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Combining topography and chemistry to produce antibiofouling surfaces – a review

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ABSTRACT. Despite decades of research on the reduction of surface fouling from biomolecules or micro-organisms, the ultimate antibiofouling surface remains undiscovered. The recent covid-19 pandemic strengthened the crucial need for such treatments. Among the numerous approaches that are able to provide surfaces with antibiofouling properties, chemical, biological and topographical strategies have been implemented for instance in marine, medical or food industries. However, many of these methods have a biocidal effect and, with antibioresistance and biocide resistance a growing threat on humanity, strategies based on reducing adsorption of biomolecules and micro-organism are necessary for long-term solutions. Bio-inspired strategies, combining both surface chemistry and topography, are currently at the heart of the best innovative and sustainable solutions. The synergistic effect of micro/nano-structuration, together with engineered chemical or biological functionalization is believed to contribute to the development of antibiofouling surfaces. This review aims to present approaches combining hydrophobic or hydrophilic chemistries with a specific topography to avoid biofouling in various industrial environments and healthcare facilities.

Contents

1. Introduction

Surface fouling is defeating man-made devices in various fields. Water treatment[1], marine[2,3] and food industry[4] as well as the medical field[5–7] are seeking for surfaces that will prevent undesired fouling. This spontaneous deposition of molecules, macromolecules and micro-organisms on an engineered surface upon contact with a liquid medium leads to the formation of biofilms that strongly impede performance and functionality. The predominant use of curative approaches, such as antibiotics in the medical filed, or biocides in marine environments, is no longer desirable. Throughout decades of massive administration of antibiotics to human and animal feedstock, more and more resistant bacterial strains have emerged and spread all over the globe. World Health Organization (WHO) recently labelled the arising antibioresistance as the most urgent health threat of our time.[8] And the European Commission forecasts no less than 10 million deaths per year attributed to antibioresistance in 2050 if today's tendency is not hampered.[9] Biocide resistance is also on the rise[10] and the important use of tributyltin since the 1960's has caused tremendous damage to the marine environment.[11,12] Since its prohibition in 2008, more environmentally friendly solutions have been investigated. The scientific community is putting in tremendous efforts in the search for alternative strategies that do not rely only on curative approaches. Their

focus is now rather on preventive approaches which tackle the initial steps of biofilm development: the adsorption of biomolecules and subsequent micro-organisms adhesion. In this manuscript, the term *antibiofouling* describes the ability of a surface to impede fouling from biological molecules, macro-molecules and/or micro-organisms, while *antifouling* is used for general fouling with any type of chemical substance or particle, including inorganic structures. Preventive approaches to fight surface fouling are now predominantly investigated and can be classified according to three different mechanisms: (i) active molecule-releasing and (ii) contact-killing surfaces, that prevent micro-organism growth both on and near surfaces, and (iii) anti-adhesive surfaces that prevent molecule, macromolecule and micro-organisms adhesion. These three antibiofouling mechanisms can be achieved with five different types of surface modification, as detailed in Figure 1.

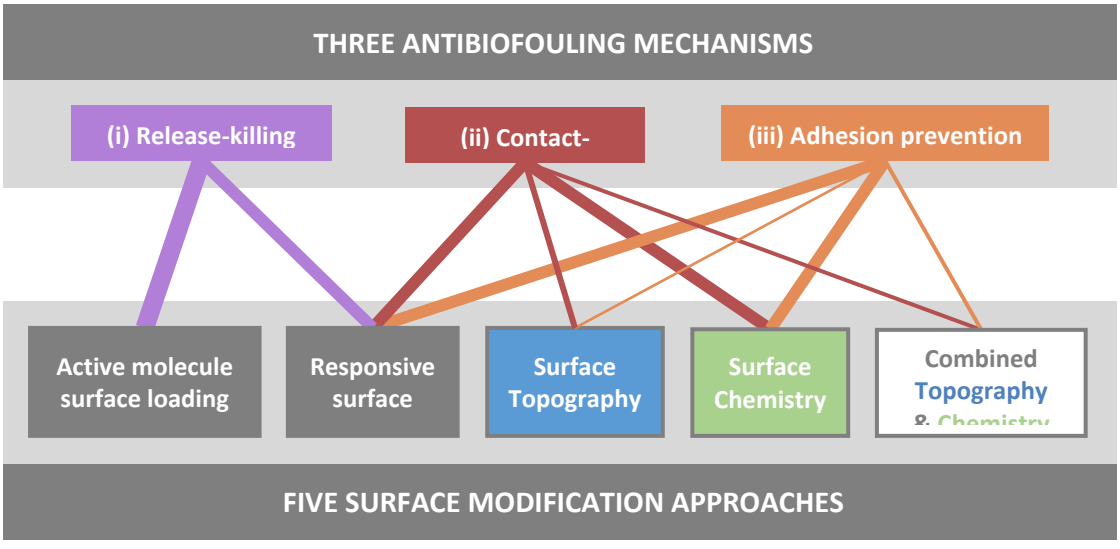


Figure 1: Three antibiofouling mechanisms linked to corresponding types of surface modification. The thickness of the links gives an estimation of the amount of research articles on the topics.

(i) In order to fight surface fouling with a limited quantity of antibiotics or biocides, a first mechanism is active molecule releasing-surfaces. Antibiotic and biocide release will kill the micro-organisms before they reach the surface and form biofilms. The release can be spontaneous in *active molecule surface loading* approaches, or triggered by a specific physico-chemical stimuli (pH, temperature, UV irradiation, enzymatic activity…) in *responsive surface* approaches. However, these approaches are limited in time, only affect micro-organisms and do not prevent biomolecular fouling, and still face the issue of antibioresistance, biocide resistance and damage to the environment. Only short term specific applications will benefit from this mechanism.[3,13,14]

(ii). A second mechanism relies on contact-killing. *Surface chemistry* approaches allow immobilization of active molecules onto the surface, leading to micro-organisms being killed upon contact or adhesion. In *responsive surface* approaches, the immobilized active molecule action can be triggered upon a specific physico-chemical stimuli. Some responsive surfaces are also able to eliminate the accumulation of dead cells that would progressively impede their contact-killing effect. But this contact-killing effect can also be obtained without the use of active molecules. Inspired by numerous natural surfaces in plants and the animal kingdom, engineered surface

topography (nanopillars, microblades, nanospikes…) is able to, in some cases, cause mechanical stress on adhered micro-organisms, leading to membrane failure and eventually cell death.[15–17] Hence, *combined surface topography and chemistry* approaches are also able to achieve contact-killing mechanism, with potential synergistic effects that are reviewed in this manuscript.

(iii). At last, only the adhesion prevention mechanism prevents both biomolecules and micro-organism fouling since they are engineered to prevent the interaction between the foulants and the surface. For instance, superhydrophobic surfaces obtained by *surface chemistry* or *combined topography and chemistry* approaches will avoid surface fouling since the foulants are confined to the liquid phase which has a limited contact area with the surface. Similarly, zwitterion molecules or polymers can provide surfaces with superhydrophilic properties, forming a dense hydration layer that can also prevent fouling. Plus, depending on physico-chemical stimuli, *responsive surface* approaches offer similar adhesion prevention mechanisms. [18–20]

All these surface modifications tune the surface properties in terms of topography and/or chemical composition. Moreover, the still on-going study of natural surfaces in plants, insects and the animal

kingdom have revealed numerous natural antibiofouling strategies that rely on the combination of a specific surface topography with a particular surface chemistry.The published literature over the past 5 years offers approximately five hundred reviews on the *antifouling* topic. Within this overwhelming amount of review articles that cover the afore-mentioned antibiofouling mechanisms, approximately 60 of them were selected based on their title and abstracts. They were classified in table S1 of the Supporting information, according to the type of surface modification approach detailed in Figure 1 (*active molecule surface loading*, *surface chemistry, surface topography, responsive surface* and *combined topography and chemistry).* Less than ten mention *combined topography and chemistry* approaches, and never as the core topic of the review.[4,21–27] Up to our knowledge, none of them specifically focused only on this approach. This manuscript aims to fill this gap and provide these works with their own specific review. However, these research articles are not easily identified since authors do not always indicate the combined aspect of their surface modifications. The research projects described in this review were then selected by using three successive filters: firstly, *surface topography* approaches over the last 5 years were explored. Secondly, the articles in which *surface chemistry* was used to complement the *surface topography* were isolated. And thirdly, only the works that exposed the engineered surfaces to

biomolecular and/or micro-organisms fouling were selected. Even if they can be sometimes a source of inspiration for developing antibiofouling surfaces, research topics such as anti-corrosion or self-cleaning surfaces, were mainly left aside.

The in-depth analysis of the selected works led to several levels of classification following a bottom-up process, as detailed in Figure 2. The first one is the nature of the substrate that is to be provided with antibiofouling property: metals and their oxides and hydroxides, glass and silicon-based materials, and polymers. Secondly, the articles are classified depending on the method used to tune the substrate topography (step 1), either by modifying the substrate itself (endogenous topography), or by using an additive strategy and adding another material (exogenous topography). The third level relates to the surface chemistry modification: a vast majority of approaches complement the topography with a chemical layer (step 2), but some approaches simultaneously tune the substrate topography while producing the chemical layer (step 1&2).

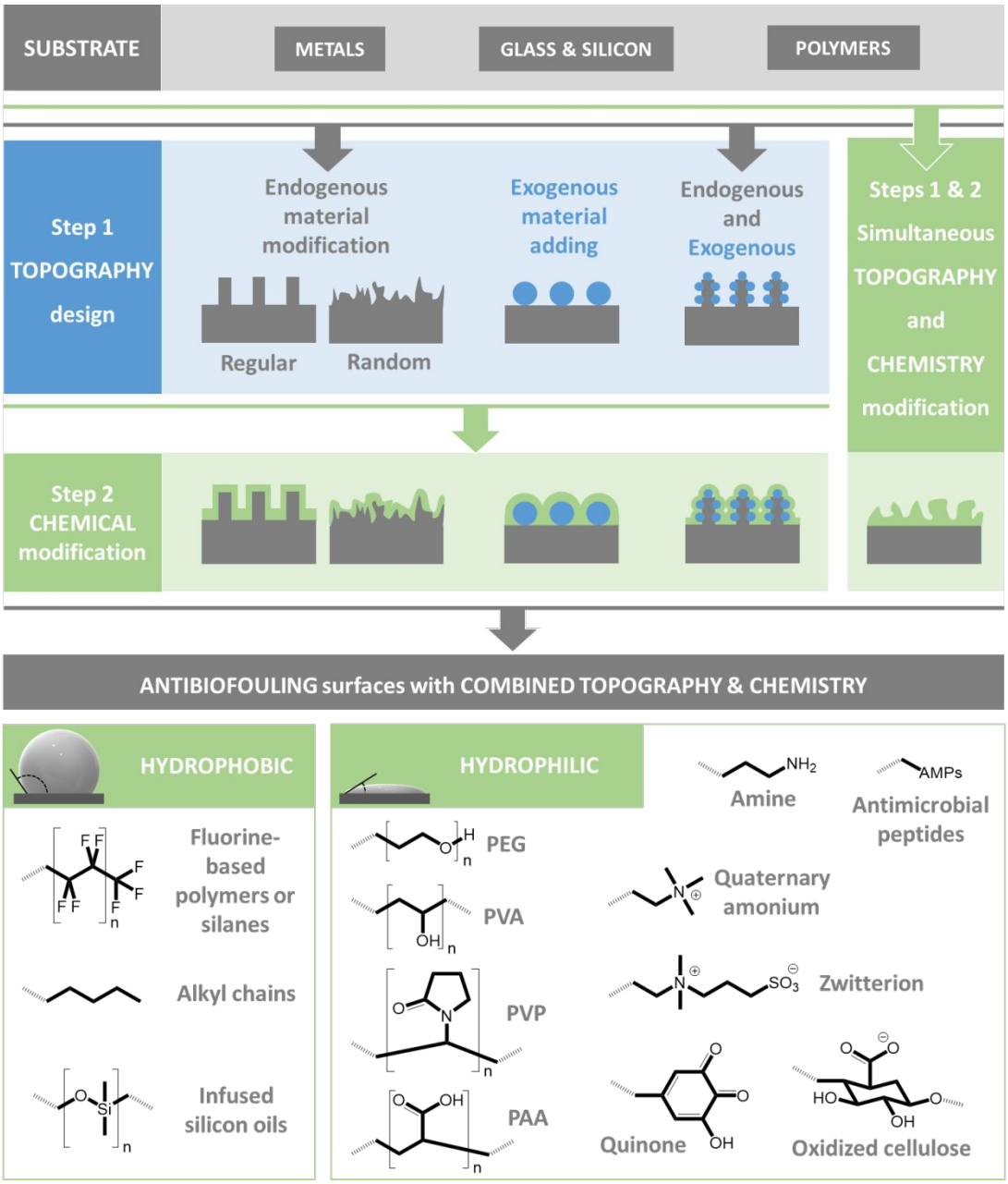


Figure 2: Combining topography and chemistry to obtain antibiofouling surfaces on different substrates (metals, glass and silicon, polymers). The first step consists in designing regular or random topography. In the second step a specific chemistry is added. It is also possible to obtain topography simultaneously with the surface chemistry modification process. In the next figures, the blue overlay will indicate the topography design, while the green overlay will indicate the chemistry modification.

Whatever the approach the resulting engineered surface from the combination of topography and chemistry will either fall into hydrophilic or hydrophobic surface. For hydrophobic approaches a

very limited amount of chemical entities are used: fluorine-based moieties and alkyl chains have been used for a long time in order to produce hydrophobic and superhydrophobic surfaces. More recently, surfaces infused with silicon oils have been developed and used as self-cleaning surfaces (often referred as slippery liquid infused surfaces, SLIS). Some research teams also used them in antibiofouling applications. Conversely, for hydrophilic approaches, chemical entities are numerous as exposed on Figure 2. Ranging from simple functional groups such as amine or carboxylic acids to polymers and ionic compounds, hydrophilic approaches are at the heart of today's most innovative antibiofouling research works. This manuscript is thus separated into two chapters, the first one detailing the hydrophobic approaches, and the second one focusing on the hydrophilic ones. This review is written from an applicative engineer perspective, the sub-chapters are thus organized according to the nature of the surface to be treated: metals, glass and silicon-based or polymers. The conclusion and outlook will provide the reader with recommendations regarding further development of antibiofouling surfaces.

2. Combined topography and hydrophobicity for adhesion prevention

A majority of topographical hydrophobic approaches use fluorine-based compounds as a chemical layer to increase the hydrophobicity. This is why the subchapter will not be organized regarding

the type of chemistry used on the engineered surface but rather according to the method of designing the topography: endogenous, exogenous or a combination of both, as detailed on Figure 2. Whatever the method, the same objective remains: decrease the contact area between the surface and the liquid medium in order to prevent fouling interactions with biomolecules or micro-organisms. As described in Figure 3, different models of surface wetting have been developed and are widely discussed in the literature.[28,29] The Cassie-Baxter regime is predominantly cited in this sub-chapter since it is the best way to prevent the liquid from fully wetting the surface. This regime is almost exclusively reached when a hydrophobic chemical entity is used in combination with the topography design.

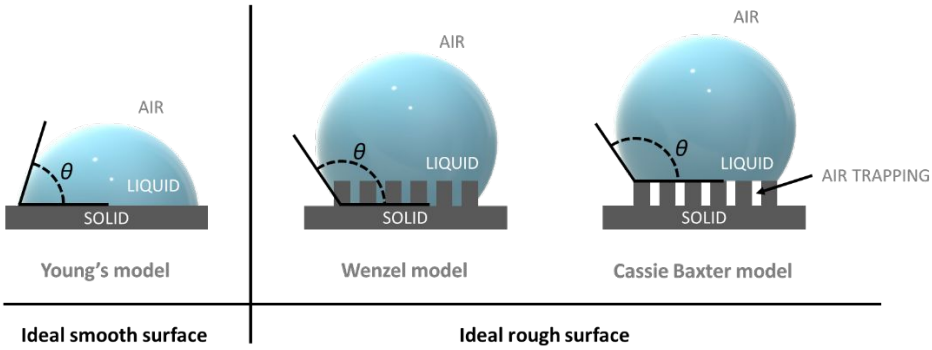


Figure 3: Surface wetting regimes and contact angle θ measurements on ideal smooth surfaces and rough surfaces.

In this chapter, only the production technique of the topographical features really differs from one study to another. This angle is going to lead our story for each category of substrate: metals, silicon-

based samples and polymers. In addition, a few studies introduce approaches that are compatible with various substrate types. A specific subchapter is dedicated to them. All the approaches are detailed in Table S2 of the Supplementary information.

2.1. Metallic substrates

Metallic surfaces that are potentially exposed to biofouling are encountered in various fields of activity, such as marine industry, food preparation facilities and healthcare.

2.1.1. Endogenous topography: micro/nanostructure designed from the metallic substrate

In order to tune the topography, the most straightforward methods rely on the direct modification of the metals surface itself. Micro/nanostructure can be produced through different approaches of aqueous phase treatments and etching techniques which provide the surface with engineered topography. These micro/nanostructures are referred as endogenous topographies.

2.1.1.1. Aqueous phase treatment

A simple way to modify the topography of metallic substrates is the formation of oxide and hydroxide layers at their surface. Upon immersion in boiling water, acidic or alkaline solutions or a combination of these, metallic oxides, that are produced at the surface of the substrates, form

hierarchical structures. Aluminium, magnesium or copper substrates are predominantly represented in the following reviewed articles. Using a subsequent step of chemical surface modification with hydrophobic compounds, some research teams managed to use combined topographical and chemical approaches to obtain superhydrophobic substrates. For instance, commercial aluminium sheets were enhanced with hierarchical micro/nano topographies produced by strong acid etching followed by immersion in boiling water. Subsequently, 1*H*,1*H*,2*H*,2*H*-perfluorodecyltrichlorosilane also known as FDTS was used to chemically functionalize the structured Al surfaces, as depicted on Figure 4A.[30] During boiling water treatment, the average roughness increased from 5 to 65 nm with the formation of Bohemite under the form of nanoplatelets on top of the existing microprotusions. Only the combination of micro and nanoscale roughness with hydrophobic silane grafting provided the surface with superhydrophobic properties which resulted in a drastic decrease of bovine serum albumin (BSA) adsorption. An 80% relative reduction in adhered bacteria was measured, regardless of the bacterial strain and their outer layer properties (*Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Staphylococcus aureus*). Finally, cytotoxicity of the samples was assessed through MTT assay and relative complete cell compatibility (HeLa cells) was validated, confirming the benefits of such a treatment for *in vivo*

applications. More recently, Mandal and co-workers studied the modification of an aluminium alloy through micro-imprinting to obtain square micropillars, followed by hot water treatment which covered the pillars with flake-like AlO(OH) bohemite nanostructures. Finally, a perfluoro-silane layer was deposited by chemical vapor deposition (CVD) on top on the nanostructure. The superhydrophobic Cassie-Baxter regime was achieved and allowed for a drastic decrease of *Escherichia coli* growth.[31,32]

Copper hydroxide can also be produced to tune the surface topography. A copper mesh was modified through the formation of $Cu(OH)_2$ nanowires at its surface, followed by Cu based metallic organic framework (MOF) production and finally polydimethylsiloxane (PDMS) deposition on the micro/nano structure as depicted in Figure 4B. Hierarchical mushroom-like structures were obtained as confirmed by scanning electronic microscopy (SEM) images. Water contact angles above 150˚ and sliding angles below 4˚ were measured. Antifouling and self-cleaning properties were validated against products such as, milk, coffee, tea, cola and juice. In addition, dirt and salts were easily removed from the substrate leaving no trace. But more importantly, drag reduction also benefited from the treatments applied to the Cu mesh, making it a promising material for innovative marine vehicle development.[33]

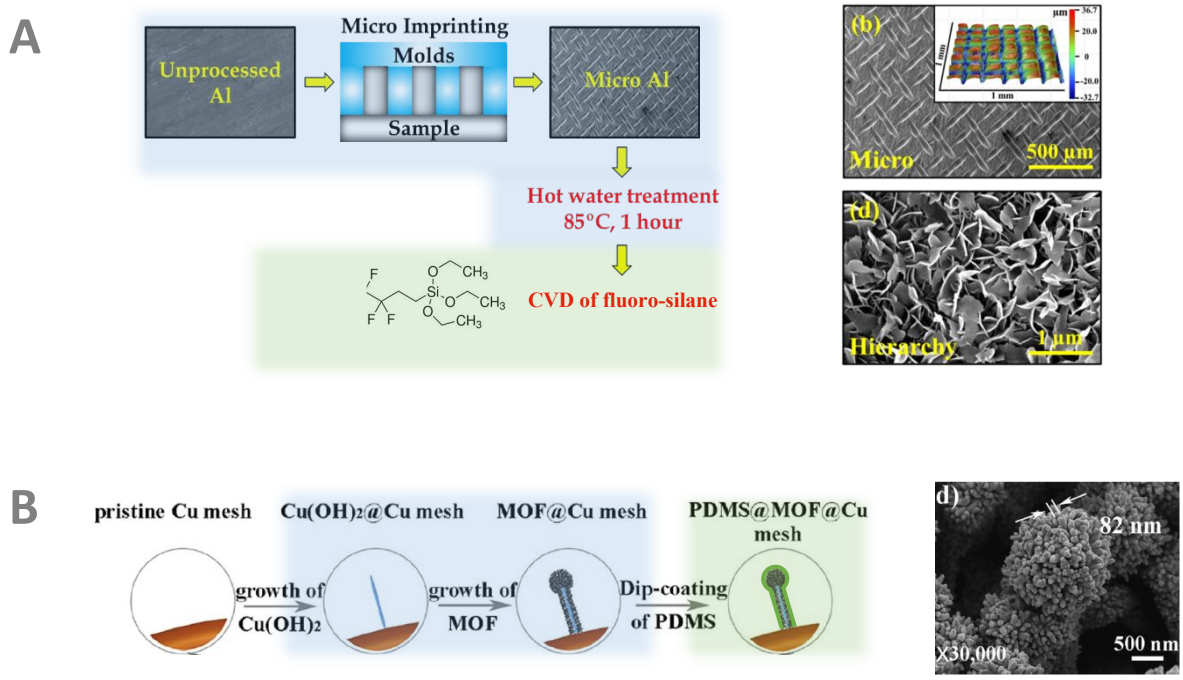


Figure 4: Combined approaches using metal oxide and hydroxide for topography design and detailed surface chemistry adopted. A: Imprinted aluminum micro-pillars covered with bohemite obtained by hot boiling water treatment, followed by FOTES CVD (adapted with permission from reference [32], Copyright 2022 Elsevier), B: super-hydrophobic PDMS/metal-organic-framework copper mesh (adapted with permission from reference [33], Copyright 2011 Elsevier). Blue and green overlay indicate topography and chemistry modifications, respectively.

2.1.1.2. Laser etching

Laser-based techniques are highly represented for modifying metals' topography.[34,35] Aluminium and stainless steel substrates are easily modified with this technique. For instance, Li *et al* used Laser Interference Patterning on stainless steel to create micro and nano structures mimicking the gecko surface.[36] This surface patterning created superhydrophilic substrates with a water contact angle (WCA) close to 0°, in accordance to the Wenzel model (Figure 3). However, the following *in situ* polymerisation of a mixture of polydopamine and octadecylamine monomers led to the

formation of small flocules and a WCA of 157.3˚, confirming superhydrophobicity (see Figure 5A). A 1-log reduction of bacterial growth was observed for *E. coli* (about 90% inhibition), a 2-log reduction was obtained against *S. aureus*, for which an inhibition efficacy of over 99% could be observed. The difference in bacterial membrane structure between Gram positive and Gram negative is used to explain this result. To assess the long-term use of theses substrates, abrasion tests were carried out with sandpaper, and 6-month storage in air also took place. Neither of these experiments considerably affected the properties of the surfaces.

Taking inspiration from lotus leaves, Zouaghi and co-workers used femtosecond laser ablation onto stainless steel surface to produce micro and nano topography. Here, the surface was coated with a perfluorosilane in an organic solvent, resulting in a first combined approach called LL (lotus-like).[37] A second approach consisted in impregnating this LL substrate with an perfluorinated oil in order to obtain a slippery liquid infused surface (SLIS) also known as SLIPS (for slippery liquid infused porous surface), as depicted in

Figure 5B. Antibiofouling tests were performed in a pilot pasteurizer with a model fluid composed of 1 wt% of whey protein, in a temperature range representing dairy industry conditions (65-85˚C). Although a complete suppression of fouling was observed for SLIPS, an increase in fouling was

detected for LL. The wide open topography of LL substrates explained the fouling increase, large and deep holes of *ca.* 10 to 20 μm were easily filled by foulants and the role of chemical layer was impeded, as explained by the authors.[38] The SLIPS substrate beneficiated from the infused hydrophobic oil which behaved like a smooth liquid surface. However, the SLIPS approach failed durability testing after only one cycle in the pasteurizer. An optimized topography to increase oil retention and the use of an alternative oil more suitable to the food industry are cited as perspectives.

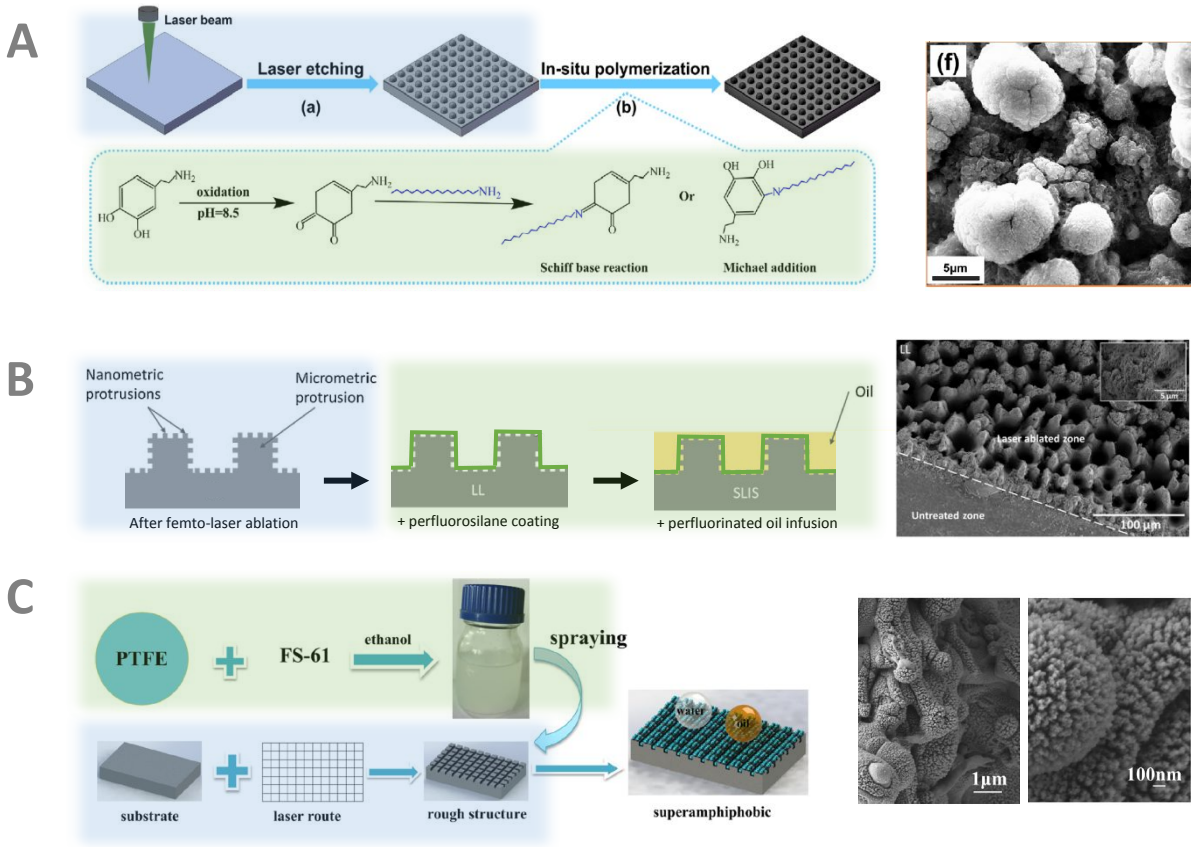


Figure 5: Combined approaches using laser techniques for topograhpy design and detailed surface chemistry adopted. A: Laser Interference Patterning on stainless steel, followed by polymerization of octadecylamine and polydopamine (adapted with permission from reference [36], Copyright 2019 Elsevier). B: femtosecond laser ablation onto stainless steel followed by perfluorosilane coating and perfluorinated oil infusion (adapted with permission from reference [38], Copyright Elsevier 2019). C: UV laser etching on aluminum and stainless steel, coated with PTFE nanoparticles (adapted with permission from reference [39], Copyright 2021 Elsevier). Blue and green overlay indicate topography and chemistry modifications, respectively.

Ultraviolet (UV) laser etching was also used on aluminium and stainless steel metallic substrates to produce topographic features folllowing vertical and horizontal lines with 30 μm spacing. Then, a coating composed of polytetrafluoroethylene (PTFE) nanoparticles and surfactant was sprayed with N_2 gas onto the etched metallic surfaces, before a final thermal treatment (Figure 5C). SEM

imaging revealed the micro and nano-sized topographical features. Chemical characterization with energy dispersive spectroscopy confirmed the homogeneous covering with the spraying technique. The wettability was evaluated against several different liquids (water (pH 0 and 14), ethanol solutions, rapeseed oil, ethylene glycol, propylene glycol and cyclohexane) that all reached contact angles above 150˚, confirming superamphiphobic properties. The combination of surface topography and hydrophobic chemistry leads to antifouling properties and has potential drag-reduction properties. Moreover, the mechanical robustness of the coating was confirmed after abrasion tests which led to a very small loss of super-amphiphobic properties. The micro topography withstood the abrasion and both nano topography and chemical functions were preserved.[39]

2.1.1.3. Reactive ion etching

Reactive ion etching (RIE) was implemented on stainless steel by Cao and co-workers to produce rectangular micropillars with different arrangements and spacing. A peptide coating was applied through immersion, and resulted in a hydrophobic surface that decreased the adhesion of marine algae *Chlorella pyrenoidosa* and *Phaeodactylum tricornutum*. The synergy between topography and chemical peptide layer was confirmed.[40] High power electro-etching in sodium chloride

solution has also been used to produce micropillars on stainless steel surface, followed by vapor deposition of various FDA-approved food-contact coatings: Ni–P-PTFE, Lectrofluor® 641, CrN, TiN, and Dursan®. Among them, the patented Dursan® coating process offered the most promising fouling resistance against *L. monocytogenes*, but the combination with micropillars gave roughly the same results as on flat samples.[41]

2.1.2. Exogenous topography: micro/nanostructure through additive strategies on metals

Additive strategies give access to more diverse topography geometries. By incorporating various micro or nano objects to the metallic surface, some research teams developed antibiofouling surfaces with more complex topographies. These are referred to as exogenous topographies.

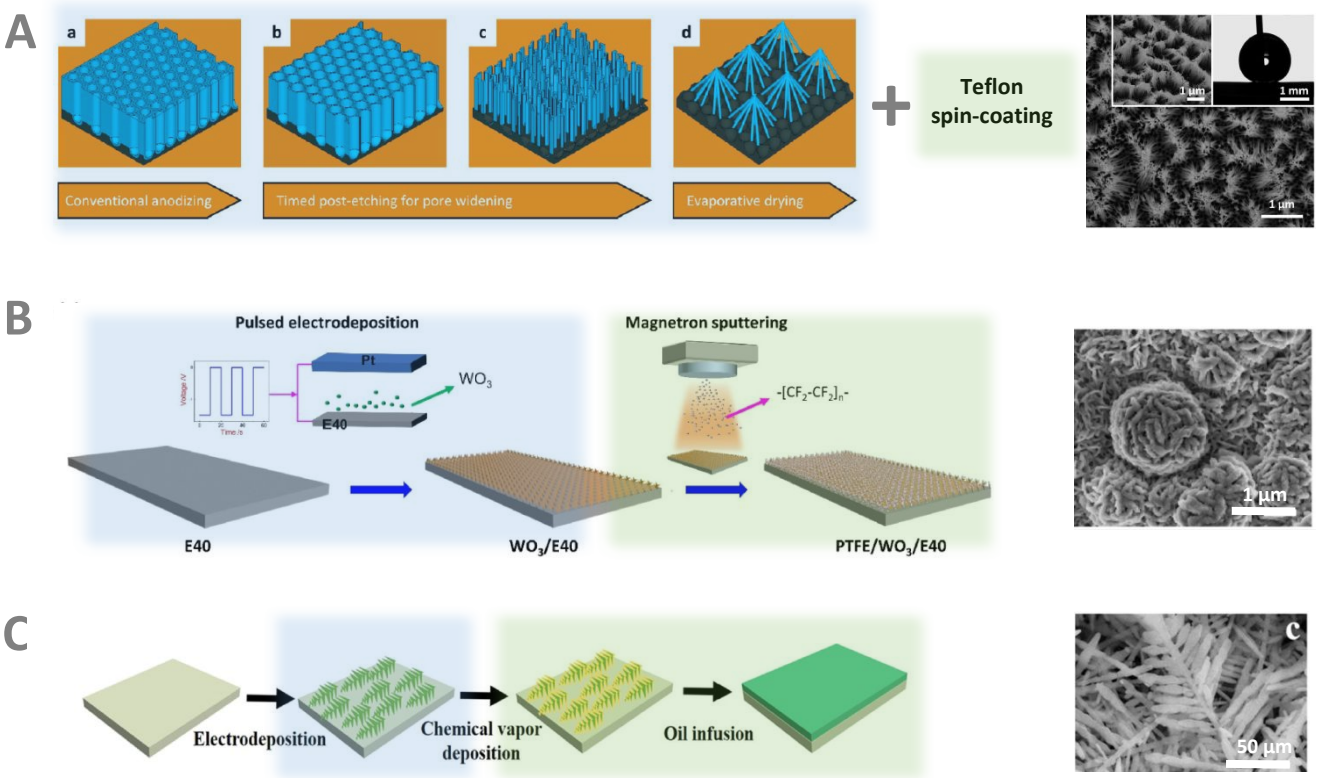
2.1.2.1. Electro-deposition.

By using a metallic substrate as an electrode, electro-deposition of diverse conducting substances can be achieved. For instance, using copper foil as an electrode exposed to a phosphate containing electrolyte, Bao *et al* produced microflower-like structures composed of copper and phosphate ions complexes. Although no biological anti-fouling experiments were conducted, a superhydrophobic self-cleaning and anti-corrosion surface was obtained after dodecylamine coating.[42] Inspired by

similar research,,[43,44] the team of Chang-Hwan Choi chose aluminium foil to be anodized in an oxalic acid solution to obtain a nanoporous structure that was thinned down with phosphoric acid treatment, resulting in disconnected nanopillars. After evaporation under controlled conditions, clusters of nanopillars assembled into conical nanostructures. A Teflon™ coating was finally applied to obtain a superhydrophobic surface (Figure 6A) which was submitted to biofouling tests against *E. coli* and *S. aureus* in static and dynamic conditions.[45] Up to 4-log reductions were obtained upon bacterial adhesion testing for conical pillars covered with Teflon™ only, confirming the synergy between the nanotopography and surface chemistry. A more recent study used $Na_2WO_4 \cdot 2H_2O$ electrolyte to create flower-like nanosheets through electro deposition onto polished E40 steel. The treatment was followed by high vacuum sputtering of PTFE and resulted in a superhydrophobic micro/nano structured PTFE/WO_3 coated E40 steel substrate (Figure 6B) with anti-pollution, anti-icing and antibiofouling properties (also obtained on Cu, Mg and Ti alloys). *Shewanella algae* adhesion was completely avoided over 14 days immersion in the bacterial suspension, while raw E40 steel and PTFE coated steel were covered with bacteria. The superhydrophobicity and electrostatic repulsion arising from the synergistic combination of micro/nano-structure and PTFE coating are believed to explain such results.[46] However, the WO_3

coated-only steel was not part of the antifouling characterized samples. It could have helped to better distinguishing contributions of micro/nano-structure *vs* chemical surface composition for explaining antibiofouling results. Ouyang and co-workers grew dendritic Ag micro/nanostructures through Ag electro-deposition onto Titanium substrates, followed by dodecanethiol vapor deposition and dimethyl silicone oil infusion to produce a Slippery Liquid-Infused Porous Surface (SLIPS) (Figure 6C). A reduction by 4 orders of magnitude of diatom *Navicula minima* and green algae *Chlorella vulgaris* was achieved upon 14 days of incubation.[47]

Figure 6: Combined approaches using electro-deposition based methods for topography design. A: clusters of nanopillars assembled into conical nanostructures obtained from anodization of aluminum foil and phosphoric acid treatment with a TeflonTM top layer (adapted with permission from reference [45]. Copyright 2017 American Chemical Society). B: flower-like nanosheets produced with Na2WO4·2H2O electrolyte on polished steel, covered with PTFE sputtered layer (adapted with permission from reference [46], Copyright 2022 Elsevier). C: liquid-infused superhydrophobic dendritic silver matrix on titanium (adapted with permission from reference [47], Copyright 2019 Elsevier). Blue and green overlay indicate topography and chemistry modifications, respectively.



Beyond electrolyte-based electro-deposition treatments, it is also possible to coat conductive polymers and obtain an antibiofouling effect. Stainless steel surfaces were turned superhydrophobic by electrodeposition of hydrophobic and conducting poly(3,4-ethylenedioxythiophene) (PEDOT) under the form of nanofibers.[48] Bacterial adhesion and biofilm

growth were investigated against *Pseudomonas aeruginosa* PAO1 and *Listeria monocytogenes* CIP 103574 (commonly found in medical facilities and food industry environments). The smallest value of deposition charge (1 mC.cm-2, without nanofibers), did not reduce the bioadhesion. On the contrary, higher deposition charge (35 $mC.cm^{-2}$), producing expanding vertical nanofibers, reduced the bioadhesion by 3-4 log. This result confirmed that the superhydrophobic chemistry alone was not enough to reduce the bacterial bioadhesion. A proiminent surface topography was necessary to achieve bacterial adhesion reduction. Biofilm growth was also performed and biofilm biovolume were measured. The same conclusions arised on the importance of surface topography to limit biofilm development.

2.1.2.2. Other methods

Leaving aside electro-deposition, the next three articles use different exogenous methods to create topography. The first approach relies on the production of layered double hydroxide (LDH) films. Aluminium alloys were coated with lithium-aluminium (Li-Al) LDH films. This is known as hydrotalcite preparation. The samples were functionalized with 4-amino-2-((hydrazine methylene) amino)-4-oxobutanoic acid (AOA) and 1*H*,1*H*,2*H*,2*H*-perfluorooctyltriethoxysilane (PFOTES). This method produced films with hydrophobicity, antibiofouling and anti-corrosion properties.[49]

SEM analysis showed a nest-like rough structure for these films with vertically-grown crosslinked nanoplates. These films showed good anti-adhesive properties towards *E. coli*, *Bacillus subtilis* and sulfate reducing bacteria, with repellency over 96% for each species. Antibacterial activity against Gram-positive, Gram-negative and anaerobic bacteria is provided by the guanadino group of the AOA. Combined with the surface roughness and hydrophobicity, this leads to surfaces with high antibiofouling capacities. Using atmospheric pressure plasma spraying (APPS), the liquid precursor hexamethydisiloxane was deposited onto foodgrade stainless steel. Process parameters were studied in a first paper which revealed the influence of the precursor flow on the surface roughness and morphology of the resulting coated surface (denoted as PL).[37] This refers to the *Step 1&2 Simultaneous topography and chemistry* approach described on Figure 2. The particular chemical surface composition, combined with the random nanostructures revealed by atomic force microscopy (AFM), led to a strong reduction of fouling upon two consecutive runs in a pilot pasteurizer. A second study was conducted to compare this PL sample with lotus-like (LL) and SLIPS samples that were described earlier in the previous *endogenous* section. Upon the fouling test in the pasteurizer, LL and SLIPS surfaces failed to overcome the durability of PL surfaces over the two consecutive runs.[38] Different bacterial strains were tested on PL samples only and

compared to bare stainless steel surface: a very mild reduction of *S. aureus* adhesion was observed, but a strong reduction of bacterial adhesion for rod-shaped bacteria was obtained: 58% and 80% for *L. monocytogenes* and *Salmonella enterica* respectively. The round-shaped bacteria are able to penetrate into the microspaces of the grain structures of the PL surface, while rod-shaped bacteria cannot, and thus have less anchoring spots, leading to reduced adhesion. However, authors did not discuss the viable or dead state of the adhered bacteria that usually allow for further understanding of the anti-adhesion and/or contact bactericidal effect.

Finally, Selim and co-workers used alumina or zinc nanorods associated with PDMS on steel in order to fight against marine fouling. In a first study, graphene oxide-alumina nanorod hybrid sheets were enhanced with exfoliated PDMS chains. The optimal amount of 1 wt% nanofiller ensured the best dispersion of the nanoparticles. The resulting coating exhibited superhydrophobicity and fouling resistance. After 28 days *in vitro* exposure to *Micrococcus sp.* (Gram-positive), *Pseudomonas putida* (Gram-negative) or *Aspergillus niger* (fungus), a sharp reduction of cell viability was observed. Fouling resistance was also confirmed with a three-month field assay in marine waters.[50] In another study, zinc oxide nanorods were embedded in a PDMS matrix to produce a similar superhydrophobic coating on steel. The same bacteria and fungus were

used for fouling resistance tests and, again, an optimized amount of nanofiller was detected at 0.5% above and below which the properties were lost. A 6-month field trial assay in natural seawater confirmed the *in vitro* tests. In both of these studies, the micro/nano-roughness combined to low energy surface chemistry is called to explain the results.[51]

2.2. Glass and silicon substrates

Regarding glass and silicon substrates, fewer articles dealing with combined topography and chemistry approaches were encountered. The first one uses endogenous topography, produced through laser patterning, while the second one uses both endogenous (reactive ion etching) and exogenous topography with addition of another material (crystal seading). All the others use different exogenous topographies.

Lee *et al* addressed biofouling on endoscope lenses. In order to prevent bacterial infection and fogging while achieving high mechanical durability, the lens was provided with a lubricant-infused directly engraved nano/micro-structured surface (LIDENS).[52] Femtosecond laser patterning was first applied to the devices to obtain nanostructured surfaces. A coating of fluorinated self-assembly monolayer was then added before infusion of the perfluorocarbon-based lubricant whose affinity with the surface is increased with the fluorocarbon chains (see Figure 7A). The LIDENS coating

showed very good anti-adhesive effects towards blood which rolled off the surface without leaving any trace. Fluorescent microscopy also demonstrated low adhesion towards albumin and fibrinogen. In addition, tape-peeling and linear abrasion tests confirmed the robustness of the LIDENS coating.

The next approach engraved the raw substrate to create micro-topography (endogenous), but also used a new material to produce the nano-topography on top of it (exogenous). Inspired by the lotus-leaf effect, silicon wafers were subjected to RIE to produce micro-cylinders. Zinc oxide crystal seads were then spincoated onto the microstructured surface allowing for the growth of Zinc salt nanoneedles through low temperature hydrothermal reaction. Finally, a fluoroalkylsilane coating was deposited by immersion in the silane solution, as depicted in Figure 7B. The resulting surface exhibited superhydrophobicity with the Cassie-Baxter regime upon contact with liquid. A 99% bacterial repellency was obtained even after 24h exposure to a bacterial suspension of *E. coli*, compared to the flat untreated silicon wafer.[53] Moreover, the few bacteria that eventually adhered onto the substrates were easily killed by the nanoneedles, as confirmed by their shrunken morphologies (obtained by SEM) and non-viable state (by live/dead™ staining). The combination

of a topographical approach and relevant chemical surface treatment produced a synergistic antibacterial solution.

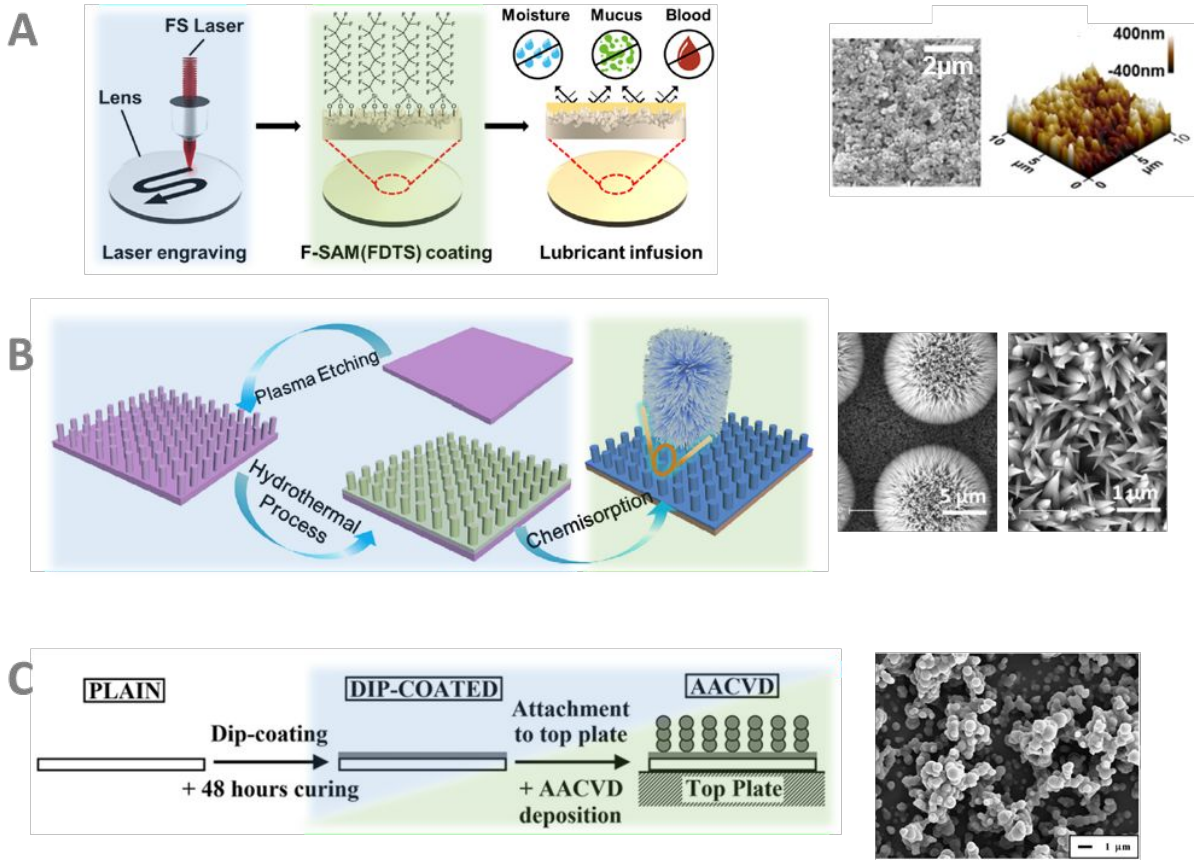


Figure 7: Combined approaches on glass and silicon-based substrates. A:endoscope lense with micro/nanostructure produced by femto-second laser ablation, covered with a fluorinated silane and infused with a perfluorocarbon-based lubricant (adapted from reference [52]). B: micro-cylinders produced by etching of silicon wafer and covered with zinc salts nanoneedles coated with a fluoroalkylsilane (adapted with permission from [53], Copyright 2020 Elsevier). C: glass slides covered with a silicone elastomer and aerosol assisted chemical vapor deposition (adapted with permission from [54], Copyright 2011 Elsevier). Blue and green overlay indicate topography and chemistry modifications, respectively.

In the following articles, exogenous materials are introduced to design both the topography and the chemistry.

Silane chemistry is of primary interest when silicon-based substrates are to be chemically modified. Privett *et al* used nanostructured fluorinated silica colloids, fluoroalkoxysilane (heptadecafluoro-1,1,2,2-tetrahydrodecyl)-trimethoxysilane (17FTMS) and methyltrimethoxysilane (MTMOS) to develop superhydrophobic xerogel coatings which showed anti-adhesive properties towards *S. aureus* and *P. aeruginosa*.[55] The particles showed both micro and nanoscale size. Acid-catalysed hydrolysis and condensation was then performed to obtain 17FTMS/MTMOS films with or without particles. The synergic combination of colloids and the fluorinated xerogel resulted in a superhydrophobic surface. Soaking in water over 15 days did not affect the WCA, suggesting the coatings were stable. These surfaces reduced bacterial adhesion by 99% for *S. aureus* and 98.2% for *P. aeruginosa*.

In addition to liquid phase chemistry, vapor phase approaches were also used to tune silicon-based substrates. Hence chemical vapor deposition techniques are able to bring both the topography and the chemistry. In the first example, glass slides were covered with a silicone elastomer film through dip-coating and subsequent aerosol assisted chemical vapor deposition (AACVD) of Sylgard® 184 silicon elastomer.[54] This process allowed for the formation of micro-scale random topographic features, as described in Figure 7C. The bacterial adhesion on modified glass slides was evaluated

with *E. coli* and *S. aureus* through live/dead™ staining assay in 30 ml of 10^7 colony forming unit (CFU)/ml bacterial suspensions, maintained for 1 hour in static conditions. Non-adherent bacteria were then removed and *BacLight*™ Bacterial Viability Staining kit was used to detect adhered bacteria with fluorescence microscopy. The total amount of live and dead adhered bacteria was drastically decreased on the modified glass slides, presumably because the aqueous bacterial suspension is repelled by these surfaces.

An atmospheric plasma polymer coating was used to treat silicon wafers and produced a microstructured topography while also imparting hydrophobic and superhydrophobic properties to the surface, that prevent bacterial adhesion.[56] A mixture of docecyl acrylate and 1*H*,1*H*,2*H*,2*H*-perfluorodecyl acrylate precursor was used. AFM imaging revealed a heterogeneous globular grain structure. The wettability was studied with contact angle measurements to monitor the transition from hydrophobic Wenzel regime to superhydrophobic Cassie-Baxter regime. The core of the study lies in the fact that the authors performed statistical analysis to compare the influence of different parameters on bacterial adhesion. These parameters were either related to the surface (topography, chemistry, wettability) or to the bacterial medium in which the substrate was incubated (bacteria species, culture, medium composition). The main result indicated that bacterial

colonization is by far predominantly influenced by culture conditions rather than surface properties. This input is precious for researchers that tackle antibiofouling surface development since it encourages them to use various medium conditions to assess precisely the antibiofouling properties. The second result indicates that the superhydrophobic substrates were the more effective at preventing bacterial adhesion, even after static or hydrodynamic long term culture. This type of statistical analysis of the influence of culture conditions could be done for every type of surface treatment that is developed to fight bacterial fouling.

2.3. Polymer substrates

As for a few of the metallic substrates, the following approaches dealing with polymeric substrates can be separated into endogenous and exogenous topography. Molding techniques and plasma treatments are highly represented in the former category, while co-polymers and inorganic structures are used in the latter to design the topography.

2.3.1. Endogenous topography: micro/nanostructure designed from polymers

2.3.1.1. Molding

Polymers are soft matter compared to metal and silicon-derived materials. Topographical features can thus be easily obtained with simple thermal treatment of molding/templating processes, as it is

described in the next studies. Inspired by the pitcher plant, Ware and co-workers tuned the topography of Teflon™ coated on polyethylene substrates with a simple thermal treatment at 160˚C to produce micro-wrinkles in which a silicon oil was then infused. The resulting superhydrophobic surface demonstrated a 99% adhesion inhibition against *Pseudoalteromonas spp.* bacteria. The inhibition was still above 76% after 2 weeks exposure to seawater. A complementary field test was performed for 7 weeks in the ocean and the surface was only covered at 23% when reference samples were fully covered with marine fouling.[57] The article also contains a brief overview of a dozen studies related to lubricant infused surfaces that were tested against biological foulants such as bacteria.

Dolid *et al* combined a shark-skin pattern on PDMS with a peptide-based coating to obtain functional surfaces that repel bacteria.[58] A silicon wafer master produced by photolithography was used to mold the structured shark-skin patterned surface, and a dopamine and peptide-based mixture was then used to coat the PDMS substrates by a spraying technique, as depicted in Figure 8A. The water contact angle reached 119˚. Upon testing against *E. coli* adhesion, it was shown that the chemically and topographically modified surfaces reduced bacterial adhesion by 85% in comparison to bare substrates. With *S. epidermidis*, adhesion reduction reached 72%. Dynamic

assays were also carried out with *E. coli* and demonstrated that no adhesion occurred on the peptide-coated and patterned substrates.

2.3.1.2. Plasma treatment

Plasma treatment can easily and rapidly modify the topography of polymers. In the next studies, different plasma treatments are used to modify the topography of polymer substrates. Oxygen plasma treatment is a very common process and can easily modify polymers' topography. But other gases are able to form plasma, and their combination with fluorinated carbon compounds lead to topography modification as well as hydrophobization.

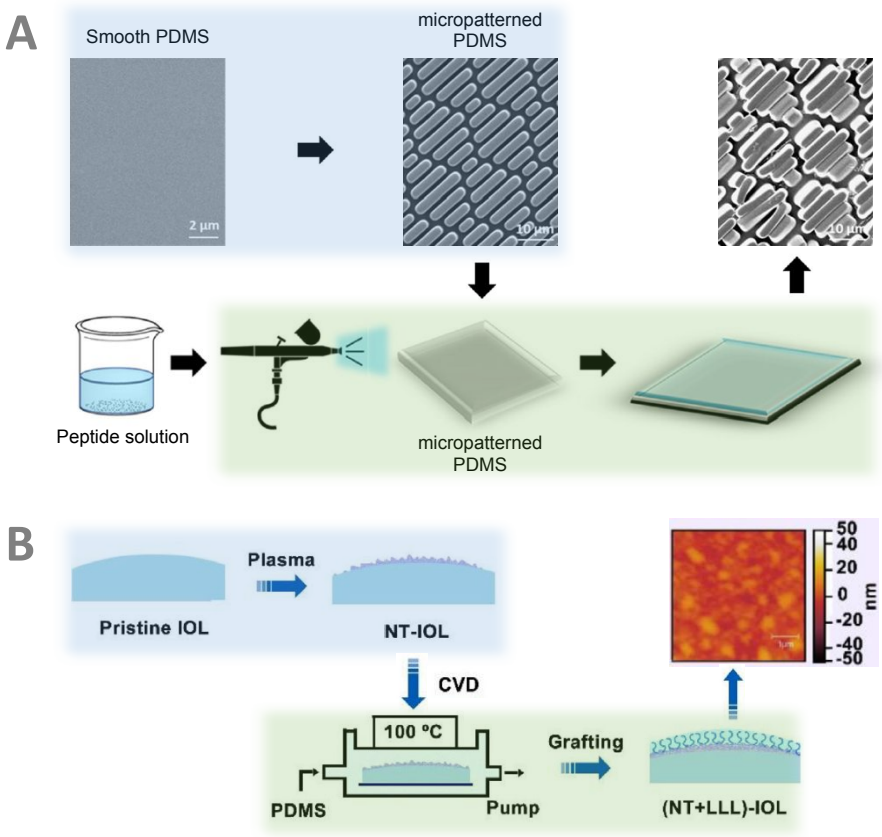


Figure 8: Combined approach with endogenous topography design. A: shark-skin pattern on PDMS with a peptide-based coating (adapted with permission from reference [58], Copyright Elsevier 2020). B: intra-ocular lense with nanotopography produced by oxygen plasma and covered with PDMS brushes to obtain a liquid-like suface (adapted with permission from reference [59], Copyright Elsevier 2021). Blue and green overlay indicate topography and chemistry modifications, respectively.

In order to prevent posterior capsule opacification (PCO) after cataract surgery, caused by adhesion of residual lens epithelial cells, researchers from Sun Yat-sen University imparted an intraocular lens (IOL) with nanotopography combined with PDMS brushes impregnated with silicon oil.[59] An oxygen plasma treatment on the hydrophobic acrylic IOL formed the nanotopography. The PDMS brushes were then tethered through a CVD system with the silicon oil (Figure 8B). The free end of the grafted polymer chain formed a liquid-like coating. AFM confirmed the superior roughness of

the prepared surfaces. The enhanced IOL was also as transparent and mechanically resistant as the pristine IOL. Anti-bioadhesion and cell viability experiments as well as animal testing complemented with statistical analysis were performed. Bioadhesion is reduced the most when topography and the chemical liquid-like layer are used simultaneously. The same outcome was confirmed for cell viability. After 60 days of *in vivo* experiments, the enhanced IOL demonstrated excellent biocompatibility and anti-PCO effect.

Oxygen plasma micro/nano-texturation was also performed on poly(methyl-methacrylate) (PMMA) transparent sheets. Combined with metal-sputtering and/or hydrophobic film deposition, antibiofouling and antimicrobial properties were obtained.[60] Two different hydrophobic coatings were finally used: octafluorocyclobutane (C4F8) that was deposited through plasma again, and perfluorooctyltrichlorosilane (pFOTS) through vapor deposition after oxygen plasma activation. For this review, the focus here covers only the textured PMMA sheets modified with hydrophobic coatings only (no metals). These samples were immersed in a bacterial suspension of unicellular Gram-negative cyanobacteria *Synechococcus sp.* for 72 hours in order to study bacterial adhesion. A resulting coverage of less than 1.5% was detected, suggesting efficient anti-adhesive properties. However, the author did not discuss the potential synergistic effect of the micro/nano-texture and

hydrophobic coatings. Experiments with hydrophobic coatings on PMMA without the micro/nano texture would have helped on this matter.

Argon and Argon/CF_4 plasmas were used to modify polycarbonate substrates. The Argon/CF_4 treatment imparted both topography and specific surface chemistry that reduced bacterial and microalgae adhesion.[61] AFM measurements revealed that Ar plasma alone was not able to modify the polycarbonate substrates topography. Only Ar/CF_4 plasmas increased the roughness significantly. Bioadhesion tests were performed in flow-cells with bacterial (two Gram negative marine bacteria, *Paracoccus sp.* 4M6 and *Pseudoalteromonas sp.* 5M6) and diatom (two axenic microalgae strains, *Cylindrotheca closterium* AC-170 and *Porphyridium purpureum* AC-122) cultures. Bacteria were exposed 2 h to the surface while 24 h exposure with 12 h-12 h light-dark cycle was carried out with microalgae. The main outcome is that only the Ar/CF_4 treated polycarbonate with higher content of CF_4 managed to reduce the adhesion of the tested micro-organisms (65% to 90% reductions). The authors claim the combination of surface chemistry and nano-topography explains such a result. The stability of the modified substrates was also evaluated with contact angle measurements after 1 hour-treatment with 2.6% bleach, and no effect was detected.

2.3.2. Exogenous topography: micro/nanostructure through additive strategies on polymers

Polymer surface topography can also be modified by the deposition of a polymer of different nature, but inorganic structures are also used as exogenous material to tune the topography.

Inspired by frog skin, this approach consisted in coating a PDMS layer with a block copolymer of polystyrene (PS) and polylactic acid (PLA). Upon an hydrolytic treatment, the PLA blocks were degraded generating microwrinkled surfaces due to the kinetic release of local strains along the multilayer composite. In addition, the volumes freed from PLA blocks formed a nanoporous structure with co-continuous nanochannels. Finally, a silicon oil was infused into the porous structure thanks to capillary forces in order to produce a wrinkled SLIPS.[62] Antibiofouling properties were assessed against the green algae species *Chlorella* sp. DT through cell coverage analysis after immersion in a suspension in static conditions for 7 days. Further evaluation was performed in fresh seawater for 7 days with blue-green algae species (*Arthrospira platensis* and *Synechococcus lividus*), seawater algae species (*Isochrysis galbana*, *Tetraselmis ehui*) and filamental cyanobacteria under different culture conditions that mimick the natural environments of these microorganisms. Without the silicon oil (topographical approach only), in static condition

assays, antibiofouling performance was slightly improved when increasing wrinkle interspaces. The author explains this tendency by indicating that the 15 μm green algae has less attachment points with increasing the wrinkle wavelength. However, performance dramatically improved after silicon oil infusion, especially for the largest (75 μm) wrinkle wavelength. This illustrates the beneficial effects of the combination of both topography and chemistry for antibiofouling performance. Testing in dynamic conditions lead to similar results. The authors also tested an oil-infused substrate without the wrinkling structure (chemical approach only). Its performance was lower than substrates with combined approaches. However, it appeared that the lubricant is hard to retain in dynamic conditions. Finally, optical transparency, anti-icing and self-cleaning properties were demonstrated for the wrinkled oil infused substrates, confirming their high potential for sensors or optical devices in marine industry.

Another example of topography modification with added material relied on the growth of Nickel hydroxide $Ni(OH)_2$ onto a cotton fabric, followed by immersion in stearic acid solution and thermal treatment to produce nickel stearate broccoli-like micro-structures. The modified cotton fabric was turned superhydrophobic (160˚), and suppressed bacterial growth of Gram-positive *S. aureus* and Gram-negative *E. coli*, as well as fungal growth of *Candida albicans* even if the antibacterial

mechanism remains unclear (Ni^{2+} release is suggested to play a role).[63] Cotton fabric was also modified with SiO_2 nanoparticles enhanced with photodynamic activity of chlorin e6 (Ce6) and functionalized with perfluoroalkyl-silane as described in Figure 9A. The textile's antibiofouling property was evaluated against suspensions of Gram-positive *S. aureus* and Gram-negative *E. coli*. Immersion and spraying in the dark were the two methods of exposure to the microorganisms, modelling waterborne and airborne bacterial contamination, respectively. The synergistic effect of superhydrophobic coating with perfluoroalkyl-silane and air trapping by hierarchical nanostructures was proposed as an explanation for the significant reduction of bacterial adhesion (*ca.* 90%) for both strains in the immersion approach. Similar results were obtained for the spraying approach. Remaining bacteria elimination was expected to be eradicated by the photodynamic activity of Ce6 that generates reactive oxygen species (ROS) upon visible light illumination. The modified cotton textiles demonstrated a clear 100% killing rate against both *S. aureus* and *E. coli* after 45 min of light illumination. Finally, modified textile fibers were exposed to whole blood and managed to entirely repel the complex medium upon roll-off experiments.[64]

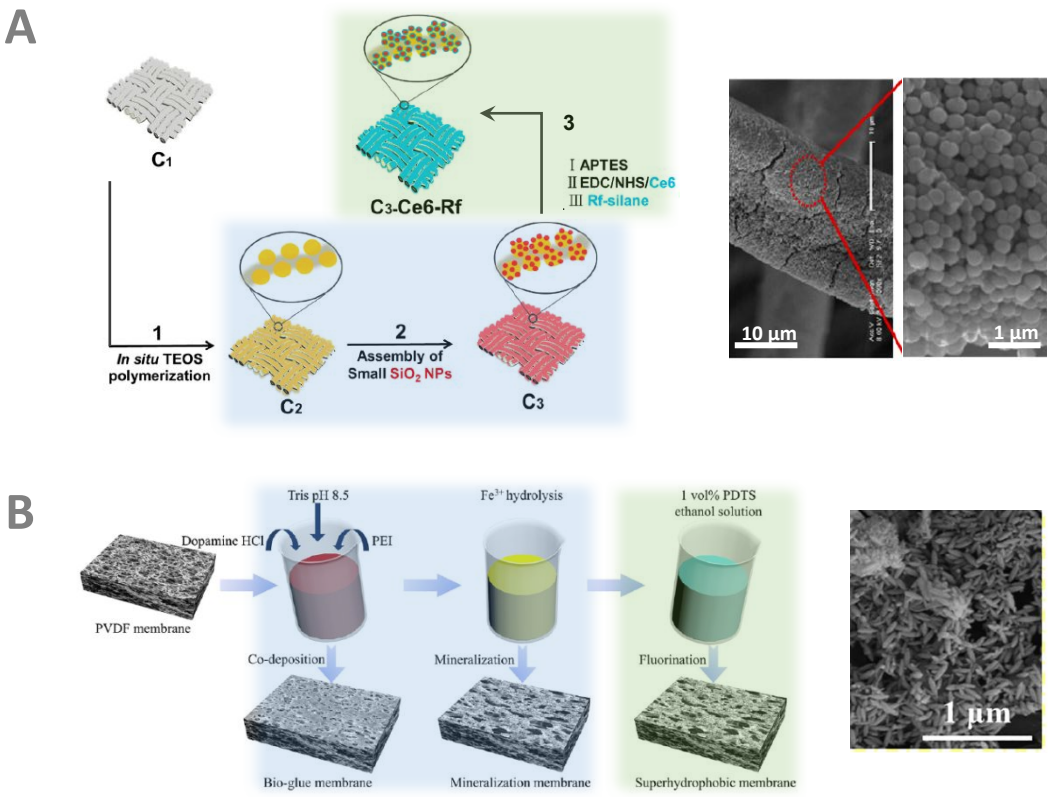


Figure 9: Combined approach for exogenous topography design. A: cotton fabric enhanced with SiO_2 nanoparticles further coated with chlorin e6 and perfluoroalkylsilane (adapted with permission with reference [64], Copyright 2019 American Chemical Society). B:PVDF membrane treated with β-FeOOH nanorods embedded in a polymer matrix, covered with a perfluorosilane (adapted with permission from reference [65], Copyright Elsevier). Blue and green overlay indicate topography and chemistry modifications, respectively.

The final article of this sub-chapter deals with a polyvinylidene fluoride (PVDF) membrane modified through mussel-inspired strategy: the co-deposition of polydopamine and polyethylenimine as bioglue to embed β-FeOOH nanorods. A final top layer chemistry of perfluorosilane was also used to further improve the superhydrophobic properties (see Figure

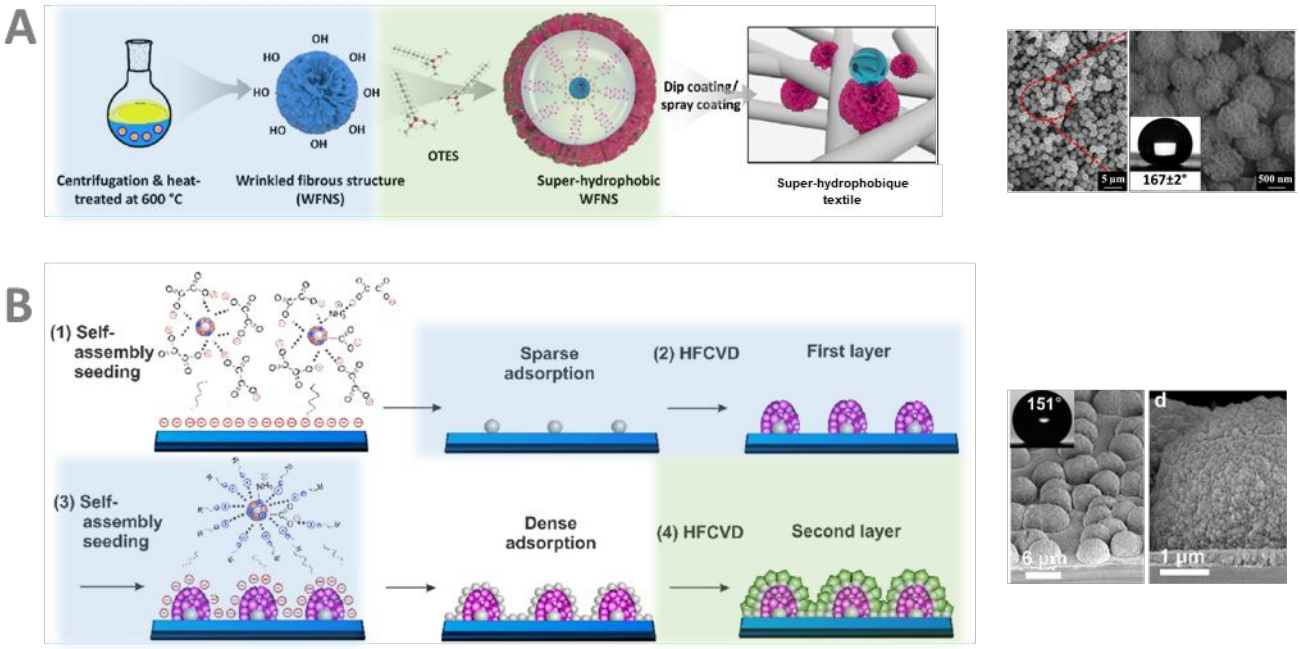
9B).[65] Roll off angles below 6˚ were measured. Moreover, thermal and mechanical resistance were evaluated for an hour against ultrasonic treatment, or 85˚C aqueous medium. Contact angles were not affected at all. The performance of direct contact membrane distillation (DCMD) was performed with the pristine and enhanced membranes. Model wastewaters were used: a mixture of NaCl, $CaCl_2$ and $NaHCO_3$ or NaCl and sodium dodecyl sulfate. The superhydrophobic membrane outperformed the pristine membrane in every case with delayed compromised flux and no salt crystallization. Even after 60h long DCMD testing, the nanorods were still present and the membrane still functional. According to the author, the clear contribution of both the structured nanorods and the chemical fluor layer contributed to reach the Cassie-Baxter regime that prevents membrane wetting and explains such results.

2.4. Multi-substrate approaches

In this last subchapter the focus is given to the research articles that offer a combined topography and chemistry approach for antibiofouling surface modification that have been successfully applied to substrates of different nature. Indeed, from an applicative engineer perspective, such approaches are of great interest since they might be used in various industrial fields, regardless of the nature of

the materials to be protected. These approaches inherently fall into the exogenous topography category.

A robust superhydrophobic coating was developed through the use of wrinkled fibrous nano silica functionnalized with octyltriethoxysilane (OTES), as depicted in Figure 10A. Various substrates (PVDF, glass, aluminium foil, fabric and paper) were treated with the wrinkled fibrous nano silica dispersions by spray (hard substrates) or dip coating (soft substrates). The superhydrophobicity was confirmed by contact angle measurements with daily liquid products such as honey, milk, coffee, yogurt and juice. The robustness of the coating was demonstrated through abrasion testing, finger wiping, tape adhesion and bending as well as before and after exposition to harsh environmental conditions (UV light, organic solvents and salts, high temperatures). Also, preliminary antifungal properties were revealed after exposition of a modified fabric to fungal species under favorable conditions. The combination of the hydrophobic properties with the surface roughness of the coral-reef like structure (and inherent air gaps) prevented the adhesion of micro-organisms and drastically reduced the availability of nutrient in the liquid phase close to the surface.[66]



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644 *Figure 10: Multisubstrates combined chemical and topographical approaches. A: wrinkled nano silica*
645 *functionnalized with octyltriethoxysilane deposited on textile, aluminium foil, glass, PVDF, fabric and*
646 *paper (adapted with permission from reference [66], Copyright 2020 Elsevier). B: hot filament chemical*
647 *vapor deposition for micro and nano sized diamond hemispheres, covered with perfluorosilane (adapted*
648 *with permission from reference [67], Copyright 2020 American Chemical Society). Blue and green overlay*
649 *indicate topography and chemistry modifications, respectively.*

650 Fang *et al* developed SLIPS with a one-step alcohol-assisted femtosecond laser irradiation that is

651 able to create porous micro/nanostructures on different substrates: stainless steel, nickel, glass and

652 polymer.[68] Fluoroalkylsilane modification was then carried out to reach superhydrophobic and

653 oleophilic surfaces. Indeed, this surface coating modified the WCA from 13˚ on porous stainless

654 steel, up to 143˚. After silicon oil infusion onto the hydrophobic surface, the adhesion properties

655 were further modified, showing much lower adhesion to water droplets. This was demonstrated for

various solutions with different components and viscosity: water, milk, ink, egg white, and especially blood, which all simply slip down the tilted SLIPS. The substrates were tested in the presence of green algae, a common fouling specie in marine applications. It was shown that the combination of laser-irradiated structure and silicon oil lubricant was essential for obtaining a good antibiofouling performance after seven days exposure to the green algae.

An antibacterial, self-cleaning and antibiofouling coating was obtained on commercial titanium alloys, silicon, quartz and ceramic substrates.[67] The bottom-up process based on hot filament chemical vapor deposition (HFCVD) allowed for the modification of complex geometries and large scale substrates. A pre-seeding of the substrates was performed with detonation nanodiamond, followed by the HFCVD process that triggered the growth of diamond hemispheres. This procedure was repeated one time to grow an additional, smaller, diamond structure onto the first one. Finally the samples were chemically modified in liquid FDTS after an oxygen plasma treatment (see Figure 10B). Antibacterial activity was evaluated against *P. aeruginosa* (MCCC1A00099) and *E. coli* (ATCC 25922) by using live/dead™ staining after 24 hours incubation. These tests confirmed the crucial role of the structured diamond film with *ca.* 90% and 99% reduction in bacterial adhesion compared to untreated substrates for *P. aeruginosa* and *E. coli*, respectively. In addition, two

biofouling tests with marine contaminants *C. vulgaris* (FACHB 44) and *Ulothrix speciosa* (FACHB 494) were conducted. Again, the structured and fluorinated samples demonstrated the best antibiofouling results compared to untreated samples, but also compared to the samples modified with either topography or chemistry alone. Thus it is the synergistic effect of topography and surface chemistry that allows for such antibiofouling effect.

As a conclusion, in a vast majority, the combined topography and chemistry hydrophobic approaches to produce antibiofouling surfaces lead to superhydrophobic wettability, often achieving Cassie-Baxter regime. In most articles, this result is obtained only by combining topography with a specific surface chemistry. The antibiofouling property thus arises from the prevention adhesion mechanism cited in Figure 1. However, despite the various topography designing techniques, the hydrophobic chemical entities employed are limited to either fluorine-based polymers or silanes, alkyl chains or infused silicon or fluorine-based oils. The next chapter will demonstrate how wide the hydrophilic chemical entities library is for antibiofouling surface development with combined topography and chemistry approaches.

3. Combined topography and hydrophilicity for multiple antibiofouling mechanisms

As explained in the introduction, superhydrophilic surfaces can also be used for antibiofouling surface development. In this chapter we will focus on research articles where superwettability has been achieved by combining topography and chemistry with the aim to repel biomolecules and microorganisms. Many different techniques have been used to develop the functional topography and deposit the chemistry of interest. All the approaches described in this chapter are detailed in Table S3 of the Supporting information.

Superhydrophilic surfaces have been less explored for antibiofouling applications than superhydrophobic one. This can explain why less common ground can be found in the literature and why there is such a variety of solutions. In addition, as it can be seen in Figure 2, there is a wide range of chemical approaches leading to hydrophilic antibiofouling surfaces. This can make it challenging to find links between the various articles. However, as in the previous chapter concerning hydrophobic approaches, three types of substrates have been studied: metals, glass and polymers. This will be used to structure this part of the review, thus creating three sub-chapters.

3.1. Metallic substrates

Metallic substrates are not a common material used for hydrophilic-based approaches, oppositely to hydrophobic strategies. However, these surfaces show very different characteristics, demonstrating the diversity of hydrophilic strategies for antibiofouling studies on metals.

The first example of such surfaces are TiO_2 nanotubes coated with a Poly(ethylene) glycol (PEG)-silane, which showed different activities against fibrinogen and *S. aureus* depending on the size of the nanotubes. For this study, An and co-workers used potentiostatic anodization of Titanium to create the nanotubular effect. Two dimensions were created: nanotubes of 20 and 80 nm diameter (TN20 and TN80 respectively). This was followed by a reaction with a PEG-silane solution allowing the nanotubes to achieve better hydrophilicity (see Figure 11B). Although TN80 was more hydrophilic with a WCA of 19˚, TN20 was the only surface which showed both low adhesion of model foulant fibrinogen and low friction coefficient. *S. aureus* was used to test the bacterial adhesion. Surprisingly, PEG-coated TN20 showed a high adhesion, similar to Ti and PEG-coated Ti, whereas all the other substrates, including PEG-coated TN80, repelled the bacteria. It seems that, depending on the size of the nanotubes, and therefore, on the available surface contact area, the antibiofouling effect can be inhibited.[69]

This has also been shown through the study of marine diatoms on zwitterion-coated structured stainless steel substrates. Here, unlike the previous study where the topography of the initial substrate was modified, an exogenous material was added to create the topography. Indeed, the initial substrates were coated with aluminium through flame spray technique and micropatterned with a shielding steel mesh. A layer of PDMS was then formed on the samples and allowed for subsequent chemical functionalization with the zwitterionic molecule [2-(Methacryloyloxy)ethyl]-dimethyl-(3-sulfopropyl)-ammonium hydroxide (pSB) through 3,4-dihydroxyphenylalanine (DOPA) binding. Bovine Calf Serum proteins were used to simulate the conditioning layer formation on the substrates. An antibiofouling activity was observed but was fully attributed to the hydration layer brought by the pSB and the electrostatic interaction between bovine proteins and dipole moment of the sulfobetaine groups. No influence of the topography was detected. The antimicrobial effect of the substrates was studied with marine diatoms *Cylindrotheca closterium* which were incubated with the samples presenting both chemical and topographical modifications, in an artificial seawater-based medium. Confocal laser scanning microscopyshowed no adhesion to the protuberances. However, pSB modification of reference flat samples resulted in a lower density of diatoms. It is thought that the increase of the specific surface area of the patterned

substrates is responsible for the higher adhesion of diatoms. A hypothesis that can be raised is that the protuberances are too big in comparison to the size of the tested micro-organisms.[70]

One last type of metallic surface that has shown promise in antibiofouling applications due to its hydrophilicity is bioinspired self-cleaning mucus-like hierarchical ciliary bionic antifouling surfaces (SMCAS). These complex surfaces made of polyamide microfibers covered with carbon nanotubes (CNT) and poly(vinyl alcohol) (PVA) hydrogel particles, that mimic the skin of marine species, were designed by Ren *et al* with electrostatic flocking technology and solution spray (see Figure 11A) to impart the so-called camouflage effect to steel surfaces, making them hard to be recognised by the various foulants. Marine bacteria *Marinobacter lipolyticus* SM19(T) and microalgae *Nitzchia closterium f. minutissima* were used to evaluate anti-adhesion performance of the SMCAS surface. After 24 hours of co-culture, SMCAS integrally suppressed the bacterial adhesion, showing better results than model PVA/CNT hydrogel which reduced the bacterial adhesion to 2.0 x 10^3 cells/cm against 5.6 x10^5 cells/cm on silicon. The efficacy of SMCAS, explained by enhanced water-retaining, was also shown upon microalgae contact for as long as 3 weeks. Concomitantly, microfibers swaying along with the flow of seawater contributed to remove the adhered contaminants.[71]

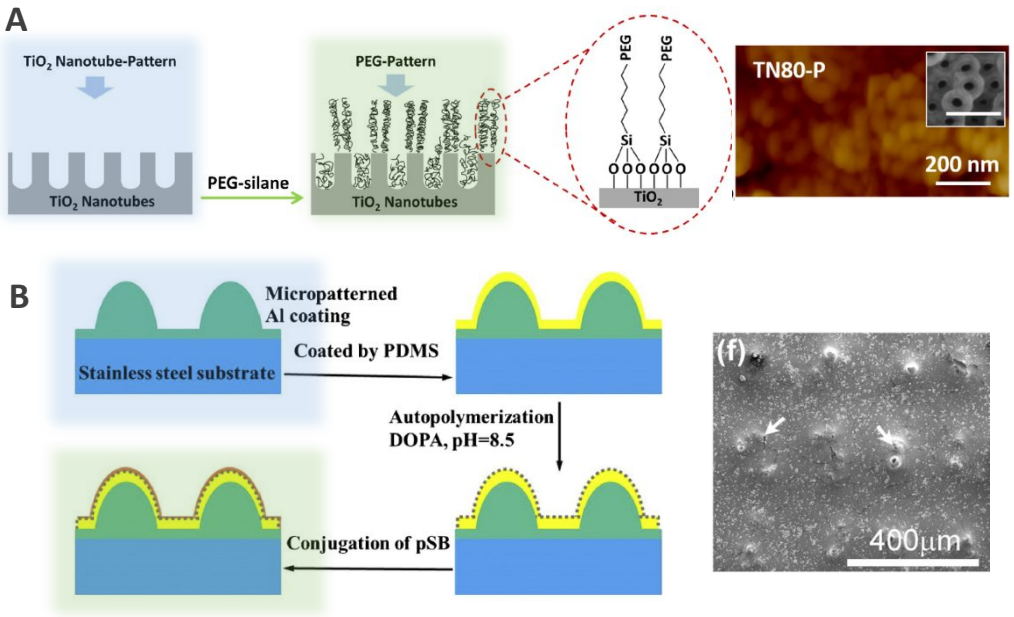


Figure 11: Antibiofouling stategies combining hydrophilic polymers and topography on metallic substrates. A: PEG silane on nanotubes (adapted with permission from reference [69], Copyright 2019 Elsevier). B: Micropatterned Al coatings with zwitterion surface modification(adapted with permission from reference [70], Copyright 2016 Elsevier). Blue and green overlay indicate topography and chemistry modifications, respectively.

3.2. Glass substrates

In this chapter, modified glass substrates with a hydrophilic antibiofouling activity will be described. The first three articles concern surfaces where endogenous topography has been created. The following articles use an exogenous material to tune the topography. They also show surface chemistry with a bactericidal effect on tested microorganisms, on top of the anti-adhesive effect caused by the hydrophilic coating on topography. This has enabled the creation of surfaces which

can kill bacteria as well as impede their adhesion. The following articles use an exogenous material to tune the topography.

For example, nisin is an antimicrobial peptide with a hydrophilic end that has been combined to microstructured glass to create efficient substrates against bacteria and diatoms. This study was carried out by Lou and co-workers who began by structuring glass through ion etching before functionalizing with nisin. This peptide binding protocol led to strong coatings which were stable in sterile artificial sea water even after 10 days. The antibiofouling activity was assessed against bacteria *Bacillus sp.* and diatoms *P. tricornutum*. The quadrangle-shaped microstructure alone promoted bacterial fouling as the interspaces were bigger than the cells. However, with the nisin immobilization, antibacterial effect was confirmed. Nevertheless, the synergistic effect of microstructure and surface chemistry appeared hard to find for bacterial fouling. Against diatoms, on the other hand, which are bigger than bacteria (10 μm vs 1-2 μm), the anti-adhesion effect of the microstructure alone was stronger. With the nisin peptide treatment, an even better anti-adhesion effect was detected, proving the synergistic effect of the combined approach against algal foulants. Also, it was shown that an increased depth of the microstructure enhanced the anti-adhesion effect of both untreated and nisin-treated glass microstructures against the diatoms.[72]

Polyacrylic acid (PAA) has also been used for its antibacterial effect. However, it has been shown to have a gram-dependant efficiency. In a study by Chen *et al*, layer-by-layer deposition of polyelectrolytes polyvinylamine (PVAm) and PAA was the chosen method for obtaining a functional coating and femto-second laser pulsing was used to acquire micro and nano-patterned borosilicate glass (see Figure 12B). When testing with *E. coli* K-12 and *S. aureus* 208, it was confirmed that the positive charge surface enhanced bacterial collection. *E. coli* adhesion increased faster than *S. aureus* owing to its higher outer-membrane charge. Live/Dead™ staining after a 4 h incubation confirmed the bactericidal activity. It was suggested that the nanostructures contributed more to the bactericidal effect than the microstructures. However, no damage was observed on mammalian cells.[73]

The same difference of adhesion depending on the type of bacteria was demonstrated with a film of poly-(acrylic acid-co-(poly(ethylene glycol)diacrylate)) (poly(AAC-co-PEGDA)). Here, the hydrogel was spin-coated onto functionalized cover slips and then treated with an argon plasma to develop micro-sized wrinkles. The acrylic acid was efficiently bactericidal against both *S. aureus* and *E. coli*, and the wrinkles contributed to lowering the amount of live microorganisms. However the engineered surfaces were slightly more efficient on Gram-positive *S. aureus*.[74]

Liu and co-workers produced a superhydrophilic layer of Poly(sulfobetaine methacrylate) (PSBMA) by sub-surface initiated atomic transfer radical polymerization (SSI-ATRP) onto a glass substrate. This technique allowed for the *simultaneous* tuning of both *topography and chemistry* (as described in Figure 2). Micro-sized wrinkles were obtained, with size parameters depending on the reaction time. A first study reveals the performance of the PSBMA structured surface against marine environment conditions[75]. Static antibiofouling was assessed with red algae *Porphyridium sp.* and diatoms *Navicula sp.* for several hours. The resulting micro-organism densities were reduced by two orders of magnitude for SSI-ATRP produced surfaces compared to blank surfaces. Furthermore, on structured surfaces resulting densities were 4 to 6 times smaller than on unstructured ones, indicating the beneficial synergistic effect of superhydrophilic surface chemistry and microsized topography. Ocean field assays over 45 days were performed. According to the author, the engineered surfaces better resisted the biofouling even if the available pictures seem complicated to compare. The SSI-ATRP also improved the long-term stability of the polymer layer.[75]

The same team used the SSI-ATRP produced PSBMA layer in another study where the adhesion of different types of foulants was investigated: macromolecules (BSA, lysozyme and fibrinogen),

bacteria (*E. coli* and *B. subtilis*) and diatoms (*Chaetoceros calcitrans*).[76] Here, a walnut-shell-like microsized surface topography was obtained. It was shown that a 2 μm PSBMA layer prevents macromolecular fouling, while a 5-10 μm thickness is more efficient against bacteria and diatoms. After a longer reaction time (8 h instead of 1, 2 or 4), the regular walnut-shell-like structures became irregular blocks and antibiofouling properties were lost.[76]

PSBMA was also chosen to create zwitterionic electrostatic flocking surfaces (ZEFS). Unlike the two formerly mentioned articles, here the topographical and chemical modifications were reached through separate steps. The topography was first obtained by depositing nylon fibers onto glass substrates by electrostatic flocking. A thin film of PSBMA was then wrapped around the microfibers by radical polymerization catalyzed by Fe (see Figure 12A). It was demonstrated that the diatoms *N. closterium f. minutissima* adhered very little to the fibers due to the low contact area caused by their morphology. Further tests were carried out using common mussel species *Mytilus edulis*, capable of choosing where to attach to the surface though exploration and thread secretion. On a test board composed of glass, PDMS and ZEFS, the mussels avoided the zwitterionic coated fibers, and preferentially stuck to glass.[77]

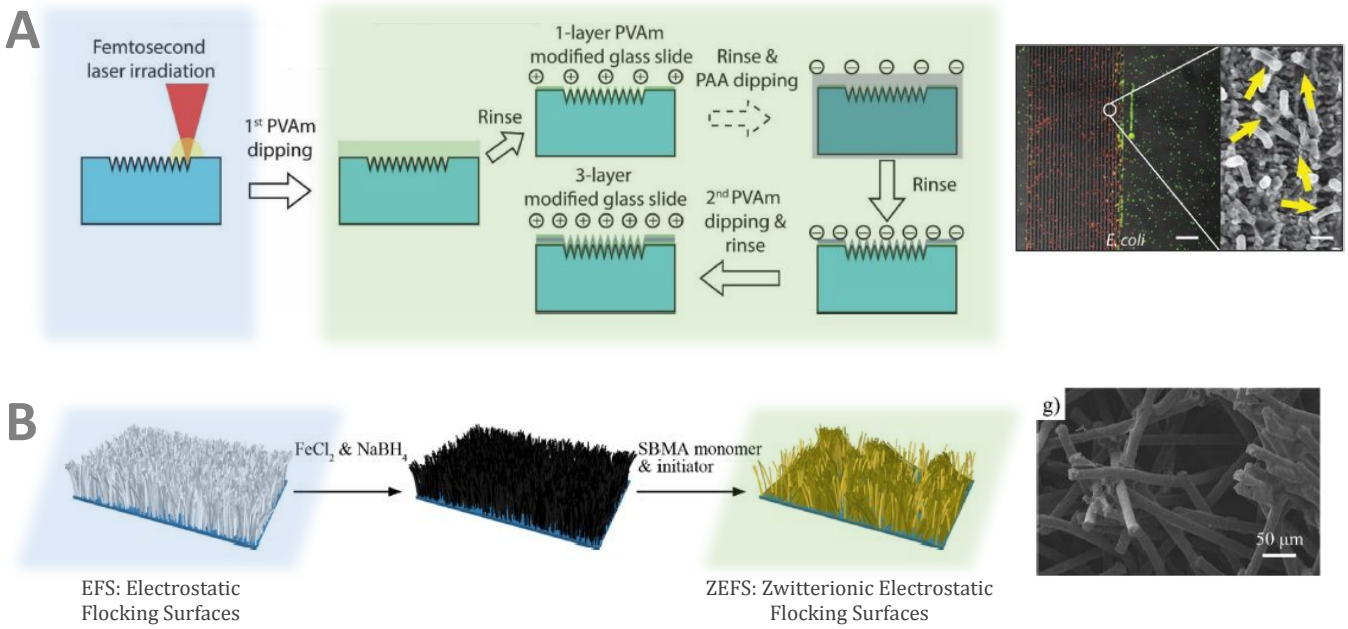


Figure 12: Fighting biofouling with hydrophilic coatings and topography on glass substrates. A: Layer-by-layer deposition of polyelectrolytes PVAm and PAA on nanopatterned borosilicate glass (adapted with permission from reference [73], Copyright 2020 Elsevier). B: zwitterionic electrostatic flocking surface produced with PSBMA (adapted with permission from reference [77], Copyright 2021 Elsevier). Blue and green overlay indicate topography and chemistry modifications, respectively.

3.3. Polymer substrates

Polymer substrates are the most represented in the chapter focusing on hydrophilic combined approaches. In nearly two thirds of the research articles in this chapter, the initial material is a polymer. However, as well as the wide diversity found in the production of topography and the surface chemistry, there is also a large range of polymers themselves. These different polymers can have different physico-chemical properties and are therefore not all suited for the same applications. To facilitate reading, in this subchapter, the articles have not been organized

depending on the polymers, but rather on the application they were chosen for: marine industry, water filtration, medical devices.

3.3.1.1. Marine industry

In this paragraph, the articles all aim to develop strategies for the marine industry where biofouling can have a significant economic impact. Some teams use biomimetic materials, as sea species have developed complex skin, shell or leaf surfaces to repel other, smaller organisms. Interestingly, they all use PDMS as the initial substrate which is directly modified to obtain the desired topography.

In the first article, PDMS films were stretched and plasma-treated to obtain a wrinkled surface. Silanization was then performed followed by surface-initiated atom transfer radical polymerization (SI-ATRP) to produce poly(ethylene glycol)methacrylate (POEGMA) or poly(3-sulfopropyl-methacrylate) potassium salt (PSPMA) brushes on the structured surface. The growth of the polymer brushes did not have an impact on the structure. *Ulva* zoospores and microalgae *Chlorella* were mixed in the same batch at different concentrations to evaluate the marine antibiofouling of the different samples. In static conditions over 7 days, the PDMS wrinkled surface was able to reduce the amount of adhered *Chlorella* more than *Ulva* since the zoospores are smaller than the wrinkled surface size. The POEGMA and PSPMA layers on flat PDMS also showed reduced cell

densities. The combination of wrinkles and polymer brushes led to the smallest cell densities. PSPMA-modified PDMS (both smooth and wrinkled) was more efficient than the surface modified with POEGMA brushes against *Ulva* zoospores. However, there was no significant differences between the two polymers against *Chlorella*. In dynamic conditions, very little biofouling from *Chlorella* was detected: from ~240 cells/mm² on PDMS to under 20 cells/mm² on the modified substrates. Finally, a sea water assay was performed for 2 months and clearly showed the superior antibiofouling effect of SI-ATRP-modified wrinkled PDMS compared to wrinkled-only or bare PDMS. Again, both polymer brushes showed similar antibiofouling effects.[78]

Brzozowska's team took inspiration from marine decapod crab *Myomenippe hardwickii* and replicated its surface composed of big and small features allowing it to repel species of various sizes. To enhance the antibiofouling effect, the biomimicking structure was combined with surface chemistry. Two strategies were carried out: modification with zwitterionic sulfobetaine polymer brushes and layer-by-layer coating of poly(isobutylene-alt-maleic anhydride) and polyethyleneimine (PEI) (Figure 13A). Tests were carried out with cyprids *Amphibalanus amphitrite* and diatoms *Amphora coffeaeformis*. For both species, the lowest adhesion was achieved with zwitterion brushes on patterned surfaces. This article also highlights the difference

between *in vitro* antibiofouling experiments and tests carried out in the field where hydrodynamics have a non-negligible effect.[79]

A similar approach consisted of mimicking the topography of algae *Laminaria japonica* by molding PDMS. Layer-by-layer coatings were also applied. In this case, they were composed of sodium alginate and (guanidine-hexamethylenediamine-Polyethyleneimine) (poly(GHPEI)) (Figure 13B). Structuring and surface chemistry modification both led to better hydrophilicity in comparison to bare PDMS. The most hydrophilic, with a WCA of 35˚, was the (GHPEI-ALG)-coated structured substrate. The prepared samples were tested against diatoms *N. closterium* and *P. tricornutum*. Structured surfaces repelled diatoms better than smooth ones. However, the combination of topography and chemistry gave the most effective surfaces, with a decrease in diatom density from nearly 1200 diatoms/mm² on smooth PDMS to under 10 diatoms/mm² on the complex surface. Over a period of 14 days, the developed material also inhibited diatom growth contrarily to other materials. Antibacterial activity was also studied with *E. coli* and was evaluated to be roughly 96%.[80]

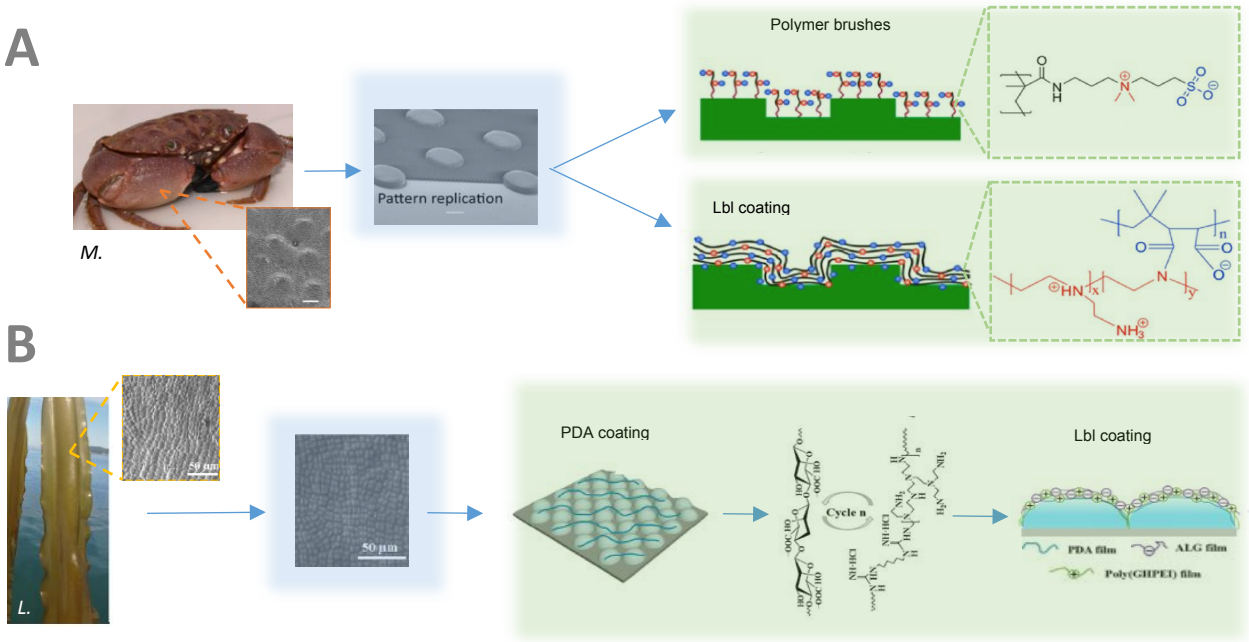


Figure 13: Bioinspired combinations of chemistry and topography on PDMS to fight marine biofouling. A: Biomimicking marine decapod crab M. hardwickii structure and modifying through polymer brushes or layer-by-layer coating (adapted with permission from reference [79], Copyright 2014 American Chemical Society). B: Layer-by-layer coatings on molded PDMS inspired by algae L. japonica (adapted with permission from reference [80], Copyright 2020 Elsevier). Blue and green overlay indicate topography and chemistry modifications, respectively.

3.3.1.2. Water filtration

We have seen so far many different applications of antibiofouling surfaces but one important industry remains to be looked at: water filtration. Indeed, to avoid contamination of drinking water, it is vital that the polymer membranes that are used resist the formation of biofilm. Hydrophilic coatings have a true importance in this field to enhance the water separation. This is what will be studied in the next paragraph which is organised by type of polymer membrane used as the initial substrate.

The first one we will concentrate on is the polyamide (PA) membrane which has been chemically and topographically modified by various teams, leading to efficient materials for water treatment without biofilm formation.

Weinman and Husson for instance, structured PA membranes with nano lines and grooves by thermal embossing, and coated them with poly(ethyleneglycol) diglycidyl ether (PEGDE) (Figure 14A). In comparison to pristine membranes, for which the flux was reduced by over 20% over a period of 2 h, the patterned membranes did not have such a negative effect on the desired application, with a maximum reduction of 8%. The PEGDE coating caused a slight flux reduction on the patterned membranes but this impact did not increase with its concentration (5 or 15 wt%). In all experiments the salt rejection remained close to the 95% specified by the manufacturer. To test the antibiofouling capacity of these membranes, sodium alginate was used as a model foulant. It was demonstrated, by quantifying the flux over time, that both the patterning and the chemical coating decreased the fouling on the membranes. The combination of both surface hydrophilicity and improved hydrodynamics induced by the lines and grooves, gave the best results.[81]

Choi's team, who had previously studied antibiofouling techniques based on cylindrical TiO_2 pillars on PA membranes,[82] further improved their technique by upgrading the structuration of the

membranes to shark skin inspired topography, namely Sharklet™. They reached thin film composite microstructured membranes using a series of steps including phase separation micromolding and layered interfacial polymerization.[83–85] The structure was then combined with coating of hydrophilic tannic acid, deposited from the liquid-phase, giving the membrane an anti-adhesif effect (Figure 14B).[85] Study of the modified membranes revealed NaCl rejection and permeability towards water were very similar between uncoated and coated membranes. In fact, the water permeance was slightly improved due to the hydrophilicity of the coatings. As with the nanopillar arrays from their previous study,[82] the sharkskin nanostructure coupled with a chemical coating of tannic acid led to a decrease in *P. aeruginosa* attachment, shown qualitatively by live/dead™ imaging. In dynamic conditions, an isolated vortex is created by the Sharkskin protrusions, decreasing furthermore the ability of *P. aeruginosa* to adhere to any surface[84]. In their publication from January 2022, Zhao *et al.* also used tannic acid on nanofiltration membranes for its antibiofouling effect. They deposited it on a polyacrylonitrile membrane modified with Glutaraldehyde (GA)-crosslinked PEI-SBMA to give it a microstructure which was tuned by varying the concentrations of GA.[86]

Another material with physico-chemical properties that allow the fabrication of membranes is polysulfone (PSF). Various types of PSF membranes exist and have raised interest in the scientific community.

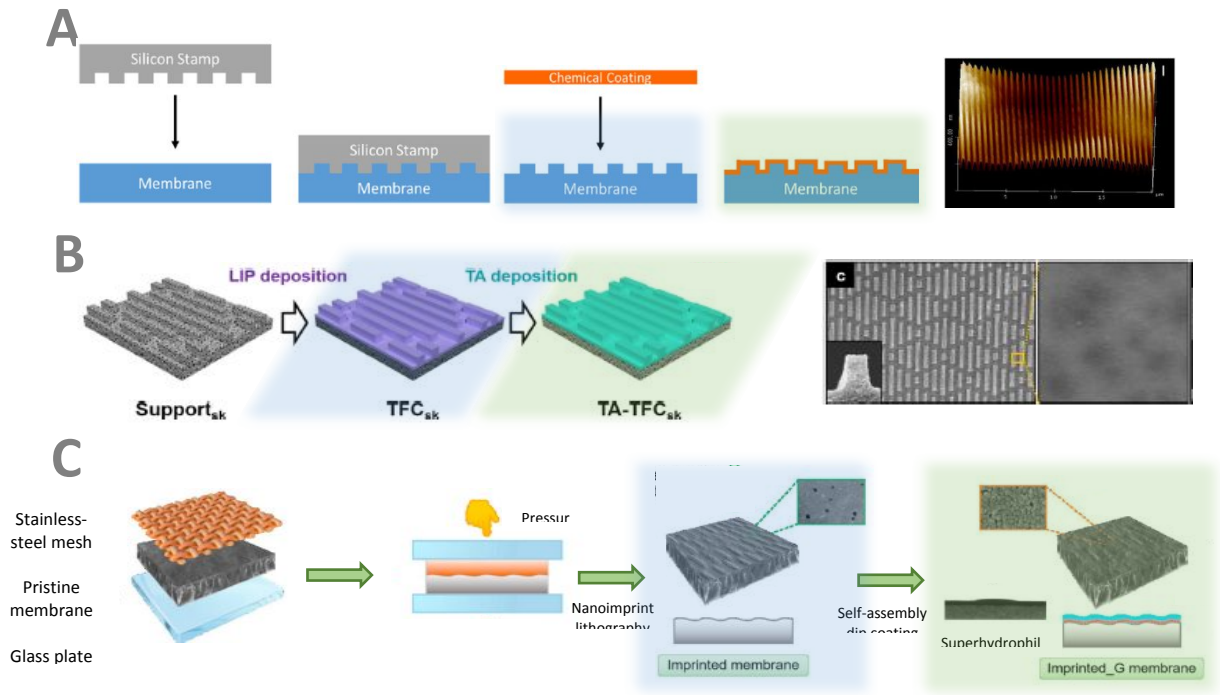
In a first study, a Polyethersulfone (PES) membrane was coated with a mixture of cellulose nanofibrils (CNF) and PVA. This treatment imparted PES membranes with both nano-textured roughness and charged surface chemistry. PVA was added to crosslink the film and improve its adhesion to the substrate, decreasing the average roughness from around 30 µm to 10 µm. According to the author, a smaller specific surface area is expected to better prevent molecule adhesion. On the contrary of the wettability, which did not change, conserving the membrane's efficiency; the surface charge was impacted by the coating: ζ-potential was reduced from -20 mV to -40 mV around the plateau at pH 5, indicating a higher amount of negatively charged hydroxyl and aldehyde groups. BSA adsorption on the coated membrane was evaluated using quartz crystal microbalance with dissipation monitoring (QCM-D) and was shown to be very limited. It is believed that the abundant hydrophilic groups of PVA/CNF layer suppress the interactions with the protein. A biofilm study with *E. coli* revealed that the bacterial coverage was also almost eliminated. In this case, the promising results can be explained by the combination of both surface

chemistry, which promotes electrostatic repulsion of bacteria and a bactericidal effect, and tuned surface roughness, which reduces the specific surface area.[87]

Lin and his team also chose to begin with PSF membranes, modifying them with a combination of tannic acid (TA), PEI and (3-amino-1-propanesulfonic acid), otherwise known as taurine. Indeed, these three molecules were co-deposited at the surface of the membrane, before interfacial polymerization with trimesoyl-chloride. Turing striped structures were formed with 0.2% taurine content during the interfacial polymerisation. Humic acid, sodium alginate and BSA were chosen as model foulants. Flux recovery ratio was close to 98% against humic acid confirming excellent antibiofouling effect. Sodium alginate and BSA tests gave slightly lower antibiofouling performance (with a flux recovery ratio of 90% and 93% respectively), partly explained by higher molecular weights. Here again, it is the combination of both chemistry and topography that led to the best designed ultrafiltration membrane: the strong hydration layer arising from the zwitterionic nature of taurine prevented the adsorption of model organic foulants, and meanwhile, the hydrophilic striped surface allowed for a mild enhancement of water flux as a consequence of increased specific surface area.[88] In a similar study from the same research team, interfacial polymerization was combined to a sol-gel reaction in order to explore a new approach to limit

biofouling.[89] This led to controlled pore size and an increase in water permeability and selectivity of the membrane. The surface was also enriched with hydroxyls that increased the hydrophilicity and decreased the biofouling of BSA.

Finally, the last type of membrane that was found to be relevant for this review is the PVDF membrane.



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967 *Figure 14: Combining topography and hydrophilic coatings to combat biofouling on polymeric*
968 *membranes for water treatment. A: Structured Polyamide (PA) membrane coated with*
969 *Poly(ethyleneglycol)diglycidylether (PEGDE) (adapted with permission from reference [81], Copyright 2016*
970 *Elsevier). B: PA membrane modified with Sharklet™ topography and coated with tannic acid (adapted*
971 *with permission from reference [85], Copyright 2021 Elsevier). C: Nanoimprint lithography and self-*
972 *assembly dip-coating to modify PVDF membranes (adapted with permission from reference [90], Copyright*
973 *Elsevier 2020). Blue and green overlay indicate topography and chemistry modifications, respectively.*

974 For example, microporous PVDF membranes have been coated with poly(N-vinyl-pyrrolidone)

975 (PVP) by initiated Chemical Vapor Deposition (iCVD). In this case, to increase the adhesion of the

976 hydrophilic PVP onto the membrane, a prime layer of crosslinking agent poly (ethylene glycol

977 diacrylate) (PEGDA) was deposited before coating with copolymer poly(VP-co-EGDA). Different

978 ratios of crosslinking were tested and the effect on FTIR and WCA were analysed. The latter

979 reached nearly 0°, as the water droplets got absorbed by the membrane in less than 3 s. It is thought

that this superwettability is only achieved by combining the two factors: the hydrophilicity of the PVP coatings on the one hand, and on the other hand, the porous structure that allows the water droplets to spread rapidly throughout the membrane. Antibiofouling was tested using model protein BSA and fluorescently stained *E. coli*. The amount of BSA was reduced from 36 µg/cm to under 2.2 µg/cm upon coating the PVDF membrane. This quantity was slightly increased after durability tests but still remained 90% lower than adsorption on pristine membranes. However, for these estimations, only the apparent surface area was studied. It is thought that the internal pores have a large surface area, thus decreasing furthermore the actual protein adsorption.[91]

Furthermore, in an article by Ma and co-workers, the PVDF substrates were enhanced by modification of topography and grafting of nanoparticles decorated with hydrophilic chemical functions. A micro scale surface pattern was formed through imprinting with a stainless steel mesh. Further nano scale topography was achieved by adding an exogenous material. Indeed, the imprinted membrane was dipped into a suspension of amine-terminated SiO_2 nanoparticles (see Figure 14C). Simultaneously, amine functions that are not involved in the surface binding thus represent the new surface chemistry of the membrane. It was noted that nanoparticle functionalisation alone lead to high roughness, which was wiped out when combined with micro-

scale imprinting. Full wetting of water droplets observed during contact angle measurements demonstrated the superhydrophilic nature of the modified membrane. Antibiofouling properties were evaluated in both static conditions against bacteria suspensions (*Bacillus thuringiensis* and *E. coli)* at 10^8 CFU/mL, and in dynamic conditions upon filtration tests with a practical mixed liquor sample in a full-scale aerobic membrane bioreactor. SEM analysis was used to detect the presence of bacteria. Fewer seemed to be detected on the modified membrane after rinsing, although no quantitative analysis was carried out. For the filtration tests, flux recovery measurements were performed to quantify the antibiofouling performance against the mixed liquor. The modified membrane offered a 45% higher flux recovery compared to pristine membranes, which is explained by the hydration layer arising from the superhydrophilicity, and the wave-like micro-structure that promotes turbulent flow, both reducing the adhesion of foulants to the membrane.[90]

3.3.1.3. Medical devices

Polymers are also often used in the medical field as they have many advantages in comparison to other materials. In the case of medical devices, developing strategies to stop biofilm formation on the polymeric surface is even more critical as it can often lead to nosocomial infections.

In this study, Park *et al* used a cellulose acetate (CA) solution which was drop-cast on a PDMS master mold resulting in a flexible CA nanoneedle array. After plasma treatment, an aqueous solution of 2-methacryloryloxyethyl phosphorylcholine (MPC) was spin-coated onto the array before drying in a convection oven. WCA proved the superhydrophilicity of the modified CA surface, with angles decreasing from 70˚ to 9˚. Antibiofouling properties were evaluated against *E. coli* and *B. subtilis* suspensions in which they were incubated for 3 to 30 hours before live/dead™ staining for fluorescence microscopy observations. Quantitative assays were also performed to confirm the antibacterial effect of the optically transparent substrates. The decrease of the density of detectable bacteria in fluorescence microscopy was mainly attributed to the chemical modification with MPC, while the live/dead™ staining assay confirmed that the nanoneedles were responsible for the bactericidal effect, by penetrating or stretching the bacterial membrane.[92] The same team also modified poly(ethylene glycol) dimethacrylate (PEGDMA) nanoneedles which swell in wet conditions. Interestingly, they maintained their shape upon swelling, and similarly to the CA nanoneedles, the best antibiofouling effect was obtained for the sample that combined the chemical surface modification and the presence of nanoneedle topography. With the intrinsic antibiofouling properties of PEGMA, MPC-PEGMA nanoneedle hybrids proved to be tough

antibiofouling surfaces as a local destruction of the topography or zwitterionic MPC coating was not sufficient to totally impede the antiadhesive properties of the substrates.[93]

Intraocular lenses have also been modified to avoid bacterial infection and minimize corneal cell attachment after cataract treatment. The lenses were altered by depositing a polymeric nanopillar array covered with ionic antibacterial polymer. The nanopillar array was produced by stamping a mix of polyurethane (PU) and Norland Optical Adhesive 63 polymer (PU/NOA63), onto a mold designed by photolithography. Then, iCVD was used to deposit a 50 nm thick layer of a copolymer of 4-vinylbenzyl chloride and 2-(dimethylamino)ethyl methacrylate. Thus, quaternary ammonium compounds (QACs) were introduced onto the surface of nanopillars. The antibacterial efficiency was measured against *S. aureus*. The nanopillar array alone demonstrated a 50% efficiency compared to flat PU/NOA63 polymer film, but it is only with the copolymer deposited on top that the antibacterial efficiency rised to almost 100%, confirming a profitable synergy between surface topography and chemistry. Upon adhesion, bacterial cells were captured in between the nanopillars, causing the latter to bend. The QACs available at the surface of the nanopillars are known to destabilize the bacterial membrane. When the nanopillars gradually restore their upright orientation, the bacteria slide down, and their membrane suffers deformation and then rupture.

However, the engineered substrate showed biocompatibility for up to 7 days towards human corneal endothelial cells.[94]

4. Conclusion & perspectives

As we have seen throughout this study, biofilm is a problem encountered in many different applications, ranging from medical devices to the marine industry. With antibioresistance and biocide resistance on the rise, and World Health Organization urging to take action, new antibacterial and antibiofouling strategies need to be developed. Concern is also arising over the toxicity of bactericidal nanoparticles or metallic compounds, making the use of such substances questionable. Thus, combining other solutions such as organic polymers and topography can be an efficient mode of action.

More precisely, macromolecules with hydrophobic or hydrophilic properties show great interest for their ability to stop bacterial adhesion, and their activity can be enhanced by coating them on micro or nanostructured surfaces. In addition to increasing the wettability effect of certain substances, some structured surfaces can cause bacterial membranes to rupture through mechanical deformation. Others can lead to hydrodynamic fluxes which inhibit bacterial sedimentation and

thus, biofouling. Precise control over the size and shape of the used structures could enable better understanding of their effect on bacterial adhesion and could also facilitate the adaptation of the surfaces to different strains of bacteria. Some structures could have opposite and non-desired effects and serve as bacterial traps. Concerning hydrophilic substances, depending on their nature, bactericidal properties can also be observed. All of these mechanisms are represented in Figure 15 which highlights the diversity of action of hydrophilicity-based approaches in comparison to hydrophobic strategies based on the Cassie-Baxter regime.

As emphasized by the organisation of this review, the initial material used for creating these antibiofouling surfaces with a combined approach can be metallic, glass or a variety of polymers. The adaptability to various substrates is interesting to address the wide range of applications where antibiofouling surfaces are needed.

However, despite all the different solutions discovered while writing this review and summarized in Table S2 and S3, there seems to be a lack of statistical experiments. Indeed, here, independent experiments have been carried out with one combination of polymer and topography and one or two species of bacteria. This lack of systematic studies has been noticed by other teams and projects are arising. Indeed, Linklater *et al* have published in February 2022 a first statistical study of the

effect of different nanopillar polymers on *P. aeruginosa* and *S. aureus.*[95] Furthermore, oppositely to *in vitro* experiments, in natural environments, one species of bacteria, or one marine species is rarely found alone, rather in a mixture with many other organisms. Only a few of the articles in this review have mentioned experiments carried out with natural samples. Therefore we can wonder whether transposing any of these modified surfaces to other applications would prove efficient or if the substrate would always have to be adapted to the field of interest and to the particular device.

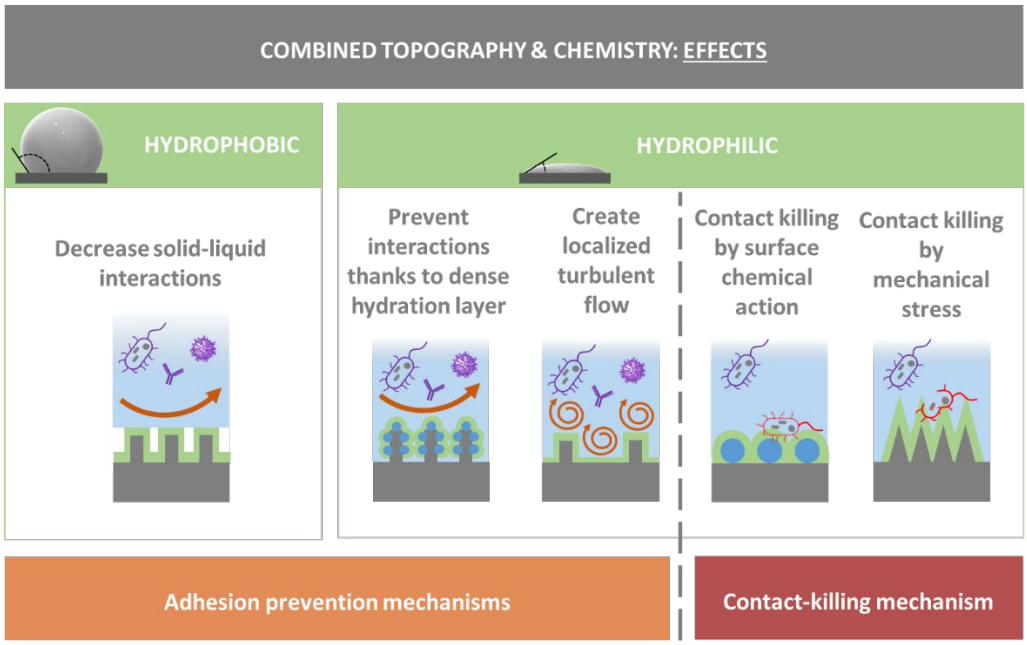

Figure 15: Diverse effects of surface modification approaches for antibiofouling, and corresponding mechanisms

To verify the biocompatibility of these surfaces created with the prospect of replacing possible toxic solutions, cytotoxicity experiments need to be carried out in parallel. This aspect can be

critical in some domains such as medical implants, where a risk of damaging human cells is unconceivable. It is also important in the marine industry to protect the natural fauna and flora. In this review, most of the publications using hydrophobicity to inhibit biofilm formation use fluorine-based chemicals. However, concern over the negative impacts of some fluorine-containing compounds could lead to an increase in fluorine-free surface development in the near future.

Finally, the question of the robustness and durability of these surfaces should also be studied to verify their applicability *in vivo*. Indeed, biofilm is created rapidly but becomes stronger overtime. For a device left in a liquid medium over several months, it is very important that its efficiency does not degrade in that time. These durability assays should also be adapted depending on the application as the stress applied to a device could be very different.

Overall, although complimentary research still needs to be carried out to respond to the yet unanswered questions, combining chemistry and topography seems to be a promising strategy to reach environmentally friendly, biocompatible and antibiofouling surfaces.

SUPPORTING INFORMATION:

Table S1 showing recent review articles on antibiofouling surfaces and overview tables (S2 & S3) summarizing the combined strategies described in this manuscript.

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Author Contributions

The manuscript was written through contributions of all authors. Miss Whiteley and Mr. Durand were in charge of the gathering and analysis of the relevant articles, and of the writing of the manuscript. Mr. Mailley participated in the reviewing process and brought insights for the manuscript structure, in addition to corrections. Mr. Nonglaton participated to the development of the manuscript structure and scope, in addition to corrections. All authors have given approval to the final version of the manuscript.

‡These authors contributed equally.

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Notes

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ABBREVIATIONS

Abbreviations are all explained in the text

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