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Review

How microbes read the map: Effects of implant topography on bacterial adhesion and biofilm formation

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ABSTRACT

Microbes have remarkable capabilities to attach to the surface of implanted medical devices and form biofilms that adversely impact device function and increase the risk of multidrug-resistant infections. The physicochemical properties of biomaterials have long been known to play an important role in biofilm formation. More recently, a series of discoveries in the natural world have stimulated great interest in the use of 3D surface topography to engineer antifouling materials that resist bacterial colonization. There is also increasing evidence that some medical device surface topographies, such as those designed for tissue integration, may unintentionally promote microbial attachment. Despite a number of reviews on surface topography and biofilm control, there is a missing link between how bacteria sense and respond to 3D surface topographies and the rational design of antifouling materials. Motivated by this gap, we present a review of how bacteria interact with surface topographies, and what can be learned from current laboratory studies of microbial adhesion and biofilm formation on specific topographic features and medical devices. We also address specific biocompatibility considerations and discuss how to improve the assessment of the anti-biofilm performance of topographic surfaces. We conclude that 3D surface topography, whether intended or unintended, is an important consideration in the rational design of safe medical devices. Future research on next-generation smart antifouling materials could benefit from a greater focus on translation to real-world applications.

1. Introduction

Microbes have remarkable capabilities to attach to biomaterial surfaces and form multi-cellular structures known as biofilms, which can affect the safe use and function of medical devices in humans [1–4]. Biofilms are complex microbial communities typically attached to a surface and embedded in a 3D extracellular matrix consisting of exopolysaccharides, proteins, and extracellular DNA. The biofilm matrix protects embedded bacterial cells by preventing the penetration of certain antibiotics and host immune cells [3,5]. The association between medical device-associated infections and biofilms of multidrug-resistant organisms has recently been established by large-scale clinical data [6]. Biofilm formation begins with bacteria-material interactions, which facilitate the attachment to the surface, followed by extracellular matrix formation and biofilm maturation. Material properties that are known to affect biofilm formation can be chemical (surface chemistry), physical

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(charge, hydrophobicity, topography, viscoelasticity, stiffness), and biological [such as specific host proteins, anti-quorum sensing agents, and inhibitors of c-di GMP (a master bacterial signaling molecule that regulates the motility/sessility switch)] [7–24]. Chemical and physical properties of the substrate material have a significant and broad-spectrum impact on biofilm formation and thus are promising targets for engineering antifouling materials.

In recent years the importance of surface topography in microbial adhesion has come to the fore [7,16–22] not only as a promising area of research but also for its importance in real-world medical challenges. One example with significant implications for women's health is the link between surface topography and incidence of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), which occurs predominately with textured implants (with micron-scale recessive topography) rather than smooth implants [25]. Although it is not yet understood why textured implants are associated with BIA-ALCL [26], a number of research publications suggest that bacterial colonization on textured breast implants may contribute to T-cell hyperplasia and consequently BIA-ALCL development [1,26–31]. There is significant public debate, and both regulatory agencies [32] and standards organizations [33–35] worldwide are considering if surface topography should be considered in risk classification.

Given the important role of bacterial biofilms in medical device-associated infections, there has been significant research on how bacteria interact with 3D surface topographies and how to design surface topography as a strategy to create antifouling and contact killing materials. Recent studies have reported a number of strategies to prevent bacterial attachment and remove established biofilms by engineering static, dynamic, and active topographies (Fig. 1). However, most of the studies to date are empirical and lack rational designs guided by principles based on fundamental understanding. We believe that the field will benefit from a better connection that integrates research on how bacteria sense and respond to 3D surface topographies with research that investigate how surfaces can be engineered to prevent biofilm formation. Translating the basic scientific understanding of how bacteria read the map to the real-world application for medical devices requires not only an understanding of what types of 3D surface topology are antifouling and what types should be avoided but also the knowledge of how the complex *in vivo* milieu (or medically specific environmental conditions) affects the performance of the devices in humans. In this review, we discuss the following specific questions:

- What has been learned from laboratory studies of microbial adhesion and biofilm formation on specific topographies?
- How do bacteria sense and interact with micro and nano-topographies? And how can this help future design?
- What do preclinical studies of topographic surfaces on implants tell us?
- What are the unique biocompatibility considerations for topographic surfaces?
- How can laboratory testing better predict the real-world performance of topographic surfaces?

Our goal is to provide a critical analysis of how microbes read the 3D topographic map and how this can be translated into medical device design and testing. Thus, this review focuses on the physical factors of topography and does not address chemical approaches such as antibiotic coatings. As we move from bench to bedside, we attempt to summarize what is currently known about this topic, identify gaps, and point the way forward towards the rational design of safer medical devices.

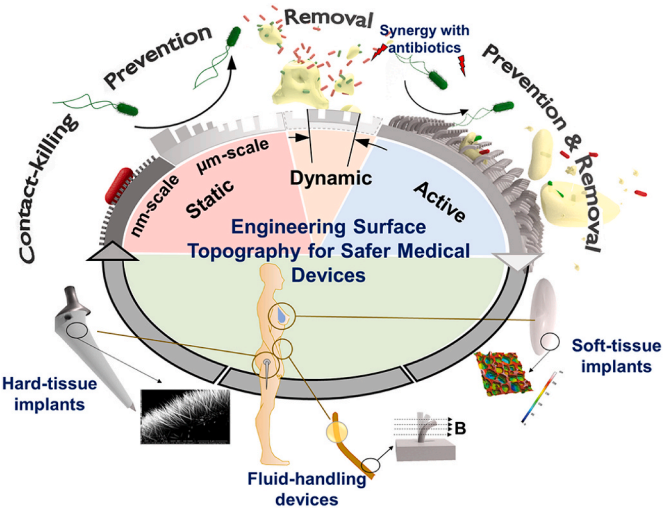


Fig. 1. Overview of surface topographies and biofilm control. Prior research has demonstrated contact killing by stiff nanopillars, biofilm prevention by static micron-scale topographies, removal of mature biofilms by dynamic surface topographies, and long-term biofilm control using active topographies. The lower section of the schematic shows examples of medical devices that have engineered topographies. Orthopedic device modified with TiO_2 nanowire [36] and catheter with active topographies [37] were shown to be antifouling. In comparison, breast implants with textured surfaces were associated with bacterial colonization, emphasizing the importance of topography to the safety of medical devices and the need for rational design [38]. SEM images of orthopedic devices modified with TiO_2 nanowires and nano-wells on breast implants are reprinted from references with permission [36,38].

2. What has been learned from laboratory studies of microbial adhesion and biofilm formation on specific topographies?

A large number of studies have been conducted to investigate how micron- and nano-scale topographies affect cell adhesion and biofilm formation, and to explore the possibility of promoting host tissue growth while inhibiting bacterial adhesion. The vast majority of studies to date have been focused on static topographies, including both protrusive and recessive features, with either well-defined or relatively random size and distribution. The features reported to date have been tested on both polymeric and metallic materials, from nm to μm scale, and include both designed topographies and bioinspired features mimicking those on plant leaves [39], shark skin [40], and insect wings [41]. While certain features were found to promote bacterial attachment and biofilm formation, most studies aimed to identify antifouling materials. In general, micron-scale topographies do not have bactericidal effects but may inhibit bacterial adhesion through specific effects on bacteria-material interactions. In contrast, a number of nano-scale topographies have bactericidal effects by directly damaging bacterial membranes (Fig. 2).

2.1. Static micron-scale topographies hinder biofilm formation by affecting bacteria-surface interactions

Micron-scale topographies have been shown to affect the attachment and biofilm formation of different bacterial strains on varying materials such as poly(methyl methacrylate) (PMMA) [42], polystyrene [43], polyethylene glycol (PEG) hydrogel [44], polyethylene terephthalate (PET) [45], Si [46,47], optical fiber [48], and Ti [49]. Some of the designs were inspired by naturally existing antifouling surfaces. For example, micron-scale topographies were created by mimicking the micropatterns on shark skin [40] for antifouling activities.

The size, shape, and distribution of topographic patterns all play an important role in bacterial attachment. Many topographic features have been shown to inhibit bacterial biofilm formation such as line patterns [40,55,56], irregular micro pits [49], honeycombs [46,50,51], cylindrical wells [44,48], ridges [39,50,57,58], and pillars with shapes of square [43,47,59,60] or hexagon [42,61]. Although these studies differ in the pattern dimension and layout, substrate material, and the bacterial strains tested, it is a common observation that bacterial adhesion

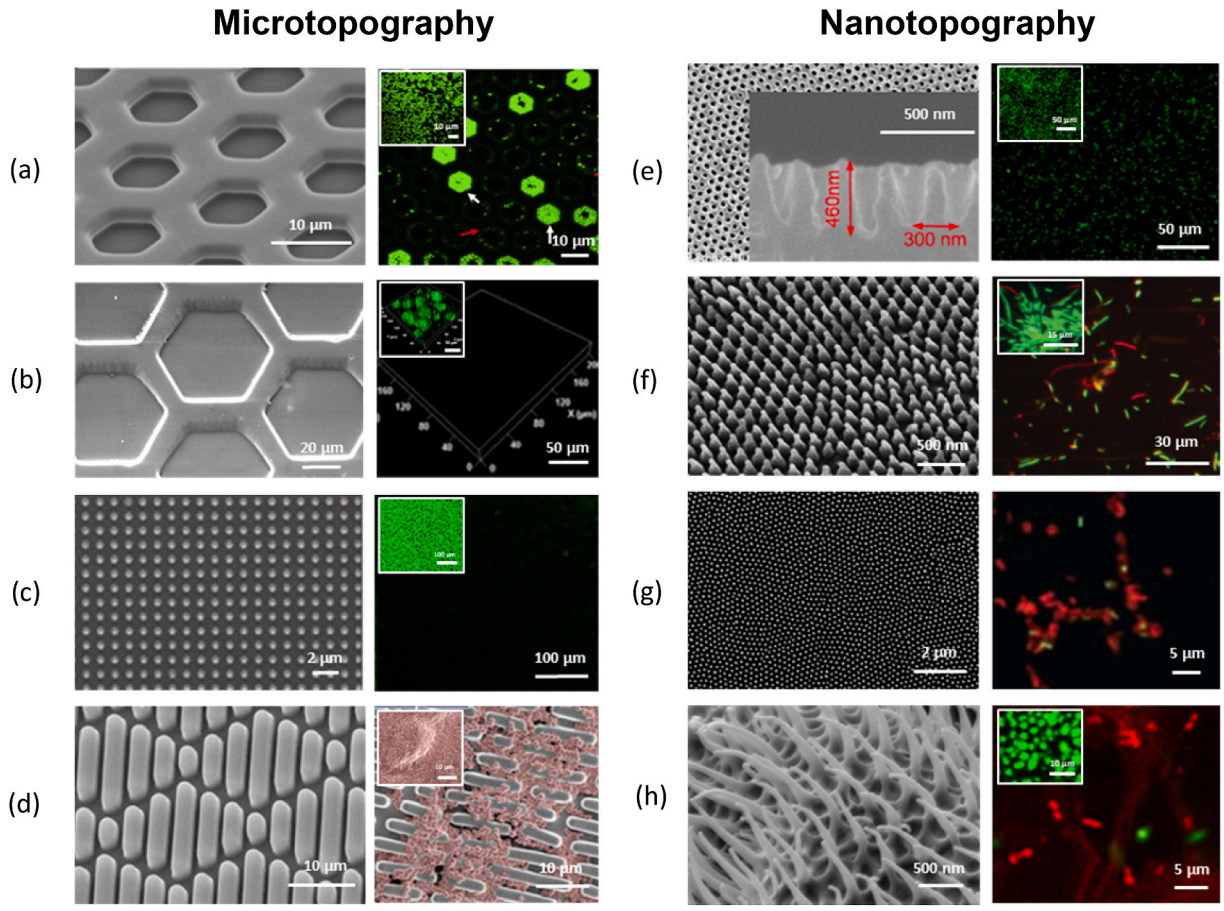


Fig. 2. Controlling bacterial attachment by using micron- and nano-scale topographies. (a–d) SEM images (left) and fluorescent microscopic images (right) of bacterial attachment on hexagonal PDMS pits (a), hexagonal PDMS pillars (b), micropillars (c), and Sharklet™ patterned surfaces (d). Live cells are stained with green fluorescent SYTO9 (a–c) or highlighted with red color (d). Images reproduced with permission from Refs. [40,47,50,51]. (e–h) Bacterial attachment on nano-topographies. SEM images (left) and fluorescent microscopic images (right) of bacterial attachment on engineered surfaces with parabolic nanostructures (e), nanopillars (f), and natural surfaces of cicada wings (g) and gecko skins (h). Live cells are green as stained by fluorescent SYTO9 while dead cells are red with the stain of propidium iodide. Image reproduced with permission from Refs. [41,52–54]. The SEM image of (b) was taken for this review article. The small images show cell attachment on flat control surfaces. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

decreases as the size of the topographic pattern gets smaller [50,56–59]. An exception is the report [39] on biomimetic surfaces of spinach leaves. The authors observed no difference in the number of adherent bacteria between unpatterned and patterned (~50 μm wrinkle with 6.88 μm R_{rms}) surfaces. In addition to static conditions, Graham et al. [62] demonstrated that micron-scale circular holes can reduce the attachment of *E. coli* in a microfluidic device by more than 4 times compared to the flat control.

Besides attachment, static topographies can also affect the physiology of bacterial cells that contribute to biofilm formation and associated antibiotic resistance. For example, *E. coli* cell cluster formation on narrow (5 μm wide) line patterns is 14 times less than that on flat surfaces [63]. Biofilm-inhibiting topographies can also reduce bacterial conjugation [64].

2.2. Nanotopographies can kill bacteria through mechanical forces

Unlike the micron-scale topographies that mainly affect bacterial attachment, some nanoscale topographies have bactericidal effects by piercing through the cell membrane. A number of studies were inspired by nanofeatures on insect wings. For example, hexagonally arranged nanopillars on Clanger cicada (*Psaltoda claripennis*) wings can kill bacterial cells in contact [65]. Further study using atomic force microscopy (AFM) revealed that these nanopillars penetrate bacterial membranes and kill the cells within 3 min. The effects were found to be physical because coating the surface with gold did not change the effects [53]. These nanotopographies were found to kill Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Escherichia coli*, and *P. fluorescens*, but not Gram-positive bacteria, which have thicker cell walls and thus are more rigid [66]. This is consistent with the report of Nguyen et al. [67] and the finding that cell rigidity plays a role in membrane damage by nanopillars [65]. Some nanotopographies have been shown to kill both Gram-negative and Gram-positive cells [68]. Linklater et al. [69] and Ivanova et al. [70] reported strong bactericidal effects of nanofeatures on vertically aligned carbon nanotube and black silicon against Gram-negative and Gram-positive bacteria, with up to 99.3% reduction at a rate of 450,000 cells/min/cm^2. Au nanostructures including pillars, rings, and nuggets all showed >99% reduction of methicillin-resistant *S. aureus* [71].

In addition to cicada wings, the skin of the box-patterned gecko (*Lucasium* sp.) with its spinules (hairs) [54] and nanotextures on dragonfly wings (*Orthetrum villosovittatum*) [72] are also antibacterial and self-cleaning. The surfaces were found to kill Gram-negative bacteria but not human stem cells [54,73]. These activities have inspired researchers to create similar features to reduce bacterial colonization on biomaterials such as Ti [74,75]. The methods to create nano-scale features have been well summarized in a recent review [22]. A number of different nano-scale features have been studied to dates such as nanopillars [66,70] and nano spikes [76] on Si surfaces generated by plasma etching, diamond [77,78] and gold [71] substrates treated by

anodization and plasma etching, carbon nanotubes created by chemical vapor deposition (CVD) [79], aluminum substrate etched by sodium hydroxide (NaOH) solution [80], nanowires and nano-size spikes made by hydrothermal processing [81–84], and nano rough Ti surfaces created by electron beam evaporation [85].

Compared to inorganic materials, fewer studies have been conducted with polymers presenting nanostructures. Some examples are anti-fouling nanopillars on polyurethane (PU) [86] and nanostructured PMMA film with both antireflective and antimicrobial properties [52].

Bactericidal effects of nanospikes and nanopillars and biofilm inhibition were also overserved under flow; e.g., a bacterial killing rate of $2.3X10^3$ colony forming units (CFU)/min/cm^2 was obtained in a microfluidic device with nano-structured black silicon [76]. Besides the general fouling control, nanotopographies have been shown to affect the population balance between bacterial species. Bhattacharjee et al. [87] used a flow cell system to investigate the effects of nanopillars and found that *E. coli* biofilm became more dominant than *P. aeruginosa* as the height of nanopillar increased. This population shift also led to higher susceptibility to rifampicin.

Overall, a number of bioinspired and synthetic systems of micron- and nano-scale topographies have been engineered and exhibited effective antifouling activities. However, a vast majority of studies to date are rather empirical (by mimicking naturally existing features or screening a set of designs) and the roles of bacterial factors are not well explored. Further development in this field will benefit from a more in-depth understanding of bacteria-material interactions, especially how bacteria sense and respond to such surface features (how bacteria read the map) as summarized below.

3. How do bacteria sense and interact with micro and nanotopographies? And how can this help future design?

A number of studies reported evidence that bacteria can actively explore and respond to micron-scale surface topography during attachment. On surfaces with micron-sized recessive wells, *E. coli* cells exhibited preferential orientation to maximize surface contact [88]. Similarly, Hochbaum et al. [89] noticed that as the distance between protruding features varied from 4 μm to sub-micron size, the orientation of the attached cell changed from perpendicular to parallel to the post lattice protruding from the surface to place itself in the confined well area and maximize the contact.

Without the ability to see and hear, "touch" plays an essential role in the interaction between a bacterial cell and surface topographic features, and the following steps of biofilm formation. Bacteria have a variety of structures for sensing the physical properties of a surface including flagella [61,90], pili [61,91,92], mechano-sensitive channels on the cytoplasmic membrane [93,94], and specific proteins or receptors on the outer membrane [70,95,96]. Understanding how bacteria respond to surface properties is essential to the rational design of anti-fouling materials.

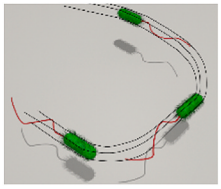
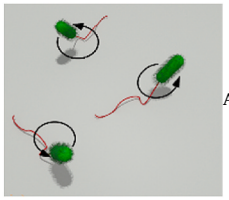
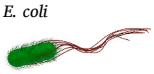
3.1. Bacterial flagella play a key role in sensing and responding to surface topographies

Bacterial flagella are typically 5–20 μm long with a flagellum [97,98] acting as a helical propeller, adhesins acting as a hook at the base of the flagellum, and a basal body working as a rotary motor [99,100]. Previous studies have shown that flagella play important roles in bacterial sensing and interaction with surface topographies (Table 1).

Paradigmatic bacteria (with multiple evenly distributed flagella [105]) such as *E. coli* control motility through "run" [with flagella assembled into a bundle and rotating counterclockwise (CCW)] and "tumble" [with clockwise (CW) rotation of separated flagella] [106]. Upon resuming CCW from tumbling, the buckling of the flagellar hook compresses the filament into a bundle, and the cell is reoriented [107]. For bacteria with polar flagella (such as *Vibrio*, *Pseudomonas*, *Aeromonas*, and *Shewanella*), their swimming modes switch from run-and-tumble to run-reverse-flick. Instead of breaking the bundle formed during CCW rotation, the motor reversal to CW will pull the cell backward. Flagella-driven motility enables bacterial cells to "touch" a surface.

Interaction between bacterial flagella and surface topography affects both the motility before attachment and rotation of cells after the initial

Table 1
Summary of bacterial flagella and their roles in sensing and responding to 3D surface topographies. The drawing of cell movement is adapted from [110] with permission.

Motility (only one flagellum is shown for clarity)	Model organism	Surface topographies		Bacterial response	Ref.
 Near-surface swimming	*E. coli* (4–10 flagella) 	Dome-shaped topographies (diameter > 1 μm)		Flagella-mediated motion switches from "run" to "random walk" as a combined result of a run and tumble when *E. coli* cells encounter obstacles.	[61]
		Channels/grooves between protruding features (with a width around 1.3 μm)		Flagella-mediated motility diminishes when the width of channels decreases to less than 1.3-times of the cell body diameter.	[101]
	B. subtilis (~20 flagella) 	Channels or grooves between protruding patterns	Width = 90 μm	Bacteria swim in the channel in a random pattern or "turbulent state" (e.g., a mixed pattern of jets and swirls).	[102]
			Width = 70 μm	Bacteria swim more unidirectionally in confined space.	[102]
	P. aeruginosa (monotrichous flagellum) 	Protrusive hemispheres	Diameter = 4 μm	Bacteria prefer to swim along the top of hemispheres.	[103]
			Diameter = 8 μm	Bacteria prefer to travel in the grooves.	[103]
 Alignment of flagella and Surface-anchored spinning	*P. fluorescens* (monotrichous flagellum) 	Line-shaped topographic patterns (with pattern width of 550 nm, height of 120 nm, and 750 nm spacing)		Flagella aligned more perpendicularly to the direction of nano-scale grids to interact with the neighboring cells.	[104]
	E. coli 	Line-shaped topographic patterns (5 μm tall) vs. flat surfaces		Anchored spinning differs between attachment on flat surfaces (regular circular motion) and the side of protruding patterns (irregular movement)	[63]

attachment (Table 1). When the flagella of *E. coli* attach to a flat surface, the cell body moves in a clockwise circle before settling [108]. In comparison, when *E. coli* cells encounter obstacles (such as dome-shaped topographies with a diameter >1 μm [61] or confined in the grooves between protruding features), their movement will switch to random walk as the combined results of run and tumble. This is thought to allow *E. coli* cells to sense and respond to surface topography. For instance, when the space between protruding features get smaller, the frequency of bacterial tumbling increases due to the drag force on the channel wall sensed by bacterial flagella during rotation [109]. When the width of channels further decreases to less than 1.3-times of the diameter of the cell body (~1.3 μm), the flagella-mediated motility of *E. coli* diminishes [101]. Although *E. coli* could still penetrate the channel by elongation and growth, it is extremely difficult for the cells to get into this narrow channel. Effects of confinement on motility were also observed for *Bacillus subtilis*, a peritrichously flagellated bacteria like *E. coli*. The movement pattern of *B. subtilis* varies when the width of the channel (or inter-pattern distance) decreases from 90 to 35 μm [102]. Specifically, the motility of *B. subtilis* transits from a "turbulent" state when the channel width is 90 μm to stable circulation when the channel width is approximately 70 μm. On surfaces with protrusive hemispheres, *P. aeruginosa* cells exhibit a preference in swimming along the top of hemispheres with 4 μm diameter but traveling in the grooves between bigger hemispheres (with a diameter of 8 μm) [103]. In a flow cell system, *E. coli* cells that are 1 μm away from microwells (10 μm in diameter, 5 μm in-depth, and 7 μm in spacing) exhibited faster movement than on a flat surface (with average velocities of 25.5 vs. 17.3 μm s^{-1}). In contrast, micropillars (5 μm diameter, 15 μm height, and 20 μm spacing) lowered cell motility compared to flat surfaces and those with microwells [59].

Besides flagella-mediated motility, the adhesion of flagellar filaments around surface topographies is also critical to bacteria-surface interaction. For example, the flagella of *P. aeruginosa* cells allow not only near-surface swimming but also surface-anchored spinning [110]. Adhesion of *P. aeruginosa* flagella to a solid surface is the first step of cell adhesion [111]. Subsequently, the mechanical signals sensed by the tethered flagella are thought to determine whether *P. aeruginosa* cells will proceed to the irreversible attachment. On gold surface modified with a grid of 550 nm width separated by 750 nm wide and 120 nm deep channels, the flagella of *P. fluorescens* prefer to align perpendicularly to the grid to reach the neighboring cells [104].

The important role that flagella play in surface attachment provides insights for the rational design of non-fouling topographies. When the flagella of *E. coli* attach on a flat surface, the cell body moves in a clockwise circle before settling [108]. However, this pattern of rotation is disrupted when *E. coli* flagella tethering to the side of 5 μm-tall line-shaped topographic features [63]. This causes the attached cells to align more perpendicularly to the orientation of the line pattern, presumably to reduce the stress on flagella [63]. Comparison with mutants revealed that the flagella and motility genes (*fli*C and *motB*) are involved in the preference of cell orientation on narrow line patterns [63]. Based on these findings, the authors proposed a set of criteria for the rational design of micron-scale antifouling topographies and achieved an 84% reduction of *E. coli* biofilm formation compared to the flat control [63].

In addition to the effects of topography on bacterial attachment, the field will benefit from additional mechanistic studies on how these interactions affect the physiology of bacterial cells. This is important for the rational design of antifouling materials. Moreover, the number and rotation of flagella vary among different bacterial species, and some bacteria do not have flagella, e.g. *S. aureus*. Thus, targeting flagella-driven motilities is likely to have limited efficacy for controlling certain species, and alternative designs may need to be tailored for specific applications with particular pathogens of concern. Besides flagella, other surface appendages such as pili can also facilitate bacterial adhesion to a surface [110,112,113]. However, their role in sensing surface topographies is largely unexplored, which deserves future study.

3.2. Nanoscale topographies have bactericidal effects by targeting bacterial membranes

Bacterial membranes play an important role in interaction with nanoscale topographies. Kelleher et al. [114] found that the nanostructures on the wings of three different Cicada species were all hydrophobic with low surface energy. A biophysical model revealed that the damage to the cell in contact is due to the stretch of cell membrane in the regions suspended between pillars [65]. A mechanical mechanism has been proposed that bacterial membranes can be ruptured by nanopillars like a "bed of nails" [20,41,53,70,115]. Some of the nanopillars require a shear force caused by the movement of cells to achieve killing [72]. Dickson et al. [41] reported that smaller and closely spaced pillars are more effective in bacterial killing. The effects were attributed to increase in stress with more contact with pillars. The optimal distance between pillars was proposed to be 130–380 nm. In comparison, Wu et al. [116] reported a different trend using Ormostamp surfaces. While the optimal inter-pillar distance is in the same range (170 nm), higher pillar density (130 nm inter-pillar distance) showed less bactericidal effects. Also, the Ormostamp surfaces with ~40 pillars/μm^2 exhibited higher bactericidal effects killing almost all the attached Gram-positive *S. aureus* cells. A biophysical model [116] showed that, while high pillar density increases stretching points, the short distance between pillars reduces the contact between the bacterial membrane and vertical pillar walls and thus the shear force. According to this model, the pillar arrays with inhomogeneous height can increase the stretch of bacterial membranes. Such effects have also been observed for surfaces with nanocones [77]. The difference in reported results might be due to the substrate materials. The chemical property of the surface material can affect the interaction with bacterial membrane and consequently the contact between pillar walls. Additional factors to consider include the mechanical properties of different bacterial membranes, other shear forces generated by flow or cell motility, and movement of the substrate. Such effects have not been well explored and should be a topic for future studies.

Concurrent with the bactericidal effects, nanotopographies have been shown to affect bacterial physiology and morphology. For example, single-walled nanotubes (SWNTs) are effective in killing *E. coli* and found to induce the expression of stress-related genes encoding σ^S (general stress response factor) and σ^E (heat shock response factor) [79]. On modified PMMA films with nanopillars, attached *E. coli* cells appear to be longer and flatter than those on flat surfaces. The elongation (filamentous growth) is thought to indicate the stress of these cells [117–120].

3.3. Topography-induced changes in surface wettability affect bacterial attachment

Modification of surface topography can alter the wettability of a surface [121–123], which has significant effects on bacterial adhesion. By creating topographic features, it is possible to trap air bubbles and render the surface hydrophobic and antifouling [59], because it can repel liquid droplets along with bacteria. However, because the contact angle is measured based on the liquid droplet with an interface with air, superhydrophobic surfaces may not be effective in fouling control when fully submerged in a liquid [11], especially when the scale of the topographic features is comparable to the size of bacterial cells.

Friedlander et al. [90] reported that poly(dimethyl siloxane) (PDMS) surfaces patterned with hexagonal features (with 2.7 μm height, 3 μm diameter, and 440 nm spacing) can delay the wetting of the surface in M63+ medium by approximately 4 h (Fig. 3b). This is because the topographic features trap air pockets in the Cassie-Baxter wetting state. However, *E. coli* can make initial attachment by inserting flagella into the grooves between the hexagonal features. This facilitates the transition from Cassie-Baxter to Wenzel wetting state and changes the wettability of the surface, promoting biofilm formation [90] (Fig. 3).

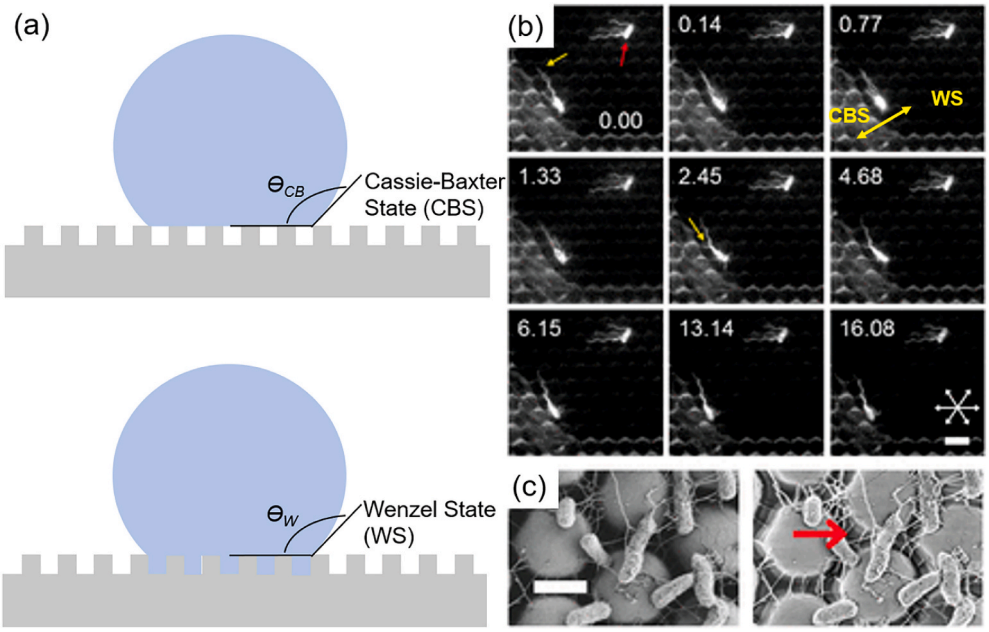


Fig. 3. Topography-induced changes in surface wettability affect bacterial attachment. (a) Effects of surface topographies on surface wettability. (b) Surface wettability changed when the PDMS surfaces were submerged into the M63+ with fluorescently labeled *E. coli* cells. (c) *E. coli* flagella can reach into the grooves (extra area provided by hexagon-shaped protruding features) to facilitate bacterial adhesion [90]. Microscopic images are reproduced with permission from Ref. [90].

3.4. Models need to incorporate the effects of topographic features

Future development of antifouling surfaces will benefit from models that can quantitatively simulate bacteria-material interactions and the associated biofilm formation. A number of models can describe the interaction between bacterial cells and a flat surface, but few models include the topographic features of the surface. Classic DLVO (Derjaguin-Landau-Verwey-Overbeek) theory describes the force between a bacterial cell and the surface based on Lifshitz-van der Waals attractive forces (dominant in the vicinity of the surface) and electrostatic interactions (dominant away from the surface) [124]. van Oss modified the DLVO theory as extended DLVO theory (XDLVO) to also consider short-range interactions including hydrogen bonding and ion pair formation [125]. These theories help understand and predict bacterial adhesion but assume flat surfaces. The surface element integration (SEI) technique and Derjaguin's integration were developed later to describe the interaction between particles and substratum with topographic features [115,126,127].

Schumacher et al. [128] defined engineered roughness index (ERI) as a term to predict colonization of a surface with topographic features. ERI is calculated as ERI = $(r \times df)/f_D$, where r is Wenzel's roughness factor (actual surface area/projected planar surface area); f_D is a fraction of recessed surface area/projected planar surface, also related to the Cassie-Baxter relationship for wetting); df is the degree of freedom of movement (1 for line patterns and 2 for interacting grids). The ERI value was found to correlate inversely with the settlement of microorganisms. Intrinsically, the definition of ERI is based on the overall protrusive and recessive areas, which does not capture the specific topographic features especially for surfaces with inhomogeneous distribution/dimension of topographic features. This presents a limitation in predicting fouling behavior [18,62]. To account for the deformation of topographic features and mechanical properties of the substrate materials, a "nano force gradient" was defined. The force required to cause a 10% lateral deflection of topographic features during the settling of microbes is estimated as $F = 3EIy/L^3$ (Fig. 4). In this equation, E is the modulus of elasticity; L is the height of features; I is a rectangular moment of area; y is the end deflection distance. The study showed that the nano force gradient is inversely correlated with attachment and some modifications have been made to improve this model [129]. In summary, existing theories help predict microbial adhesion, but these models do not include biological factors such as bacterial cell morphology, surface appendages, and motility that are important to colonization.

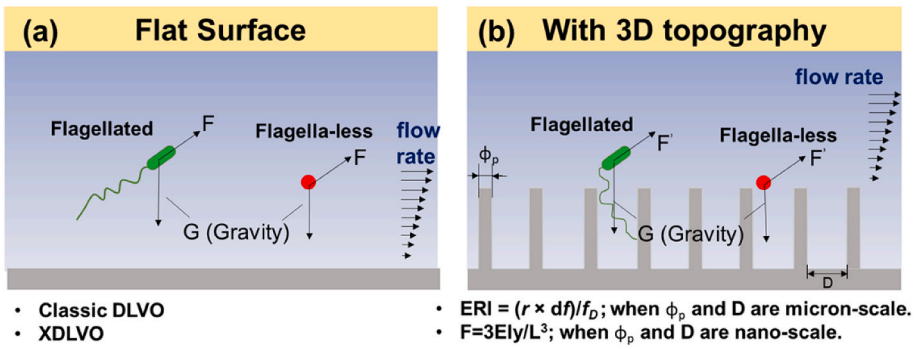


Fig. 4. Models to predict bacterial adhesion on surfaces with or without 3D topography. (a) For bacterial cells approaching a flat surface, thermodynamic models such as the classic and van Oss modified the DLVO theory have been used to quantitatively simulate bacteria-material interactions [124,125]. In this figure, F is the total force from the flow, Lifshitz-van der Waals attractive forces, propulsive forces (for flagellated cells), etc. (b) When the surface is modified with topographic features, engineered roughness index (ERI) and the model of "nano force gradient" have been developed to predict bacterial response to surfaces modified with micron-scale or nano-scale features, respectively [128,130]. F′ represents the combined force of repellent and attractive forces generated by the surface topography.

3.5. Dynamic topographies can remove established biofilms

To ensure the safety of medical devices, it is important to obtain long-term biofilm control because devices like urinary catheters are constantly challenged by microbial pathogens, and some catheters need to stay for weeks if the patients have conditions that do not allow frequent changes. Even for implanted medical devices, the infection can occur long after the implantation (e.g. 3–24 months) [131]. An important consideration, and potential drawback to static topographic features, is that effective biofilm control depends on the direct interaction between bacteria and the surface. Although static topographies with specific micron or nano-scale features may initially prevent bacterial adhesion and biofilm formation, cells that manage to attach tend to multiply and overcome these features over time. For surfaces that have bactericidal effects, it is also possible that dead cells may protect other cells that attach to them rather than the original topographic features.

When live cells manage to attach, static topographies do not move and thus cannot respond. Multiple studies have shown that bacteria can attach to surfaces by overcoming unfavorable topographies [45,63,88,90,104]. Thus, it will be difficult to achieve long-term fouling control based on static topographies alone. However, these designs can be leveraged along with other strategies, e.g., dynamic systems or drug-eluting materials, to obtain long-lasting effects.

One strategy to address the limitation of static topographies and remove established biofilms is to create dynamic topographies. Epstein et al. [132] developed a synthetic platform that can create up to 2 μm dynamic wrinkles of PDMS through uniaxial mechanical strain and demonstrated up to 80% removal of 24 h *P. aeruginosa* biofilms. Shivapooja et al. produced active topography by applying pneumatic actuation [133] or electrical voltage [134] to the surfaces and obtained more than 90% removal of *E. coli* biofilms and 80% removal of *Cobetia marina* biofilms. Gu et al. [51] recently engineered a dynamic substrate using *tert*-butylacrylate-based shape memory polymer with microscale hexagonal topography. The patterns alone reduced 48 h biofilm formation by ~50%. By triggering on-demand shape recovery with mild heating (to 40 °C), dynamic changes in patterned surface topography led to effective removal of established biofilms of *P. aeruginosa*, *E. coli*, and *S. aureus* (up to 3 logs). The cells became more susceptible to antibiotics after detachment [135]. Levering et al. [136] reported a different design of on-demand fouling-release urinary catheter, which can detach mature *P. mirabilis* biofilm by up to 90% through hydraulic and pneumatic actuation. The dynamic systems based on pneumatic actuation and shape recovery may have applications in fluid handling devices, especially the complications associated with urinary catheters where clogging by biofilms is a major issue. Besides biofilm removal, movement of the substrate has been shown to enhance the effects of static bactericidal topographies. For example, the bactericidal effects of Titania (TiO_2) nanowire arrays were found to be stronger on upright surfaces with shaking compared to static cultures [84]. Similarly, on surfaces with nanofeatures, bacterial motility may contribute to the killing effects. Nano-topography exhibited cell piercing activities regardless of the motility of cells but was more effective when the mechanical motion was part of the interaction between the device and microbes [84].

3.6. Programmable and stimuli-responsive strategies have the potential for long-term biofilm control

In addition to high-level tolerance to antimicrobials and host immune factors, biofilm-associated infections also present a great challenge to diagnosis due to the lack of biofilm-specific markers (see Ref. [137] for a recent review). The vast majority of antifouling surfaces designed to date are “idle” and lack the capability to respond to microbial adhesion and biofilm formation. Recently, Gu et al. [37] engineered magnetically driven active topographies for long-term biofilm control (Fig. 5). By creating micron-sized pillars with super-paramagnetic nanoparticles loaded in the pillar tips, the surfaces

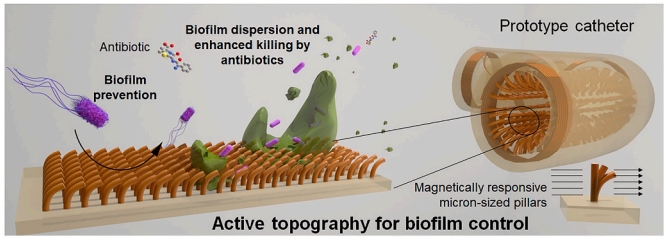


Fig. 5. Active topography for long-term biofilm control. Antifouling activities were obtained by the programmable beating of micron-sized pillars driven by a tunable magnetic field [37]. The image was created for this review article.

can both repel bacteria from attaching and remove established biofilms by tuning the beating frequency and bending angle (thus beating force) of the pillars. A prototype catheter was engineered based on this design, which remained clean for more than 30 days with the flow of artificial urine medium and the continuous challenge of uropathogenic *E. coli* (UPEC), while the flat and static controls were blocked by UPEC biofilms within 5 and 3 days, respectively. The magnetic field is generated by the coil embedded in the catheter wall, thus the modification does not change the profile of the device. This technology may potentially improve urinary catheters and other liquid handling devices. Additionally, Leulmi Pichot et al. [138] reported 70% reduction of *E. coli* biofilm formation using magnetic cantilevers grafted on a substrate, actuated by a stirrer and magnets. The design of smart medical devices also needs the capability to detect biofilm formation *in situ*. One possibility is to integrate impedimetric sensors into medical devices. Huiszoon et al. [139] engineered a microfluidic chip with an electrode/probe. This device combines real-time monitoring and a threshold activated bacterial killing by generating an electric field. The group applied this technology to a urinary catheter with wireless monitoring. This is an exciting field that deserves further study and development. Integration of wireless control technology [140] and machine learning may ultimately bring smart and safe medical devices that can self-detect infection and activate biofilm control in response.

4. What do preclinical studies of topographic surfaces on implants tell us?

Preclinical studies of topographic surface modifications of biomedical device materials can be organized based on their locations of use, such as breast implants, bone implants, catheters, and oral implants. These studies focused specifically on the testing application of the topography to real-world medical devices, often using more realistic real-world *in vitro* conditions or *in vivo* testing to evaluate effectiveness. It is important to understand how the performance obtained under these conditions may hint potential weaknesses for a specific topographic strategy.

4.1. Some tissue-integrative topography may present an increased potential for biofilms

Textured breast implants, with recessive topographies that have depths around tens to hundreds of microns, were first introduced due to the high capsular contracture incidence rate with severe fibrosis on smooth breast implants [141,142]. For textured breast implant devices, topographic features can be fabricated by three different methods: salt-loss, imprinted, and foam. These methods, which are ideal for the mass production of textured implants, produce non-uniform features. Although textured breast implants can reduce the incidence of capsular contracture, more concerns have been raised recently due to the correlation between textured implants and anaplastic large cell lymphoma (ALCL). Jones et al. [143] conducted *in vitro* tests using 11 commercial textured breast implants and stated that up to two orders of magnitude

more cells of *S. epidermidis*, *S. aureus*, *P. aeruginosa*, and *Ralstonia pickettii*, attached on textured implants in 24 h than smooth implants due to the increase in the surface area. However, it is not yet known if this increase translates into clinically significant differences. More studies on materials-cell interaction are needed to reveal what features present hot spots for bacterial colonization and how this contributes to ALCL.

4.2. Rationally designed topography can reduce bacterial attachment more than random surface roughening

Surface roughening by etching or salt-out is easy to scale up, but these processes do not provide well-defined surface topographies. In a previous study to create nanostructures on catheter surfaces with plasma treatment, the plasma-treated catheters were found to have more *S. aureus* attachment than control catheters due to the increase in contact area [144]. Tebbs et al. [145] also reported that catheters with smoother surfaces had less *S. epidermidis* attachment (5.5-fold) than those with irregular surfaces. As shown in fundamental studies discussed earlier in this review, bacteria switch between motility and sessility through interaction with the surface. It is possible that random topographic features contain "hot spots" for bacterial attachment, which facilitates further colonization and biofilm formation even over unfavorable topographies. Compared to general roughening, surface modifications with well-defined topographic features have been shown to have strong antifouling activities [37,40,41]. Further testing of these features *in vivo* is needed to guide the design of safer medical devices. It is also important to develop advanced processes to apply such well-defined topographies in large scale manufacturing, especially metallic medical devices with complex structures.

Different materials for dental implants have also been studied [146–154] such as Ti and Zirconia. In general, dental implants can be roughened by acid-etching, machining, grit-blasting, and by using laser-modified methods (see Refs. [154–156] for recent reviews). Similar to the discussion above, these methods only control the overall roughness and do not create specific (uniform) surface topographies, and thus is not a major part of the present review. Future work is needed to identify the types of topographies that are effective in reducing the colonization of dental implants. Unlike orthopedic implants, dental materials can be physically cleaned frequently and are more exposed to fluidic flow. This is helpful for the strategies based on static topographies because the small number of attached cells can be removed before developing more established biofilms.

5. What are the unique biocompatibility considerations for topographic surfaces?

Surface topography along with hydrophobicity/wettability and surface free charges may affect the interactions of proteins with the surface, which is critical for the binding of host cells through integrins and further biological responses [157]. Subsequently, aggregation of macrophages and foreign-body giant cells results in recruiting fibroblasts and the formation of fibrous capsules around the implant. This process is known as a foreign-body reaction and has an impact on the biocompatibility of the implant [158]. Thus, the design of antifouling topographies should also consider the effects on host cells.

5.1. Surface topography affects the orientation of the cytoskeleton and cellular functions

Surface texturing and topographic features such as ridges, grooves, curvatures, pits, and pillars identified as biologically relevant structures may significantly affect the adsorption of proteins on the surface of

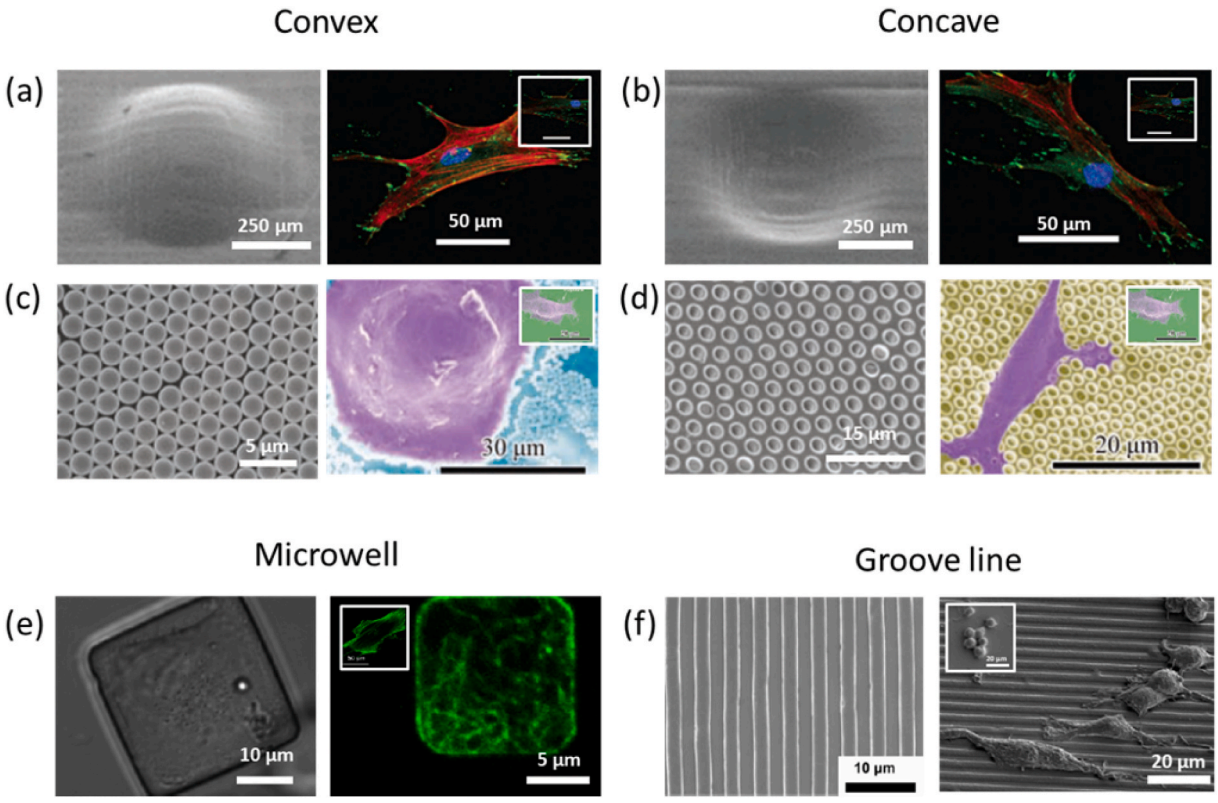


Fig. 6. Effects of surface topography on mammalian cell morphology. Figures show the scanning electron microscopy (SEM) images and immunofluorescent images of cells on different topographic features. Inserted small images show the cells on flat control surfaces. (a&b) hMSCs (vinculin: green; F-actin: red; nuclei: blue). (c&d) HeLa cells (cells: purple; periodic colloidal crystal array (PCCA): blue; honeycomb array membrane (HCM): yellow). (e) Fibroblast cells (nuclei: blue; actin filament: green). (f) Macrophages. Scale bars are as indicated. Image reproduced with permission from Refs. [160–163]. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

biomaterials. The design of these features in terms of size, shape, curvature, spacing, and nano-topography can also impact the cell-surface interactions by manipulation of the cytoskeleton resembling the *in vivo* environment, as shown in Fig. 6 [159–163]. According to the "contact guidance" concept developed by Weiss et al. [164], cells explore the surrounding environment by extending their filopodia in order to align themselves with the topographic features. In this phenomenon, the actin filaments spread out in 2D on flat surfaces, while textured surfaces provide a 3D landscape for cells which is more biologically relevant.

For example, Wang et al. [165] demonstrated that the integration of micro features onto polymethyl methacrylate (PMMA) with chemical treatment significantly increased fibroblast proliferation/attachment and may modulate the growth of mammalian cells. In another study, fibroblasts cultured on smooth silicon exhibited higher proliferation compared to micro-grooved silicon [166]. Recessive micron-scale topography (3–5 μm hexagon/square side) was found to reduce fibroblast adhesion and interfere with the activation of macrophages [167]. It was found that the proliferation rate of fibroblasts is independent of groove size, and ridge width can influence the cell alignment [168]. With an increase in groove width, cell orientation becomes more random. However, as far as cells are larger than the width of the grooves they are capable of spanning several groove/ridge boundaries and orient themselves with the direction of the grooves [169]. For pits wider than 25 μm, cells tend to migrate and spread out to fit inside the pits. With nano-pits cells may show more motility with a higher amount of filopodia, which can be due to the higher adsorption of proteins in nano-pits [170]. Tissue response to surface topography also involves changes in gene expression related to cell signaling, translation, and extracellular matrix formation [171].

Several studies reported the effects of nanotopographies on cell adhesion and cell differentiation [172,173]. Generally, downregulation of genes that encode for extracellular matrix (ECM) proteins, chemokines, transcription factors, integrin, and growth factor signaling was observed on anti-fouling pit/pillar surfaces [174]. For other types of topographical features such as curvatures, the sharpness of edges, and the degree of curvatures may affect the protein adsorption and focal adhesion of cells. For example, an increase in protein adsorption was observed after increasing the curvature of spheres (15–165 nm). On these types of features cells were found to extend around the curved geometry by distorting their cytoskeleton [175].

5.2. Can tissue integrating topography be tuned to resist bacterial attachment?

For many long-term implants, it is important to identify surface topographies that promote tissue growth and integration while repelling microbes. A number of studies reported different effects of nanostructures on bacteria and mammalian cells and the possibility to selectively kill bacteria than mammalian cells [54,73,84,176–178]. For example, poly (ethylene glycol) hydrogel patch with an appropriate pore size (~2–5 μm) promote tissue-cell interactions but with the inhibition of bacterial adhesion [44]. For titanium materials which can be used for orthopedic implants, the anodized Ti nanotubes (80 nm pore size) [179] and nanodiamond (120 nm) coated 3D printed Ti surfaces [177] are able to promote human cell adhesion while inhibiting bacterial colonization. Hydrothermally treated Ti nanowire was investigated *in vitro* using *E. coli*, *S. aureus*, and *in vivo* using rabbits. Kapat et al. [180] reported up to 93.3% reduction of *E. coli* and 85.6% reduction of *S. aureus in vitro* and no infections were observed *in vivo* for 12 weeks, consistent with the killing effect of modified Ti surfaces *in vitro* reported by Tsimbouri et al. [181]. One study on nanostructured Si_3N_4 implants for bone devices reported up to a 4.4-fold reduction of cell adhesion compared to smooth control *in vitro* and enhanced bacterial killing by macrophages and osseointegration *in vivo* [182]. On the other hand, a couple of studies indicate the cytotoxicity and potential DNA damage and chromosomal aberrations induced by TiO_2 nanotubes [183]. Park et al. [184] reported that cell adhesion and proliferation were significantly impaired on TiO_2 nanotubes with diameters larger than 50 nm which resulted in cell death. Also, no difference was found between micro-structured locking compression plates (LCPs) and electropolished LCPs in both *in vitro* tests and *in vivo* tests using rabbit humerus [185].

On some topographic surfaces, proteins may fill valleys between protrusions and reduce the roughness, which has been reported to increase the adhesion of cells in comparison to smooth surfaces [186,187]. However, the random arrangement of cells on rough surfaces results in the randomly oriented collagen fibers and a decrease in fibroblast growth [188]. Moderately rough surfaces (S_a > 1–2 μm), and hydroxyapatite coating was reported to establish stronger osteointegration and less fibrous capsule formation on orthopedic devices [189]. Lan et al. [190] investigated the biocompatibility of $ScCO_2$-treated TiO_2 nanotubes and reported higher biocompatibility for the 15 nm-diameter nanotubes than the as-grown sample. Similarly, TiO_2 nanotubes with micro-nano composite porous structures exhibited a rougher surface and enhanced biocompatibility and osteogenic activity in comparison with the highly ordered layer [191]. Structures with nanopore diameters of 80–120 nm also have good osteogenic activity [59].

Despite the aforementioned reports, topographies that are effective against bacterial colonization but favor tissue integration are not well developed. The studies in this field have been largely guided by the principle of "race for surface", which indicates that a surface covered by host cells will essentially be protected from bacterial colonization [192]. A previous study by Mezey et al. [193] also showed that mesenchymal stem cells can have intrinsic antimicrobial properties. Based on these principles, surfaces that favor mammalian cell adhesion are desired. Co-culture systems that simulate such competition [194] can help understand what designs are better to protect the host. Meanwhile, it is well recognized now that bacteria can cause infections even long after implantation. Long-term *in-vivo* studies are needed to understand how bacteria, host cells, and the implanted biomaterial interact both at the time of initial contact and in late-term infection.

5.3. Unique mechanical forces and particulates should be given adequate consideration

Most biocompatibility investigations of novel medical-relevant surface topographies reported in the literature focus only on the cytocompatibility of cells on the biomaterial surface. However, according to ISO 10993-1: Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process the biocompatibility endpoints required for medical devices should be evaluated based on their nature of body contact and contact duration. For particular medical products, different biological endpoints may require evaluation including, Cytotoxicity (per ISO 10993-5), Sensitization (per ISO 10993-10), Irritation or intracutaneous reactivity (per ISO 10993-10); Acute systemic toxicity (per ISO 10993-11); Material-mediated pyrogenicity (per ISO 10993-11), Subacute/Subchronic Toxicity (per ISO 10993-11), Genotoxicity (per ISO 10993-5), Implantation (per ISO 10993-6); Hemocompatibility (per ISO 10993-4), Chronic toxicity (per ISO 10993-11), Carcinogenicity (per ISO 10993-5), and Reproductive/Developmental Toxicity (per ISO 10993-3) [195].

It is also important to consider if a topographic surface introduces new risks [33]. In particular, these may include increased mechanical forces on surrounding tissue or the formation of new particulates during use. This risk may be a result of not only static interactions but also more dynamic forces that are encountered when the body is in motion. To a large degree, this will depend on the anatomy and physiology where the implant will be used. Some adverse events associated with biomedical devices such as metal-on-metal orthopedics have been due to a failure to adequately consider the impact of these dynamic interactions on novel materials. Future studies are needed to investigate if and how implants with modified surface topography affect the release of ions and particles and the impacts on the host. The field also needs more *in vitro* and *in vivo*

models for such studies.

6. How can laboratory testing better predict the real-world performance of topographic surfaces?

There is a significant gap between *in vitro* testing performance and *in vivo* outcomes which makes it challenging to accurately identify and prioritize topographic strategies for further development. Unfortunately, testing at present is limited by the absence of reference topographic surfaces with clinically validated effectiveness data, which could be used to benchmark against. Even if such controls existed, they would also need to overcome the challenge of heterogeneity in medical device applications due to different anatomy/physiology depending on where/how the device is used. At present, there is no simple "one size fits all" approach for *in vitro* testing that has been recognized to provide a clear answer as to how a novel topography might help prevent biofilm-associated infections. There are a number of parameters that may have an impact on the ability to predict real-world performance (Fig. 7) [196–211].

6.1. Consider the effects of topography on protein absorption and wettability

In the *in vivo* environment, the adsorption and activity of host proteins significantly affect bacterial attachment and biocompatibility of materials. Thus, pre-conditioning surfaces with real-world soil are often used in biofilm testing. Singh et al. [202,212] demonstrated that adhesion of *E. coli* and *S. aureus* decreases (by 50% and 66%, respectively) as the surface roughness increases above 20 nm due to the increase in adsorption of Bovine Serum Albumin (BSA), which compromises the effect of nanofeatures. Consistently, nanoporous alumina-multiwalled carbon nanotubes (NAMC) have lower BSA adsorption than the flat alumina and thus reduced biofilms of *E. coli* and *S. aureus* [213]. On another hand, surface curvature associated with topographic features may increase the contact area and alter the secondary structure of adsorbed protein molecules unpredictably [214–217]. For example, albumin, but not fibrinogen, is less ordered on surfaces with high curvature [175]. These changes may affect bacterial attachment and the physiology of attached cells or may lead to other deleterious effects on device function.

The quality, type, and conformation of absorbed proteins are all important to bacterial attachment. Some specific proteins such as collagen [218] and fibronectin [219,220] play a more dominant role in bacterial attachment than other factors due to the high binding affinity with adhesins that certain pathogens produce. Thus, it is also important

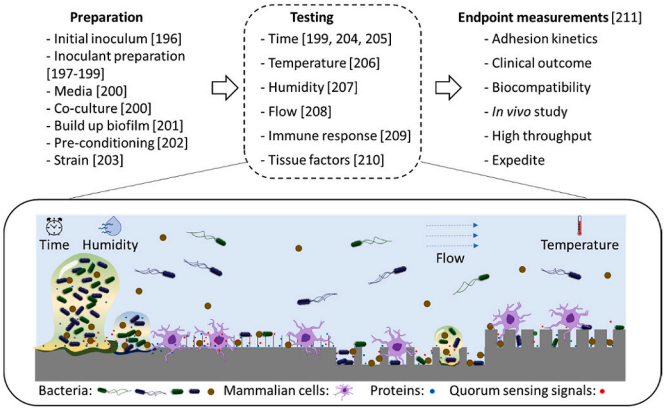


Fig. 7. Schematic of parameters and endpoints that can have a significant effect on preclinical testing of medical device surface topography. The figure shows *in vivo* factors associated with implantable medical devices that should be considered in the tests of novel surface topographic features.

to consider how manufacturing and sterilization processes may impact the chemical and mechanical properties of a topographic material. In some cases, it is possible that changes brought about by these processes may affect protein adsorption or wettability.

6.2. Consider the effects of the organism, inoculum type, and duration of testing

Most *in vitro* studies are conducted with standard lab strains that are known to make good biofilms. However, great biofilm-producing strains are not always the most pathogenic *in vivo* [221–223]. Many infections also involve multiple species [224,225]. For example, the microbiome found on breast implants is diverse and even depends on the geographic location [226,227], and the microbiome of dental implants plays a critical role in success or failure [228]. From prior *in vitro* tests on implants with multiple species, dynamic and spatial variations in bacterial populations have been observed on dental implants in addition to the positive correlation between biomass and surface roughness [229–232]. Further research with co-culture systems is needed to determine where a single organism can be used and where it is necessary to incorporate polymicrobial testing.

The type of inoculum used for biofilm testing can also result in significantly different outcomes. A common practice is to break up any clusters of cells using sonication before inoculation, to achieve more reproducible and uniform biofilm formation on surfaces. While this may be valuable for reproducibility and ease of interpretation, it may also remove a real-world aspect of contamination by clusters of cells. Melaugh et al. [197–199] studied how inoculation with pre-formed biofilm chunks may result in significantly different antimicrobial performance. These aggregates of bacteria may also be more resistant to nanoscale bactericidal surface topography.

The selection of inoculum size has roots in the field of sterility where a high-level disinfectant or preservative requires a sufficiently large bioburden challenge and log reduction to ensure that it will be effective even in the worst-case scenario. Most biofilm testing in the literature also uses a large inoculum (10^6–10^8 CFU). But for passive microscale topographic surfaces that prevent biofilm but do not kill bacteria, the use of a large starting inoculum makes it difficult to assess *in vivo* performance. As few as 100 bacteria can cause an infection when there is an implanted biomaterial [233]. Since most basic science studies of bacterial interactions with topography claim a 90% reduction or less, *in vivo* and clinical research is needed to characterize the bioburden in real-world applications.

Another important parameter to consider is the duration of the biofilm test. Many *in vitro* tests are only run for a few hours or overnight, yet for many infections such as those associated with orthopedic devices [205], there is no cut-off point between an early, intermediate, or late infection. It is not clear if an antimicrobial effect sustained for a few hours or even a few days *in vitro* can achieve a significant reduction in the infection rate. Contamination may come from the patient's skin, where it is already in a biofilm matrix [199,204], The topographic materials may be bio-fouled as part of the host response or overgrown by rapidly multiplying bacteria. Longer-term test formats are needed to assess if topographic surfaces can achieve the anticipated reduction in biofilm.

6.3. It is important to incorporate tissue-based models

During surgical insertion of a device, commensal bacteria or biofilm from epithelial tissue may be introduced into the surgical site, potentially leading to infection [234]. The presence of a foreign material appears to increase the risk of adjacent tissue colonization by microbes. Surgical sites may be compromised by inflammation and wound response, and provide an environment rich in blood and other nutrients. Bacteria can colonize necrotic tissues around a device until they achieve a sufficient bioburden to overcome surface topography strategies. The

presence of a tissue environment is known to influence biofilm formation [235] and contains tissue factors that promote colonization [236]. Therefore, testing the performance of topographic features in contact with the tissue environment is an important consideration.

In recent years, a number of biofilm models have emerged that combine tissue with biomaterials to more realistically simulate the *in vivo* environments [208,237–240]. This work shows significant differences in the performance of antimicrobial biomaterials between a coupon or flow-cell based test methods and tissue-based test methods. In particular, drug-eluting materials can protect tissues surrounding a device for longer than non-eluting materials. Thus, active topographic strategies coupled with drug release may better protect tissue in the surgical site and more effectively prevent infection. Tissue models can include *ex vivo* tissue such as porcine skin, "live" human skin obtained during clinical procedures and used immediately with a compatible physiologic medium, as well as live tissue constructs or microphysiological systems. Tissue models are more complex than abiotic testing, but the tradeoff of enhanced realism is often worth the additional cost in time and expense, especially given steep increases in cost and ethical considerations for stepping up to an animal study. Each type of tissue approach has specific advantages or disadvantages. The use of *ex vivo* tissue is the simplest approach but has a limited life depending on decontamination during preparation [210]. Live tissue models can provide longer testing times but may lack certain structural or biological factors found in real tissue such as commensal strains, antimicrobial peptides, and EPS-degrading enzymes [241]. The use of tissue-based models will reveal potential differences in the performance of passive and active topographic strategies and guide the development of topographic approaches that have greater real-world efficacy.

6.4. Use appropriate endpoints for detecting adhesion and biofilm on implants with topographic features

Many biofilm standards are designed to grow reproducible thick, uniform lawns, but do not have specified endpoints and associated detection methods to be used. These biofilms appear to differ from those observed on explanted devices and tissue samples from *in vivo* studies. To understand what types of early-stage interactions take place and the roles of surface topographies, it may also be helpful to study early-stage adhesion rates and microbial response to specific topographic features, especially under the conditions that mimic *in vivo* environments. Measurement of adhesion kinetics (a plot of the number of cells adhered to a surface vs. time) has not been correlated with clinical outcomes but is highly sensitive to material differences. Early-stage adhesion may also correlate with the number of cells found after a few hours of overnight biofilm growth [242]. Since clinical explants appear to have much smaller numbers of cells than one would find in most *in vitro* biofilm testing, there is a need to understand what aspects of bacterial attachment, such as attachment strength, niche areas in the material, biocompatibility, etc. are related to successful survival and infection *in vivo*. These endpoints could potentially provide a better estimation of clinical performance for topographic materials.

Numerous methods have been used in the literature to quantify various properties of biofilms [211,243], the scope of which is beyond this review. While the gold standard for quantification is colony counting, it is important to consider potential errors caused by viable but non-culturable cells (VBNC) [244]. Some common alternative methodologies employed include microscopy or spectroscopy in combination with stains, antibodies, or bacteria that are engineered to produce fluorescent or luminescent signals. SEM provides high-resolution images, but this method is destructive as the samples need to be dehydrated. Microscopy can image larger areas than SEM but is still subject to a number of related challenges. Autofluorescence from different materials must be addressed in order to successfully quantify bacterial load. The curvature of surfaces can make it difficult or even impossible to obtain quantitative images. For complex medical devices, there may be surfaces that can't be reached without destructive techniques and significant effort in sample preparation, which may be suitable for extractionless approaches to biofilm detection [245]. For *in vivo* studies, *in vivo* imaging system (IVIS) type time-lapse luminescence measurements can provide valuable information on pathogenesis mechanisms with relatively small numbers of animals [246]. Bacterial viability determined by GFP fluorescence, luminescence, or live/dead staining may not always be reliable and should be confirmed by plating and culturing. A recent review of biofilm detection can be found at [137].

As a higher throughput alternative to microscopy for studying topographic medical surfaces, spectroscopic measurements of samples in microplates are especially useful for sample coupons or clear, three-dimensional materials such as hydrogels where the entire volume of a sample can be interrogated, and the results integrated into a single measurement. It can be used for studying adhesion on surfaces at various time points [247–249]. Sample coupons in these models can also be removed and scraped for plating and culturing to verify results obtained spectroscopically. The use of microplate readers allows for a range of spectroscopic interrogation [250] combined with various intracellular markers or biofilm stains, antibodies, lectins, etc. This includes native ultraviolet (UV) fluorescence [251], quantitative luminescence, fluorescence resonance energy transfer (FRET) [252], two-photon [253], and time-gated and time-resolved modalities such as fluorescence lifetime imaging (FLIM) [254]. The high throughput and reproducibility obtained with microplate-based biofilm studies can help expedite early-stage research, followed by more complex mechanistic studies using confocal microscopy.

7. Concluding remarks and future perspectives

The rational design of topographic materials for medical devices has the potential to help reduce bacterial attachment, prevent biofilm formation, and kill bacterial pathogens. While initial developments in this field were inspired by anti-fouling surfaces in nature, innovative new strategies have adapted these concepts for the specific requirements of use in humans. Most studies to date focused on short-term biofilm prevention. Further research is needed to obtain long-term biofilm control especially the strategies against established biofilms. Three promising areas of investigation at present include dynamic/active materials that can remove established biofilms, programmable/stimuli responsive topography that reduces the potential for toxicity, and dual-function topography that promotes tissue integration while reducing bacterial attachment. While there have been many empirical studies of topographic libraries, our knowledge to predict how bacteria interact with topographic materials is rather limited. To achieve rational design, it is important to understand the interplay between the implant, microbes, and host cells. Closing this knowledge gap is important for developing rational design principles.

Moreover, our understanding of topographic material performance is based almost exclusively on *in vitro* testing and needs to be put in perspective to real-world performance in human use. Our analysis of preclinical test methods shows that a major contributor to this lack of understanding is the gap between current *in vitro* methods and what is known about the *in vivo* environment and pathogenesis. The use of a more realistic preclinical test will help prioritize rational designs with the greatest potential to improve the safety and efficacy of medical devices. There is also a need for additional study of the unique biocompatibility considerations facing topographic surfaces, among which dynamic mechanical forces and particulates stand out as particular concerns.

Gains in the translational science of topographic surfaces will also translate into community-wide standard methods that can be used to reduce the risk of product development, accelerate the product pipeline, and ensure a clear regulatory pathway. With further development, antifouling topographies may provide promising solutions for engineering smart and safe medical devices, which are essential in an era of

rapidly increasing antibiotic resistance.

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The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services. The findings and conclusions in this paper have not been formally disseminated by the US Food and Drug Administration and should not be construed to represent any agency determination or policy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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