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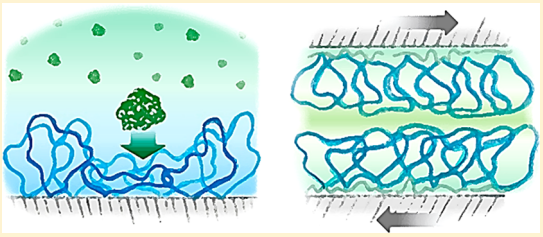
Bioinert and Lubricious Surfaces by Macromolecular Design

Wenqing Yan,[†] Shivaprakash N. Ramakrishna,[†] Matteo Romio,[†,‡] and Edmondo M. Benetti*[,†,‡]

[†]Polymer Surfaces Group, Laboratory for Surface Science and Technology, Department of Materials, Swiss Federal Institute of Technology (ETH Zürich), Vladimir-Prelog-Weg 1-5/10, CH-8093 Zurich, Switzerland

[‡]Biointerfaces, Swiss Federal Laboratories for Materials Science and Technology (Empa), Lerchenfeldstrasse 5, CH-9014 St. Gallen, Switzerland

ABSTRACT: The modification of a variety of biomaterials and medical devices often encompasses the generation of biopassive and lubricious layers on their exposed surfaces. This is valid when the synthetic supports are required to integrate within physiological media without altering their interfacial composition and when the minimization of shear stress prevents or reduces damage to the surrounding environment. In many of these cases, hydrophilic polymer brushes assembled from surface-interacting polymer adsorbates or directly grown by surface-initiated polymerizations (SIP) are chosen. Although growing efforts by polymer chemists have been focusing on varying the composition of polymer brushes in order to attain increasingly bioinert and lubricious surfaces, the precise modulation of polymer architecture has simultaneously enabled us to substantially broaden the tuning potential for the above-mentioned properties. This feature article concentrates on reviewing this latter strategy, comparatively analyzing how polymer brush parameters such as molecular weight and grafting density, the application of block copolymers, the introduction of branching and cross-links, or the variation of polymer topology beyond the simple, linear chains determine highly technologically relevant properties, such as biopassivity and lubrication.



INTRODUCTION

The design of biomaterials, medical devices, and sensors often encompasses surface functionalization strategies aiming to impart to them well-defined interfacial physicochemical properties. These determine the way the functionalized materials interact with their application medium and, in most of the formulations, largely influence their performance.

The assembly of functional polymers yielding "polymer brush" layers[1] or, alternatively, the growth of polymer brushes from premodified supports through surface-initiated polymerization (SIP)[2,3] methods has emerged as among the most versatile and efficient strategies for generating surfaces with tunable properties.

During the past decade, we have dedicated intense effort to establishing robust fabrication protocols to generate polymer brushes with precise architecture and well-defined composition, especially concentrating on the influence of these two parameters on the biopassive and tribological properties of the obtained coatings.

The combination of high resistance toward nonspecific protein adsorption and lubrication is often highly required on the exposed surface of biomaterials. On one hand, hampering the formation of a protein layer would prevent microbial contamination or an adverse immune response toward a synthetic construct when this is applied within physiological environments.[4−7] On the other hand, the presence of a lubricious coating would increase the comfort and prevent wounding when a modified device is placed in contact with tissues, such as in the case of contact lenses or catheters.[8−10]

A large number of hydrophilic polymers forming dense brush assemblies on surfaces can meet these needs because of the interplay between enthalpic and entropic effects. These are respectively determined by the association of water molecules within the brush structure and the distinctive, stretched conformation characterizing densely grafted chains.[11−14] Hence, dense and hydrated polymer brushes efficiently prevent the nonspecific adhesion of biomolecules (and larger biomolecular entities) because of their unfavorable dehydration and the loss of conformational entropy involved when biomolecules adhere to the surface.[4,11−14]

In addition, the interplay between high water content and the osmotic pressure generated within the brush provides fluid lubrication and load-bearing capacity, substantially reducing friction when a shearing countersurface is applied (Figure 1).[15−19]

The design principle for biopassive and lubricious polymer brushes has primarily relied on a careful tuning of polymer composition, which allows one to enhance the hydration capacity of the assemblies while minimizing the presence of chemical functionalities that could trigger specific or nonspecific interactions with the surrounding biological environment. Through this strategy, in addition to poly(ethylene glycol) (PEG)[13,21−23] and its derivatives, several other polymers have progressively emerged as starting materials for fabricating brushes with improved antifouling properties and

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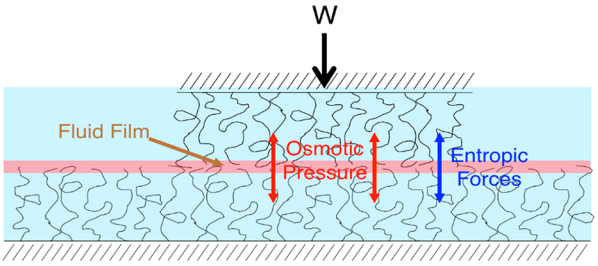

Figure 1. The lubricity of polymer brushes is due to a combination of osmotic pressure within the grafted assemblies, and resistance to interpenetration between opposing brushes. Reproduced from ref 20, copyright 2019 John Wiley and Sons.

enhanced lubricity. These include polyzwitterions,[24−27] poly(acrylamide)s and poly(methacrylamide)s,[28−32] poly(2-alkyl-2-oxaoline)s (PAOXAs),[33,34] and very recently poly(2-alkyl-2-oxazine)s (PAOZIs).[35]

However, their composition, polymer architecture (i.e., branching or topology), and structural properties (i.e., grafting density and/or thickness) represent additional parameters strongly affecting the physicochemical properties of brush assemblies, consequently determining their resistance toward biological contamination as well as their nanotribological properties.

In this article, we summarize our recent efforts in the macromolecular design of polymer-brush interfaces, especially focusing on how polymer topology and the structural properties of the assemblies can be varied in order to modulate technologically relevant interfacial properties of the generated surfaces. In particular, we concentrate on the bioinertness of polymer brushes, intended as protein and cell repellence, and lubrication properties of the grafted films.

While additionally reporting the most prominent, recent works by others, where polymer structure−brush property relationships have been dissected, the main objective of this feature article is thus to derive from experimental work some general design principles, which for a given chemistry would enable us to independently tune highly technologically relevant properties of polymer brushes, such as biopassivity and lubrication. Although we are aware that a comprehensive theoretical description of the brush structural parameters regulating these properties has been derived from several fundamental works, including simulations,[14−17,36−42] the focus of this report is rather on those studies that through experiments could rationalize the determinants for such interfacial properties of polymer brushes.

MODULATION OF POLYMER-BRUSH THICKNESS AND GRAFTING DENSITY

The independent variation of the structural properties of homopolymer brushes represents a powerful tool for modulating their interaction with biological environments and tuning their lubrication properties. The main structural variables that can be readily adjusted in order to vary these characteristics are the molecular weight of the brushes, which directly correlates to brush thickness, and their grafting density (σ).[14−16,43,44]

It is important to emphasize that the nonspecific adhesion of proteins can provide an indirect indication of the way polymer-brush interfaces would interact with larger biological objects, such as cells and bacteria.[13,14,41,42,45] Nevertheless, enlarging resistance toward protein adsorption to generalized antifouling behavior might be not valid for several systems.

The values of σ mainly determine the primary adsorption of proteins on polymer brushes (i.e., the nonspecific interaction between the biomolecules and the underlying substrate).[14,41,42] A variation of grafted-polymer coverage thus regulates the extent of protein intercalation within the brush assembly, with low-σ brushes enabling relevant surface contamination especially by small globular proteins such as albumin (Figure 2).

In contrast, tuning the brush thickness, which for a given σ is directly correlated to the molecular weight of the grafted polymer, determines secondary protein adsorption.[14,41,42] This phenomenon arises from long-range interactions between biomolecules approaching the brush−medium interface and the underlying substrate, and it can be efficiently hindered when the brush thickness is finely adjusted, for instance, by fabricating brushes via surface-initiated controlled radical polymerization (SI-CRP).[2] Hence, the fabrication of sufficiently thick and densely grafted brushes can ensure an efficient and durable resistance toward nonspecific protein contamination.

When in addition to biopassivity high lubrication is sought, the composition of polymer brushes (i.e., their hydrophilic character) should be carefully considered while tuning the structural properties of the grafted assemblies. Friction progressively decreases with increasing brush thickness in the case of highly hydrophilic brushes, such as those based on polyzwitterions, due to the increment in the amount of water associated with the grafts with increasing their molecular weight (Figure 3).[46−49]

In contrast, brushes presenting an amphiphilic character, especially those based on poly(ethylene glycol) (PEG) and its derivatives, often showed an opposite behavior. This is the case of poly[(oligoethylene glycol)methacrylate] (POEGMA) brushes synthesized by surface-initiated atom transfer radical

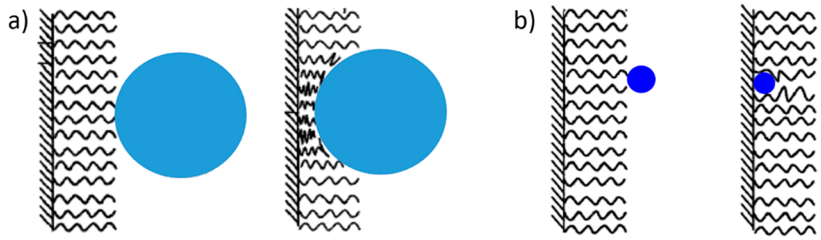

Figure 2. Large proteins can adsorb the outer edge on polymer brushes via secondary adsorption (a). In contrast, small proteins can intercalate within the brush structure undergoing primary adsorption (b). Reproduced from ref 14, copyright 1999 American Chemical Society.

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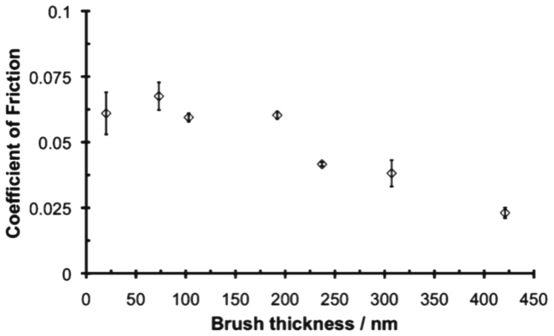

Figure 3. Coefficient of friction (μ) obtained by LFM on poly[2-(methacryloyloxy)ethylphosphorylcholine] (PMPC) brushes was shown to decrease with increasing brush thickness. Reproduced from ref 49, copyright 2011 American Chemical Society.

polymerization (SI-ATRP), which present an amphiphilic character in water, and showed a progressive increment in friction with increasing brush thickness when analyzed by lateral force microscopy (LFM) (Figure 4).[50] This phenomenon was ascribed to the increment in mechanical energy dissipation that arises while shearing progressively thicker POEGMA brushes, which feature just a limited amount of solvent within their structure, and display adhesive hydrophobic interactions toward the atomic force microscopy (AFM) colloidal probe.

Similar results were recorded while studying the nanotribological properties of poly(*N*-isopropylacrylamide) (PNIPAM) brushes below and above their lower critical solution temperature (LCST).[51] Below LCST, highly swollen PNIPAM brushes were characterized by an increment in lubricity with increasing thickness, due to the higher content of fluid lubricant incorporated within thicker brushes. In contrast, above LCST, PNIPAM brushes are poorly hydrated and friction increases with their thickness, due to the rising of dissipative forces when a shearing AFM probe is applied.

Differently from what has been observed while varying brush thickness, a variation of σ produced a similar effect on the nanotribological properties of hydrophilic and amphiphilic brushes. On both these types of assemblies, an increase in surface coverage of grafted chains was mirrored by a concomitant reduction in friction. Generally, denser brushes displayed an augmented load-bearing capacity because of the higher osmotic pressure generated within their structure with respect to that exerted by their more loosely grafted counterparts.[52,53] In addition, when polymer brushes are sheared against structurally identical brush-functionalized surfaces, an increment in grafting density translated into a reduction of interpenetration between opposing brushes,[16,54] leading to a diminution of dissipative collisions between sheared chains, and a simultaneous decrease in the resulting friction (Figure 5).[52,55,56]

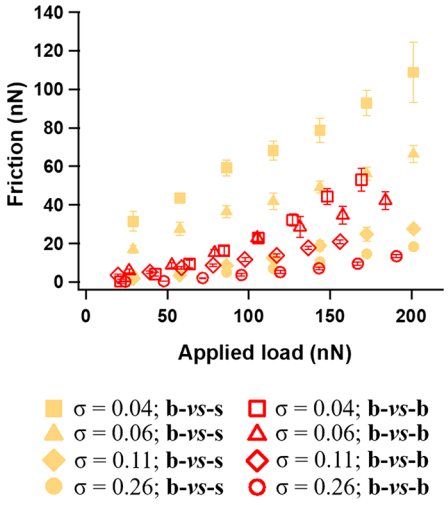

Figure 5. Friction-vs-applied load (F_fL) profiles recorded by LFM on poly(2-ethyl-2-oxazoline) (PEOXA) brushes presenting different values of σ. A reduction in friction was observed by increasing σ both when PEOXA brushes were sheared against a bare, silica-based colloidal AFM probe (b-vs-s), and when an identical brush was applied as countersurface (b-vs-b). Reproduced from ref 52, copyright 2018 American Chemical Society.

MIXED AND COPOLYMER BRUSHES

The fabrication of polymer brushes including compositionally diverse homopolymer, random or block copolymer grafts

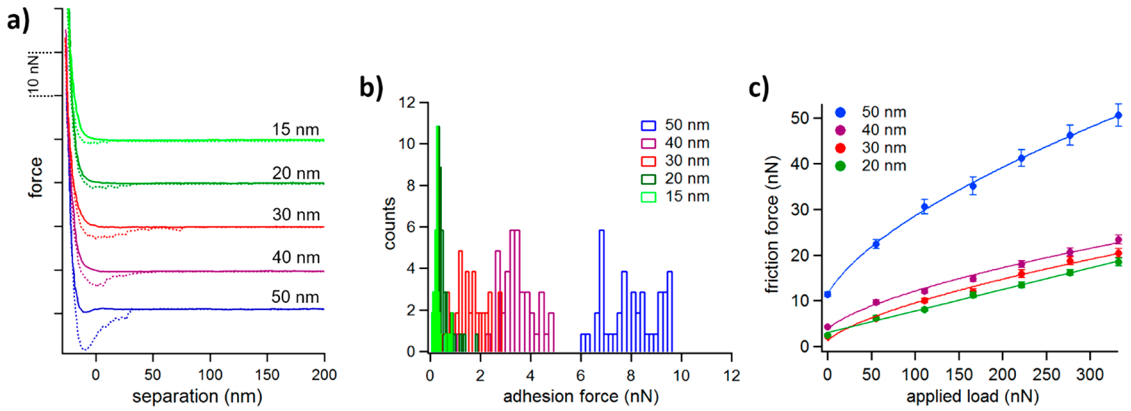

Figure 4. (a) Force-vs-separation (FS) profiles recorded on POEGMA brushes presenting different dry thicknesses (indicated in black along each FS profile). (b) Adhesion was shown to increase with brush thickness due to hydrophobic interactions between the silica-based AFM colloidal probe and POEGMA brushes. (c) Friction-vs-applied load profiles (F_fL) recorded by LFM highlighted how mechanical energy dissipation increased with increasing brush thickness, leading to a simultaneous increment in friction. Reproduced with permission from ref 50, copyright 2015 John Wiley and Sons.

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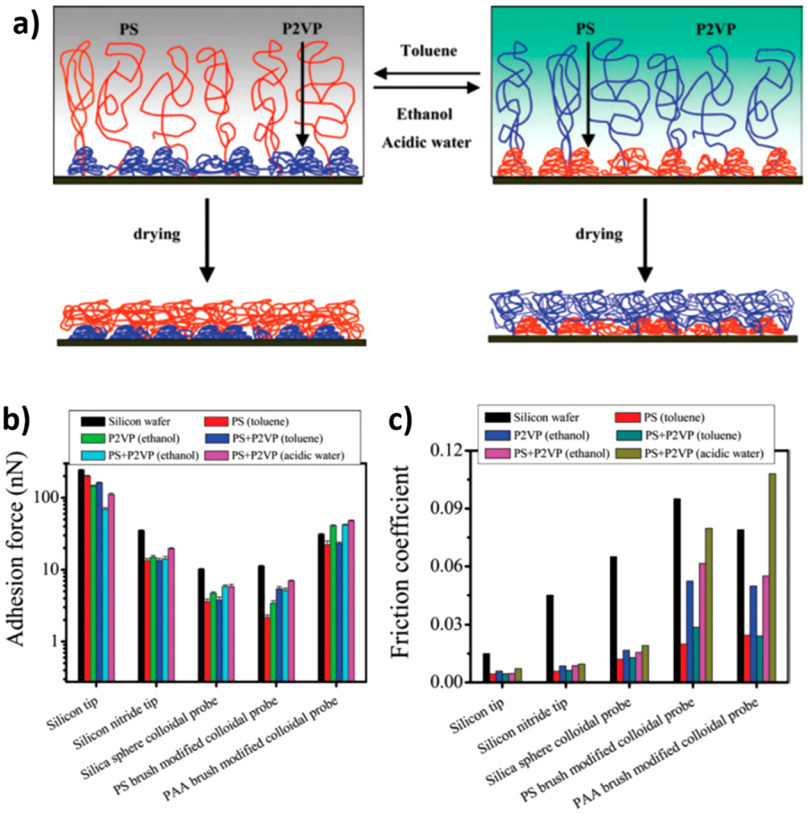

Figure 6. (a) The interfacial morphology of polystyrene (PS)-poly(2-vinylpyridine) (P2VP) mixed brushes was modulated by treating them with selective solvents. In this way, and by simultaneously varying the composition of the brush grafted on the AFM colloidal probe, both adhesive properties (b) and friction (c) could be tuned. Reproduced from ref 84, copyright 2008 Royal Society of Chemistry.

enables to precisely tune the biopassive and nanotribological properties of the generated surfaces.

After the seminal works by Stamm and Minko, where the morphological and interfacial physicochemical properties of mixed brushes in response to selective solvents were thoroughly investigated,[57−62] increasing efforts have been subsequently dedicated in synthesizing structurally similar assemblies capable of shifting their affinity toward proteins and/or their nanotribological properties.

Mixed brushes featuring tunable biopassivity were successfully synthesized following a general design principle, where two chemically different grafts are sequentially grafted to a functional surface,[61] or consecutively grown by SI-CRP from initiator-bearing substrates.[63−70] In most of these cases, mixed brushes comprised a biopassive component intercalated with an additional graft-type capable of changing its swelling properties or charge density in response to a variation in temperature, pH or ionic strength.

In the exemplary cases of ionizable poly(acrylic acid) or poly(methacrylic acid) (PAA and PMAA, respectively) grafts mixed with PEG[71,72] or poly(2-methyl-2-oxazoline) (PMOXA)[73,74] analogues, pH and ionic strength could be varied in order to modulate the exposure of the nonionic and biopassive components at the interface, finally enabling the capture and successive release of proteins from the surrounding medium.

Through this strategy, and via the fine adjustment of molecular weight and relative content of PEG grafts within PAA/PEG mixed brushes, the selective and reversible physisorption of defined biomolecules from mixtures of different protein types could be additionally accomplished.[75]

Alternatively, by combining thermoresponsive PNIPAM grafts with PAA analogues, switching of the affinity toward proteins could be triggered by varying the temperature of the medium, and it could further amplified by tuning of the relative content of each component at the surface.[76]

Switching of bioadhesion on polymer brushes could be also accomplished by synthesizing random copolymer grafts that incorporate different relative contents of amphiphilic, hydrophobic and charged comonomers. Similarly to the case of mixed brushes, where the overall composition of the assemblies was tuned in order to amplify switching of properties, a careful adjustment of the relative content of each comonomer was exploited to enhance the variation of interfacial properties of the generated brush in response to a temperature change, efficiently shifting the character of the surface from biorepellent to bioadhesive. This strategy was successfully exploited by Okano et al. in order to stimulate the adhesion of different cells and subsequently release them following proliferation, yielding freestanding cell sheets, or to trigger attachment and release from the surface of a particular cell type from mixtures.[77−83]

Mixed brushes featuring two immiscible polymer graft that can be selectively swollen in different solvent environments were additionally applied to modulate adhesion and friction at surfaces. In particular, grafted assemblies including polystyrene (PS) and poly(2-vinylpyridine) (P2VP) could significantly vary their morphology and interfacial composition in response to the exposure to selective solvents (toluene and ethanol/water) (Figure 6a).[84] In this way, adhesive and lubrication properties could be shifted by an order of magnitude, and further tuned as a function of the composition of the probe

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used as countersurface for the adhesion/friction force measurements (Figure 6b,c).

A significant alteration of the interfacial physicochemical properties of polymer brushes could be accomplished by mixing two nonionic grafts that are both soluble in water, such as PEG and PMOXA or poly(2-ethyl-2-oxazoline) (PEOXA).[85] Surface dilution of a grafted component with a compositionally different analogue led to an increment in the hydration of the entire assembly, with a consequent improvement in its resistance toward protein contamination. Moreover, in combination with the increased brush swelling achieved through mixing, the inclusion of PEG grafts that are characterized by a low glass transition temperature (T_g) within PMOXA and PEOXA brushes (with $T_g \geq 70$ °C) significantly reduced friction with respect to that measured on the corresponding homopolymer films, especially when relatively high pressures were applied (Figure 7).[35]

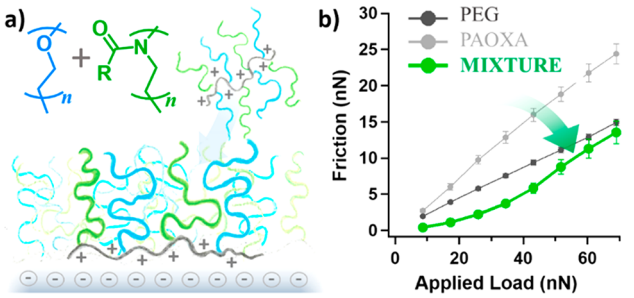

Figure 7. Mixed brushes featuring PEG and PAOXA grafts (a) showed an improved lubricity if compared to PEG- and PAOXA-based single-component brushes (b). Reproduced from ref 85, copyright 2018 American Chemical Society.

Besides studying the properties of grafts presenting two or more components mixed on the same substrate, the immiscibility between chemically diverse homopolymer brushes grafted from different surfaces allowed de Beer et al. to substantially hinder brush interpenetration when these two assemblies are sheared one against each other.[36] The consequent reduction of dissipative forces between opposing grafts sliding in opposite directions[17,18,37] generated a substantial reduction in the coefficient of friction (μ) if compared to that measured by shearing identical, interpenetrating brushes.

It is also important to emphasize that a comparable suppression of brush interdigitation, with a concurrent improvement in lubricity, could be potentially accomplished by substituting one of the two countersurfaces with a responsive brush capable of varying its swelling and conformation in response to a physical stimulus, such as a shift in pH or temperature.[37,86]

An alternative approach for broadening the functional character of polymer brushes and expand their physicochemical properties has encompassed the application of (multi)-block copolymer grafts, typically synthesized by sequential SI-CRP methods.[2]

Especially in the designing of biointerfaces, hierarchical brush structures including a substrate-bound, biopassive block, and functional/bioactive interfacial segments have been applied for regulating the adhesion of cells and bacteria. This general design enabled the fabrication of coatings capable of repelling bacteria, as well as displaying bactericidal properties.[87,88] Similar block copolymer brushes have been applied to functionalize the surface of biosensors, where just one brush block can selectively bind analytes from solution.[89−92]

Alternatively, functional block copolymer brushes have been exploited to trigger the adhesion of cells and simultaneously modulate their response.[93−97] Generally, within these brush formulations one or more brush segments feature a biopassive character, although their tunable physical properties are exploited to regulate the behavior of cells, whose attachment to the surface is stimulated by the presence of functional cues on the other blocks.

Block copolymer brushes characterized by an alternation of biopassive and cell-adhesive blocks were applied to modulate the surface exposure of covalently bound peptides, which were "buried" by interfacial brush segments of different molecular weights,[93,94] and whose presentation at the interface could be altered when the bioinert segments feature temperature-dependent swelling properties.[98]

Following this strategy, the morphology of adhering cells and their attachment on the brush interface could be precisely adjusted, suggesting possible strategies to influence cell's

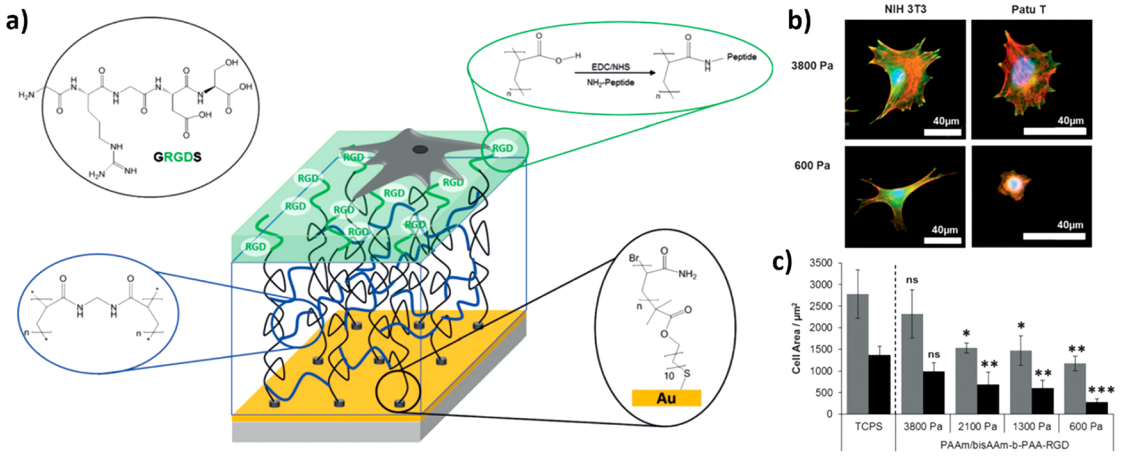

Figure 8. (a) Block copolymer brushes featuring a substrate bound, cross-linked polyacrylamide (PAAm) brush hydrogel with variable stiffness, and an interfacial PAA brush functionalized with peptide-based cues were applied to study the attachment of different cell types and their cytoskeleton organization (b,c). Reproduced from ref 99, copyright 2016 John Wiley and Sons.

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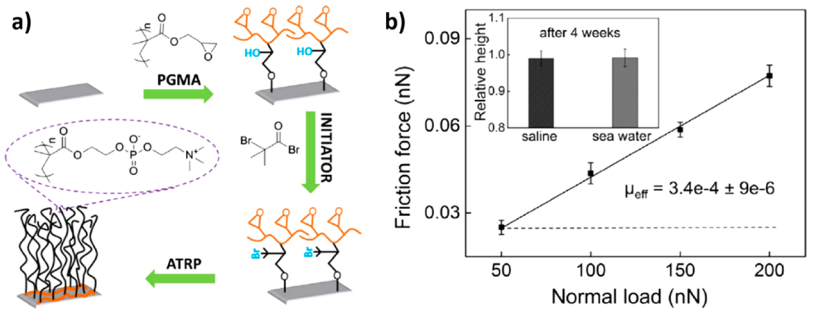

Figure 9. PMPC brushes grafted by SI-ATRP from initiator-bearing poly(glycidyl methacrylate) (PGMA) underlayers (a) preserve their structural properties even after 4 weeks of incubation in salty waters, and maintain their lubricious character, as evidenced by LFM measurements (b). Reproduced from ref 101, copyright 2017 Elsevier Ltd..

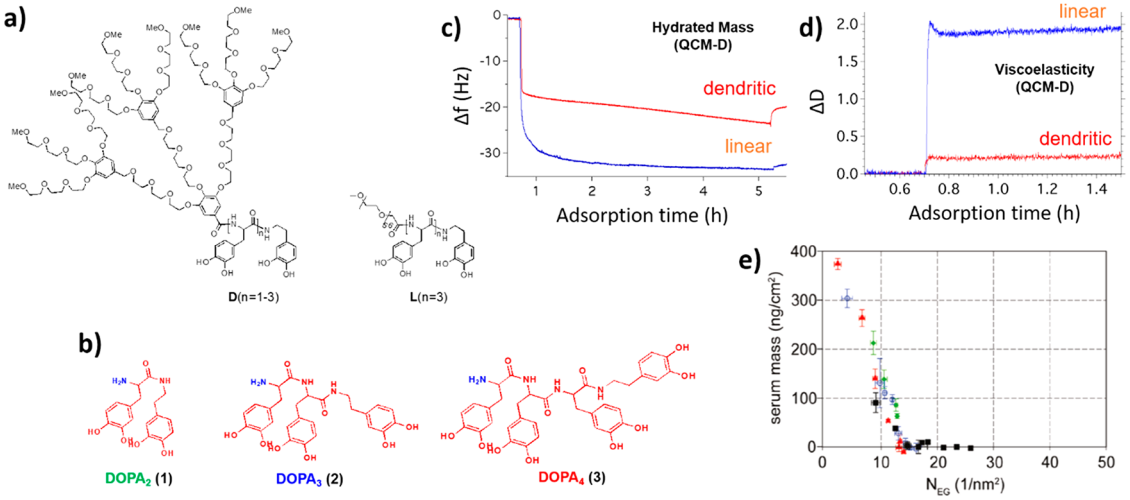

Figure 10. Dendronized PEG adsorbates (a) presenting multicatechol anchors (b) formed brushes on TiO_2 surfaces that featured lower swelling compared to linear PEG analogues (c) and higher rigidity (d), as measured by monitoring frequency (Δf) and dissipation (ΔD) shifts with quartz crystal microbalance with dissipation (QCM-D). However, both linear and dendronized PEG brushes showed a comparable biopassivity when exposed to full human serum (FHS) (e), as recorded by variable angle spectroscopic ellipsometry (VASE) on assemblies featuring different polymer surface coverages (expressed as number of ethylene glycol units, N_{EG}, per nm^2). Reproduced from ref 107, copyright 2011 American Chemical Society.

behavior (proliferation and/or differentiation) on biomaterials previously modified with different brush architectures.

The influence of the physicochemical properties of cell-adhesive brush films on the settlement of different cell types could be dissected by designing block copolymer brushes including a substrate-bound brush block with variable degree of cross-linking and an interfacial linear brush decorated with cell-adhesive cues.[99] In particular, Schönherr et al. demonstrated how the nanomechanical properties of polyacrylamide (PAAm) brushes could be precisely varied by tuning of the relative concentration of acrylamide/bis(acrylamide) during SI-ATRP (Figure 8a). Simultaneously, an interfacial brush based on PAA functionalized with arginine-glycine-aspartic acid (RGD)-containing peptides guaranteed a comparable cell-adhesive character to the exposed surface. In this way, the effect of underlying brush' stiffness on the behavior of both fibroblasts and cancer cells could be addressed independently of the morphology and composition of the interface (Figure 8b,c).

In addition to the fabrication of protein- or cell-responsive surfaces, block copolymer brushes including a hydrophobic, substrate-bound block and hydrophilic interfacial segments were applied in order to increase the long-term stability of polymer brush coatings within particularly aggressive media, such as cell culture solutions or salty waters, and to preserve their distinctive interfacial properties, otherwise undergoing a progressive alteration during brush degradation.

For instance, the resistance of poly(sulfobetaine methacrylamide) (PSBMAm)[100] and poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) brushes[101] toward hydrolytic degradation and degrafting could be significantly improved by including hydrophobic brush blocks as protective layers bound to the underlying substrates. The presence of either poly(methyl methacrylate) (PMMA), polystyrene (PS) or poly(glycidyl methacrylate) (PGMA) segments, all of which formed a collapsed, substrate-bound layer, preserved the structural integrity of the highly swollen PSBMAm and PMPC grafts at the interface, maintaining their attractive biopassive and lubrication properties (Figure 9).[101]

In a similar way, the stability of PMAA[102] and POEGMA[103] brushes was significantly improved by the presence of substrate-bound PMMA blocks, which protected the underlying initiator functions from hydrolysis. Especially POEGMA-*b*-PMMA block copolymer brushes showed comparable biopassive properties and lubricity with respect to POEGMA homopolymer analogues, whereas the hydrophobic PMMA underlayer improved the structural stability of the entire films by several days under cell culture media at 37 °C.[103]

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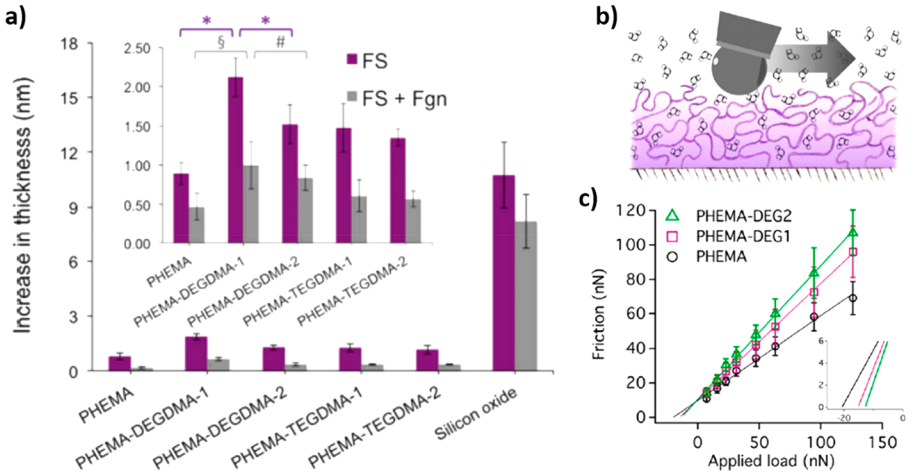

Figure 11. Adsorbed protein thickness on the different poly(hydroxyethyl methacrylate) (PHEMA) brushes and brush hydrogels measured by VASE following 90 min of incubation in FHS (violet bars) and FHS with added fibrinogen (Fgn) (gray bars). * indicates a statistically significant difference analyzed by ANOVA test $P < 0.0001$, § refers to $P < 0.001$, and # indicates $P < 0.05$. Reproduced from ref 119, copyright 2016 American Chemical Society. The values of μ recorded on PHEMA brushes and brush hydrogels by LFM (b) could be precisely modulated by varying the content of the di(ethylene glycol)dimethacrylate (DEGDMA) cross-linker between 1 and 2 mol %. Reproduced from ref 120, copyright 2017 American Chemical Society.

BRANCHED AND CROSS-LINKED POLYMER BRUSHES

Polymer adsorbates featuring a branched architecture were applied to generate biopassive, brush-like assemblies on a variety of inorganic and organic substrates. The most prominent examples included hyperbranched polyglycerol (hPG)[104,105] and PEG adsorbates.[106−108]

Assemblies featuring hPG dendrons and dendrimers showed excellent resistance toward the nonspecific surface contamination by proteins, cells and bacteria, often surpassing the antifouling properties displayed by linear polyglycerol brushes, and in several cases matching those showed by densely grafted PEG analogues.[109−112]

Dendronized PEG adsorbates assembled on TiO_2 surfaces via catechol-based anchors formed brushes that were less hydrated and more rigid (less viscoelastic) with respect to their linear PEG counterparts (Figure 10).[107] However, dendronized PEG brushes showed a resistance toward the adsorption of undiluted full human serum (FHS) comparable to that showed by highly swollen linear PEG assemblies. These results suggested that hydration might not represent a strict determinant for biopassivity in the case of brushes presenting an hyperbranched structure, which could thus compensate their reduced swelling with a concomitant increment in surface passivation.

The biopassive properties displayed by grafted-from polymer brushes featuring side chains with different degree of branching further highlighted the effect of brush architecture on its resistance toward nonspecific biological contamination. In particular, the groups of Haag and Huck compared the antifouling properties of glycerol-containing linear polymethacrylate brushes synthesized by SI-ATRP with those displayed by analogous grafts featuring linear, first- and second-generation dendritic polyglycerol side chains.[113] From this comparative analysis, brushes including branched side chains were characterized by excellent biopassivity within FHS and undiluted blood plasma, with first-generation polygycerol-bearing brushes outperforming all the other tested coatings.

In addition to branching, an alternative approach to modulate both biopassivity and lubrication properties relied on the introduction of covalent or physical cross-links between surface-grafted chains.

Brush-hydrogels of diverse compositions and including different concentrations of cross-links could be easily synthesized by SI-ATRP, mixing mono and bifunctional monomers within the polymerization mixture.[114−118] Due to the intrinsic architecture of polymer brushes, which are characterized by polymer grafts immobilized by one chain end to the same substrate, the introduction of even a relatively low concentration of cross-linker, or a slight variation in its content, translated into a significant shift of the interfacial physicochemical properties of the resulting films.

For instance, cross-linking poly(hydroxyethyl methacrylate) (PHEMA) brushes with ∼1 mol % of di(ethylene glycol) dimethacrylate (DEGDMA) reduced by nearly 20% the swelling ratio of the brushes, and significantly reduced their conformational freedom.[119] These changes in brush structure and properties eventually led to a 2-fold increment in the amount of proteins physisorbed on brush-hydrogels from FHS, if compared to that recorded on the corresponding linear PHEMA brushes presenting comparable dry thickness (Figure 11a).

Interestingly, the substitution of DEGDMA with an equimolar amount of longer, tetra(ethylene glycol)dimethacrylate (TEGDMA) reduced the loss of biopassive properties observed on PHEMA-DEGDMA brush-hydrogels, presumably due to the increment in the overall content of water-associating ethylene glycol units within the films.

Irrespective of their composition, the introduction of covalent cross-links between grafts and the simultaneous decrease in the content of fluid lubricant within the films caused a significant increase in friction. As an example, the μ measured in water by LFM on PHEMA brushes increased from 0.49 to 0.67 and 0.76 when the grafted chains were cross-linked by 1 and 2 mol % of DEGDMA, respectively (Figure 11b,c).[120]

A more pronounced reduction in lubricity was observed in the case of more hydrophilic polymer grafts,[30,121,122] such as

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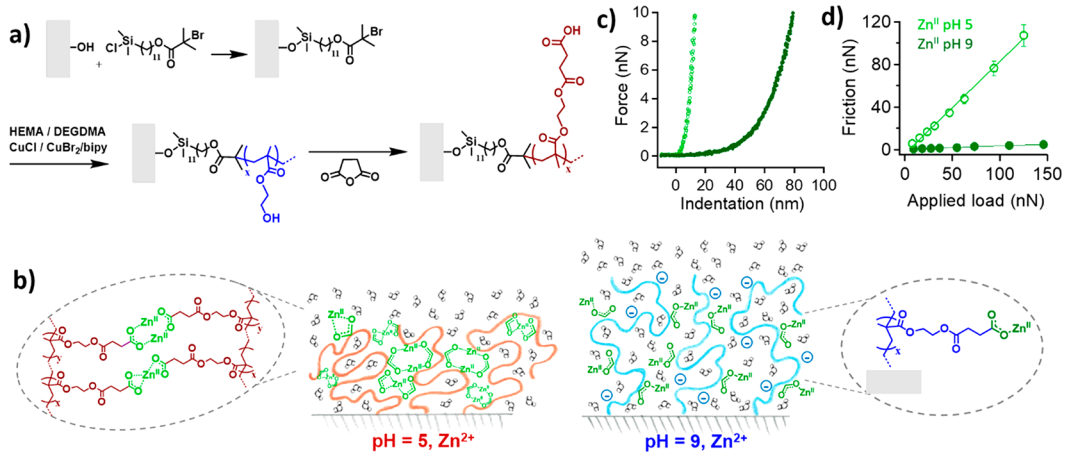

Figure 12. PHEMA-SA brushes were synthesized by SI-ATRP followed by derivatization with succinic anhydride (a). When PHEMA-SA brushes were treated with 10 mM Zn^{2+} solution at pH 5, bridging and chelating complexes were formed, while in 10 mM Zn^{2+} at pH 9, brush networks presenting monodentate conjugates were obtained (b). Force vs indentation (FI) and F_fL profiles recorded by AFM on PHEMA-SA-Zn^{II} brushes highlight how the swelling and lubrication properties were determined by the formation of different types of cross-links between the PHEMA-SA grafts. Reproduced from ref 126, copyright 2017 American Chemical Society.

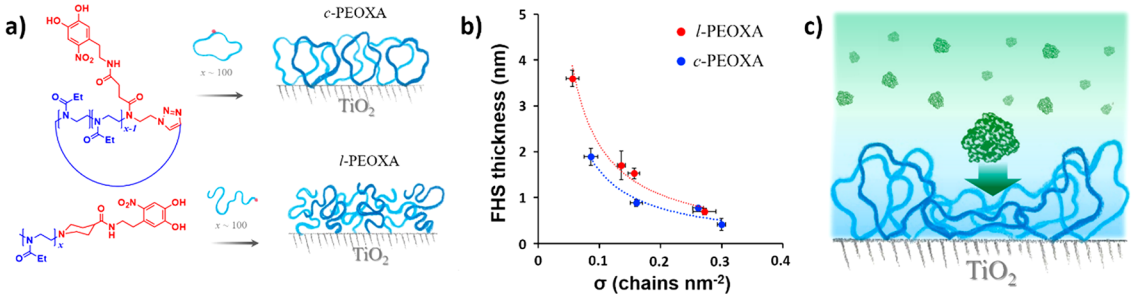

Figure 13. (a) Linear and cyclic PEOXA adsorbates featuring catechol anchors assembled on TiO_2 surfaces yielding topologically different PEOXA brushes (indicated as *l*-PEOXA and *c*-PEOXA, respectively). (b) *c*-PEOXA brushes showed improved biopassivity toward FHS across a wide range of grafting densities with respect to *l*-PEOXA analogues. (c) The increased resistance toward nonspecific protein contamination by cyclic brushes is ascribed to the additional steric barrier provided by the cyclic topology of the grafts. Reproduced from ref 52, copyright 2018, American Chemical Society.

PAAm brushes synthesized by surface-initiated photoiniferter-mediated polymerization (SI-PIMP),[123,124] and cross-linked by 0.1−5 mol % bis(acrylamide) (bisAAm).[30,122] In particular, PAAm brush-hydrogels presenting 5 mol % bisAAm showed a 10-fold decrease in swelling properties in water and a concomitant increment in μ by more than an order of magnitude.

Besides the fabrication of covalent brush networks, the design of polymer brushes that could be reversibly cross-linked through the formation of organometallic complexes between linear grafts enabled the fabrication of surfaces presenting switchable swelling and nanotribological properties.[125−127] In the chemically simplest case, linear PHEMA brushes bearing succinic acid−based side chains (PHEMA-SA) could be reversibly cross-linked by treatment with divalent metal ions, such as Zn^{II} and Ca^{II} (Figure 12a).[126] Tuning of the pH during the formation of the polymer−metal complexes enabled the synthesis of either mono- or bidentate bridges between the grafts (Figure 12b), generating brush networks with pronounced differences in swelling and lubrication properties (Figure 12c,d). Brush networks including Zn^{II} ions thus showed a reversible shift in μ from 0.8, when more strongly cross-linked dehydrated structures were formed via bidentate complexes, to 0.03, in the case of more compliant and swollen networks based on monodentate bridges (Figure 12d).

POLYMER BRUSHES PRESENTING CYCLIC AND LOOP TOPOLOGIES

Recent studies from our group have highlighted that shifting the topology of polymer brushes from a simple, linear chain to their cyclic counterparts, while keeping their composition and molecular weight constant, determined a pronounced alteration of biopassivity and lubrication.[52,53,55,128−133]

Because of their more compact molecular dimensions,[134−137] cyclic polymer adsorbates assembling on inorganic and organic substrates tend to generate much denser brushes with respect to their linear analogues, providing an exceptional steric stabilization to the functionalized surfaces. This "topological effect" translates into films that exhibit enhanced resistance toward biological contamination as a result of the exceptional osmotic pressure originating from dense cyclic brushes, as demonstrated for PEOXA and PMOXA assemblies on TiO_2,[52,53,55,132,133] F_2O_3,[140] and SiO_x surfaces.[128]

It is important to emphasize that the steric constraints introduced during the cyclization of polymer adsorbates provide an additional barrier toward nonspecific interaction with adsorbing biomolecules, determining a slight but significant improvement in biopassivity for cyclic brushes across a wide range of surface densities when compared to

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structurally and chemically identical linear analogues (Figure 13).[52,55]

The absence of interfacial chain ends, which is intrinsic in the cyclic topology, additionally hinders brush interpenetration when opposing assemblies are compressed and sheared against each other,[18,19,138,139] providing to cyclic brushes superlubricious character.[52,132,133] As a result of the combined effects of the suppression of dissipative forces between cyclic-brush countersurfaces and increased steric stabilization of the underlying substrates, which leads to an improved load-bearing capacity, even amphiphilic cyclic PEOXA brushes in water provide values of μ of as low as 10^{-3}, nearly reaching the lubricity typically displayed by highly hydrophilic polyzwitterionic-based linear analogues (Figure 14).[26]

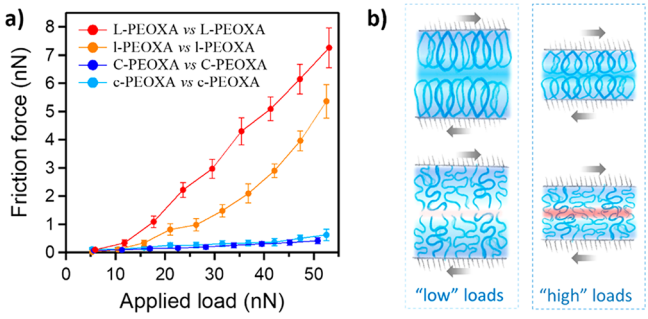

Figure 14. (a) F_fL profiles recorded by LFM while shearing PEOXA brushes against topologically identical brush-bearing countersurfaces (b). In (a), the F_fL profiles for 10 and 5 kDa linear PEOXA brushes (*L* and *l*-PEOXA, respectively) are compared to those recorded while shearing cyclic PEOXA bushes of 10 and 5 kDa (*C*- and *c*-PEOXA, respectively). Reproduced from ref 53, copyright 2017 American Chemical Society.

The unique biopassivity and lubricity of polymer brushes constituted by cyclic macromolecules triggered their application on supports where both of these properties are highly required, such as in the case of articular cartilage. Especially during degenerative syndromes that alter the content of natural biolubricants present in the synovial fluid,[140−144] as in the case of osteoarthritis (OA), tissue-adhesive graft copolymers[145] forming a cyclic brush layer on the exposed collagenous surface of cartilage were demonstrated to re-establish its lubrication properties and protect it from the enzymatic degradation connected to OA progression.[129]

Biopassive and nanotribological characteristics similar to those displayed by cyclic brushes could be observed on "loop"-forming grafts, usually assembled on surfaces from telechelic polymer-based or multifunctional copolymer adsorbates.[53,146−155] Interestingly, even a relatively low surface concentration of residual linear chain ends exposed at the interface was identified as a factor strongly influencing the lubricious character of loop brushes. Simultaneously, increasing the loops-to-linear "tails" ratio was accompanied by the progressive improvement of both biopassivity and lubrication, gradually approximating the interfacial properties of cyclic brushes (Figure 15).[53]

CONCLUSIONS AND PERSPECTIVES

During the past decade of research, increasing effort has been spent on designing polymer interfaces on solid surfaces with molecular precision in order to modulate interfacial physicochemical properties that are fundamental in the fabrication, modification, and performance of devices, ranging from sensors to tissue engineering supports. The reduction of nonspecific biological contamination and lubrication have represented two of the most required properties, especially when synthetic materials are expected to integrate within physiological media without altering their interfacial composition and if a minimization of the mechanical stress toward the surrounding environment when shear is applied is sought.

To meet these needs, the composition of polymer-brush-based coatings has been progressively optimized in order to reach full biopassivity within highly contaminating media, such as blood and serum, reduce polymer degradation even after long incubation times, and simultaneously increment lubricity. Although attaining increasingly bioinert and lubricious surfaces has encompassed the application of highly hydrated polymer brushes, for instance, featuring polyzwitterions,[156] the modulation of polymer-brush architecture has concomitantly emerged as an additional method to broaden the tuning potential for the above-mentioned properties.

In particular, while keeping the composition of a polymer assembly constant, the translation of topology effects under the confinement of a grafting surface has enabled us to significantly alter interfacial physicochemical properties that determine the performance of polymer brushes within physiological environments.

In our work, we demonstrated that the application of branched or looped polymer architectures substantially altered the steric stabilization and viscoelasticity of brush assemblies,

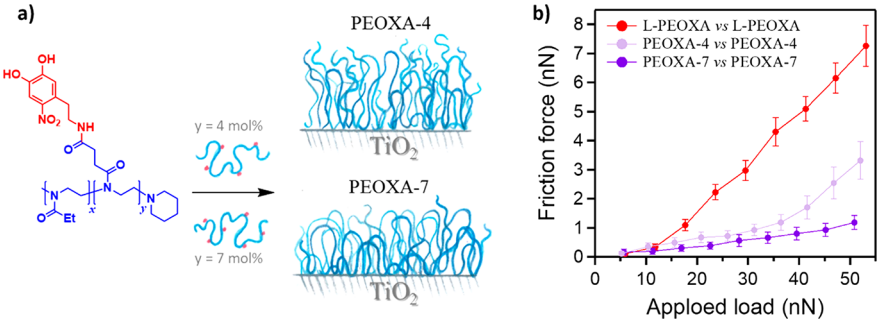

Figure 15. (a) PEOXA brushes featuring a mixture of loops and linear tails are assembled on TiO_2 surfaces from random PEOXA copolymers including 4 and 7 mol % catechol-bearing comonomers (indicated as PEOXA-4 and PEOXA-7, respectively). In (b), F_fL profiles of linear PEOXA brushes of 10 kDa (*L*-PEOXA) are compared to those recorded on PEOXA-4 and PEOXA-7. Reproduced from ref 53, copyright 2017 American Chemical Society.

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providing a more efficient barrier toward nonspecific contamination by biomolecules and suggesting new approaches to suppressing mechanical energy dissipation under shear and reducing friction.

The introduction of covalent or physical cross-links between grafts, yielding brush gels or hydrogels, enabled us to precisely tune the nanomechanical and nanotribological properties of the obtained films and provided a tool to modulate their swelling properties.

Alternatively, the application of block copolymers and mixed brushes enlarged the tuning potential for interfacial composition and allowed one to generate assemblies that can vary their nanomorphology in response to selective solvent environments, often improving the structural stability of the entire coating within aggressive media.

Despite the wealth of possibilities in the molecular structuring of polymer brushes, even the most sophisticated polymer architectures have been always characterized by a constant or "quenched" structure, which enabled limited conformational transitions in response to a variation in temperature or solvent quality. Hence, it has become progressively evident that one of the next challenges that will involve polymer and materials chemists will deal with the realization of soft-matter interfaces characterized by a "dynamic" architecture that can remodel itself via topological transformations of its macromolecular constituents,[157,158] in this way modulating surface interaction with the surrounding medium.

Simultaneously, a growing need for controlled SI-CRP processes, compatible with ambient conditions and scalable to large and morphologically different substrates, has emerged. Following closely the development of oxygen-tolerant reversible deactivation radical polymerization (RDRP) processes in solution,[159] several methods enabling the living growth of polymer brushes in the presence of oxygen that are applicable on extremely large substrates while using just microliter volumes of reaction mixtures were proposed.[160−166]

Collectively, all of these ongoing and future challenges involve experts from different fields of chemistry, physics, and materials science, who are concentrating not only on defining new chemistries for the fabrication of polymeric biointerfaces but also developing coating processes and establishing robust analytical methods for dissecting interfacial properties.

AUTHOR INFORMATION

Corresponding Author

*E-mail: edmondo.benetti@mat.ethz.ch.

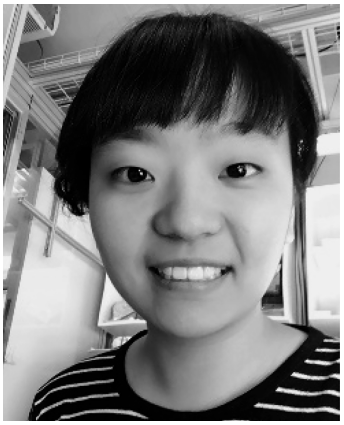
ORCID

Edmondo M. Benetti: 0000-0002-5657-5714

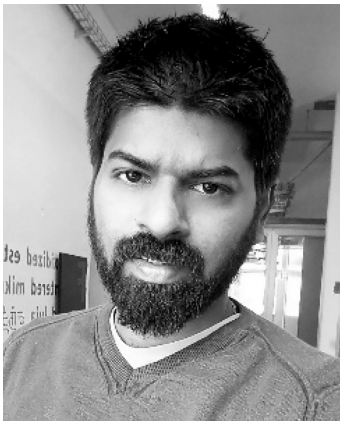
Notes

The authors declare no competing financial interest.

Biographies



Wenqing Yan studied polymer science at the University of Freiburg (Germany), where she received her master's degree in 2017. She is currently a Ph.D. student in the Laboratory for Surface Science and Technology in the Department of Materials at ETH Zürich.



Shivaprakash N. Ramakrishna completed his bachelor's and master's degrees at Kuvempu University, Karnataka (India). He received his Ph.D. degree in 2013 in the Department of Materials, ETH Zürich. He worked as a postdoctoral researcher in the Laboratory for Surface Science and Technology from 2013 to 2015. Currently, he is a senior scientist in the same laboratory, focusing his research on surface science, nanotribology, nanomechanics, and soft matter.

Matteo Romio studied chemistry at the University of Padova (Italy), where he also received his Ph.D. in 2016. Since 2019, he has been a postdoctoral researcher in the Polymer Surfaces Group at the Swiss Federal Laboratories for Materials Science and Technology (Empa) and the Department of Materials, ETH Zürich.

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Edmondo M. Benetti graduated in chemistry at the University of Padova (Italy) in 2004 and carried out his Ph.D. research at the University of Twente (The Netherlands), working in the Department of Materials Science and Technology of Polymers (2009). He joined the Department of Materials at ETH in 2009 as a postdoctoral researcher (ETH fellow) working in the groups of Prof. Nicholas D. Spencer and Prof. Marcus Textor. Since 2014, he has been a senior scientist and group leader, coordinating the activities of the Polymer Surfaces Group, which is now active between the Department of Materials at ETH Zürich and the Swiss Federal Laboratories for Materials Science and Technology (Empa). His research interests are focusing on controlled polymerization applied to interfaces and the fabrication and physicochemical characterization of synthetic biointerfaces.

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