. Antibiofilm surfaces typically function through dynamic chain reorientation (e.g., enabled by statistical amphiphilic copolymer coatings), immobilization of antibiofilm enzymes, or enzyme-mimicking polymers. Furthermore, multifunctional surfaces combine the aforementioned mechanisms. Moreover, we highlighted several significant challenges in the development and implementation of these coatings, including functional cross-linker utilization, zwitterionic material design, monomer library expansion, and the development of new antibacterial strategies. We also emphasize the importance of standardization in antibacterial assays to ensure accurate and consistent comparisons across various antibacterial coatings. By addressing these challenges and embracing the opportunities in the development of vapor-deposited antibacterial polymer materials, this Perspective intends to spur continued research and innovation in this crucial area.

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Notes

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REFERENCES

(1) Xu, J.; Lee, H. Anti-Biofouling Strategies for Long-Term Continuous Use of Implantable Biosensors. *Chemosensors* **2020**, *8* (3), 66.

(2) Carrascosa, C.; Raheem, D.; Ramos, F.; Saraiva, A.; Raposo, A. Microbial Biofilms in the Food Industry—a Comprehensive Review. *Int. J. Environ. Res. Public Health* **2021**, *18* (4), 2014.

(3) Zhang, X.; Ma, J.; Zheng, J.; Dai, R.; Wang, X.; Wang, Z. Recent Advances in Nature-Inspired Antifouling Membranes for Water Purification. *Chemical Engineering Journal* **2022**, *432*, No. 134425.

(4) Byrnes, T. A.; Dunn, R. J. K. Boating-and Shipping-Related Environmental Impacts and Example Management Measures: A Review. *J. Mar Sci. Eng.* **2020**, *8* (11), 908.

(5) Mack, D.; Rohde, H.; Harris, L. G.; Davies, A. P.; Horstkotte, M. A.; Knobloch, J. K. M. Biofilm Formation in Medical Device-Related Infection. *International Journal of Artificial Organs* **2006**, *29* (4), 343−359.

(6) Patel, R. Biofilms and Antimicrobial Resistance. *Clin. Orthop. Relat. Res.* **2005**, *437* (437), 41−47.

(7) Maan, A. M. C.; Hofman, A. H.; de Vos, W. M.; Kamperman, M. Recent Developments and Practical Feasibility of Polymer-Based Antifouling Coatings. *Adv. Funct Mater.* **2020**, *30* (32), 2000936.

(8) Khlyustova, A.; Cheng, Y.; Yang, R. Vapor-Deposited Functional Polymer Thin Films in Biological Applications. *J. Mater. Chem. B* **2020**, *8* (31), 6588−6609.

(9) Chen, P.; Lang, J.; Zhou, Y.; Khlyustova, A.; Zhang, Z.; Ma, X.; Liu, S.; Cheng, Y.; Yang, R. An Imidazolium-Based Zwitterionic Polymer for Antiviral and Antibacterial Dual Functional Coatings. *Sci. Adv.* **2022**, *8* (2), 1−12.

(10) Khlyustova, A.; Yang, R. Initiated Chemical Vapor Deposition Kinetics of Poly(4-Aminostyrene. *Front Bioeng Biotechnol* **2021**, *9*, 1−7.

(11) Gleason, K. K. Designing Organic and Hybrid Surfaces and Devices with Initiated Chemical Vapor Deposition (iCVD). *Adv. Mater.* **2024**, *36* (8), 2306665.

(12) Mariappan, D. D.; Kim, S.; Zhao, J.; Zhao, H.; Muecke, U.; Gleason, K.; Akinwande, A. I.; Hart, A. J. Ultrathin High-Mobility SWCNT Transistors with Electrodes Printed by Nanoporous Stamp Flexography. *ACS Appl. Nano Mater.* **2023**, *6* (7), 5075−5080.

(13) Zhao, J.; Gleason, K. K. Solvent-Less Vapor-Phase Fabrication of Membranes for Sustainable Separation Processes. *Engineering* **2020**, *6* (12), 1432−1442.

(14) Ivanova, E. P.; Hasan, J.; Webb, H. K.; Truong, V. K.; Watson, G. S.; Watson, J. A.; Baulin, V. A.; Pogodin, S.; Wang, J. Y.; Tobin, M. J.; Löbbe, C.; Crawford, R. J. Natural Bactericidal Surfaces: Mechanical Rupture of Pseudomonas Aeruginosa Cells by Cicada Wings. *Small* **2012**, *8* (16), 2489−2494.

(15) Chien, H. W.; Chen, X. Y.; Tsai, W. P.; Lee, M. Inhibition of Biofilm Formation by Rough Shark Skin-Patterned Surfaces. *Colloids Surf. B Biointerfaces* **2020**, *186*, No. 110738.

(16) Luo, L.; Zhou, Y.; Xu, X.; Shi, W.; Hu, J.; Li, G.; Qu, X.; Guo, Y.; Tian, X.; Zaman, A.; Hui, D.; Zhou, Z. Progress in Construction of Bio-Inspired Physico-Antimicrobial Surfaces. *Nanotechnol Rev.* **2020**, *9* (1), 1562−1575.

(17) Choi, G.; Song, Y.; Lim, H.; Lee, S. H.; Lee, H. K.; Lee, E.; Choi, B. G.; Lee, J. J.; Im, S. G.; Lee, K. G. Antibacterial Nanopillar Array for an Implantable Intraocular Lens. *Adv. Healthc Mater.* **2020**, *9* (18), 1−9.

(18) Chen, N.; Kim, D. H.; Kovacik, P.; Sojoudi, H.; Wang, M.; Gleason, K. K. Polymer Thin Films and Surface Modification by Chemical Vapor Deposition: Recent Progress. *Annu. Rev. Chem. Biomol Eng.* **2016**, *7* (iCVD), 373−393.

(19) Choudhury, R. R.; Gohil, J. M.; Mohanty, S.; Nayak, S. K. Antifouling, Fouling Release and Antimicrobial Materials for Surface Modification of Reverse Osmosis and Nanofiltration Membranes. *J. Mater. Chem. A Mater.* **2018**, *6* (2), 313−333.

(20) Golda-Cepa, M.; Engvall, K.; Hakkarainen, M.; Kotarba, A. Recent Progress on Parylene C Polymer for Biomedical Applications: A Review. *Prog. Org. Coat.* **2020**, *140*, No. 105493.

(21) Lahiri, D.; Nag, M.; Dey, A.; Sarkar, T.; Ray, R. R.; Rebezov, M.; Shariati, M. A.; Thiruvengadam, M.; Simal-Gandara, J. Immobilized Enzymes as Potent Antibiofilm Agent. *Biotechnol Prog.* **2022**, *38* (5), 1−10.

(22) Berne, C.; Ellison, C. K.; Ducret, A.; Brun, Y. V. Bacterial Adhesion at the Single-Cell Level. *Nat. Rev. Microbiol* **2018**, *16* (10), 616−627.
(23) Sauer, K.; Stoodley, P.; Goeres, D. M.; Hall-Stoodley, L.; Burmølle, M.; Stewart, P. S.; Bjarnsholt, T. The Biofilm Life Cycle: Expanding the Conceptual Model of Biofilm Formation. *Nat. Rev. Microbiol* **2022**, *20* (10), 608−620.
(24) Gu, Y.; Yu, L.; Mou, J.; Wu, D.; Xu, M.; Zhou, P.; Ren, Y. Research Strategies to Develop Environmentally Friendly Marine Antifouling Coatings. *Mar. Drugs* **2020**, *18* (7), 371.
(25) Nayak, K.; Kumar, A.; Tripathi, B. P. Molecular Grafting and Zwitterionization Based Antifouling and Underwater Superoleophobic PVDF Membranes for Oil/Water Separation. *J. Membr. Sci.* **2022**, *643*, No. 120038.
(26) Cheng, Y.; Khlyustova, A.; Chen, P.; Yang, R. Kinetics of All-Dry Free Radical Polymerization under Nanoconfinement. *Macromolecules* **2020**, *53* (24), 10699−10710.
(27) Khlyustova, A.; Cheng, Y.; Yang, R. Membrane Pore Size Distribution by Design via Kinetic Engineering Using Initiated Chemical Vapor Deposition. *Macromolecules* **2023**, *56* (16), 6492−6500.
(28) Vasudev, M. C.; Anderson, K. D.; Bunning, T. J.; Tsukruk, V. V.; Naik, R. R. Exploration of Plasma-Enhanced Chemical Vapor Deposition as a Method for Thin-Film Fabrication with Biological Applications. *ACS Appl. Mater. Interfaces* **2013**, *5* (10), 3983−3994.
(29) Yi, K.; Liu, D.; Chen, X.; Yang, J.; Wei, D.; Liu, Y.; Wei, D. Plasma-Enhanced Chemical Vapor Deposition of Two-Dimensional Materials for Applications. *Acc. Chem. Res.* **2021**, *54* (4), 1011−1022.
(30) Goda, T.; Konno, T.; Takai, M.; Ishihara, K. Photoinduced Phospholipid Polymer Grafting on Parylene Film: Advanced Lubrication and Antibiofouling Properties. *Colloids Surf. B Biointerfaces* **2007**, *54* (1), 67−73.
(31) Tan, C. P.; Craighead, H. G. Surface Engineering and Patterning Using Parylene for Biological Applications. *Materials* **2010**, *3* (3), 1803−1832.
(32) Hassan, Z.; Varadharajan, D.; Zippel, C.; Begum, S.; Lahann, J.; Bräse, S. Design Strategies for Structurally Controlled Polymer Surfaces via Cyclophane-Based CVD Polymerization and Post-CVD Fabrication. *Adv. Mater.* **2022**, *34* (37), 2201761.
(33) Golda-Cepa, M.; Chorylek, A.; Chytrosz, P.; Brzychczy-Wloch, M.; Jaworska, J.; Kasperczyk, J.; Hakkarainen, M.; Engvall, K.; Kotarba, A. Multifunctional PLGA/Parylene C Coating for Implant Materials: An Integral Approach for Biointerface Optimization. *ACS Appl. Mater. Interfaces* **2016**, *8* (34), 22093−22105.
(34) Bing, W.; Cai, Y.; Jin, H.; Tian, L.; Tian, L.; Yin, Y.; Teng, Y.; Wang, P.; Hou, Z.; Bai, X. An Antiadhesion and Antibacterial Platform Based on Parylene F Coatings. *Prog. Org. Coat.* **2021**, *151*, No. 106021.
(35) Tian, L.; Yin, Y.; Zhao, J.; Jin, H.; Shang, Y.; Yan, S.; Dong, S. Parylene F Coatings for Combating Marine Biofouling. *Mater. Lett.* **2021**, *285*, No. 129141.
(36) Khlyustova, A.; Yang, R. Initiated Chemical Vapor Deposition Kinetics of Poly(4-Aminostyrene. *Front Bioeng Biotechnol* **2021**, *9* (April), 1−10.
(37) Zorman, C.; Roberts, R. C.; Chen, L. Additive Processes for Semiconductors and Dielectric Materials. In *MEMS Materials and Processes Handbook*; Ghodssi, R., Lin, P., Eds.; Springer, 2011; pp 50−52. .
(38) Wong, T. S.; Kang, S. H.; Tang, S. K. Y.; Smythe, E. J.; Hatton, B. D.; Grinthal, A.; Aizenberg, J. Bioinspired Self-Repairing Slippery Surfaces with Pressure-Stable Omniphobicity. *Nature* **2011**, *477* (7365), 443−447.
(39) Song, F.; Koo, H.; Ren, D. Effects of Material Properties on Bacterial Adhesion and Biofilm Formation. *J. Dent Res.* **2015**, *94* (8), 1027−1034.
(40) Leng, C.; Sun, S.; Zhang, K.; Jiang, S.; Chen, Z. Molecular Level Studies on Interfacial Hydration of Zwitterionic and Other Antifouling Polymers in Situ. *Acta Biomaterialia* **2016**, *40*, 6.
(41) Chen, S.; Zheng, J.; Li, L.; Jiang, S. Strong Resistance of Phosphorylcholine Self-Assembled Monolayers to Protein Adsorption: Insights into Nonfouling Properties of Zwitterionic Materials. *J. Am. Chem. Soc.* **2005**, *127* (41), 14473−14478.
(42) Leonardi, A. K.; Ober, C. K. Polymer-Based Marine Antifouling and Fouling Release Surfaces: Strategies for Synthesis and Modification. *Annu. Rev. Chem. Biomol Eng.* **2019**, *10* (1), 241−264.
(43) Shao, Q.; Jiang, S. Molecular Understanding and Design of Zwitterionic Materials. *Advanced Materials* **2015**, *27* (1), 15−26.
(44) Lau, K. H. A.; Bang, J.; Hawker, C. J.; Kim, D. H.; Knoll, W. Modulation of Protein-Surface Interactions on Nanopatterned Polymer Films. *Biomacromolecules* **2009**, *10* (5), 1061−1066.
(45) Callow, J. A.; Callow, M. E. Trends in the Development of Environmentally Friendly Fouling-Resistant Marine Coatings. *Nat. Commun.* **2011**, 244.
(46) Calabrese, D. R.; Wenning, B.; Finlay, J. A.; Callow, M. E.; Callow, J. A.; Fischer, D.; Ober, C. K. Amphiphilic Oligopeptides Grafted to PDMS-Based Diblock Copolymers for Use in Antifouling and Fouling Release Coatings. *Polym. Adv. Technol.* **2015**, *26*, 829.
(47) Patterson, A. L.; Wenning, B.; Rizis, G.; Calabrese, D. R.; Finlay, J. A.; Franco, S. C.; Zuckermann, R. N.; Clare, A. S.; Kramer, E. J.; Ober, C. K.; Segalman, R. A. Role of Backbone Chemistry and Monomer Sequence in Amphiphilic Oligopeptide- and Oligopeptoid-Functionalized PDMS- and PEO-Based Block Copolymers for Marine Antifouling and Fouling Release Coatings. *Macromolecules* **2017**, *50*, 2656.
(48) Reichstein, W.; Sommer, L.; Veziroglu, S.; Sayin, S.; Schröder, S.; Mishra, Y. K.; Saygili, E. İ.; Karayürek, F.; Açil, Y.; Wiltfang, J.; Gülses, A.; Faupel, F.; Aktas, O. C. Initiated Chemical Vapor Deposition (Icvd) Functionalized Polylactic Acid−Marine Algae Composite Patch for Bone Tissue Engineering. *Polymers (Basel)* **2021**, *13* (2), 186.
(49) Liu, W.; Su, C.; Su, P.; Yang, H.; Lu, P.; Du, Z.; Ye, Y. Sub-20 Nm Bilayer Hydrophilic Poly(Vinyl Pyrrolidone) Coatings for Antifouling Nanofiltration Membranes. *Macromol. Mater. Eng.* **2021**, *306* (6), 1−7.
(50) Sun, M.; Qiu, H.; Su, C.; Shi, X.; Wang, Z.; Ye, Y.; Zhu, Y. Solvent-Free Graft-From Polymerization of Polyvinylpyrrolidone Imparting Ultralow Bacterial Fouling and Improved Biocompatibility. *ACS Appl. Bio Mater.* **2019**, *2* (9), 3983−3991.
(51) Sun, M.; Wu, Q.; Xu, J.; He, F.; Brown, A. P.; Ye, Y. Vapor-Based Grafting of Crosslinked Poly(N-Vinyl Pyrrolidone) Coatings with Tuned Hydrophilicity and Anti-Biofouling Properties. *J. Mater. Chem. B* **2016**, *4* (15), 2669−2678.
(52) Subramaniam, M. N.; Goh, P. S.; Sevgili, E.; Karaman, M.; Lau, W. J.; Ismail, A. F. Hydroxypropyl Methacrylate Thin Film Coating on Polyvinylidene Fluoride Hollow Fiber Membranes via Initiated Chemical Vapor Deposition. *Eur. Polym. J.* **2020**, *122*, 109360.
(53) Wang, H.; Shi, X.; Gao, A.; Lin, H.; Chen, Y.; Ye, Y.; He, J.; Liu, F.; Deng, G. Heparin Free Coating on PLA Membranes for Enhanced Hemocompatibility via ICVD. *Appl. Surf. Sci.* **2018**, *433*, 869−878.
(54) Zhang, R.; Shi, X.; Huang, X.; Zhao, J.; Lu, P.; He, Y.; Liu, F.; Liu, W.; Ye, Y. Vapor-Based Hybrid Grafting of Heparin-like Coating for Dialysis Membranes with Enhanced Hemocompatibility. *J. Membr. Sci.* **2023**, *685* (June), 121963.
(55) Zhu, M.; Mao, Y. Vapor-Deposited Janus Membranes with Fouling Resistance for Desalination of Oil-Contaminated Wastewater. *Adv. Mater. Interfaces* **2022**, *9* (2), 1−9.
(56) Donadt, T. B.; Yang, R. Amphiphilic Polymer Thin Films with Enhanced Resistance to Biofilm Formation at the Solid−Liquid−Air Interface. *Adv. Mater. Interfaces* **2021**, *8* (5), 1−7.
(57) Yang, R.; Moni, P.; Gleason, K. K. Ultrathin Zwitterionic Coatings for Roughness-Independent Underwater Superoleophobicity and Gravity-Driven Oil-Water Separation. *Adv. Mater. Interfaces* **2015**, *2* (2), 1−5.
(58) Baxamusa, S. H.; Gleason, K. K. Random Copolymer Films with Molecular-Scale Compositional Heterogeneities That Interfere with Protein Adsorption. *Adv. Funct Mater.* **2009**, *19* (21), 3489−3496.

https://doi.org/10.1021/cbe.4c00043
Chem Bio Eng. 2024, 1, 516−534

(59) Wang, T. J.; Lin, W. P.; Guo, S. P. Increased Hydrophilicity and Anti-Fouling Effect of Orthokeratology Lenses Coated with NVP and PEGMA by Plasma-Enhanced Chemical Vapor Deposition. *J. Coat. Technol. Res.* **2023**, *21* (2), 737−745.
(60) Yang, R.; Gleason, K. K. Ultrathin Antifouling Coatings with Stable Surface Zwitterionic Functionality by Initiated Chemical Vapor Deposition (ICVD). *Langmuir* **2012**, *28* (33), 12266−12274.
(61) Yang, R.; Xu, J.; Ozaydin-Ince, G.; Wong, S. Y.; Gleason, K. K. Surface-Tethered Zwitterionic Ultrathin Antifouling Coatings on Reverse Osmosis Membranes by Initiated Chemical Vapor Deposition. *Chem. Mater.* **2011**, *23* (5), 1263−1272.
(62) Janakiraman, S.; Farrell, S. L.; Hsieh, C. Y.; Smolin, Y. Y.; Soroush, M.; Lau, K. K. S. Kinetic Analysis of the Initiated Chemical Vapor Deposition of Poly(Vinylpyrrolidone) and Poly(4-Vinylpyridine). *Thin Solid Films* **2015**, *595*, 244−250.
(63) Yang, R.; Gleason, K. K. Ultrathin Antifouling Coatings with Stable Surface Zwitterionic Functionality by Initiated Chemical Vapor Deposition (ICVD). *Langmuir* **2012**, *28* (33), 12266−12274.
(64) Coclite, A. M.; Howden, R. M.; Borrelli, D. C.; Petruczok, C. D.; Yang, R.; Yagüe, J. L.; Ugur, A.; Chen, N.; Lee, S.; Jo, W. J.; Liu, A.; Wang, X.; Gleason, K. K. 25th Anniversary Article: CVD Polymers: A New Paradigm for Surface Modification and Device Fabrication. *Advanced Materials* **2013**, *25* (38), 5392−5423.
(65) Huang, C. J.; Li, Y.; Jiang, S. Zwitterionic Polymer-Based Platform with Two-Layer Architecture for Ultra Low Fouling and High Protein Loading. *Anal Chem.* **2012**, *84* (7), 3440−3445.
(66) Le, N. L.; Duong, P. H. H.; Pulido, B. A.; Nunes, S. P. Zwitterionic Triamine Monomer for the Fabrication of Thin-Film Composite Membranes. *Ind. Eng. Chem. Res.* **2021**, *60* (1), 583−592.
(67) Zhang, R.; Shi, X.; Huang, X.; Zhao, J.; Lu, P.; He, Y.; Liu, F.; Liu, W.; Ye, Y. Vapor-Based Hybrid Grafting of Heparin-like Coating for Dialysis Membranes with Enhanced Hemocompatibility. *J. Membr. Sci.* **2023**, *685* (June), 121963.
(68) Yang, R.; Xu, J.; Ozaydin-Ince, G.; Wong, S. Y.; Gleason, K. K. Surface-Tethered Zwitterionic Ultrathin Antifouling Coatings on Reverse Osmosis Membranes by Initiated Chemical Vapor Deposition. *Chem. Mater.* **2011**, *23* (5), 1263−1272.
(69) Shafi, H. Z.; Wang, M.; Gleason, K. K.; Khan, Z. Synthesis of Surface-Anchored Stable Zwitterionic Films for Inhibition of Biofouling. *Mater. Chem. Phys.* **2020**, *239*, No. 121971.
(70) Yang, R.; Goktekin, E.; Wang, M.; Gleason, K. K. Molecular Fouling Resistance of Zwitterionic and Amphiphilic Initiated Chemically Vapor-Deposited (ICVD) Thin Films. *J. Biomater Sci. Polym. Ed* **2014**, *25* (14−15), 1687−1702.
(71) Chen, P.; Lang, J.; Zhou, Y.; Khlyustova, A.; Zhang, Z.; Ma, X.; Liu, S.; Cheng, Y.; Yang, R. An Imidazolium-Based Zwitterionic Polymer for Antiviral and Antibacterial Dual Functional Coatings. *Sci. Adv.* **2022**, *8* (2), 1−12.
(72) Qian, S.; Zhang, S.; Pan, Q.; Sun, Q.; Song, R.; Zhang, Y.; Zhang, S.; Geng, Z.; Huang, J.; Wang, L.; He, Y.; Zhu, B. Conformable Thin Film Organic Electrochemical Transistor Array Featuring Tissue-like Softness and Ultralow Biofouling. *Appl. Surf. Sci.* **2024**, *660*, No. 160032.
(73) Zhang, S.; Qian, S. H.; Zhao, G.; Pan, Q. C.; Song, R.; Zhang, T.; Zhang, S.; Geng, Z.; Huang, J.; Wang, L.; Zhu, B. Intrinsically Antifouling, Soft and Conformal Bioelectronic from Scalable Fabrication of Thin-Film OECT Arrays by Zwitterionic Polymers. *Chem. Eng. J.* **2024**, *483*, No. 148980.
(74) Stalin, S.; Chen, P.; Li, G.; Deng, Y.; Rouse, Z.; Cheng, Y.; Zhang, Z.; Biswal, P.; Jin, S.; Baker, S. P.; Yang, R.; Archer, L. A. Ultrathin Zwitterionic Polymeric Interphases for Stable Lithium Metal Anodes. *Matter* **2021**, *4* (11), 3753−3773.
(75) Khoo, Y. S.; Lau, W. J.; Liang, Y. Y.; Karaman, M.; Gürsoy, M.; Ismail, A. F. Eco-Friendly Surface Modification Approach to Develop Thin Film Nanocomposite Membrane with Improved Desalination and Antifouling Properties. *J. Adv. Res.* **2022**, *36*, 39−49.
(76) Khoo, Y. S.; Lau, W. J.; Liang, Y. Y.; Karaman, M.; Gürsoy, M.; Ismail, A. F. A Green Approach to Modify Surface Properties of Polyamide Thin Film Composite Membrane for Improved Antifouling Resistance. *Sep Purif Technol.* **2020**, *250* (March), No. 116976.
(77) Flemming, H. C.; Wingender, J. The Biofilm Matrix. *Nat. Rev. Microbiol* **2010**, *8* (9), 623−633.
(78) Chaudhary, K.; Kumar, K.; Venkatesu, P.; Masram, D. T. Protein Immobilization on Graphene Oxide or Reduced Graphene Oxide Surface and Their Applications: Influence over Activity, Structural and Thermal Stability of Protein. *Adv. Colloid Interface Sci.* **2021**, *289*, No. 102367.
(79) Soozanipour, A.; Taheri-Kafrani, A. Enzyme Immobilization on Functionalized Graphene Oxide Nanosheets: Efficient and Robust Biocatalysts. *Methods Enzymol.* **2018**, *609*, 371−403.
(80) Plakunov, V. K.; Zhurina, M. V.; Gannesen, A. V.; Mart'yanov, S. V.; Nikolaev, Y. A. Antibiofilm Agents: Therminological Ambiguity and Strategy for Search. *Microbiology (Russian Federation)* **2019**, *88* (6), 747−750.
(81) Guo, W.; Ngo, H. H.; Li, J. A Mini-Review on Membrane Fouling. *Bioresour Technol.* **2012**, *122*, 27−34.
(82) Donadt, T. B.; Yang, R. Amphiphilic Polymer Thin Films with Enhanced Resistance to Biofilm Formation at the Solid−Liquid−Air Interface. *Adv. Mater. Interfaces* **2021**, *8* (5), 1−7.
(83) Khlyustova, A.; Kirsch, M.; Yang, R. Amphiphilic Copolymer Thin Films with Short Fluoroalkyl Side Chains for Antibiofilm Properties at the Solid-Liquid-Air Interface. *ACS Sustain. Chem. Eng.* **2022**, *10* (48), 15699−15713.
(84) Karygianni, L.; Hellwig, E.; Al-Ahmad, A. Multiplex Fluorescence in Situ Hybridization (M-FISH) and Confocal Laser Scanning Microscopy (CLSM) to Analyze Multispecies Oral Biofilms. *Methods Mol. Biol.* **2014**, *1147*, 65−72.
(85) Moreno-Couranjou, M.; Mauchauffé, R.; Bonot, S.; Detrembleur, C.; Choquet, P. Anti-Biofouling and Antibacterial Surfaces: Via a Multicomponent Coating Deposited from an up-Scalable Atmospheric-Pressure Plasma-Assisted CVD Process. *J. Mater. Chem. B* **2018**, *6* (4), 614−623.
(86) Donadt, T. B.; Yang, R. Amphiphilic Polymer Thin Films with Enhanced Resistance to Biofilm Formation at the Solid−Liquid−Air Interface. *Adv. Mater. Interfaces* **2021**, *8* (5), 1−7.
(87) Feng, Z.; Cheng, Y.; Khlyustova, A.; Wani, A.; Franklin, T.; Varner, J. D.; Hook, A. L.; Yang, R. Virtual High-Throughput Screening of Vapor-Deposited Amphiphilic Polymers for Inhibiting Biofilm Formation. *Adv. Mater. Technol.* **2023**, *8*, 2201533.
(88) Khlyustova, A.; Kirsch, M.; Ma, X.; Cheng, Y.; Yang, R. Surfaces with Antifouling-Antimicrobial Dual Function via Immobilization of Lysozyme on Zwitterionic Polymer Thin Films. *J. Mater. Chem. B* **2022**, *10* (14), 2728−2739.
(89) Chen, P.; Lang, J.; Franklin, T.; Yu, Z.; Yang, R. Reduced Biofilm Formation at the Air-Liquid-Solid Interface via Introduction of Surfactants. *ACS Biomater. Sci. Eng.* **2023**, *9* (7), 3923−3934.
(90) Kim, H.; Park, S.; Song, Y.; Jang, W.; Choi, K.; Lee, K. G.; Lee, E.; Im, S. G. Vapor-Phase Synthesis of a Robust Polysulfide Film for Transparent, Biocompatible, and Long-Term Stable Anti-Biofilm Coating. *Korean Journal of Chemical Engineering* **2023**, *40* (2), 412−418.
(91) Abu Elella, M. H.; Goda, E. S.; Yoon, K. R.; Hong, S. E.; Morsy, M. S.; Sadak, R. A.; Gamal, H. Novel Vapor Polymerization for Integrating Flame Retardant Textile with Multifunctional Properties. *Composites Commun.* **2021**, *24*, No. 100614.
(92) Nasrollahi, N.; Aber, S.; Vatanpour, V.; Mahmoodi, N. M. Development of Hydrophilic Microporous PES Ultrafiltration Membrane Containing CuO Nanoparticles with Improved Antifouling and Separation Performance. *Mater. Chem. Phys.* **2019**, *222*, 338−350.
(93) Selim, M. S.; Yang, H.; Wang, F. Q.; Fatthallah, N. A.; Huang, Y.; Kuga, S. Silicone/ZnO Nanorod Composite Coating as a Marine Antifouling Surface. *Appl. Surf. Sci.* **2019**, *466*, 40−50.
(94) Natarajan, S.; Lakshmi, D. S.; Thiagarajan, V.; Mrudula, P.; Chandrasekaran, N.; Mukherjee, A. Antifouling and Anti-Algal Effects of Chitosan Nanocomposite (TiO2/Ag) and Pristine (TiO2 and Ag)

https://doi.org/10.1021/cbe.4c00043
Chem Bio Eng. 2024, 1, 516−534

Films on Marine Microalgae Dunaliella Salina. *J. Environ. Chem. Eng.* **2018**, *6* (6), 6870−6880.
(95) Pourhashem, S.; Seif, A.; Saba, F.; Nezhad, E. G.; Ji, X.; Zhou, Z.; Zhai, X.; Mirzaee, M.; Duan, J.; Rashidi, A.; Hou, B. Antifouling Nanocomposite Polymer Coatings for Marine Applications: A Review on Experiments, Mechanisms, and Theoretical Studies. *J. Mater. Sci. Technol.* **2022**, *118*, 73−113.
(96) Roberts, D. A.; Poore, A. G. B.; Johnston, E. L. Ecological Consequences of Copper Contamination in Macroalgae: Effects on Epifauna and Associated Herbivores. *Environ. Toxicol Chem.* **2006**, *25* (9), 2470−2479.
(97) Srinivasan, M.; Swain, G. W. Managing the Use of Copper-Based Antifouling Paints. *Environ. Manage* **2007**, *39* (3), 423−441.
(98) Mohapatra, S.; Yutao, L.; Goh, S. G.; Ng, C.; Luhua, Y.; Tran, N. H.; Gin, K. Y. H. Quaternary Ammonium Compounds of Emerging Concern: Classification, Occurrence, Fate, Toxicity and Antimicrobial Resistance. *J. Hazard Mater.* **2023**, *445*, No. 130393.
(99) Maillard, J. Y. Bacterial Target Sites for Biocide Action. *Journal of Applied Microbiology Symposium Supplement* **2002**, *92* (1), 16S−27S.
(100) Franklin, T.; Yang, R. Vapor-Deposited Biointerfaces and Bacteria: An Evolving Conversation. *ACS Biomater. Sci. Eng.* **2020**, *6* (1), 182−197.
(101) Choi, G.; Jeong, G. M.; Oh, M. S.; Joo, M.; Im, S. G.; Jeong, K. J.; Lee, E. Robust Thin Film Surface with a Selective Antibacterial Property Enabled via a Cross-Linked Ionic Polymer Coating for Infection-Resistant Medical Applications. *ACS Biomater Sci. Eng.* **2018**, *4* (7), 2614−2622.
(102) Çıtak, E.; Testici, H.; Gürsoy, M.; Sevgili, E.; Dağı, H. T.; Öztürk, B.; Karaman, M. Vapor Deposition of Quaternary Ammonium Methacrylate Polymers with High Antimicrobial Activity: Synthetic Route, Toxicity Assessment, and Durability Analysis. *Journal of Vacuum Science & Technology A* **2020**, *38* (4), No. 043203.
(103) Song, Y.; Lee, Y. ki; Lee, Y.; Hwang, W. T.; Lee, J.; Park, S.; Park, N.; Song, H.; Kim, H.; Lee, K. G.; Kim, I. D.; Kim, Y.; Im, S. G. Anti-Viral, Anti-Bacterial, but Non-Cytotoxic Nanocoating for Reusable Face Mask with Efficient Filtration, Breathability, and Robustness in Humid Environment. *Chemical Engineering Journal* **2023**, *470* (June), No. 144224.
(104) Ding, X.; Duan, S.; Ding, X.; Liu, R.; Xu, F. J. Versatile Antibacterial Materials: An Emerging Arsenal for Combatting Bacterial Pathogens. *Adv. Funct Mater.* **2018**, *28* (40), 1−19.
(105) Lahiri, D.; Nag, M.; Sheikh, H. I.; Sarkar, T.; Edinur, H. A.; Pati, S.; Ray, R. R. Microbiologically-Synthesized Nanoparticles and Their Role in Silencing the Biofilm Signaling Cascade. *Front. Microbiol.* **2021**, *12*, 636588.
(106) Su, C.; Ye, Y.; Qiu, H.; Zhu, Y. Solvent-Free Fabrication of Self-Regenerating Antibacterial Surfaces Resisting Biofilm Formation. *ACS Appl. Mater. Interfaces* **2021**, *13* (8), 10553−10563.
(107) Jeong, G. M.; Seong, H.; Im, S. G.; Sung, B. H.; Kim, S. C.; Jeong, K. J. Coating of an Antimicrobial Peptide on Solid Substrate via Initiated Chemical Vapor Deposition. *Journal of Industrial and Engineering Chemistry* **2018**, *58*, 51−56.
(108) Kim, J.; Song, Y.; Kim, H.; Bae, N. H.; Lee, T. J.; Park, Y. M.; Lee, S. J.; Im, S. G.; Choi, B. G.; Lee, K. G. 3d Hierarchical Polyaniline−Metal Hybrid Nanopillars: Morphological Control and Its Antibacterial Application. *Nanomaterials* **2021**, *11* (10), 2716.
(109) Xu, L. Q.; Pranantyo, D.; Neoh, K. G.; Kang, E. T.; Fu, G. D. Thiol Reactive Maleimido-Containing Tannic Acid for the Bio-inspired Surface Anchoring and Post-Functionalization of Antifouling Coatings. *ACS Sustain Chem. Eng.* **2016**, *4* (8), 4264−4272.
(110) Lundberg, P.; Bruin, A.; Klijnstra, J. W.; Nyström, A. M.; Johansson, M.; Malkoch, M.; Hult, A. Poly(Ethylene Glycol)-Based Thiol-Ene Hydrogel Coatings?Curing Chemistry, Aqueous Stability, and Potential Marine Antifouling Applications. *ACS Appl. Mater. Interfaces* **2010**, *2* (3), 903−912.
(111) Chang, R.-Y.; Li, R.; Wang, W.; Geng, W.-H.; Li, N.; Jing, L.-C.; Yang, Z.-X.; Li, J.; Geng, H.-Z. Electrical Responsiveness of Carboxylate Multi-Walled Carbon Nanotube Cross-Linked Composite Anti-Fouling Membranes to Organic Pollutants. *J. Membr. Sci.* **2024**, *693*, No. 122360.
(112) Coclite, A. M.; Howden, R. M.; Borrelli, D. C.; Petruczok, C. D.; Yang, R.; Yagüe, J. L.; Ugur, A.; Chen, N.; Lee, S.; Jo, W. J.; Liu, A.; Wang, X.; Gleason, K. K. 25th Anniversary Article: CVD Polymers: A New Paradigm for Surface Modification and Device Fabrication. *Advanced Materials* **2013**, *25* (38), 5392−5423.
(113) Ferre, R.; Melo, M. N.; Correia, A. D.; Feliu, L.; Bardaji, E.; Planas, M.; Castanho, M. Synergistic Effects of the Membrane Actions of Cecropin-Melittin Antimicrobial Hybrid Peptide BP100. *Biophys J.* **2009**, *96* (5), 1815−1827.
(114) Xiao, M.; Jasensky, J.; Gerszberg, J.; Chen, J.; Tian, J.; Lin, T.; Lu, T.; Lahann, J.; Chen, Z. Chemically Immobilized Antimicrobial Peptide on Polymer and Self-Assembled Monolayer Substrates. *Langmuir* **2018**, *34* (43), 12889−12896.
(115) Romo-Rico, J.; Murali Krishna, S.; Golledge, J.; Hayles, A.; Vasilev, K.; Jacob, M. V. Plasma Polymers from Oregano Secondary Metabolites: Antibacterial and Biocompatible Plant-Based Polymers. *Plasma Process. Polymers* **2022**, *19* (7), 2100220.
(116) Kumar, A.; Mills, S.; Bazaka, K.; Bajema, N.; Atkinson, I.; Jacob, M. V. Biodegradable Optically Transparent Terpinen-4-Ol Thin Films for Marine Antifouling Applications. *Surf. Coat. Technol.* **2018**, *349*, 426−433.
(117) Kumar, A.; Al-Jumaili, A.; Prasad, K.; Bazaka, K.; Mulvey, P.; Warner, J.; Jacob, M. V. Pulse Plasma Deposition of Terpinen-4-Ol: An Insight into Polymerization Mechanism and Enhanced Antibacterial Response of Developed Thin Films. *Plasma Chemistry and Plasma Processing* **2020**, *40* (1), 339−355.
(118) Kumar, A.; Al-Jumaili, A.; Bazaka, K.; Mulvey, P.; Warner, J.; Jacob, M. V. In-Situ Surface Modification of Terpinen-4-Ol Plasma Polymers for Increased Antibacterial Activity. *Materials* **2020**, *13* (3), 586.
(119) Khoo, Y. S.; Seah, M. Q.; Lau, W. J.; Liang, Y. Y.; Karaman, M.; Gürsoy, M.; Meng, J.; Gao, H.; Ismail, A. F. Environmentally Friendly Approach for the Fabrication of Polyamide Thin Film Nanocomposite Membrane with Enhanced Antifouling and Antibacterial Properties. *Sep. Purif. Technol.* **2021**, *260*, No. 118249.
(120) Hasan, J.; Crawford, R. J.; Ivanova, E. P. Antibacterial Surfaces: The Quest for a New Generation of Biomaterials. *Trends Biotechnol* **2013**, *31* (5), 295−304.
(121) Kelleher, S. M.; Habimana, O.; Lawler, J.; O'reilly, B.; Daniels, S.; Casey, E.; Cowley, A. Cicada Wing Surface Topography: An Investigation into the Bactericidal Properties of Nanostructural Features. *ACS Appl. Mater. Interfaces* **2016**, *8* (24), 14966−14974.
(122) Ye, J.; Deng, J.; Chen, Y.; Yang, T.; Zhu, Y.; Wu, C.; Wu, T.; Jia, J.; Cheng, X.; Wang, X. Cicada and Catkin Inspired Dual Biomimetic Antibacterial Structure for the Surface Modification of Implant Material. *Biomater Sci.* **2019**, *7* (7), 2826−2832.
(123) Jaggessar, A.; Shahali, H.; Mathew, A.; Yarlagadda, P. K. D. V. Bio-Mimicking Nano and Micro-Structured Surface Fabrication for Antibacterial Properties in Medical Implants. *J. Nanobiotechnology* **2017**, *15* (1), 1−20.
(124) Xue, F.; Liu, J.; Guo, L.; Zhang, L.; Li, Q. Theoretical Study on the Bactericidal Nature of Nanopatterned Surfaces. *J. Theor Biol.* **2015**, *385*, 1−7.
(125) Gupta, M.; Kapur, V.; Pinkerton, N. M.; Gleason, K. K. Initiated Chemical Vapor Deposition (ICVD) of Conformal Polymeric Nanocoatings for the Surface Modification of High-Aspect-Ratio Pores. *Chem. Mater.* **2008**, *20* (4), 1646−1651.
(126) Choi, G.; Song, Y.; Lim, H.; Lee, S. H.; Lee, H. K.; Lee, E.; Choi, B. G.; Lee, J. J.; Im, S. G.; Lee, K. G. Antibacterial Nanopillar Array for an Implantable Intraocular Lens. *Adv. Healthc Mater.* **2020**, *9* (18), 1−9.
(127) Gürsoy, M.; Testici, H.; Çıtak, E.; Kaya, M.; Türk Dağı, H.; Öztürk, B.; Karaman, M. Biomimetic Surfaces Prepared by Soft Lithography and Vapour Deposition for Hydrophobic and Antibacterial Performance. *Materials Technology* **2022**, *37* (8), 745−752.
(128) Li, Y.; Ning, C. Latest Research Progress of Marine Microbiological Corrosion and Bio-Fouling, and New Approaches

of Marine Anti-Corrosion and Anti-Fouling. *Bioact. Mater.* **2019**, *4*, 189−195.
(129) Zhi, B.; Song, Q.; Mao, Y. Vapor Deposition of Polyionic Nanocoatings for Reduction of Microglia Adhesion†. *RSC Adv.* **2018**, *8* (9), 4779−4785.
(130) Su, C.; Hu, Y.; Song, Q.; Ye, Y.; Gao, L.; Li, P.; Ye, T. Initiated Chemical Vapor Deposition of Graded Polymer Coatings Enabling Antibacterial, Antifouling, and Biocompatible Surfaces. *ACS Appl. Mater. Interfaces* **2020**, *12* (16), 18978−18986.
(131) Kim, H.; Song, Y.; Park, S.; Kim, Y.; Mun, H.; Kim, J.; Kim, S.; Lee, K. G.; Im, S. G. Synthesis of a Stretchable Polyampholyte Hydrophilic Film with Compositional Gradient for Long-Term Stable, Substrate-Independent Fouling-Resistant Coating. *Adv. Funct. Mater.* **2022**, *32* (26), 2113253.
(132) Song, Q.; Zhao, R.; Liu, T.; Gao, L.; Su, C.; Ye, Y.; Chan, S. Y.; Liu, X.; Wang, K.; Li, P.; Huang, W. One-Step Vapor Deposition of Fluorinated Polycationic Coating to Fabricate Antifouling and Anti-Infective Textile against Drug-Resistant Bacteria and Viruses. *Chem. Eng. J.* **2021**, *418*, 129368.
(133) Donadt, T. B.; Yang, R. Amphiphilic Polymer Thin Films with Enhanced Resistance to Biofilm Formation at the Solid−Liquid−Air Interface. *Adv. Mater. Interfaces* **2021**, *8* (5), 1−7.
(134) Yang, R.; Xu, J.; Ozaydin-Ince, G.; Wong, S. Y.; Gleason, K. K. Surface-Tethered Zwitterionic Ultrathin Antifouling Coatings on Reverse Osmosis Membranes by Initiated Chemical Vapor Deposition. *Chem. Mater.* **2011**, *23* (5), 1263−1272.
(135) Shao, Q.; Jiang, S. Molecular Understanding and Design of Zwitterionic Materials. *Advanced Materials* **2015**, *27* (1), 15−26.
(136) Franklin, T.; Wu, Y.; Lang, J.; Li, S.; Yang, R. Design of Polymeric Thin Films to Direct Microbial Biofilm Growth, Virulence, and Metabolism. *Biomacromolecules* **2021**, *22* (12), 4933−4944.
(137) Chen, P.; Zhang, Z.; Rouse, Z.; Baker, S. P.; Yeo, J.; Yang, R. Engineering Solvation in Initiated Chemical Vapour Deposition for Control over Polymerization Kinetics and Material Properties. *Nat. Synthesis* **2023**, *2*, 373.
(138) Mengel, S. D.; Guo, W.; Wu, G.; Finlay, J. A.; Allen, P.; Clare, A. S.; Medhi, R.; Chen, Z.; Ober, C. K.; Segalman, R. A. Diffusely Charged Polymeric Zwitterions as Loosely Hydrated Marine Antifouling Coatings. *Langmuir* **2024**, *40*, 282.
(139) Azzaroni, O.; Brown, A. A.; Huck, W. T. S. UCST Wetting Transitions of Polyzwitterionic Brushes Driven by Self-Association. *Angewandte Chemie - International Edition* **2006**, *45* (11), 1770−1774.
(140) Shao, Q.; Jiang, S. Influence of Charged Groups on the Properties of Zwitterionic Moieties: A Molecular Simulation Study. *J. Phys. Chem. B* **2014**, *118* (27), 7630−7637.
(141) Sun, L.; Yuan, G.; Gao, L.; Yang, J.; Chhowalla, M.; Gharahcheshmeh, M. H.; Gleason, K. K.; Choi, Y. S.; Hong, B. H.; Liu, Z. Chemical Vapour Deposition. *Nat. Rev. Methods Primers* **2021**, *1*, 5.
(142) Shen, C.-H. *Diagnostic Molecular Biology*; Academic Press: London, UK, 2019.
(143) Magana, M.; Sereti, C.; Ioannidis, A.; Mitchell, C. A.; Ball, A. R.; Magiorkinis, E.; Chatzipanagiotou, S.; Hamblin, M. R.; Hadjifrangiskou, M.; Tegos, G. P. Options and Limitations in Clinical Investigation of Bacterial Biofilms. *Clin. Microbiol. Rev.* **2018**, *31* (3), No. e00084-16.
(144) O'Toole, G. A. Microtiter Dish Biofilm Formation Assay. *J. Visualized Exp.* **2011**, *47*, 3−5.
(145) Perni, S.; Preedy, E. C.; Prokopovich, P. Success and Failure of Colloidal Approaches in Adhesion of Microorganisms to Surfaces. *Adv. Colloid Interface Sci.* **2014**, *206*, 265.
(146) Boles, B. R.; Singh, P. K. Endogenous Oxidative Stress Produces Diversity and Adaptability in Biofilm Communities. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 12503.
(147) Nguyen, P. Q.; Botyanszki, Z.; Tay, P. K. R.; Joshi, N. S. Programmable Biofilm-Based Materials from Engineered Curli Nanofibres. *Nat. Commun.* **2014**, *5*, 1−10.
(148) Huang, J.; Liu, S.; Zhang, C.; Wang, X.; Pu, J.; Ba, F.; Xue, S.; Ye, H.; Zhao, T.; Li, K.; Wang, Y.; Zhang, J.; Wang, L.; Fan, C.; Lu, T. K.; Zhong, C. Programmable and Printable Bacillus Subtilis Biofilms as Engineered Living Materials. *Nat. Chem. Biol.* **2019**, *15* (1), 34−41.

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