Engineering and Application Perspectives on Designing Antimicrobial Surface

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Abstract

Infections, contaminations, and biofouling resulted from micro- and/or macro- organisms remained a prominent threat to the public health, food industry, and aqua/marine-related applications. Considering environmental and drug resistance concerns as well as insufficient efficacy on biofilms associated with conventional disinfecting reagents, developing an antimicrobial surface potentially improved the antimicrobial performance by directly working on the microbes surrounding the surface area. Here we provide an engineering perspective on the logic of choosing materials and strategies for designing antimicrobial surfaces, as well as an application perspective on their potential impacts. In particular, we analyze and discuss requirements and expectations for specific applications and provide insights on potential misconnection between the antimicrobial solution and its targeted applications. Given the high translational barrier for antimicrobial surfaces, future research would benefit from a comprehensive understanding of working mechanisms for potential materials/strategies, and challenges/requirements for a targeted application.

Keywords: Antimicrobial, biocide, interface, coating, microbe-resistance

Introduction

The adhesion of microbes on surfaces has caused prominent health, environmental, and societal issues. Significant effort and investment have been made to deal with the contamination/fouling of micro- or macro- organisms on indwelling medical devices[1], food processing industry[2], ship hulls and marine devices[3], etc. Take the threat to public health, for example, an annual of 1.7 million people suffered from healthcare-associated infections (HCAI) in the USA, and about 90, 000 died due to the infection each year.[4]

Conventional ways to disinfect (kill or inhibit) microorganisms involve antimicrobial reagents, including antibiotics, fungicides, antiviral drugs, as well as a wide selection of non-pharmaceutical chemicals. Extensive use of these reagents caused the concern of environmental pollution and potential microbial drug

resistance.[5] Furthermore, once microbes were attached and concentrated on a surface, a notorious biofilm would be developed. Conventional antimicrobial agents such as antibiotics were known for treating planktonic microbe infection but became insufficient to inhibit or eliminate a biofilm.[6] Part of the reasons have been attributed to the biofilm matrix which provides a protective diffusion barrier for antimicrobial reagents.[7-8] The applied reagents, typically in solution form, also have limitations in achieving high and durable local concentrations on the surface, preventing an effective treatment of biofilm.[9-10]

For most of the application scenarios (e.g., implanted medical devices, food packaging, vessels submerged into fresh or saltwater, etc.), the infection, biofouling, and/or biofilm formation typically happened on the substrate surface interfacing with the microbe environment. Compared to conventional bulk disinfection methods, engineering an antimicrobial surface in these cases potentially made more sense by directly treating the incoming and/or colonized microbes surrounding the surface area, resulting in an improved antimicrobial efficacy.[8, 10]

There are multiple strategies to construct an antimicrobial surface, including the approach integrating biocides onto the surface (microbicidal surface)[11-12], integrating materials showing microbe resistance properties (microbe resistance surface)[13-14], and potential combination of the two approach[15-16] (Figure 1). Prior reviews have focused on antimicrobial materials, their functioning mechanisms, and test results.[17-20] As a deviation from previous reviews, we provide an engineering perspective on the logic of choosing materials and strategies for designing antimicrobial surfaces, as well as an application perspective on their potential impacts (e.g., environmental, longevity/durability, capability to extend use). Majority discussions involve examples, either from the research field or industry, within the past five years. When possible, we provide insight on potential misconnection between a particular antimicrobial surface and its potential targeted applications, and desired properties/performance from the application standpoint. These perspectives are crucial given the high translational barrier in this field.

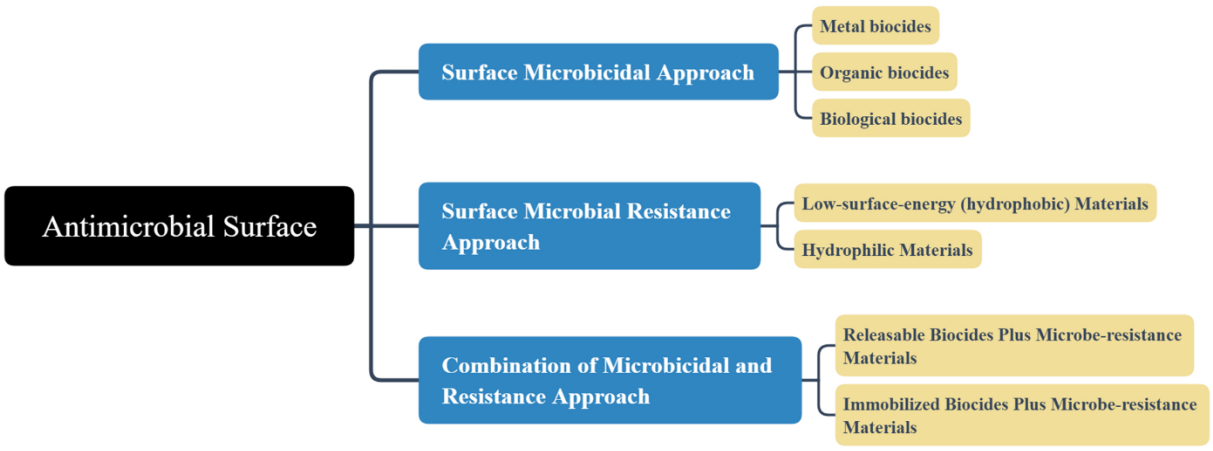

Figure 1. Design strategies for antimicrobial surface.

Surface Microbicidal Approach

The most commonly used antimicrobial approach is by incorporating materials/reagents with biocidal properties onto a surface and performing antimicrobial functions through releasing biocide[21-23] or contact killing [24-26]. An immediate convenience of this strategy is that a wide selection of biocides is available; many of them might have been approved by regulatory agencies and are ready to be formulated for specific applications.

For a typical biocides releasing process, biocide was released from the coating layer into the solid/liquid interface and the liquid phase and formed a toxic atmosphere with biocide concentration decreasing from the interference to the environment.[7] Locally, the surface biocide concentration can easily exceed the minimal inhibitory concentration (MIC) and the biocide can effectively kill the approaching microbes and prevent their contamination on the surface.[10] A major concern with this approach is that the biocide released pollute the environment, such as water, to some extent.[27-28] This may or may not be an issue depending on the type of the biocides and the local regulatory standards. Additionally, once the biocide is consumed, the surface loses the antimicrobial property.[29] The functioning duration of an antimicrobial surface is one of the key application-specific factors. This may require re-prepare the surface for biocide reloading, such as a paint removal and re-painting process.

For a contact killing process, biocide was typically covalently or firmly immobilized on the top surface and killed the microbes attempting to adsorb on the surface. Compared with the biocide releasing process, contact killing has limited biocide leakage to the environment and only functions when the microorganisms contact to the surface.[29] Common bactericidal mechanism is through physical damage, such as by destroying the bacterial membranes.[9, 30] The benefits of this approach are that no or limited toxic compound

being released, which is environmentally friendly.[31] Besides, compared to the biocide releasing strategy, contact killing, in theory, can function for a relatively longer time, assuming that the surface can be reactivated after the killed microbes are removed.[10] Nevertheless, surface absorption by contaminators such as bacterial fragments and/or inorganic or organic pollutants can disable the antimicrobial capability of these surface-immobilized biocides; This typically resulted in fouling gradually.[32-34]

Different from the traditional classification based on antimicrobial mechanisms [29-30], below we classified some commonly used biocidal reagents based on their material types, including metal derivatives[21, 35, 36], organic biocides[11-12, 22, 37], and biological biocides[34, 38] (this is for the convenience of biocide selections for a particular application scenario), and discussed their characters/functional mechanisms, reagent-stability, and pros and cons in terms of multiple aspects closely relating to their applications.

Metal Biocides

Metal-based biocides are among the most popular for a broad range of applications, including industrial, agricultural, marine, residential, and medical-related, and can be either deposited[39-40] or adsorbed[41-42] on a substrate. Copper oxidants[43-45], for example, are the main active ingredients in an antifouling marine coating,[46] which is nowadays classified as self-polished coating (SPC)[47]. The copper-based biocide was mixed with a base paint and deposited/applied on the substrate through a curing process. The paint includes polymer matrix providing mechanical support for the coating and the biocide contained is responsible for the antimicrobial or antifouling functions. The antimicrobial SPC, in general, has good durability despite the top surface layer continuously being polished/removed. The duration for copper-based biocide to function is determined by the amount of biocide trapped, the type of coating matrix, self-polishing rate, and the coating thickness (e.g., several layers of paint). In practice, the commercial copper-based SPC can function from months to years, which was subjected to variations caused by the longevity of coated vessels in water and the surrounding water conditions (temperature, salinity, etc.). Nevertheless, once the biocide is consumed, there is no way for reloading, and the remaining polymer coating has to be removed, followed by re-prepare the substrate for a new paint.

Before the copper oxidants were adopted for marine antifouling coating, tin-based biocide, such as organic tin complexes (Tributyltin, TBT), was the gold standard performing superior antifouling functions that can hardly be achieved even by any current antifouling paints, including those copper based[48-49]. Nevertheless, tin-based biocide was banned by the International Maritime Organization for biocidal surface applications in 2003 because it was very toxic to the shellfish and the toxicity can be transferred and enriched to other marine organisms even to human beings.[48, 50-51] The copper biocide has a safer profile than tin biocide, but

toxic concern for marine environment remains, with regulation coming into place for certain vessel coating applications in California and Washington State of the US.[52]

Comparatively, the silver-based biocide has an efficient antimicrobial property meanwhile with a relatively safer profile in living bodies.[35,36] A typical silver-based coating can be obtained through surface reduction process particularly for a small scale surface[53]. For large scale surfaces, they can be coated with silver nanoparticles (Ag NPs) based coatings [54-55] which is a more cost-effective option. Nanoparticle coatings had an increased specific surface area and further improved the antibacterial efficiency of silver[54]. It should be noted that silver-based antimicrobial performance has been widely documented, but limited results available for long-term performance.[35,15] Theoretically, the Ag NPs were trapped by the 3D structure of a coating matrix (such as polymer/gel-based)[56] and oxidized to Ag^+ very slowly[57]. But without a chemical linkage[58], the retention of the Ag NPs within the coating matrix could be weak, limiting their antimicrobial performance for a long term. Generally, the silver-based antimicrobial materials, under certain lab-test conditions, can function for several days[59-60], and with proper encapsulation for months.[61-62] Caution should be made that real application condition is still needed to evaluate the time frame of the release of biocides and its long-term performance.

With limited types of metal biocides available, current research in this area focused more on improving efficacy, such as through nano-scale preparation, and on controllable release, such as by tuning the adsorption to/retention by the substrate and/or through encapsulation. On the list of metal biocides, Zn and Ag are under more intensive study due to the lower toxicity compared to traditional Cu and Sn.

Organic Biocides

Organic biocides are small molecules or macromolecules exhibit antimicrobial properties. Different from the biological biocides, the organic biocides are mostly designed artificially and produced by the chemical industry in large scales. There are a lot more choices of organic biocides compared with metal biocides, including small biocidal molecules such as antibiotics[37,63] and triclosan[11], econea[64-65] and high molecular weight polymers such as chitosans[66-67], N-halamine polymers[68], sulfonium salts[69]. The organic biocides could be encapsulated by polymers[37, 70], or directly immobilized to surfaces [11-12].

In a typical encapsulation strategy, organic biocides could be directly mixed with the coating matrix materials before curing[71], or nano/micrometer-sized capsules could be formed with the biocide encapsulated before formulated into the coating matrix or immobilized onto the substrate.[71-72] The biocide release could be a purely diffusion dependent process which could be further determined by hydrophobicity/hydrophilicity and molecular weight of the biocide and potential interaction with the polymer matrix. Or the release could be controlled through potential degradation of the matrix

polymers/capsules[73-74] (4,5-Dichloro-2-n-octyl-4-isothiazoline-3-one in polysaccharide reported to several days[75]; 3-iodo-2propynyl butyl carbamate in polymethylmethacrylate (PMMA) reported to last for 15 years[74]). A potential benefit of organic biocides is their release to the environment could be considered "safe" given that they are degraded into non-toxic products. Econea is one of them which strongly resists barnacles meanwhile is quickly degraded in sea water[65], and has been extensively used in many of current marine antifouling paint formulations. Nevertheless, as a general issue to any biocide releasing approach, organic biocides released can be hard to be recharged, resulting in a loss of surface antimicrobial functions over time. It should be noted that under certain conditions, the loss of antimicrobial/antifouling functionalities might happen suddenly without warning, a potential combinatory effect of biocide release and degradation, which might cause unexpected troubles.

When organic biocides are immobilized onto the surface, they perform contact killing functions.[11-12, 76] The immobilization could be achieved by grafting polymer chains onto a substrate followed by anchoring the organic biocidal molecules to the terminal functional groups of the polymer through chemical reactions.[12, 77] A covalent linkage between the biocide and the polymer base is preferred to strengthen the immobilization. This leads to no/minimum release of biocide to the environment[31], and a working antimicrobial surface for a relatively long period[78]. Potential degradation mechanism for the organic biocides should be considered when designing the contact killing surface, which might limit the longevity of the antimicrobial performance. Potential contamination/absorption of bacterial cells or fragments on the biocide surface should also be considered since they compromised the immediate contact between the biocide and live microbes, deteriorating the bactericidal functions over time.[15, 19, 79-80]

Cationic polymers, such as the chitosan[66-67] and poly quaternary ammonium salt[81-82] are well known antimicrobial materials working though the contact killing mechanism.[9, 30] The polymer chain appeared to penetrate the cell wall of the bacteria, leading to a cytoplasmic leakage and killing the cells.[83-84] Length and density of the cationic polymer chains are considered critical parameters of modulating the penetration and thus the biocidal capability. For example, it was found that cationic polymer of 2-(dimethylamino)ethyl methacrylate (pDMAEMA) exhibited the highest antibacterial efficacy with greater than $5x10^{15}$ charges/cm^2.[25] Besides, the longer chain length (> 20 nm) of the cationic polymers improved the efficiency of killing the *E. coli* up to 20 folds compared to the polymer layer as thin as 10 nm. [25, 85] Cationic polymers would not induce drug resistance through known mechanisms, presumably there is no similar structure in nature.[85] Nevertheless, the cationic polymers had the same problem of non-specific contamination/absorption as other immobilized biocides, gradually losing their antimicrobial performance due to the coverage of bacteria or microbe fragments.

Biological Biocides

Biological biocides are antimicrobial compounds obtained from living bodies and/or produced through biological engineering methods, mainly including enzymes[34, 86-87], antimicrobial peptides[38, 88-89], bacteriophages[90-92], etc. Consider the molecular size and relatively high cost compared to metal and organic biocides, biological biocides were majorly immobilized on surfaces and functioned through contact killing.

Biocidal enzymes and peptides can be covalently anchored to the terminal of a polymer brush, which was grafted on the substrate through various surface reactions.[93-94] Durable immobilization could be obtained, and so is the antimicrobial activity; a covalently linked antimicrobial peptide on surfaces was able to maintain sufficient biocidal capability for up to 6 months as published.[95] The durability of the immobilization can be further improved by enhancing the linkage between substrate and spacer polymers. Similar to the biocidal mechanism for certain organic biocides, antimicrobial enzymes, and peptides functioned by non-specifically destroying the cytomembrane, which led to cellular content leakage.[34] The stability and performance of enzymes were restricted by environmental factors including temperature[96], pH[97], ultraviolet radiation [98], etc. Lysozyme is known as more stable among traditional enzymes[99], but still has limited applicability in a complex environment such as the less stable in warm marine area[100]. Again, simple modification of biological biocides cannot resist the adhesion of the protein and/or dead microbial debris, which compromised the biocidal efficiency over time.[34, 101]

Bacteriophages have been introduced as a biocide and immobilized onto surfaces in more recent years.[90-92, 102] They were immobilized though physisorption[103], electrostatic interactions[104] and covalent bonds[92], and functioned as a virus by infecting the microbes through surface contact. During the immobilization, the orientation of the bacteriophages has been considered; for example to ensure their tails pointing away from the surface to improve their capability of infecting the microorganisms,[90,102] and this is because the bacteriophages inject their genetic material through the tails into the cytoplasm of the host to infect the microorganism[105]. The naturally occurred bacteriophages are environmentally friendly and can perform efficient biocidal functions for months.[91] Nevertheless, they are non-rechargeable after the infectious genetic materials within the phages are consumed. Compared with other organic and biological biocides (e.g., cationic polymers and enzymes), bacteriophages infected and fought very specific microbes as they contacted the surface. It is expected that bacterial resistance of the phages would be developed and an equilibrium between the phage/host-microbe populations would be established.[102]

Surface Microbial Resistance Approach

In addition to the surface biocidal strategy, surface can be engineered to resist the microbial adhesion/adsorption/accumulation.[29-30] Microbe adhesion is considered as the critical step of colonization,

invasion and biofilm formation, so the prevention of adhesion can reduce the bacterial virulence and resist the contamination efficiently.[106] Unlike biocidal materials, materials performing anti-adhesion or resisting function do not damage the bacteria or reduce their numbers, but resist their attachment by reducing the adhesive force,[29, 107-108] or enable ease of removal of the loosely attached microbes such as through water shearing or physical turbulence.[109] Because this is a passive strategy involving no biocide, the surface resistance approach is considered safe, environmentally friendly, and without drug resistance concerns.[29, 110] Because of the non-leaching and non-specific resisting properties, this approach potentially provides a long period of microbial/fouling resistance.[13, 111-112] Certain low-surface-energy (hydrophobic) [113-114] and hydrophilic[13, 115] materials have been used as microbial resistance surface and were discussed below.

Low-surface-energy (Hydrophobic) Materials

Theoretically, a low-surface-energy material coated surface would resist the adhesion and spreading of high-surface-energy biofoulers such as proteins, cells, and bacteria since the potential coverage of which would further increase the surface energy of the coated substrate- an unfavored process according to Gibbs law of free energy.[116] Fluorocarbon and silicone-based materials are the most widely used low-surface energy materials. They are among the few materials showing surface free energy below 30 mN/m (e.g., polytetrafluoroethylene PTFE (Teflon™): 20 mN/m[117]; polydimethylsiloxane (PDMS): 19.8 mN/m[118]). In reality, the biofoulers did adhere to the low surface energy materials, but could be relatively easier to remove compared with regular material surfaces. For example, barnacle, one of the most notable marine fouler, has drastically reduced adhesion force on PDMS (~0.05 MPa[119]; 0.069 MPa[120]) as compared to a regular plastic substrate PMMA (0.5 MPa[119]). There is a number of ways to explain the rationale for the ease of removal or fouling release. For the PTFE surface, because of its hydrophobic nature, protein tends to approach to the surface through its hydrophobic region through hydrophobic-hydrophobic interactions.[121] However, the unique lipophobic nature of PTFE[122] vs. the lipophilic nature of the protein hydrophobic domain weakened such adhesion force[123]. For the PDMS surface, there is a significant mobility of the molecular chains accounting for a higher level of surface entropy. Potential protein absorption tends to restrict the chain movement, resulting in an unfavored status of decreased surface entropy. Fluorocarbon coat such as PTFE was typically applied through a spraying or electrostatic coating followed by thermal baking/curing[124-126], a process suitable for small to medium-sized substrates (larger size is tough). Silicone-based materials have been formulated into a series of commercial paints such as those for marine fouling-release purposes and could be conveniently coated on substrates of any size through conventional painting or rolling methods. Compared to biocide based antifouling paints, silicone-based marine fouling-release paints show the advantage of environmental friendly and relative ease of cleaning, however, their market

share was quite small due to a general lower antifouling performance (e.g., fouling-release coating may require a minimum of 15 knots sailing speed for at least 70% of time in water).[127]

As a common way to improve the low-surface-energy/hydrophobic properties, the surface morphologies or roughness could be further modified such as on PTFE and PDMS surfaces. Inspired by the natural superhydrophobic phenomenon of the lotus leaves[128], nano-scale morphology has been produced on PTFE surfaces and was found to improve the fouling-release performance (e.g., more than 99% *S. aureus* was easily removed by flowing water).[124] A porous surface based on a ZnO nano framework combined with a PDMS matrix has also been developed to achieve superhydrophobicity (contact angle increased to over 150 ^{o}).[129] The increased surface roughness and potential air entrapment by the 3-D morphology reduced the contact area between the microbe and the surface, further decreasing the adhesive force in-between. A common pitfall with complex surface morphology (e.g., micro/nano roughness feature) is their subjective to mechanical damage, impacting the durability and performance of use.[113] Compared to PTFE, PDMS has a relatively higher resistance to surface abrasions or damage due to its elastic nature[129]. A desired mechanical property can also be obtained through a composite material strategy. Additional pitfall includes a gradual entrapment of fouling debris onto the rough surface, particularly the valley region, and a gradual loss of the entrapped air, leading to deteriorated fouling release performance. Furthermore, translating the complex surface morphology to real-world substrates could be challenging with potential scaling-up, inconvenience, and high cost issues.

When a porous low-surface-energy surface (e.g., wrinkled PTFE) was infused with low-surface-energy liquid (e.g., silicone oil), a surface called SLIPS (slippery porous lubricant-infused surfaces) was obtained showing superhydrophobicity with water contact angle >160^{o}.[130] High resistance to bacterial adhesion (*Pseudoalteromonas spp.*) up to 99% was achieved within 24 h incubation. Better marine antifouling performance (inhibiting algal attachment) was observed with SLIPS compared with un-infused control when tested in the waters of Sydney Harbor for over 7 weeks. Despite reasonable retention by the porous surface due to similar polarities, the silicone oil was subject to gradual leakage through diffusion and shear stress of the water, leading to the loss of antifouling performance over time.[130] Silicone oil can be recharged into the surface, but their retention shall be further improved given that oil discharge could be an environmental concern and a demand for the longevity of a coating product, particularly in the marine antifouling market.

Hydrophilic Materials

Different from low-surface-energy (superhydrophobic) strategy, certain hydrophilic polymers resist the microbial adhesion because of their strong hydration capability.[30] The tightly bound water layer around

these materials shows strong repulsive hydration forces to resist protein adsorption, as well as cells/bacteria adhesion.[29-30, 131] Note that these hydrophilic materials here would resist the fouling in the first place, different from low-surface-energy materials that do encourage fouling but allowing the ease of fouling release/removal. Typical hydrophilic/water-soluble polymers would have structural characteristics of non-ionic or zwitterionic, which enables hydrogen bonding with water or ionic solvation, respectively.[131] Among them, nonionic polyethylene glycol (PEG) and zwitterionic polymers are the most well-known for surface coatings achieving superior microbial resistance.[3, 112, 132]

PEG is one of the most popular hydrophilic polymers for a broad range of applications; it has been FDA-approved to formulate drugs for both oral and injective administrations indicating an excellent safety profile.[133-134] There is abundant oxygen within the -CH_2CH_2O- repeating unit of PEG to form a large number of hydrogen bonds with water molecules. This afforded a strongly hydrated surface once a PEG coating was formed, and was responsible for its high resistance of more than 99% of bacteria from nonspecific adhesion.[14] The microbial-resistance property could be optimized with chain length and coating density[132], and overall a flexible PEG chain and high surface coverage are preferred to achieve a maximized surface entropy and minimized coating defect. One main challenge unique to PEG coatings is their subjective to oxidative damage, prohibiting their long-term applicability.[135] In addition, known anti-PEG antibodies have been/could be developed within certain group of people, which may or may not jeopardize their applications inside the body.[136-137]

Zwitterionic polymers are characterized as balanced positively and negatively charged groups within the same repeating units. Unlike nonionic polymers such as PEG typically able to dissolve in both water and organic solvents and showing both hydrophilic and hydrophobic (amphiphilic) properties, zwitterionic polymers may only be dissolvable in water (e.g., certain carboxybetaine polymers) and show a superhydrophilic property.[131] Different from nonionic hydrophilic polymers forming hydration layer through hydrogen bonds, zwitterionic polymers provide strong hydration through ionic solvation resulted from plenty of negative and positive charges within the material.[131] Since the net charge of zwitterionic polymer is nearly zero with opposite charges homogeneously distributed, the material itself would not preferably interact with charged proteins or microbes through electrostatic interactions. A number of zwitterionic polymer surfaces prepared from 2-methacryloyloxylethyl phosphorylcholine (MPC)[138-139], sulfobetaine methacrylate (SBMA)[115, 140], and carboxybetaine methacrylate (CBMA)[13, 141] showed high antifouling performance in resisting proteins/cells/bacteria attachment. Certain report indicated that zwitterionic PCBMA coating can reduce the formation of *P. aeruginosa* biofilm by 95% and maintained such high performance for 10 days, which might function superior over other reported PEG coatings that can only delay biofilm formation for one day.[110] A potential limitation unique to zwitterionic polymers is

their solubility issue (only dissolvable in water for certain types of polymers), which might complicate potential reaction with hydrophobic materials such as when forming an amphiphilic diblock copolymer for potential coating applications.[131, 142-143] Yet a zwitterionic polymer coatings can still be applied on many substrates through surface-initiated polymerization (graft-from method)[144], and covalent linkage through terminal functional groups (graft-to method)[145].

A notable drawback for any hydrophilic coatings is their low durability in an aqueous environment; they drastically tend to dissolve in water, together with insufficient coating immobilization, resulting in a gradual loss of the coating from the substrate.[13, 141, 146] The material loss may further pose a safety concern when the coating was applied in a medical environment where they are contacting with circulating blood. For these reasons, it was rarely found any antifouling hydrophilic coatings in the market such as in medical device fields and marine coating fields. From the perspective of resisting microbe adhesion and biofilm formation, as long as the hydrophilic coating shows high antifouling performance and maintains their coating integrity on a substrate, theoretically, a biofilm should never form. Nevertheless, majority hydrophilic coatings reported to date showed a delay of biofilm formation for days but failed to resist the biofilm for a long term, which could be partly explained by the durability challenge.[141] Recently, super glue has been used to immobilize zwitterionic gel network onto a variety of common substrates and the resulting zwitterionic hydrogel coating showed unusually high durability under aqueous, shearing, and mechanical impacting conditions, and remained the high antifouling performance for 3 months.[13] Figure 2 shows the performance of this coating in resisting different microbes from adhesion and biofilm formation (nearly “zero” attachment), showing high potential to fully address the biofilm issue.

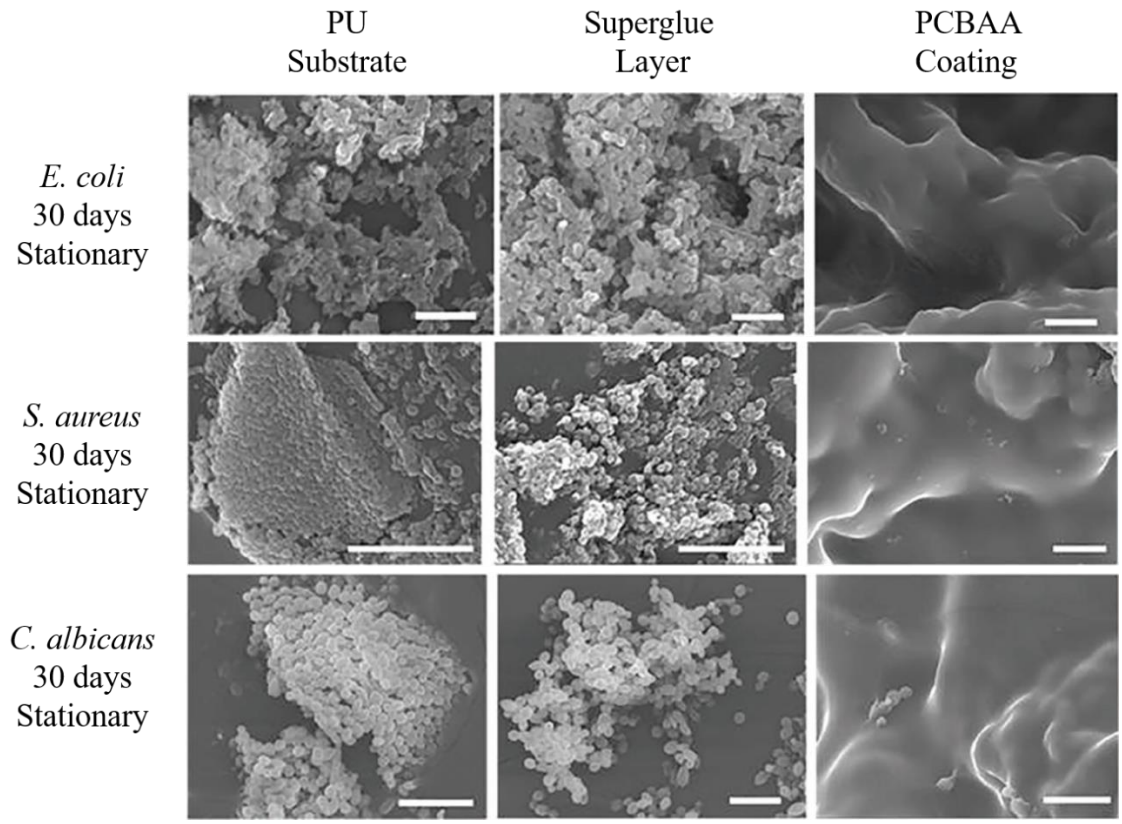

Figure 2. Surface microbial resistance of superdurable PCBAA (poly-3-((3-acrylamidopropyl) dimethylammonio)propanoate)) coating for long term performance.[13] The SEM images exhibited the microbial adhesion on the PU (polyurethane), superglue and PCBAA coating surface respectively after 30 days of stationary with different types of microbes. Reproduced with permission from ref 13. Copyright 2017, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Combination of Microbicidal and Resistance Approach

As discussed above, surface microbicidal approach and surface microbe resistance approach involve different technical, environmental, and functioning features, which further guide their applications in suitable scenarios. One can think of the potential combination of the two strategies to achieve maximum antimicrobial performance meanwhile balancing the pros and cons of each of the strategies.[30, 33, 80]. Here we discuss the possibility of combining these two approaches without compromising the performance for each, note that a bold combination may lead to unexpected results. Despite the potential improvement in antimicrobial efficacy, the combination approach will most likely increase the complexity of coating development and implementation, which requires additional justification.

Releasable Biocides Plus Microbe-resistance Materials

When a releasable biocidal material was combined with microbe-resistance material (either fouling resistance or fouling release type), there is a high chance that the released biocide plays the role of first defense by killing majority planktonic microbes (since the biocide can leave the surface) and the microbe-resistant material serves the second defense by preventing the attachment of dead microbes, a small portion of live microbes escaped from the biocide-killing, or other contaminators, or by allowing the ease of removal of the fouling attached. When the releasing rate for the biocide is slow, which is preferred to improve the longevity of microbicidal approach (e.g., as seen in commercial copper-based SPC), a fouling-resistant material would function as the first defense by resisting majority planktonic microbes from absorption and the releasable biocide serves the second defense and kills the microbes ever adhere to the surface. For a fouling-release material, it may function simultaneously with the releasable biocide while the microbes are attached on the surface.

Since releasable biocides are typically small molecules and ultimately would leave the surface, their interference with microbe-resistance materials is minimum, assuming no other materials competing the presence on surfaces with microbe-resistance materials. Thus, this combination perhaps represents the best coordination between the two strategies without sacrificing much of each of the biocidal/resistance functions. This combination also shows a potential advantage to continue performing the antimicrobial function, by resisting and/or enabling easy cleaning, after the releasing biocides were consumed up. Figure 3 shows one example of this combination[147] among many others[148], where Ag NPs were deposited within a zwitterionic PSBAA or PSBMA polymer coating. This combined approach showed a resistance of over 95% of *E. coli* from attaching to the surface, meanwhile killed up to 98% bacteria that attached.

The releasable biocides could be recharged under certain conditions, e.g., Ag NPs can be repeatedly loaded into a microbe-resistant hydrogel to sustain the antimicrobial functions[148]. These types of rechargeable surfaces might find applications for short-term usage per recharging cycle, since an effective recharging requires high diffusion property of the coating matrix, which in turn results in a faster release of the biocide out of the matrix. For long-term usage, the biocide was much stronger retained by the coating matrix; recharging the biocide would be difficult and the coating would need to be re-applied to sustain the microbicidal functions.

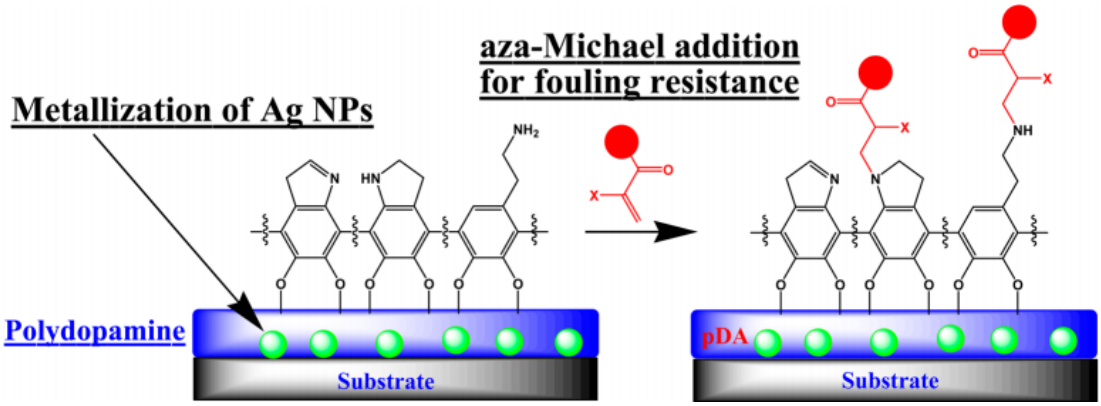

Figure 3. Releasable biocides within microbe-resistance surface for coordinated antimicrobial functions.[147] The Ag NPs (green balls) were deposited in the pDA layer (blue) *in situ* as the releasable biocide before the pDA surface was further functionalized and linked covalently to antifouling materials such as the SBAA, SBMA or PEGMA (red) to provide the microbe-resistance functions. Reproduced with permission from ref 147. Copyright 2016, American Chemical Society.

Immobilized Biocides Plus Microbe-resistance Materials

When an immobilized biocidal material was combined with microbe-resistance material (either fouling resistance or fouling release type) to form a surface coating, they would compete on their interaction with an approaching or an attached microbe. Depending on physical and chemical characters for these two materials (chain length, size, hydrophilicity/hydrophobicity), their spatial-temporal presence on the surface might be different, and this may or may not cause a compromise of each of the biocidal/resistance functions.[89, 149-150] For example, biocidal materials tend to interact with microbes while fouling resistance materials tend to repel. The presence of both on surface leads to the respective compromise of their functions. However, when biocidal materials and fouling release materials are co-presented on the surface, the compromise could be minimum since both tend to interact with microbes to some extent. Additionally, when the two types of materials are not on the same surface levels, such as the example shown in Figure 4, where zwitterionic PSBMA (fouling-resistance material) located at the outer surface and *N*-halamine (immobilized biocide) presented closer to the substrate[149], the compromise could also be minimum.

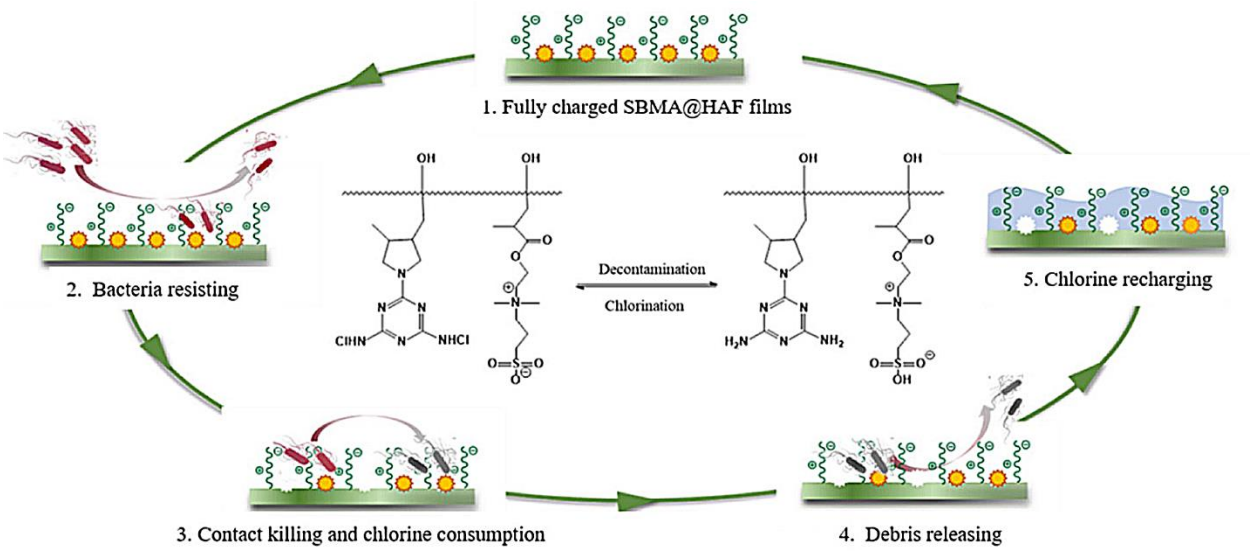

Figure 4. The immobilized biocidal *N*-halamine film integrated with the microbe-resistance PSBMA brush for coordinated antimicrobial application.[149] The HAF (immobilized rechargeable biocide) film was prepared with the modification of BPTCD (photoinitiator) before the zwitterionic polymers (green line, PSBMA, microbe-resistance coating) were grafted on the surface. The chlorine (yellow balls) on the HAF would be consumed during the contact biocidal process while the PSBMA resisted the adhesion of the bacteria/debris. The biocidal chlorine could be recharged by immersing the surface in a household bleach solution. Reproduced with permission from ref 149. Copyright 2019, American Chemical Society.

Special design of the combination approach could adjust the temporal presence of the two materials through external stimuli, allowing only majorly one type of material to appear and function at a time (to resolve potential compromise). For example, an antimicrobial surface has been engineered using immobilized cationic polymers to perform biocidal functions on attached microbes. After special treatment to hydrolyze part of the polymers, zwitterionic carboxybetaine was generated on the surface allowing release and/or easy removal of the prior contact-killed microbes.[151] Additionally, novel structured polymer surface would allow unlimited switch between cationic polymers and zwitterionic polymers through reversible ester bonds forming/breaking triggered by acidic/basic conditions, performing either microbicidal or resistance function as demanded.[16] It should be noted that the external manipulation to control the spatial-temporal presence of the two materials might be a hassle or might be demanded in a particular application scenario, which requires further validation.

Conclusion and Outlook

Overall, both microbicidal surface and microbe resistance surface could effectively address the antimicrobial requirement for a variety of applications, and some of them have already been implemented as commercial products. Current research in each of these areas and their potential combination further advanced the knowledge and technology to address the ever-increasing needs for antimicrobials. Despite enormous research publications on antimicrobial surfaces, the translational barrier was high and few of them succeeded in serving the real-world applications. Common reasons include a significantly high cost to register and approve a novel biocide with safety/environmental agencies, manufacturing barrier and difficulty to apply the coating on a real substrate, not being able to meet durability/mechanical/longevity requirement, e.g., medical devices and marine-related applications requires both coating stability and high performance for months or even years, and additional issues that might be out of the radar of researchers, such as coating removal/repair, spec to meet for targeted applications, and cost issues. It is believed that future research on antimicrobial surfaces would benefit from a comprehensive understanding of fundamentals, e.g., working mechanisms for potential materials/strategies, as well as the challenges/requirements from an application perspective.

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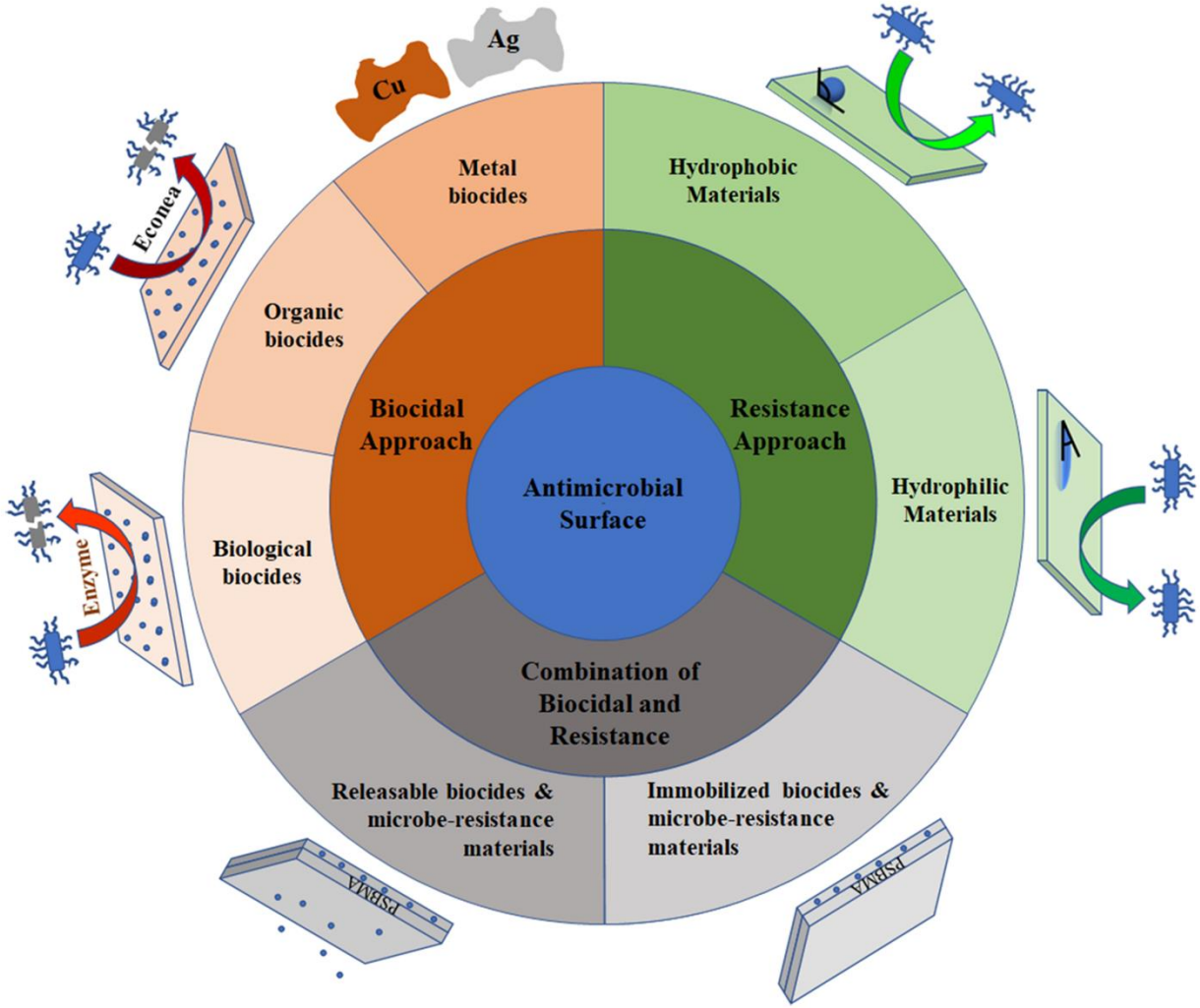
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Resistance Approach
Antimicrobial Surface
Hydrophilic Materials
Enzyme
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Combination of Biocidal and Resistance
Releasable biocides & microbe-resistance materials
Immobilized biocides & microbe-resistance materials
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