



Precision Design of Antimicrobial Surfaces

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The overall expectation from an antimicrobial surface has been high considering the need for efficiency in preventing the attachment and growth of pathogenic microbes, durability, safety to both humans and environment as well as cost-effectiveness. To date, antimicrobial surface design has been mostly conducted liberally, without rigorous consideration of establishing robust structure-activity relationships for each design strategy or of the use intended for a specific antimicrobial material. However, the variability among the domain bacteria, which is the most diverse of all, alongside the highly dynamic nature of the bacteria-surface interface have taught us that the likelihood of finding universal antimicrobial surfaces is low. In this perspective we discuss some of the current hurdles faced by research in this promising field, emphasizing the relevance and complexity of probing the bacteria-surface interface, and explain why we feel it would greatly benefit from a more streamlined *ad-hoc* approach.

Keywords: surface, antimicrobial, biofilm, interface, bacteria

ANTIMICROBIAL SURFACES—WHY ARE THEY SO IMPORTANT?

Interest in the development of antimicrobial surfaces has escalated in the last two decades. Literature searches on the Web of Science reveal impressive 3- and 6-fold increases in the number of original and review articles as well as in patents devoted to antimicrobial surfaces, from 2000 to 2010 and from 2000 to 2020, respectively. Patents alone account for 29% of the 42,691 publication universe under the keyword “antimicrobial surface.”

This interest in antimicrobial surfaces goes hand-in-hand with the 2012–2022 explosion in the global market for nanoengineered surfaces (NES) where the building sector heads the expected million USD revenues, followed by electronics and the biomedical sector (1). Within the latter, the sub-sectors of anti-bacterial sterilization and anti-biofouling radically evolved from having a negligible value in 2012 to an expected value of 106.4 and 51.7 billion USD by 2022, respectively, with an estimated total Compound Annual Growth Rate (CAGR) of 127.5% in this period.

Antimicrobial surfaces are needed to prevent the growth and spread of infectious microbes on a plethora of materials that routinely serve humans. They have become ubiquitous and indispensable in extending the shelf-life of both consumer and industrial goods as well as in reducing health risks across a wide range of sectors including health, food packaging, furniture, textiles, and the building and shipping industries (2–5). The outstanding impact of antimicrobial surfaces on boosting future technologies is predicted in the design of self-driving cars, for instance, where they will help to reduce the maintenance and downtime of key parts (6).

The need to build physical barriers between humans and infectious agents to prevent their spread within our community by contact has very recently been evidenced by the global pandemic

caused by SARS-CoV-2. Although extensive efforts have been directed toward the design of surfaces to target bacteria, little has been done to find those that efficiently kill and/or repel viruses, with the first steps toward understanding the method and duration of their surface adherence currently taking place (5, 7). At present, the remarkable evolution of community-disseminated super-resistant bacteria, alongside the scarcity of new antibacterial drugs to have reached the market in the past decades (8), represents a latent menace that threatens to cause the next global health crisis.

Overall, the expectations from an antimicrobial surface have been high. They should efficiently prevent the attachment and growth of pathogenic microbes indiscriminately thus limiting their spread by contact, be durable, harmless to human health and to the environment and cost-effective. However, can one single surface meet such a highly demanding wish list? Is the surface development process conveniently streamlined to ensure that the upcoming years will witness significant advances in the biomedical field?

ANTIMICROBIAL SURFACES THAT LEACH

By far the most straightforward strategy to design surfaces that target bacteria remains the incorporation, by physical adsorption, of an antimicrobial agent onto a polymeric matrix (2–5). Such surfaces are deemed leaching, i.e., they kill bacteria upon release of the antimicrobial agent over time. Despite being effective, leaching surfaces will eventually become inactivated once the antimicrobial agent has been exhausted and cannot therefore be regarded as long-lasting solutions. In addition, they are only as good as the agent they release, i.e., there is a limited number of antimicrobial agents that can be used due to stringent regulations.

Although the mode of action of leaching surfaces is easily ascribed to the respective agent they release, the exact load of antimicrobial agent comprised by the surface can be hard to accurately quantify, and the environmental impact of the leaching process is of concern (9). Metals and metal salts including silver, copper, zinc, and titanium dioxide are the most commonly used. They are known to act by inducing bacterial membrane disruption and oxidative stress. Long-term toxicity associated with exposure to silver is not yet fully established in humans, but its ecotoxicity is well-documented (10). Quaternary ammonium compounds (QACs), bearing permanent positive charges that disrupt bacterial membranes, lack sufficient efficiency and are prone to development of bacterial resistance (11, 12). In a similar fashion, bacteriostatic triclosan was banned over toxicity to both humans and the environment (13).

Natural antimicrobial peptides (AMPs), both bacterial and human, have also been under investigation (14). Among the diverse mechanisms of action known for AMPs, their net charges may allow for interaction with cell membranes while hydrophobic regions can maneuver into the phospholipid bilayers and in some instances result in pore formation and leakage of cell components (15). However, as AMPs are part of the innate immune system of all multicellular organisms,

the potential for resistance development cannot be overlooked, particularly if human AMPs are employed. AMPs can also be chemically grafted at the surface of polymers (14, 16–22) and in this case the leaching ability will depend upon the coupling method selected which will determine the stability of the chemical bond established. Amides are among the strongest chemical bonds whereas esterification and silanization will afford less stable bonds. A quick agar plate test is usually sufficient to rule out this leaching effect. AMPs are chemically complex molecules and therefore any translation of their outstanding antimicrobial properties will likely rely on the development of simplified synthetic counterparts.

Nonetheless, antimicrobial surfaces that leach have been successfully translated into very useful practical applications. For instance, despite the fact that roughly 1/3 of the silver present in conventional wound-dressings leaches out and becomes black due to oxidation hindering visualization of the healing process, silver-based dressings are a mainstay (23) among antimicrobial dressings, a market valued at 9.16 billion USD in 2014 and expected to exceed more than 23 billion by 2024 (24).

THE NEED TO EXPLORE THE INTERFACE WITH BACTERIA

The early 90's realization that bacteria exist in nature as biofilms as opposed to single entities and the extensive knowledge of bacterial behavior gathered thereafter (25, 26), have impacted the paradigm of antimicrobial surface design. Biofilms are very seldom eradicated by leaching antimicrobial agents alone due to the presence of the sheltering extracellular matrix. One of the best depictions of this behavior is provided by *B. subtilis* biofilms (27) which are more non-water-wetting than Teflon, presenting extreme impenetrability to liquid antimicrobials and gases.

Intensive research into the physico-chemical mechanisms specifically involved in bacterial adhesion onto surfaces has been underway (28–32) in the hope of finding key events that can be targeted for limiting early biofilm establishment. In this regard, a dissection of the interactions occurring at the interface of antimicrobial surfaces and the outermost external components of bacterial cells has become crucial in order to explain how surfaces can either kill or repel bacteria (or both) directly upon contact. Such explorations have often been complemented by computational models to predict bacterial attachment (33, 34). These surfaces are referred to as contact-active, and typically they are complex, either entailing a pattern at the surface or a random arrangement, yet their mode of action is independent of any leaching substance. They are usually perceived as potentially more ecofriendly if they are biodegradable, and more efficient if they can overcome clogging by dead bacteria and/or debris over time.

For instance, QACs and antibiofilm peptides have been immobilized at the surface of several polymers leading to contact-killing activity (35–39). The regular separation of both positive and negative charges along zwitterionic polymers successfully resulted in anti-fouling and bactericidal properties with self-cleaning capacity (40). Immobilized bacteriocins such as nisin

on various abiotic surfaces can prevent the formation of biofilms, and this approach has been explored by the food industry (41, 42). More recently, small tricyclic diterpenoids covalently bound onto nanocellulose through stable amide bonds (43, 44) rendered contact-active anionic antimicrobial surfaces capable of limiting biofilm formation.

Although hard to characterize both experimentally and theoretically, the tentative modes of action of contact-active surfaces are supported from studies regarding the activity of biosurfactants (45) and the interactions of nanoparticles with bacteria (32, 46, 47). It is likely that the surfaces are perceived by bacteria as complex polymeric matrices, unevenly branched with hydrophobic and hydrophilic regions or net charges that can intercalate into bacterial external structures, bind to surface proteins or modulate their activity through ion chelation, and/or have the ability to extract lipopolysaccharides, ultimately causing cell death. Other mechanisms may include enzymatic degradation of cellular membrane components or disruption of eDNA as well as limitation of the nutrient reservoir (48, 49). The presence of photoinduced compounds bound at the surface to kill bacteria by generation of oxidative radical species following activation has also been reported (35).

Regardless of the approach, the chemistry at the surface is a key determinant of the activity. Topographical manipulation of surfaces alone, i.e., devoid of any concomitant chemical modification, can compromise bacterial adhesion and in particular settings result in a contact-killing effect (50, 51). However, the number of materials that will entail the specific topographical features needed for the activity is limited and this strategy lacks sufficient efficiency to be regarded as a self-standing solution.

WHY ARE BACTERIA WINNING THE DAY?

The cumulative experience from the last two decades of research has taught us that bacteria-surface interfaces are outstandingly dynamic and that the likelihood of being successful with a simple approach, either leaching or non-leaching, is low. Therefore, the combination of leaching and non-leaching actions on the same surface, i.e., mixed action surfaces, has been investigated (2–5). One extreme example depicts the combination of topographical manipulation with chemical functionalization and the inclusion of a lubricating layer of liquid to build a slippery liquid-infused porous surface (SLIPS) that was able to prevent the attachment of both Gram-positive and Gram-negative bacteria for a whole week (52).

Indeed, the domain bacteria is the most diverse of all and this makes it virtually impossible to fine-tune a surface to meet the specific requirements of each bacterial strain in terms of hydrodynamics, topography-induced cell ordering, air-entrapment, chemical gradients, physicochemical force fields or cell membrane deformation, among other factors. In addition, even though bacteria use their surface structures, such as fimbriae, pili, flagella, and S-layer for adhesion to surfaces, these structures may also prevent bacteria or their membranes from coming into close contact with antimicrobial surfaces.

Bacteria have different preferences for hydrophilic and hydrophobic surfaces (53) which could relate to differences in charges and/or composition of their bacterial membranes and the extracellular polymeric matrix (EPS) they produce en route to establishing biofilms. In general, hydrophobic surfaces gain greater biofilm formation (54). As in antimicrobial drug discovery, the outer membrane of Gram-negative bacteria is a strikingly differentiating factor. The presence of lipopolysaccharide O-antigen is reported to hamper adhesion of surfaces onto bacteria by neutralizing the negative charge usually carried by the supporting cell envelope (32). Moreover, bacteria are well-prepared to adapt and evolve to survive in the presence of external stress. Finally, compared to research settings which work with primarily monoculture biofilms in controlled environments, natural biofilms also frequently host other microbes as symbionts to establish polymicrobial communities, thus challenging the performance of antimicrobial surfaces when used in real settings.

As exemplified by contact-active surfaces, a plethora of different surface chemistries will work against bacteria through manipulations of net charge, hydrophobicity, topography, or other factors, yet to date there is no clear cut structure-activity relationships that can be inferred to guide future design efforts. This is largely due to the diversity of polymer substrates, antimicrobial agents and functionalization strategies currently portrayed in the literature, which are extremely broad and essentially random, hampering what should be a systematic approach. At least one study has applied combinatorial chemistry and high-throughput screening to identify a group of structurally related polymers that limit pathogenic bacterial adhesion at their surface (55). With this approach, it is possible to focus on a single polymer class and determine, with a higher level of precision, exactly which variations in chemistry afforded the best antimicrobial properties. With this information at hand, predictive computational models can be built (29), yet their robustness is likely to be at present modest in light of the extreme complexity in accurately depicting bacteria-surface interactions.

On the other hand, while the majority of available reports focuses on finding broad-action antimicrobial surfaces, the translational value of selectively targeting one specific bacteria type remains to be determined. Clues on how to design surfaces that discriminate between Gram-positive and Gram-negative bacteria as well as fungi are available from literature on microbe detection systems (30). The fact that the activity of cationic polymers can be modulated by buffer concentration is notable.

TIME TO CONSOLIDATE TO STEP UP TO THE CHALLENGE

The intricacy of bacteria-surface interactions turns the idea of an universal antimicrobial surface into a chimera. We foresee that advancements in this field will come from focusing the design of antimicrobial surfaces on the very specific features required by its intended use. This precision design will entail a comprehensive knowledge of the microbes that need to be targeted as well as of the polymers that bear the most convenient properties for

good performance in a particular setting. These should include biopolymers such as (nano)cellulose, silk, collagen, or alginate for the sake of sustainability.

To support this endeavor, a very wide range of experimental, computational, and theoretical approaches will be mandatory where knowledge of chemistry including computational chemistry, microbiology, membrane biophysics and bioinformatics is key. In addition, the development of antimicrobial surfaces would greatly benefit from a “design of experiments approach” to streamline the process for building robust structure-activity relationships.

Our ability to continue to explore bacteria-surface interactions will dictate how much we can say of specific modes of action for each surface at the atomic level. For instance, despite significant advances in molecular dynamics to study the mode of action of small AMPs (56, 57), extending these studies to the scale and complexity of a surface is still way beyond the limits of this technique. Proteomics, transcriptomics, and mutagenesis studies will continue to be essential techniques in deciphering the interactions of antimicrobial surfaces with bacteria.

Regardless of addressing the main mode of action, the most important thing is functionality, i.e., to find surfaces that work. How broad-acting, durable, biodegradable, or cytocompatible they need to be should be dictated by their final use. Therefore, the selection of suitable control materials and bioassays that address the complexity of single-cell and multispecies biofilms is of utmost importance. Surfaces should also be screened in

combination with other techniques to target biofilms including, for instance, cold plasmas (58). Finally, however specific these insights may be for bacteria, we believe the strategy for surface design outlined herein will apply for other microbes including fungi and viruses, conveniently adapted to their particular biology.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

DM, XW, TT, and PS carried out literature searches. VM compiled the manuscript. All authors contributed to the views expressed in the article, and critically helped to write and revise the document.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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