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A recent state of art on polyoxazoline-containing antifouling coatings for biological and environmental applications

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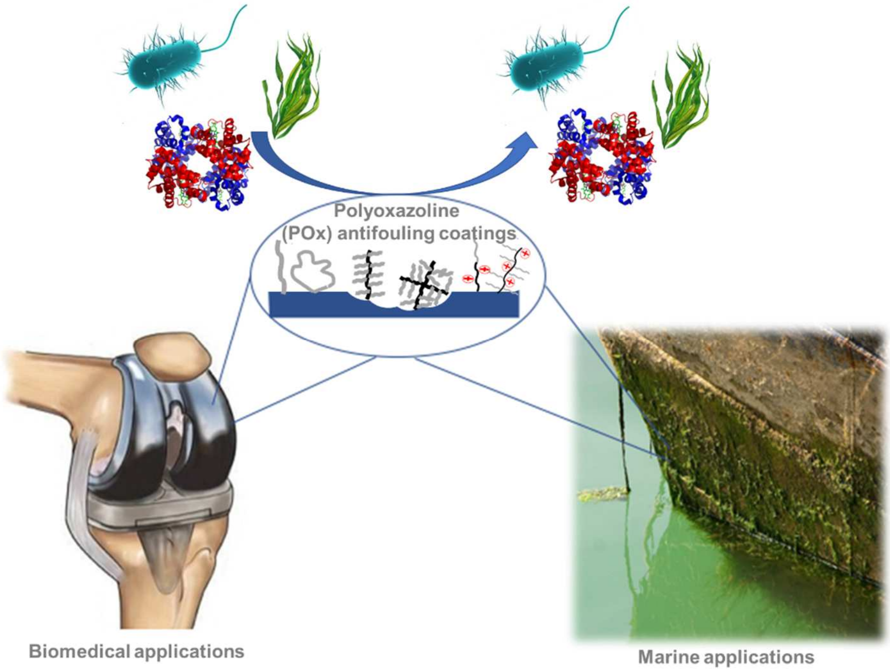
Graphical abstract



Abstract

Antifouling coatings based on polymers attracted a high interest in the last years in biomedical and marine applications. These materials prevent the adhesion of proteins, cells, bacteria or marine organisms. In particular, a range of hydrophilic polymers such as poly(ethylene glycol) (PEG) or hydrophobic ones such as silicone or fluorine are currently used for antifouling coatings. Recently, coatings based on poly(2-alkyl-2-oxazoline)s (POx) have drawn significant attention for antifouling applications due to their unique properties. They constituted a versatile class of biocompatible polymers endowed with a high ability of functionalisation through various macromolecular architectures ranging from linear, branched or brush until the cyclic chains with amazing behavior. This tutorial review highlights the correlation between POx architectures and antifouling properties for biomedical and marine applications. A brief update of the POx chemistry allowing the synthesis of well-defined macromolecular architectures, the main methods used to decorate solid surfaces by POx chains as well as the antifouling properties of POx surfaces against bacteria, proteins, cells and marine organisms will be presented.

Keywords: polyoxazoline, coating, biomedical antifouling, marine antifouling

I. Introduction

Antifouling (AF) coatings are designed in order to resist to the adhesion of proteins, cells, bacteria or marine organisms which is a key step in the initial stages of biofouling. For biomedical applications, the formation of biofilm (*via* the adhesion of residual proteins or bacteria) on biosensors, medical implants such as prosthetic devices, vascular catheters or contact lenses led to serious risks including clotting and infections. Surface functionalization of implantable medical devices with antifouling agents is an efficient strategy to prevent bacterial fouling and associated infections and obtain thromboresistant surfaces for *i.e.* blood-contacting medical devices.[1] Antifouling coatings also concern the prevention of biofouling existing on shipping vessels, heat exchangers, aquaculture cages and other submerged structures in marine environments.[2] The colonization of these surfaces begins with a biofilm (bacteria, micro-algae, etc.) then continues with the arrival of macro-algae, sessile organisms (sponges, anemones, barnacles, mussels, etc.) and mobile species (worms, crabs, shrimps, etc.). This inevitable natural phenomenon affects maritime and aquatic industries since the accumulation of marine organisms causes high frictional resistance of shipping vessels resulting in loss of 86% of a vessel's cruising speed, [2],[3] contributing to delays across the marine shipping industry as well as a corrosive environment, resulting in degradation and failure of materials and structures. The biofouling also causes ecological disasters within the transport of invasive species in other regions of the planet.[4],[5],[6],[7],[8]

Two main ways to address the challenge of antibiofouling (for both biological and marine applications) with biopassive and bioactive antifouling coatings (**Fig. 1**).[9] Biopassive antifouling coatings reduce the fouling due to a repellent character without interfering with the proliferation cycle (of bacteria or marine organisms), nor the cell metabolism.[10] Frequently, the biopassive antifouling materials are also known as fouling resistant coatings. In contrast, bioactive antifoulings produce the inactivation of adherent microorganisms or biofilms by releasing antifouling biocides (known also as fouling release mechanism), or by killing (degrading) the cells, bacteria, or microorganisms in contact by using specific molecules (named also fouling degrading mechanism).[9] Highly explored in the field of marine applications, bioactive antifouling coatings following a fouling release mechanism are based on the dispersion of biocide additives in different types of polymeric binders which release the biocide agent into the seawater over time using erodible matrix.[6],[9],[11] These foulings can release the biocide agent (*e.g.*, metallic compounds like organotin tributyl (TBT), copper in marine applications, etc.) from an insoluble or soluble polymer matrix. The insoluble polymer matrices cannot be eroded after the immersion in water, while the soluble matrices can be dissolved in seawater.[9]

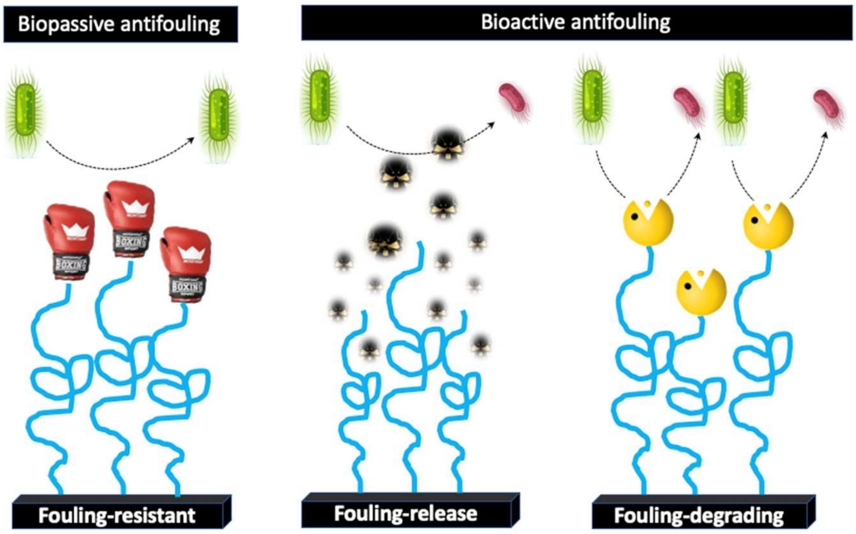


Fig. 1. Types of antifouling mechanism (blue line: polymer chain).

Polymer coatings were largely explored for antifouling applications in biomedical and marine field. The antifouling properties can be influenced by three parameters including the surface chemistry, the surface topography and the architecture of polymer coating (**Fig. 2**).[9] The surfaces in which the antifouling coatings are deposited range from wood, polymers, composites to metals depending on the application. In marine field, the protected surfaces correspond to those of hull boats mainly composed of wood, aluminium, and more recently by steel or composites based on carbon and glass fibres spread of unsaturated polyester (UP) or epoxy (EP) resins.[5],[12],[13] In biomedical field, the nature of the implant ranges from cartilage,[14],[15] thermoplastics (PE, PP, PVC, PVDF),[16] thermosets (PU,[17] silicone[18]) as well as metals (titanium, gold).[16]

It is important to note that the surface chemistry influences the way foulants interact with the surface. Three kind of fouling surfaces exist such as hydrophilic, hydrogen bond-forming and electrically neutral.[9] In this regard, hydrophilic or neutral polymers can be coated on solid surfaces. In biomedicine, antifouling polymer coatings consist of polymer backbones derived from poly(ethylene glycol) (PEG) which is considered as the gold standard for antifouling applications.[19] Other examples include fluorine containing polymers,[20] zwitterionic polymers,[21] while silicones[12] were intensively explored for marine applications.

So far, poly(2-alkyl-2-oxazoline) (abbreviated here as POx), also named poly(alkylethyleneimine) are particularly attractive for antifouling polymer coatings and that thank to major breakthroughs of Textor and Benetti groups. Many kind of surfaces were coated by POx ranging from metallic to polymer or inorganic until natural tissue like the skin.[22],[23] Inspired by PEG, POx are biocompatible and are characterized by some structural similitudes including a flexibility of backbone that avoid the attachment of pathogens on surface.[24],[25],[26] POx show less adverse immunological reactions than PEG derivatives and they are not degraded by the enzymes, so they can be efficiently used for biomedical and marine antifouling.[19],[27] Similar to PEG conjugates, POx are not biodegradable due to their substituted repetitive amide groups. They exhibit enhanced stability in biological environments, rendering them suitable for long-term applications such as antifouling coatings. Moreover, poly(2-methyl-2-oxazoline) (PMeOx) and poly(2-ethyl-2-oxazoline) (PEtOx), the hydrophilic candidates of this class of polymers, are endowed with repellent properties against bacteria, cells or marine organisms.[28],[29] Due to their hydrophilicity, PMeOx or PEtOx can be used either as hydration coatings (*i.e.*, thin hydrogels)[30],[31] either in combination with hydrophobic polymers in order to form amphiphilic polymer coatings. In addition, POx structures can be regarded as those of pseudo-peptides,[32] which give them an advantage in terms of various ways of functionalisation, in comparison to PEG, with a supplementary route of modification using the acyl group in pendent chain.[33] The high ability of POx functionalisation is a valuable tool to design various architectures (linear, cyclic, comb, brush, etc.) which can modify the antifouling performances.

The antifouling ability of hydrophilic and electrically neutral surfaces is related to the high hydration and surface energy which prevent the biofilm adsorption.[21] Oppositely, a hydrophobic behaviour provides the surface with a higher self-cleaning potential. Moreover, surface charge can also play an important role in preventing nonspecific adhesion since the positive charged surfaces will kill the organisms/cells (which are negatively charged) upon deposition.[21] In addition, surface topography can impede the settlement of microorganisms/cells by imposing size restrictions. Microorganisms prefer to settle in areas that are slightly larger than themselves in order to achieve maximum protection and high surface area contact.[9],[11] However, the investigation of surface topography on antifouling properties of polymer coatings is out of the scope of the present review.

Furthermore, the polymer architecture is another parameter to design antifouling polymer coatings. The polymer architecture (*i.e.*, linear, brush, cyclic, etc.) may influence the coverage of the surface and thus differently limit the interactions between the foulant agents and the surface. The grafting density, thickness and flexibility of the polymer brush are other essential parameters that should always be taken into account when designing such coatings.

This review deals with antifouling coatings based on various POx used in biomedical and marine applications (**Fig. 2**). The discussion is organised in four parts and begins by a description of the chemical modifications of POx and their macromolecular architectures used for antifouling coatings. The second section is dedicated to the type of bonds between POx and the solid surface. Then, some parameters such as POx length or grafting density were discussed before detailing the most elaborated section of the antifouling properties (against bacteria, proteins/cells and marine organisms) of POx reported in the last ten years.

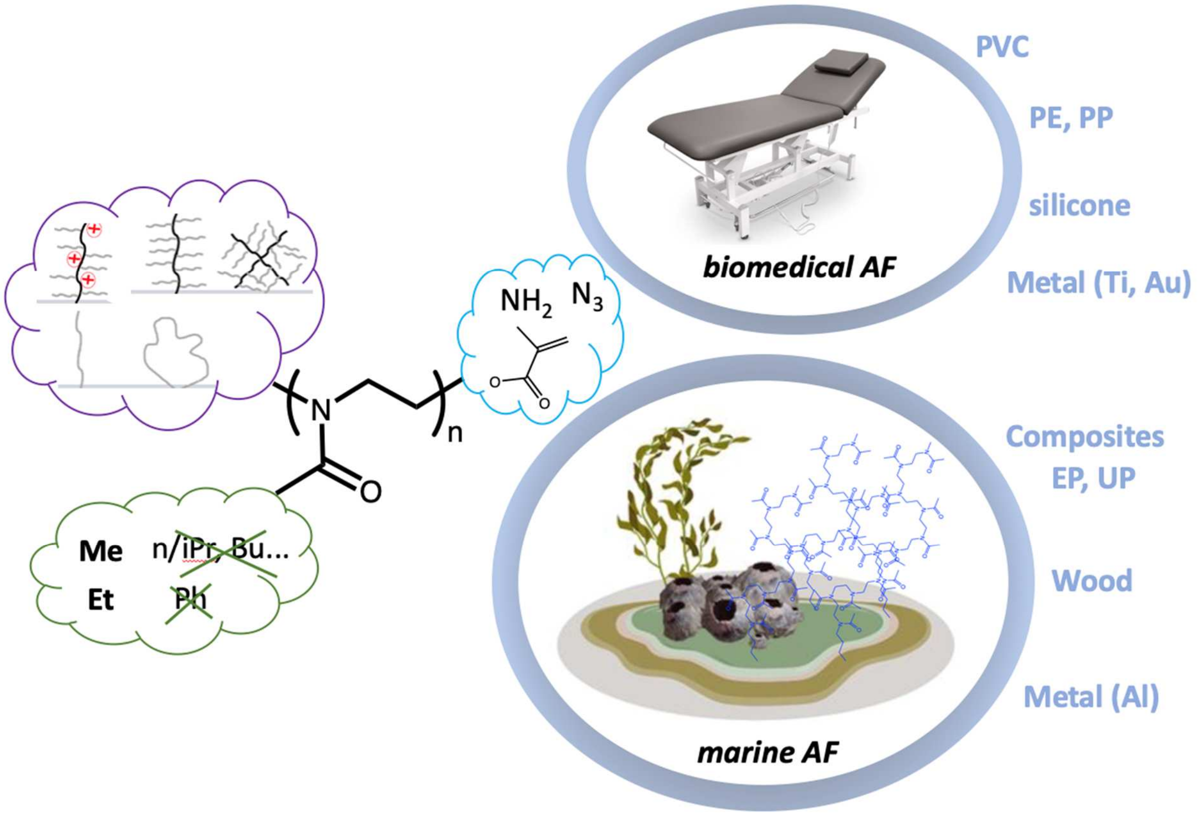


Fig. 2. Polyoxazoline design for marine and biomedical applications.

II. Tunable polyoxazolines for antifouling applications

Well-defined polyoxazolines are easily prepared by cationic ring-opening polymerization (CROP) of cyclic 2-R-2-oxazolines, qualified of living and controlled processes providing predetermined length chains according to the initial initiator/monomer ratio. Various oxazoline monomers with R substituent such as alkyl chain (Me, Et, nPr, iPr, Bu), phenyl... are marketed.[33] The CROP process requires an electrophilic initiator (noted as R_1X) in order to produce oxazolinium-ended growing chains. After a total consumption of the monomer, the growing chain can be used or killed by adding a nucleophilic terminating agent (TerH) able to react with the terminal reactive oxazolinium propagating species, according to ionic mechanism, and POx-CH_2X for covalent mechanism.[34] In both cases, the resulting POx chains bear a terminal Ter group. The family of POx is a versatile polymeric platform which can be functionalised by using different functional initiators or terminating agents, as attested by several recent reviews. [33],[35],[36],[37] To graft POx chains on the surface, the terminal route of functionalization is mainly employed to avoid any side-reaction during the propagation step of the polymerization and often requires protection and deprotection of reactive group of the initiator.[38] In the present topic, two pathways allow the surface modification by POx: i) the terminal oxazolinium-activated POx directly reacts with the reactive nucleophilic sites (Ter) of the surface (Route A) and, ii) the growing POx chains react with a terminating agent (TerH) and in a second time, they covalently bound to the complementary functions of the surface (Route B) (**Fig. 3**). We noted that another route of functionalization of POx -not employed in this topic- consists in the (partially) hydrolysis of oxazoline units into amines and generate linear poly(ethyleneimine) (L-PEI). The resulting reactive amine groups along the backbone further react with acyl units, acrylates, epoxy… [39],[40] All these chemical modifications are compatible with many metallic, polymeric, inorganic surfaces. A diametrically opposed route (Route C, **Fig. 3**) is the modification of both the core and the surface of a material by POx, especially employed for AF coatings in marine environment where the main commercial matrices mainly based on silicon are modified by a polymeric additive.

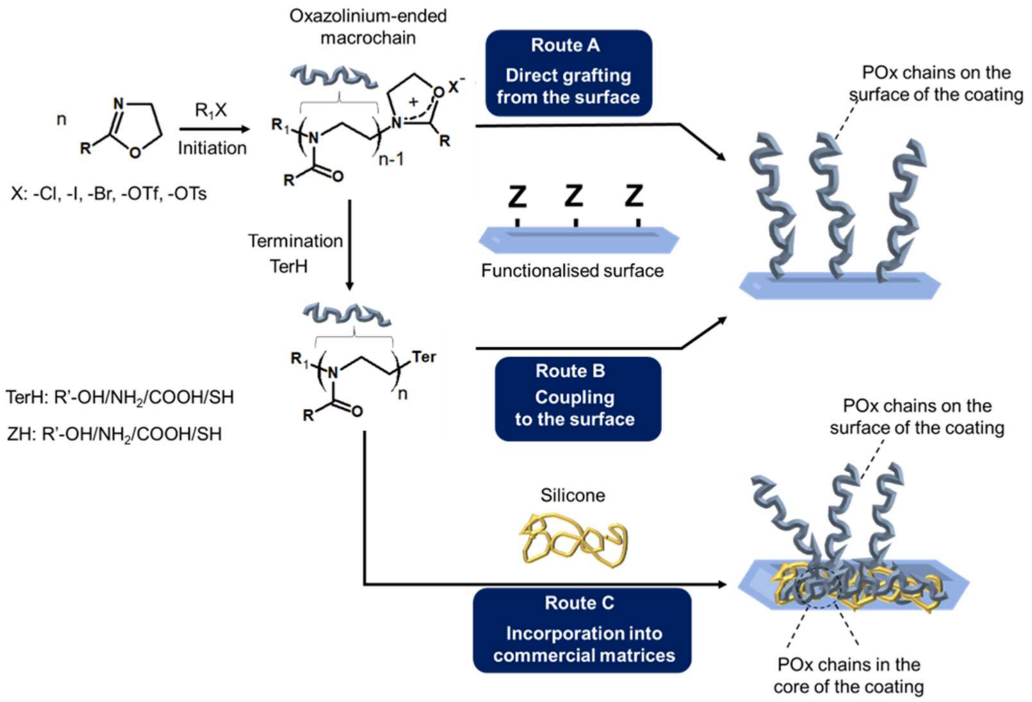


Fig. 3. Pathways to decorate a surface by POx chains.

II.1. Linear homopolymers

The most commonly macromolecular architecture of POx reported in the field of antifouling applications are the linear POx using hydrophilic monomers such as 2-methyl-2-oxazoline (MeOx) or 2-ethyl-2-oxazoline (EtOx) (**Fig. 4**). They are employed as precursors of hydrogel antifouling coatings permitting a hydration layer which could resist to the adsorption of marine organisms.[41] Surprisingly, no hydrophobic POx using PrOx, BuOx, PhOx… monomers as well as no purely polyoxazoline copolymers were reported. The use of POx chemistry in AF applications is limited to the chain-end functionalisation of linear homopolymers with various functions containing nitrogen functions, cyclic units, double C=C bonds, carboxyl (-COOH) or triethoxysilyl (-SiOEt$_3$), as it will be underlined in this section.

II.1.1. *N*-terminated linear POx

Several nitrogen-POx were described and show the multifaceted of the *N*-chemistry producing nucleophilic (amine), electrophilic (isocyanate) and click (N$_3$) reactivity. ω-amino-PMeOx or PEtOx were reported by different groups as efficient polymer coating for AF. The general strategy consists in the CROP polymerisation of the corresponding monomers using MeOTs (methyl p-toluenesulfonate) initiator followed by the end-capping with potassium phthalimide converted into amino end group by adding hydrazine monohydrate according to Gabriel reaction.[42],[43],[44] Another pathway applied by Weydert *et al.*[45] as well as Zhu *et al.*[46] used ammonia during the end-capping step of the polymerisation. However, compared to the first strategy, unwanted esterification reactions happen and decrease the reaction efficiency. Moreover, ω-N_3-POx were successfully prepared by Morgese *et al.*[47] and Yan *et al.*[44] using 2-azidoethylamine as end-capping agent at the end of CROP polymerisation. The third class of nitrogen-POx, ω-NCO-POx, is reported by Zhang *et al.*[48] as well as Du *et al.*[49] First, ω-OH-PMeOx was synthesized by CROP of MeOx, ended by sodium carbonated solution followed by the reaction of the terminal group with hexamethylene diisocyanate to yield the corresponding ω-NCO-POx. Noted the respect of 2:1 stoechiometry to avoid a dimerization of POx chains in the case of POx excess.

II. 1.2. Cyclic-terminated linear POx

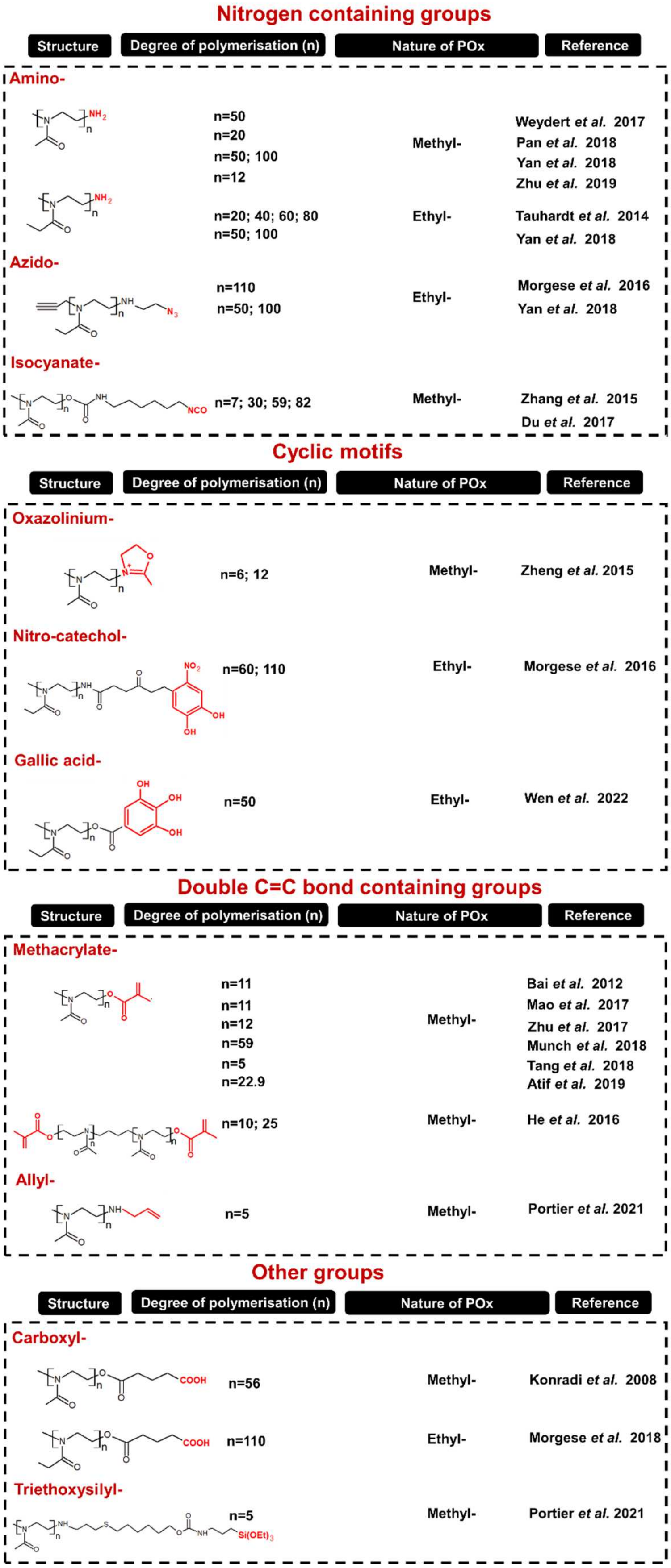
A particular terminal cyclic ring is the oxazolium unit before the termination step of the CROP which can act as reactive cyclic site for various surfaces as reported by Zheng *et al.*[50]. Otherwise, as stated by Morgese *et al.*[47] a nitro-dopamine group has been introduced in terminal position of POx chain by modification of PEtOx-NH_2 with succinic anhydride, followed by the reaction with nitro-dopamine. More recently, the esterification of PEtOx-OH with gallic acid (*i.e.*, a trihydroxy benzoic acid) followed by the oxidation of phenolic hydroxyl groups yielded a quinone-ended PEtOx.[51]

II. 1. 3. Unsaturated-terminated linear POx

The two significant examples of unsaturated end group of linear POx are the methacrylic and allylic units. The methacrylation of PMeOx has been largely explored by Schubert *et al.* to elaborate brush copolymers, as it will be further illustrated in this review. In the case of methacrylate-ended PMeOx, a common strategy involves the end-capping of oxazolinium active-ended group of PMeOx with methacrylic acid.[52],[53],[54],[55],[56],[57],[58] We noted the extensive literature on this functionalization due to the possible by-products, the uncomplete termination. Using mono or difunctional initiators, methacrylated monomers or crosslinkers can be synthesized. Furthermore, the end-capping by using allylamine led to allyl-ended PMeOx, as stated by Portier *et al.*[59] which then can be modified by thiol-ene coupling.

II. 1. 4. Other end-functionalisations of linear POx

Carboxylic acid and trialkoxysilane groups can be introduced at the end of POx backbone and crosslinked with silicone matrix specially used in marine applications. For the first case a classical route consists in the reaction of POx-OH with glutaric anhydride to produce ω-COOH ended POx (with Me or Et as alkyl pendent groups), as previously shown by Konradi *et al.*[60] and Morgese *et al.*[61] Recently, Portier *et al.* prepared triethoxysilane ended PMeOx (PMeOx-$SiOEt_3$) after the reaction between mercaptohexanol ended PMeOx with 3-(triethoxysilyl)propyl isocyanate.[59]



Nitrogen containing groups

Structure	Degree of polymerisation (n)	Nature of POx	Reference
Amino-			
	n=50 n=20 n=50; 100 n=12	Methyl-	Weydert *et al.* 2017 Pan *et al.* 2018 Yan *et al.* 2018 Zhu *et al.* 2019
	n=20; 40; 60; 80 n=50; 100	Ethyl-	Tauhardt *et al.* 2014 Yan *et al.* 2018
Azido-			
	n=110 n=50; 100	Ethyl-	Morgese *et al.* 2016 Yan *et al.* 2018
Isocyanate-			
	n=7; 30; 59; 82	Methyl-	Zhang *et al.* 2015 Du *et al.* 2017

Cyclic motifs

Structure	Degree of polymerisation (n)	Nature of POx	Reference
Oxazolinium-			
	n=6; 12	Methyl-	Zheng *et al.* 2015
Nitro-catechol-			
	n=60; 110	Ethyl-	Morgese *et al.* 2016
Gallic acid-			
	n=50	Ethyl-	Wen *et al.* 2022

Double C=C bond containing groups

Structure	Degree of polymerisation (n)	Nature of POx	Reference
Methacrylate-			
	n=11 n=11 n=12 n=59 n=5 n=22.9	Methyl-	Bai *et al.* 2012 Mao *et al.* 2017 Zhu *et al.* 2017 Munch *et al.* 2018 Tang *et al.* 2018 Atif *et al.* 2019
	n=10; 25	Methyl-	He *et al.* 2016
Allyl-			
	n=5	Methyl-	Portier *et al.* 2021

Other groups

Structure	Degree of polymerisation (n)	Nature of POx	Reference
Carboxyl-			
	n=56	Methyl-	Konradi *et al.* 2008
	n=110	Ethyl-	Morgese *et al.* 2018
Triethoxysilyl-			
	n=5	Methyl-	Portier *et al.* 2021

Fig. 4. Functionalized linear POx homopolymers.

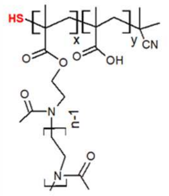
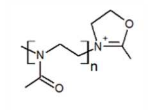
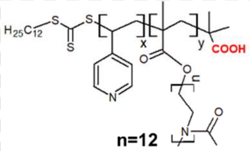
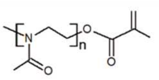
II.2. Brush copolymers

Compared to the linear polymers, the brush polymers are constituted by a polymer backbone decorated by densely packed polymeric side chains. This type of architecture creates a denser and even more impenetrable layer, which is highly desired for antifouling applications.[9] Functionalized linear POx homopolymers described previously also served for the synthesis of brush copolymers. These last can result from conventional (FRP) or controlled (CRP) radical polymerisation of methacrylated monomer which polymerized from reactive species located along a backbone. An alternative is the covalent reaction of living POx chains bearing terminal groups (*e.g.*, oxazolinium or carboxylic groups) with nucleophilic groups located along a backbone chain.

From a structural point of view, the POx containing brushes reported for antifouling applications are divided in two groups: monofunctionalised end-brushes and multiple functionalised brushes (**Fig. 5**). In the first class, the POx-containing brushes own a functional end chain as point of connection to the surface. For example, Zheng *et al.* prepared thiol-ended brushes [50] using a thiol-ended poly(methacrylic acid) (PMAA) on which oxazolinium-ended linear POx reacted with carboxylic acid groups. A second example was reported by Zhu *et al.*[55] where dithiocarbonate-end brushes were synthesized by RAFT copolymerization of 4-vinyl pyridine and methacrylate-ended linear POx by using a carboxyl-containing chain transfer agent.

In the second class, the brushes contain multiple functions along the polymer backbone. A common method consists in the RAFT copolymerization of a methacrylate-ended linear POx with a glycidyl containing methacrylate.[52],[54],[56],[58] Another approach is the modification of a functional polymer backbone (*e.g.*, containing reactive carboxyl or amino functions) by a functionalized POx. For instance, Weydert *et al.* grafted to poly(silanol acrylamide-*b*-acrylate-*b*-lysine) triblock copolymer an ω-amino-POx *via* the carboxylate groups of acrylate backbone.[45] Moreover, carboxylic-modified linear POx was grafted by amidation to the amino groups of deprotonated poly(L-lysine) (PLL), as described by Konradi *et al.*[45] and Morgese *et al.*[61]

End-functionalised

Polymer Architecture	Structure of the POx part	Nature of POx	Reference
 n=6; 12	 n=6; 12	Methyl-	Zheng *et al.* 2015
 n=12	 n=12	Methyl-	Zhu *et al.* 2017

Multiple functionalised

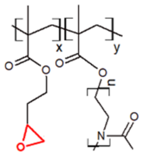
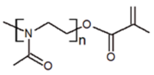
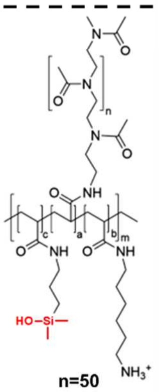
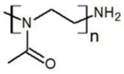
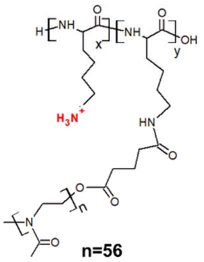
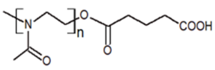
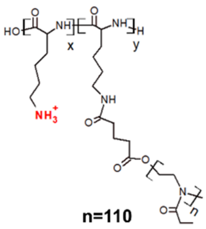
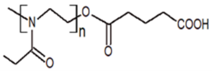
Polymer Architecture	Structure of the POx part	Nature of POx	Reference
 n=11 n=11 n=59 n=22.9	 n=11 n=11 n=59 n=22.9	Methyl-	Bai *et al.* 2012 Mao *et al.* 2017 Munch *et al.* 2018 Atif *et al.* 2019
 n=50	 n=50	Methyl-	Weydert *et al.* 2017
 n=56	 n=56	Methyl-	Konradi *et al.* 2008
 n=110	 n=110	Ethyl-	Morgese *et al.* 2018

Fig. 5. Brush polymers containing POx.

II.3. Branched and cyclic (co)polymers

Based on functionalized linear POx previously commented, branched copolymers have been reported (**Fig. 6**). The ramification comes from branched PEI (bPEI) which is connected by one of its terminal amine groups to NCO-POx as shown by Zhang *et al.*[48] while Wen *et al.*[51] used quinone terminal group.

A very sophisticated macromolecular architecture is the cyclic POx which were also designed for antifouling applications (**Fig. 6**). Compared to linear and even brush, the cyclic architectures provide a higher polymer density to the surface and in consequence an enhanced steric barrier that surpasses the typical entropic shield of a linear brush, therefore preventing the fouling. However, despite their unique features, the synthesis of cyclic architectures in large amounts is very costly and complex, which reversely limits their suitability for large-scale applications.[9] Morgese *et al.*[47] and Yan *et al.*[44] reported cyclic POx synthesised starting from a bifunctionalised POx containing α-alkyne and ω-azido groups using Huisgen intramolecular cyclisation.

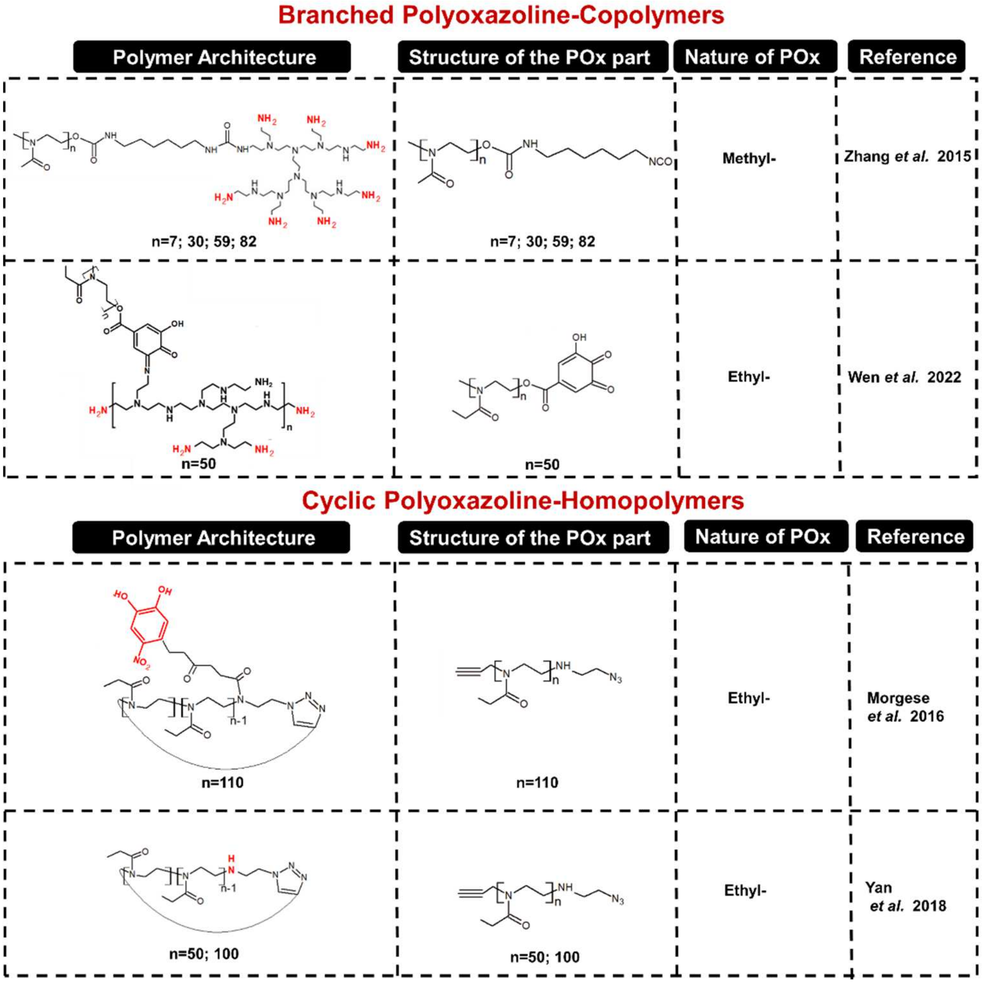


Fig. 6. Branched and cyclic POx polymers.

III. Modification of surface by polyoxazolines

The previous section emphasised the versatility of functionalisation of a variety of POx architectures reported until now in the field of antifouling applications. As mentioned before, the antifouling performances are correlated with the type of anchor between the POx chains and the surface. The first part of this section focuses on the covalent linking between various POx chains (linear, brush, branched and cyclic) and different surfaces, and point out the main chemical reactions which occur during the grafting step. The second part presents the main examples of POx-containing antifouling surfaces which are elaborated by using electrostatic interactions between POx chains and the surface.

III.1. Covalent modification of surfaces

The covalent bonding is one of the most widespread methods to connect POx to a surface. POx can be linked to the surface by *grafting to* or by *grafting from* approach. In the *grafting to* approach, functionalised POx (reactive sites symbolized by a red arrow in **Fig. 7**) reacts with the functionalised surface (reactive sites symbolized by a blue hook in **Fig. 7**) while in the *grafting from* approach, the surface contains functional groups able to initiate the polymerisation of POx where each macromonomer owns a polymerizable end-group (symbolized by a brown arrow in **Fig. 7**).

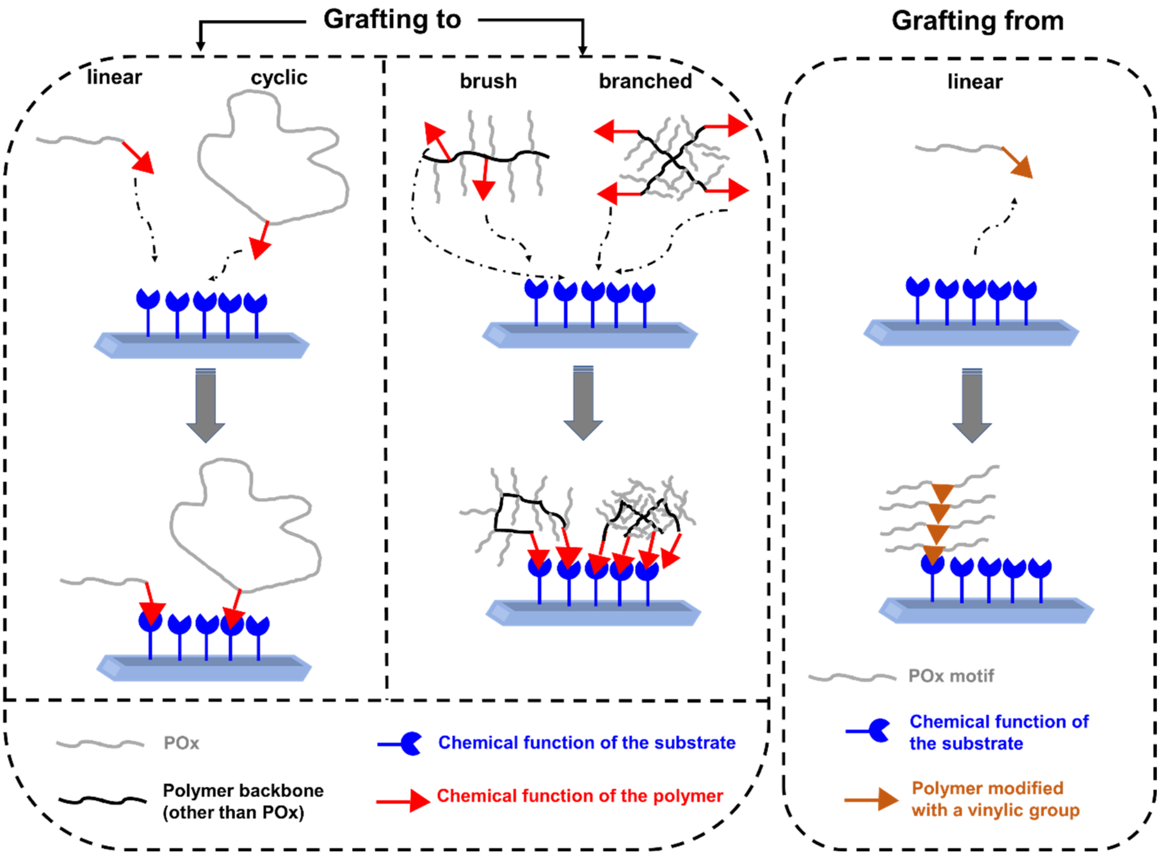


Fig. 7. General scheme of covalent bonding substrate-polymer: *grafting to* and *grafting from* approach.

III.1.1. *Grafting to* strategy

In the *grafting to* approach, the functional group of the POx is placed on the POx backbone (*e.g.*, linear and cyclic) or along another polymer backbone (*e.g.*, brush and branched) before reacting with the functional surface allowing its protection.

- ***Grafting to* by using functional groups along the POx backbone**

Previous reports indicated that functional groups along the linear or cyclic POx backbone can be grafted to various surfaces (glass, silicone or gold). In general, linear POx are covalently linked to functionalised surface bearing epoxy, amino, hydroxy, quinone, chloride or methacrylate groups (**Fig. 8**). From these, the use of epoxy functionalised surfaces (glass, silicone or gold) for the grafting of amino-containing POx is one of the most cited techniques in this field due to easiness of the synthetic pathway.[42],[44],[46]

Various surfaces containing amino or hydroxyl groups were reported by several groups to graft linear POx bearing cyclic units on surfaces. In this context, linear POx containing oxazolinium end group were connected to amino-modified silicon wafers/gold surfaces. This method, as stated by Svoboda *et al.*, is very promising since it enables the modification of surfaces by using PMeOx or PEtOx moieties with different chain lengths.[62] More recently, Wen *et al.* used free amino groups of PEI-coated PMMA surfaces with quinone groups of POx and produce imine coatings.[51] Furthermore, an efficient strategy was reported by Morgese *et al.* using phenolic end group of POx deposited on TiO_2 surfaces.[47] Another recent example reported by Portier *et al.* involved a silicone crosslinking between hydroxy activated PDMS surfaces and silanol modified PEtOx *via* siloxane bonds resulting from hydrolysis/condensation.[59] Otherwise, less examples concern the use of dopamine, chloride or methacrylate functionalised surfaces for the grafting of linear POx. For example, amino-modified POx were grafted on dopamine coated surfaces such as silicon, glass or gold.[43] Herein, the dopamine coated surface is prior oxidised in order to obtain quinone like functions which form imine bonds upon the reaction with amino-modified PMeOx. A less common method consists in the grafting of amino functionalised PEtOx on chloro-functionalised surfaces using an aromatic electrophilic substitution, as reported by Tauhardt *et al.*[42] Finally, methacrylated PMeOx photoreacted under UV radiation with a methacrylated surface to produce methacrylate coating by photo-crosslinking. [53]

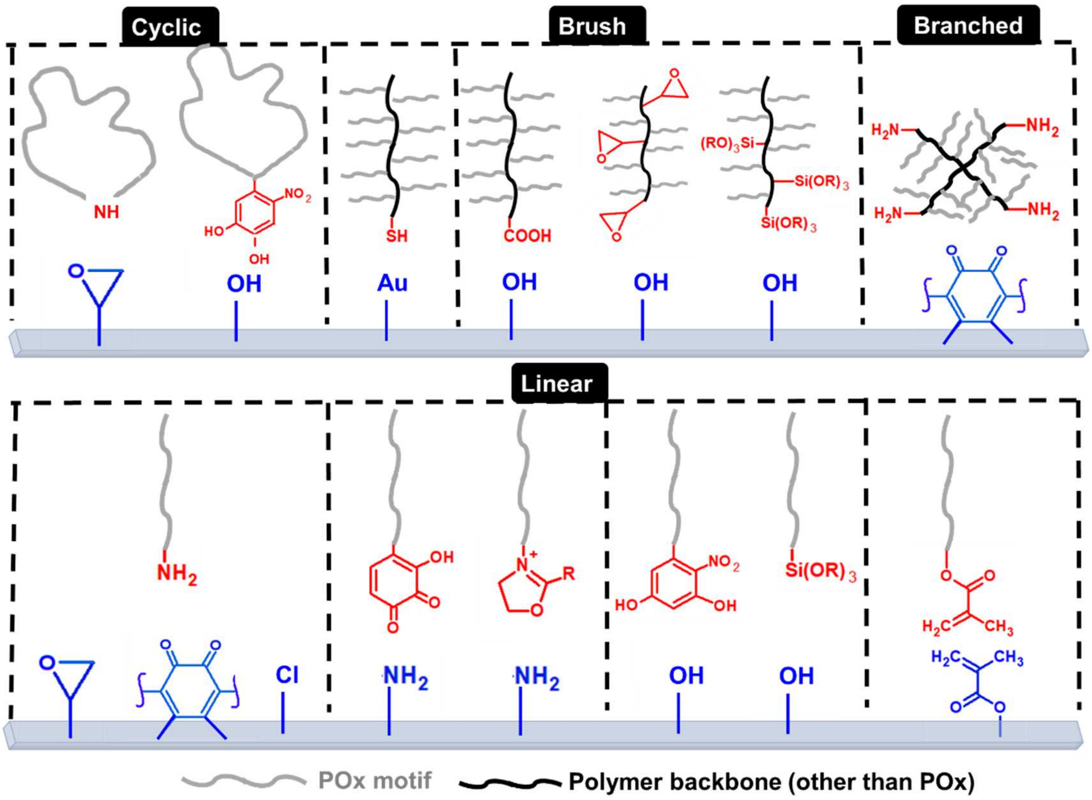


Fig. 8. Surface functionalization by linear, brush, cyclic and branched POx

While several examples of surface decoration by linear POx were reported in the literature so far, fewer examples were highlighted in the case of cyclic POx (**Fig. 8**). These architectures were particularly investigated by the group of Benetti. In general, cyclic POx covalently reacted to hydroxy or epoxy functionalised surfaces. For example, Morgese *et al.* used hydroxy activated TiO_2 surfaces with cyclic PEtOx containing phenolic groups.[53] Another strategy reported by Yan *et al.* involved secondary amino groups of cyclic PMeOx or PEtOx with epoxy modified silica surfaces.[44]

- ***Grafting to* by using functional groups along different polymer backbone than POx**

Previously it was shown that functionalised linear and cyclic POx can be linked to surfaces by using *grafting to* approach. For linear and cyclic POx, the functional group was placed onto the POx backbone. Otherwise, other architectures of POx such as brush or branched can be grafted to functionalised surfaces (**Fig. 8**). Brushes POx are generally composed of a polymer backbone and hydrophilic POx lateral arms. Similarly, branched POx copolymers are composed of a branched-shaped polymer backbone and lateral POx ramifications. For functionalized POx, the functional group involved in the grafting to the surface is attached this time to the hydrophobic polymer backbone. One or more functional groups can be attached to the main polymer backbone of the brush copolymer. For example, Zheng *et al.* prepared brush PMAA-*g*-PMeOx copolymers containing one thiol unit attached in terminal position of the PMAA backbone.[50] These thiol-ending PMAA-*g*-PMeOx brushes were furthermore functionalised on gold surfaces through gold-sulphur bonds. Moreover, mono carboxyl ended PVP-*g*-PMeOx brushes were chosen for the functionalisation of various solid surfaces including silicon, glass, gold, PDMS wafers as stated by Zhu *et al.* [55]

In another approach, the main polymer backbone of brush polymer contains multiple functional groups. Several examples illustrated the reaction of PGMA-*g*-PMeOx brushes containing pendant glycidyl groups to hydroxylated solid surfaces. Similar coated surfaces were also reported by the groups of Mao *et al.*,[54] Mumtaz *et al.*[63] as well as Munch *et al.*[56] Additionally, Weydert *et al.* prepared hydroxy activated SiO_2 surfaces involved the reaction between PLL-*g*-PMeOx brushes containing multiple silanol ending functions attached to the PLL backbone.[45]

The POx brush copolymers were intensively investigated for their grafting performances to solid surfaces in the field of antifouling. In opposition to the brush architectures, very few examples were cited in the case of branched copolymers (**Fig. 8**). For example, Zhang *et* *al.*[48] and Du *et al.*[49] showed that dopamine coated solid surfaces can be employed with amino-ended star PEI-g-PMeOx *via* imine covalent bonds.

III.1.2. Strategy of *grafting from*

Compared to *grafting to*, *grafting from* approach was less used to covalently link POx on solid surfaces. With the aim of obtaining antifouling POx surfaces, *grafting from* was applied in previous works reported by Zhang *et al.*[64] as well as by Tang *et al.* [57] (**Fig. 9**). A strategy applied by Zhang *et al.* consisted in the modification of glass surfaces with amino groups which reacted under UV with 2-isopropenyl-2-oxazoline in order to polymerize the isopropenyl groups. The resulting surface containing pendant oxazoline heterocycles (methyl, ethyl or n-propyl) was involved in CROP polymerisation in the presence of MeOTf leading to the formation of POx containing brush modified surfaces. In another approach, Tang *et al.* functionalised a gold-silicon coated surface with an ATRP bromine-ending agent which was involved in the ATRP polymerisation of a POx-methacrylate macromonomer.

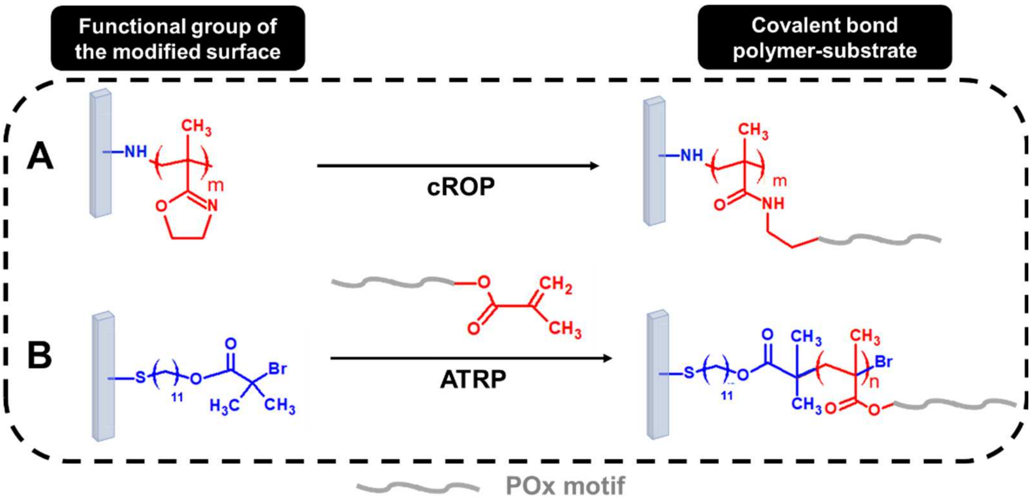


Fig. 9. Modification of surface by POx by using *grafting from* approach

III.2. Physical modification of the surface

POx can be also connected to solid surfaces by using electrostatic interactions instead of covalent bonds. In this case, different architectures with a brush or linear architectures can be deposited on solid surfaces *via* layer-by-layer (LbL) method (**Fig. 10**). This process consists in the deposition of POx derived architectures containing positive charged functions to solid surfaces which are modified with negative charged groups.

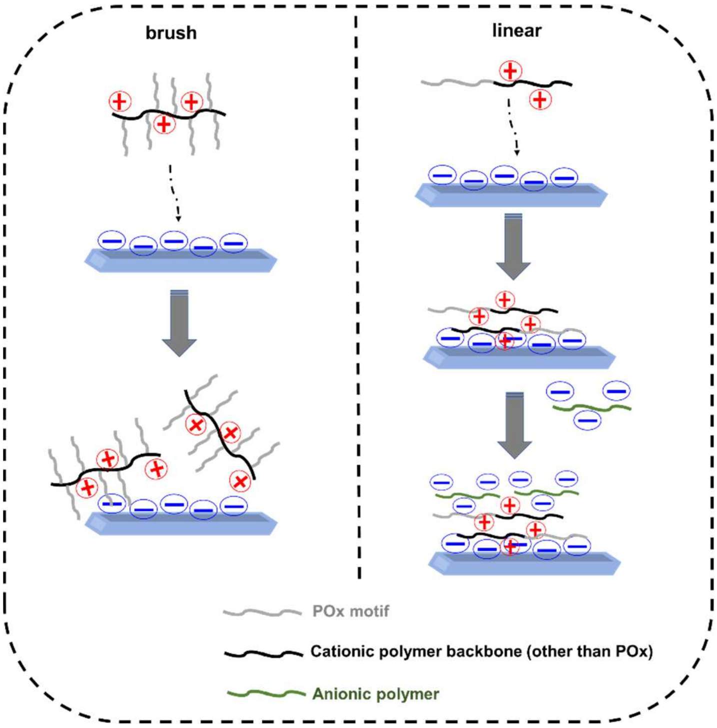


Fig. 10. General scheme of POx AF coatings by electrostatic interactions substrate-polymer.

For the reported brush copolymers, the cationic functions were attached to a polymer backbone (*i.e.*, in general PLL), whereas POx were used as extern arms. For example, Konradi *et al.* deposited brush PLL-*g*-PMeOx (number of PMeOx chains per lysine units PMeOx/PLL: 0.22) to anionic activated Nb_2O_5 coated silicon surfaces.[60] Furthermore, PLL-*g*-PMe(Et)Ox brushes were deposited *via* ammonium activated lysine groups to SiO_2 surfaces.

In addition, cationic copolymers containing POx were designed by using block copolymers composed of a POx block and a second block comporting positively charged units. These architectures were reported by Li *et al.*[65] and by He *et al.*[66] and used for the deposition on the hydroxyl activated silicon surfaces.

IV. Key parameters of POx for an efficient antifouling coating

IV.1. Hydrophilicity of grafted polymer

As shown in the previous examples, PMeOx and PEtOx were the two main polymer candidates used for antifouling coatings. This choice is related to the hydrophilic behaviour of POx which is one of the major requests to prevent the fouling process, as stated before.

Respectively, PMeOx displays a higher hydrophilicity than PEG while longer alkyl side-chains in POx led to a decrease of hydrophilicity.

IV.2. Length of polymer chains on the surface

As displayed before, a library of PMeOx and PEtOx with different DP_n were used in the preparation of antifouling coatings. The most various examples were noted in the case of linear architectures (**Fig. 4**) where PMeOx with DP_n ranging from 5 to 100 and PEtOx with DP_n between 20 and 110 were synthesised. The brush architectures in particular are composed of PMeOx as side arms, where the PMeOx chain length varied from 6 to 59, whereas additional examples were reported with PEtOx arms with a DP_n of 110 (**Fig. 5**). Moreover, PMeOx was an ideal candidate for branched architectures, where the length of PMeOx ranged between 7 and 82. Sophisticated branched or cyclic architectures (**Fig. 6**) were described when using PEtOx with DP_n ranging from 50 to 110.

IV.3. Grafting density in POx on surface

The grafting density (noted as σ) is a key parameter that might have a significant influence on the antifouling properties of POx coatings. Most of the time, the grafting density is expressed as the number of polymer chains (or sometimes as the mass of polymer) grafted per unit surface area of the substrate (*e.g.* chains/nm^2 or g/nm^2). However, the evaluation of grafting density is a challenging task because of technical reasons such as the type of the substrate or the existence of monolayers onto deposition process. For polyoxazoline coatings, as stated by several papers, a correlation between POx architecture, type of the linking with the substrate, and the grafting density is rather difficult, even impossible.[9] This section aims to take an overview of the main grafting density properties of POx coatings, in respect to the type of POx architecture (*e.g.*, linear, cyclic, brush or branched).

A general observation reported for the coatings prepared by using linear POx was that, whatever the substrate is, the grafting density decreases when increasing the DP_n of POx. For example, Svoboda *et al.* reported a significant variation of σ of oxazolinium ending POx (PMeOx and PEtOx) grafted on dopamine functionalised silicon wafers/gold substrates.[62] According to them, for PMeOx, σ varied from 1.8 ± 0.8 chains/nm^2 (DP_{19}) to 0.3 ± 0.1 chains/nm^2 (DP_{115}) while a similar trend was observed when using PEtOx. According to the authors, the decrease of the grafting density for high DP_n of POx was explained by the lower availability of reactive oxazolinium-end groups in the long polymer coils towards the amino groups of the dopamine coated surfaces. A similar tendency was reported by Morgese *et al.* for linear PEtOx containing phenolic cycles grafted on hydroxy modified TiO_2 surfaces. σ varied from 0.37 chains/nm^2 (DP $_{60}$) to 0.19 chains/nm^2 (DP$_{110}$).[47]

As for linear architectures, the cyclic POx showed the same trend of the decrease of σ when increasing the DP$_n$ of starting polymer. However, compared to linear architectures, the advantage of cyclic architectures is that they provide an enhanced steric stabilization of the surface, since for cyclic architectures, each graft loops at the grafting point. When using cyclic PEtOx with different DP grafted on epoxy substrates, Yan *et al.* reported a decrease of σ from 1.7 ± 0.3 chains/nm^2 (DP$_{51}$) to 0.8 ± 0.1 chains/nm^2 (DP$_{109}$).[44] However, for cyclic architectures with the same DP$_n$ of POx, the type of the substrate can slightly change the grafting density properties. Respectively, Morgese *et al.* reported that lower grafting densities (0.31 chains/nm^2) were obtained when using cyclic PEtOx (DP$_{109}$) grafted on hydroxyl activated TiO_2 surfaces.[47]

For brush copolymers, it is important to note that the grafting density depends on the brush length. For example, Zheng *et al.* prepared brush PMAA-g-PMeOx copolymers containing one thiol end group attached in terminal position of PMAA backbone.[50] The increasing of PMeOx length (DP$_{6\text{-}12}$) in the brushes prepared with a short PMAA (DP$_{20}$) led to a soft decrease of the surface coverage. However, the authors underlined significant differences of the surface coverage when changing the length of PMAA (DP$_{20\text{-}40}$), while using the same length of PMeOx. Respectively, (PMAA$_{20}$-*g*-PMeOx$_6$)-SH with shorter PMAA backbone provided much higher surface coverage than (PMAA$_{40}$-*g*-PMeOx$_6$)-SH brush prepared with longer PMAA backbone. The authors concluded that long length brushes are detrimental to obtain high coverage area of the gold surfaces.

In another example, the grafting performance of PGMA-*r*-PMeOx brushes (with different molar ratio PGMA/PMeOx: 1/1, 1/3 and 3/1) was expressed in terms of the thickness of the coating.[52] Respectively, the increase of PGMA content allowed to enhance the thickness of the resulting coatings from 5 nm (PGMA/PMeOx 1/3 molar ratio) to 48 nm (PGMA/PMeOx 3/1 molar ratio), which was a consequence of more covalent bonds formed between the glycidyl groups of PGMA and the hydroxylated surfaces. Similar coated surfaces were also reported by Mao *et al.* ,[54] Mumtaz *et al.*[63] and Munch *et al.*[56]

Moreover, no significant change of the grafting density was reported when using *grafting from* method instead of *grafting onto* approach. For example, Tang *et al.* reported a grafting density of 0.5 chains/nm^2 for PMeOx coatings obtained *via* grafting from approach starting from a functionalised gold-silicon coated surface modified with an ATRP bromine ending agent.[57]

V. Antifouling properties of POx surfaces

POxs were previously reported as antifouling surfaces against different micro-organisms (such as bacteria or marine organisms), as well as proteins or, in some cases, the cells. In this part, the main antifouling properties of POx are briefly correlated to POx architectures (*e.g.*, linear, cyclic, branched, brush, or positive charged linear copolymers), as illustrated in **Fig. 11**.

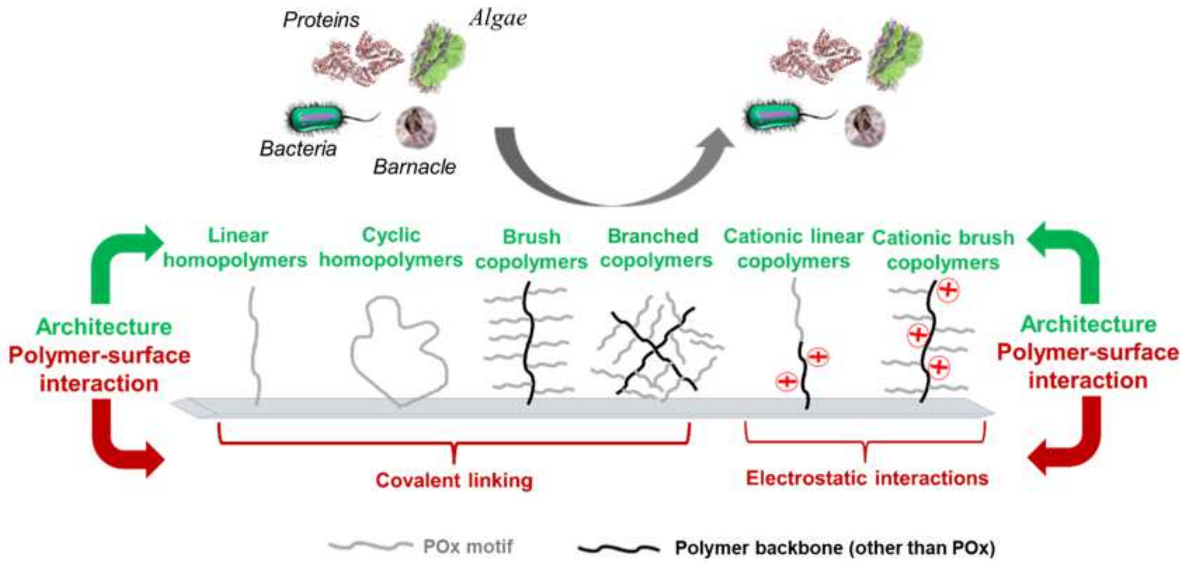


Fig. 11. Representative scheme of the scope of POx architectures in antifouling coatings.

V.1. Against bacteria

Figure 12 summarizes the main antifouling properties of POx against different bacteria. Significant contributions were reported by Tauhardt *et al.* who investigated the antifouling properties of linear PEtOx deposited on glass surfaces against five bacteria including *Aeromonas hydrophila/caviae, Sphingomonas paucimobilis, Pasteurella spp., Aeromonas salmonicida,* and *Leuconostoc spp.*[21] PEtOx coatings showed a clear reduction of the cell adhesion after 15 h (*i.e.*, up to 66%, evaluated by confocal laser scanning microscopy) compared to the pristine glass surfaces. Moreover, no significant difference related to the cell adhesion was observed between PEtOx films modified by glycidyl (named as GOPTMS) or chloro-tetraether lipid containing linkers (named as TEL). However, the percentage of dead bacteria is another property to be considered during the evaluation of the antifouling performance of a material. From this point of view, the authors underlined that the shortest length (DP_{20}) of PEtOx attached to the surface by a TEL lipid linker expressed the best compromise in terms of simultaneous lowest biofilm formation and highest amounts of dead bacteria.

Otherwise, Portier *et al.* recently studied the antifouling properties of PMeOx crosslinked in siloxane matrix against *Pseudomonas Aeruginosa* and *Staphylococcus Aureus* [59] and compared to PEG-siloxane control sample. The assays performed on *Pseudomonas Aeruginosa* showed that after 30 min, the concentration of bacteria released from PMeOx-silicone surfaces was significantly higher than that released from the uncoated PDMS surface (*i.e.*, 1430 ufc/mL *vs.* 358 ufc/mL, ufc is defined as colony forming unit). However, no significant difference related to the concentration of the released bacteria was observed in comparison with PEG-silicone coatings. Concerning *Staphylococcus Aureus*, the results showed that no bacteria were released from PDMS surfaces while a significant concentration of released bacteria was detected with PMeOx-silicone surfaces (*i.e.*, 250 ufc/mL). Nevertheless, the authors noted that the PMeOx-silicone surfaces were 5 time less effective than PEG-silicone derivatives, who released higher amounts of bacteria (*i.e.*, 1210 ufc/mL). A possible explanation stated by the authors was that PMeOx silicone coatings were less compatible with PDMS surfaces compared to PEG silicone coatings used as controls which might influence the antifouling performance against *Staphylococcus Aureus*. Even so, the main conclusion was that despite of the future improvements of PMeOx silicone coatings requested in order to obtain better antifouling results, the use of PMeOx reduced the fouling release ability in comparison to uncoated PDMS surfaces. Other POx than PMeOx and PEtOx would be more appropriate to these silicone matrices, more compatible with them.

Antifouling applications of brush POx copolymers were also tested against bacteria. For example, He *et al.* investigated the AF properties of α,ω-dimethacrylate PMeOx covalently linked to methacrylate functionalised silicon wafers against *Escherichia Coli* and *Staphylococcus Aureus*.[53] Unfortunately, after 1 h of incubation, a very soft decrease of the bio adhesion of both bacteria related to uncoated silicon wafers was detected (*i.e.*, 0.5 and 1.4% for PMeOx coatings and uncoated surfaces, respectively). A possible explanation stated by the authors was related to the low thickness of the coatings which might be a reason for the low differences of the antifouling properties. In another study, glycidyl functionalised PMeOx copolymer brushes deposited on hydroxyl modified cellulose substrates were investigated by Munch *et al.* for their AF properties against three types of bacteria, *Bacillus subtilis*, *Escherichia coli* and *Saccharomyces cerevisiae*.[46]

In addition, linear cationic copolymers containing PEtOx were reported as antifouling coatings against bacteria. Recently, Li *et al.* designed by layer-by-layer process of PAA/PEtOx-EI (7% EI) coatings deposited on glass/silicone substrates and tested their AF properties against *Escherichia coli* and *Bacillus subtilis*.[65] As control, hydrophilic polycationic PAA/PAH coatings was used. After 6 h of incubation in the presence of both bacteria, the PAA/PEtOx-EI coatings showed very low amounts of bacteria attached to the surface. However, no difference was reported related to the type of the substrate used (glass or silicone). The authors reported that the density of *Escherichia coli* for coated substrates was reduced by 98% in comparison to the control film (*i.e.,* a density of $2.0 \pm 0.6 \times 10^4$ cells/mm^2) while the density of *Bacillus subtilis* was reduced by 5% (*i.e.*, $1.0 \pm 0.3 \times 10^4$ cells/mm^2) which underlined that the PEtOx coating remarkably improved the antifouling properties. This result was additionally explained by the high surface concentration of coatings as well as the unique structural characteristics of PAA/PEtOx-EI coatings. These coatings contain fewer cationic charged secondary amino groups than PAA/PAH controls which significantly decreased the interactions with negatively charged surfaces of cell bacterial envelopes. In addition, PEtOx-EI generates a hydration layer on the coating surface which can effectively repel the bacterial attachment.

Inspired by the study of Li *et al.*,[65] He *et al.* investigated the effect of PAA/PEtOx-EI coatings deposited by LbL on the antifouling resistance against *Escherichia coli* and *Staphylococcus aureus* on hydroxy activated silicon wafers.[66] The number of deposited layers significantly influence the AF properties. A number of bilayers of PAA/PEtOx-EI ranged from 1 and 8 and led to an effective protection against *Escherichia coli*, while the use of coatings providing less than 5 bilayers was less effective to prevent the attachment of *Staphylococcus aureus*. These differences in bacterial attachment resistance were related to different cell sizes and /or cell membrane properties.

Overall, the main examples of POx AF coatings against bacteria were represented by those containing methyl or ethyl substituents and providing linear or brush architectures. Even POx AF coatings decreased significantly the number of attached bacteria in comparison to standard references such as PEG or PMDS, there is no direct correlation referenced in the literature between the DP_n of POx and the AF properties. However, in the case of coatings deposited by LbL, the increase of the number of POx layers (and thus the coating thickness) improved the AF properties against bacteria.

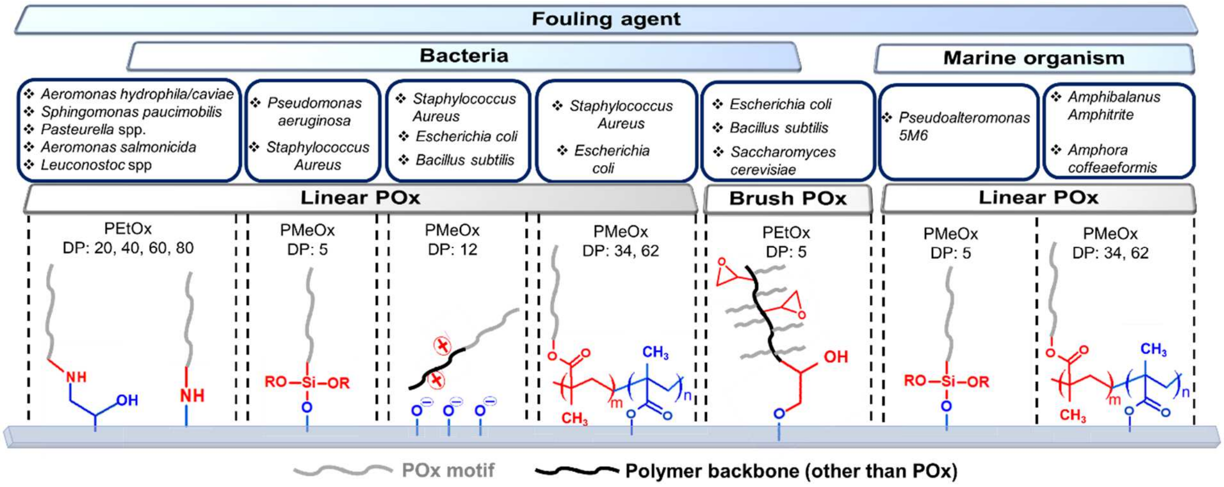


Fig. 12. Type of bacteria and marine organisms tested on POx antifouling coatings.

V.2. Against marine organisms

In comparison to the examples of POx-containing architectures used to prevent the adhesion of bacteria, very few examples of POx concern their use as antifouling materials for marine organisms (**Fig. 12**). He *et al.* reported PMeOx coatings deposited on silicon wafers for their AF properties against *Amphibalanus Amphitrite* (a cyprid larvae) and *Amphora coffeaeformis* (an algae).[53] In this regard, the amount of settled organisms (cyprid larvae and algae) on the PMeOx coatings were evaluated. The settlement of cyprid larvae on clean silicon wafers (used as reference) was close to 50% while for PMeOx coated samples it was less than 3%. Moreover, PMeOx coatings showed a different antifouling behaviour against *Amphora coffeaeformis*. In this case, a decrease of the settled algae density from 82 cells/m^2 (uncoated silicon wafer) to 40 cells/m^2 (PMeOx coated silicon wafer) was observed. The authors concluded that the PMeOx coatings were more efficient as repellents for larvae than for algae, these results being consequent with those previously obtained by the same research group. Another recent work was reported by Portier *et al.* who investigated the antifouling behaviour of linear PMeOx ended with siloxane groups covalently linked to PDMS surfaces against *Pseudoalteromonas 5M6*.[59] In this case, the formulation is based on amphiphilic POx additive incorporated into reactive silicone matrices. Compared to PEG-siloxane coatings used as control experiments, PMeOx significantly increases the concentration of released micro-organisms (*i.e.*, 2.58 × 10^3 ufc/mL for PMeOx-silicone surface, against 4.59 × 10^4 ufc/mL for PEG-silicone coatings).

V.3. Against proteins and cells

Various macromolecular architectures of POx (linear, cyclic, brush or branched) were reported as antifouling materials against proteins or cells (**Fig. 13**). First examples of linear POx were reported by Morgese *et al.*[47],[44] who used PEtOx ended by nitroquinone groups with TiO_2 surfaces as antifouling materials against fibrinogen, albumin, immunoglobulin G and full human serum. Since PEtOx has a cloud point (CP) around 60 °C, two sets of experiments, at room temperature (RT) and at the CP were conducted. A correlation between the temperature and the protein adhesion was observed for fibrinogen, albumin, and immunoglobulin G whereas no significant difference was noted when varying the DP_n of the PEtOx. An increase of polymer chain density on TiO_2 was noted with the temperature for both tested DP_n (*i.e.*, 0.18 and 0.37 chains/nm^2 at RT and CP, respectively), which was furthermore consequent with a slight decrease of the physiosorbed protein layer (*i.e.*, from 4 nm at RT to less than 0.5 nm at CP). However, with full human serum, the reduction of the deposited biofilm layer was less evident at RT and CP. A possible explanation according to Morgese *et al.* was that the full human serum is a highly contaminated medium with various proteins and enzymes which might influence the antifouling properties of PEtOx coatings.

Additional attempts were realized by Yan *et al.* who showed that SiO_2 surfaces modified by PMeOx and PEtOx can display promising repellent properties against albumin and fibrinogen.[44] After 3 h of immersion in the presence of albumin and fibrinogen, both PMeOx and PEtOx coatings reduced the adhesion of both proteins by 50%. However, no significant difference on the antifouling properties was observed when the DP_n of POx varied. By using the same chemistry, Zhu *et al.* reported PMeOx coatings on glass wafers with AF properties against bovine serum albumin (BSA).[46] A coherent relationship between the grafting density (*i.e.,* calculated from the number of anchor units on glass wafer) and the amount of adsorpted BSA protein. They observed that an increase of grafting density from 0.9 to 1.9 chains/nm^2 decreases the fluorescence intensity by 39 and 90% respectively, compared to uncoated glass wafers after 2 h of immersion in BSA. These results confirmed that a high grafting density (expressed as a high content of glycidyl units in the anchoring coating) enable the introduction of more PMeOx chains into the coating which thus improve the antifouling properties. The same authors tested PMeOx coatings deposited on silicon wafers against platelet adhesion. As for BSA, Zhu *et al.* noted that the PMeOx prevented the platelet adhesion when increasing the grafting density of the wafers, which allowed the deposition of high amounts of hydrophilic polyoxazolines.[46]

Moreover, Pan *et al.* reported the deposition of mixtures of PMeOx and PAA on dopamine coated surfaces against BSA protein.[43] The interest of PAA for AF coatings is the pH sensitivity, with a pK_a around 5, allowing the modulation of antifouling properties of coatings in different pH media. At pH 7.4, PAA with higher DP_n than that of PMeOx led to a better control of the protein adsorption/desorption behaviour (*i.e.*, a composition of PMeOx (DP_{23})/PAA (DP_{80}) adsorpted 1175.6 ng/cm^2 of BSA and desorpted 87.0% of the protein related to PMeOx coated surface used as control). When the pH > pK_a, the density of negative charges of PAA chains increases and the charged PAA chains stretch out as much as possible to reduce electrostatic repulsion between negative charges, which improves in consequence the antifouling properties.

In another study, Svoboda *et al.* reported that whatever the increase of the PMeOx length is, the adsorpted human blood plasma (HBP) decreased to about 30%.[62] Moreover, PMeOx coatings had superior AF properties than PEtOx coatings at same surface-related parameters (*i.e.*, 40% of protein adsorpted for PMeOx *vs.* 70% for PEtOx). According to them, these differences were most probably caused by steric barrier effects due to chain prolongation which boosted out the AF properties of the coatings in contact with the biological media.

Significant contributions on the AF properties of PEtOx surfaces functionalized with gallic acid (PEtOx-GA) against BSA, lysozyme and myoglobin adhesion were introduced by Wen *et al.*[51] 70% less BSA were adsorbed onto the surface compared to the uncoated surface. Moreover, after 24 h, PEtOx-GA coatings showed ~65% less adsorption of lysozyme and ~30% less adsorption of myoglobin. According to them, the differences between the amounts of absorpted proteins were explained by the fact that each protein provides a different isoelectric point and in consequence, a different ionic strength.

POx brush copolymers were the most cited architectures in the field of AF materials. For example, Zhang *et al.* prepared copolymer brushes containing different poly(2-alkyl-2-oxazoline) side chains and investigated their antifouling behaviour against the adsorption of fibronectin.[64] In particular, they studied the influence of the type of alkyl linker attached to the POx side chain (*i.e.*, methyl, ethyl, n-propyl) as well as the chain length (for PMeOx containing brushes), in correlation with the amount of the adsorpted fibronectin. The authors concluded that the increase of the hydrophobicity of the alkyl linker increases the amount of adsorpted fibronectin which was translated by a low antifouling behaviour. Consequently, low amounts of fibronectin (below 10 ng/cm^2) were adsorpted by PMeOx and PEtOx related to PnPrOx (90 ng/cm^2). The authors noticed that the increase of PMeOx chain length (from DP 6 to DP 12 and DP 18) improved AF behaviour. Short side chains decrease fibronectin adsorption (from 600 to 50 ng/cm^2) while long side chains suppress protein adsorption (less than 10 ng/cm^2).

Many examples of copolymer brushes containing POx side chains on silicon or glass wafers were reported as antifouling materials against BSA. Bai *et al.* shown that the increase of the PMeOx molar ratio in PMeOx-*r*-GMA brushes (from 1/1 to 3/1) induces a consequent decrease of the amount of adsorbed BSA (from 20 to less than 5 units).[52] These results underline that the hydrophilicity increases the protein resistance. Similar behaviour was observed by Mumtaz *et al.*[63] with silicon or glass substrates as well as by Munch *et al.*[56] who performed investigations on cellulose coated SiO_2 substrates.

Zheng *et al.* investigated AF materials against BSA, fibrinogen and lysozyme using thiol ended PMAA-*g*-PMeOx brush coatings (named $PMAA_{40}$-*g*-$PMeOx_6$-SH, $PMAA_{20}$-*g*-$PMeOx_6$-SH and $PMAA_{20}$-*g*-$PMeOx_{12}$-SH) deposited on gold surfaces.[50] Globally, the increase of PMeOx length while keeping constant low PMAA chain length produces a substantial decrease of the adsorption of the three proteins related to the uncoated gold surface (*e.g.*, the BSA adsorption decreased to 63 and 85% for $PMAA_{20}$-*g*-$PMeOx_6$-SH and $PMAA_{20}$-*g*-$PMeOx_{12}$-SH, respectively). Similar results were stated for fibrinogen. Otherwise, the authors underlined that for lysozyme, the amount of adsorbed protein was lower (*e.g.*, the BSA adsorption of 38 and 48.5% for $PMAA_{20}$-*g*-$PMeOx_6$-SH and $PMAA_{20}$-*g*-$PMeOx_{12}$-SH, respectively). These differences were explained by the electrostatic interactions which play a significant role in the antifouling performance. At physiological pH, the PMAA backbone contains carboxylate residues providing negative charges. Consequently, the polymer adsorbs positively charged proteins such as lysozyme, and repels negatively charged proteins such as fibrinogen and BSA.

In another study, Weydert *et al.* take advantage of brush copolymers providing polyacrylamide backbone and grafted PMeOx units (PAcrAm-*g*-PMeOx) modified by cationic lysine moieties and silanol groups for the covalent linking to gold surfaces.[45] PAcrAm-*g*-PMeOx reduced the nonspecific BSA binding with 90% compared to the gold surface used as reference (392 ng/cm^2). As stated by the authors, the results were relatively comparable to commercial PLL-g-PEG which are currently used as antifouling materials (*i.e.*, that reduced more than 95% the BSA binding).

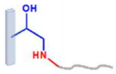
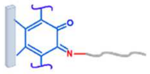
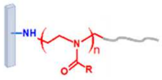
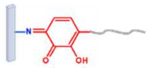
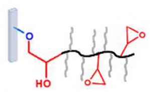
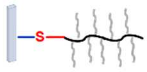
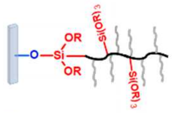
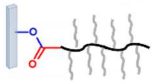
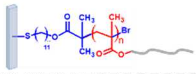
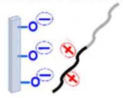
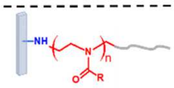
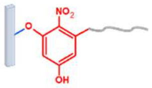
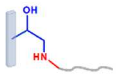
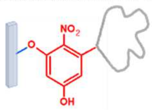
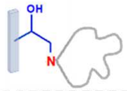
Furthermore, significant results of AF properties were reported by Zhu *et al.* who prepared coatings based on PMeOx-*g*-PVP brush copolymers under UV irradiation on silicon/glass/gold/PDMS substrates.[55] The 4-vinyl pyridine (VP) segment in copolymer promotes the thickness of coating after UV irradiation while PMeOx segment mainly improves the hydrophilicity of the coating. The UV irradiation of the resulting coatings significantly reduced the adhesion of different proteins (BSA) or cells (HUVEC, blood platelets) (*i.e.*, the fluorescence intensity decreased with more than 90% after UV irradiation). These results emphasize the efficiency of UV irradiation to crosslink the hydrophobic VP part of the brush and allowed an effective anchoring of the PMeOx chains on the substrate improving the protein resistance.

While POx brush copolymers were largely explored for AF applications against the proteins, only few examples of cyclic POx were reported in this field most certainly explained by the difficulty of access. Morgese *et al.* designed cyclic PEtOx using nitroquinone moieties on hydroxy-activated TiO_2 substrates as AF coatings against three proteins (fibrinogen, albumin and immunoglobulin G) as well as human serum.[47] These cyclic architectures emphasized a CP temperature around 52 °C corresponding to PEtOx thermo-sensitivity. The authors investigated the effect of the temperature onto the AF behaviour of the coatings. At RT, the cyclic brushes displayed the lowest amount of physiosorbed proteins and human serum (*i.e.*, the protein deposited layer was less than 1 nm for cyclic architectures). Moreover, at 52 °C, the cyclic POx showed nearly a 50% reduction of adsorpted proteins from human serum compared to the linear homologous. The authors correlated these results to the grafting density of coatings which depends on the architecture topology. More exactly, at RT, the density of grafted chains of a cyclic brush is expected to be much higher than a linear analogous, which means that the cycles are less sterically accessible towards protein adhesion, providing in consequence better antifouling properties. Then, at CP, the cyclic architectures become more compact than at RT, which thus slightly increase the packing density of the coatings (*i.e.*, 0.31 and 0.2 chains/nm^2 at CP and RT, respectively) and consequently improve the antifouling performance. Similar results were later cited by Yan *et al.* who prepared cyclic PMeOx and PEtOx with AF properties against albumin and fibrinogen proteins.[44]

As for the cyclic architectures, branched POx containing topologies were barely explored in the literature so far by Zhang *et al.*[48], Du *et al.*[49] and Wen *et al.*[51] Zhang *et al.* noted that two selected branched copolymer candidates, PEI-*g*(70)-PMeOx(5K) and PEI-*g*(70)-PMeOx(7K) (*i.e.,* where g(70) represents the average number of PMeOx chains per PEI molecule) deposited on PDA-coated glass films exhibited non-cytotoxicity and the highest resistance to protein adsorption (96–99% relative to the bare gold surface) and cell attachment (97–99% relative to the bare glass surface) as well as the complete inhibition against platelet adhesion.

Lastly, linear cationic copolymers containing POx were reported as AF materials against proteins. Konradi *et al.* studied cationic PLL backbone containing grafted PMeOx chains deposited on Nb_2O_5 substrates. PLL-*g*-PMeOx spectacularly decreased the amount of adsorpted proteins (*i.e.*, less than 2 ng/cm^2 of protein deposited for PLL-*g*-PMeOx *vs.* 229 ng/cm^2 for uncoated substrate).[60] Inspired by the work of Konradi *et al.*, Morgese *et al.* investigated PMeOx-*g*-PLL, PEtOx-*g*-PLL, as well as mixed brush copolymers consisting of a cationic PLL backbone and hydrophilic arms such as PEG and PMeOx.[61] These brushes were grafted on silica-activated surfaces by electrostatic interactions between positive charged PLL and negative charges of silica. PEG/PMeOx-*g*-PLL mixed brushes fully prevented the adsorption of different proteins from full human serum (FHS), providing similar antifouling properties to those observed for pure PMeOx-*g*-PLL coatings (*i.e.*, 0 ng/cm^2 of adsorpted FHS for both brushes). In contrast, mixed PEG/PEtOx-*g*-PLL brushes showed a substantial improvement of protein resistance compared to single PEtOx-*g*-PLL brushes (*i.e.*, 70 ng/cm^2 of adsorpted FHS for PEG/PEtOx-*g*-PLL *vs.* 320 ng/cm^2 for PEtOx-*g*-PLL). Nevertheless, compared to PMeOx containing architectures (single or mixed), PEtOx brushes are less hydrophilic and thus less effective to avoid the protein adhesion, due to possible van der Waals interaction between the PEtOx segments and the proteins.

To a large extent, these examples prove that various POx architectures were used as AF coatings against proteins and cells. As observed for bacterial AF, there is no relationship between the DP_n of POx and the amount of removed protein/cell. However, the AF ability for protein removing is highly influenced by the polymer architecture (linear, cyclic, brush, etc.) while brush and cyclic architectures were the most effective. This is because, in comparison to linear architectures, brush and cyclic POx are less sterically accessible towards protein adhesion as a result of high packing density, which thus provides better antifouling properties.

Type of removed Protein/cell	POx architecture		Surface-polymer architecture	Reference
Bovine Serum Albumin (BSA)	Linear homopolymer	PMeOx DP: 20		**Zhu *et al.* 2019**
		PMeOx DP: 23		**Pan *et al.* 2018**
		PMeOx DP: 19, 115		**Svoboda *et al.* 2019**
		PEtOx DP: 5		**Wen *et al.* 2022**
	Brush copolymer	PMeOx DP: 11, 12, 23		**Bai *et al.* 2012** **Mumtaz *et al.* 2018** **Munch *et al.* 2018** **Atif *et al.* 2019** **Mao *et al.* 2017**
		PMeOx DP: 6, 12		**Zheng *et al.* 2015**
		PMeOx DP: 52		**Weydert *et al.* 2017**
		PMeOx DP:5		**Zhu *et al.* 2017**
		PMeOx DP: 5		**Tang *et al.* 2018**
	Branched copolymer	PMeOx DP: 30, 70, 100 PEtOx DP: 5		**Du *et al.* 2017** **Wen *et al.* 2022**
	Cationic linear copolymer	PMeOx DP: 56 PMeOx DP: 100 PEtOx DP: 100		**Konradi *et al.* 2008** **Morgese *et al.* 2018**
Human Serum Albumin	Linear homopolymer	PMeOx DP: 19, 115		**Svoboda *et al.* 2019**
	Branched copolymer	PMeOx DP:6, 26, 52, 73		**Zhang *et al.* 2015**
Albumin	Linear homopolymer	PEtOx DP: 60, 110		**Morgese *et al.* 2016**
		PMeOx DP: 67,89 PEtOx DP: 53, 114		**Yan *et al.* 2018**
	Cyclic homopolymer	PEtOx DP: 110		**Morgese *et al.* 2016**
		PMeOx DP: 61, 95 PEtOx DP: 51		**Yan *et al.* 2018**

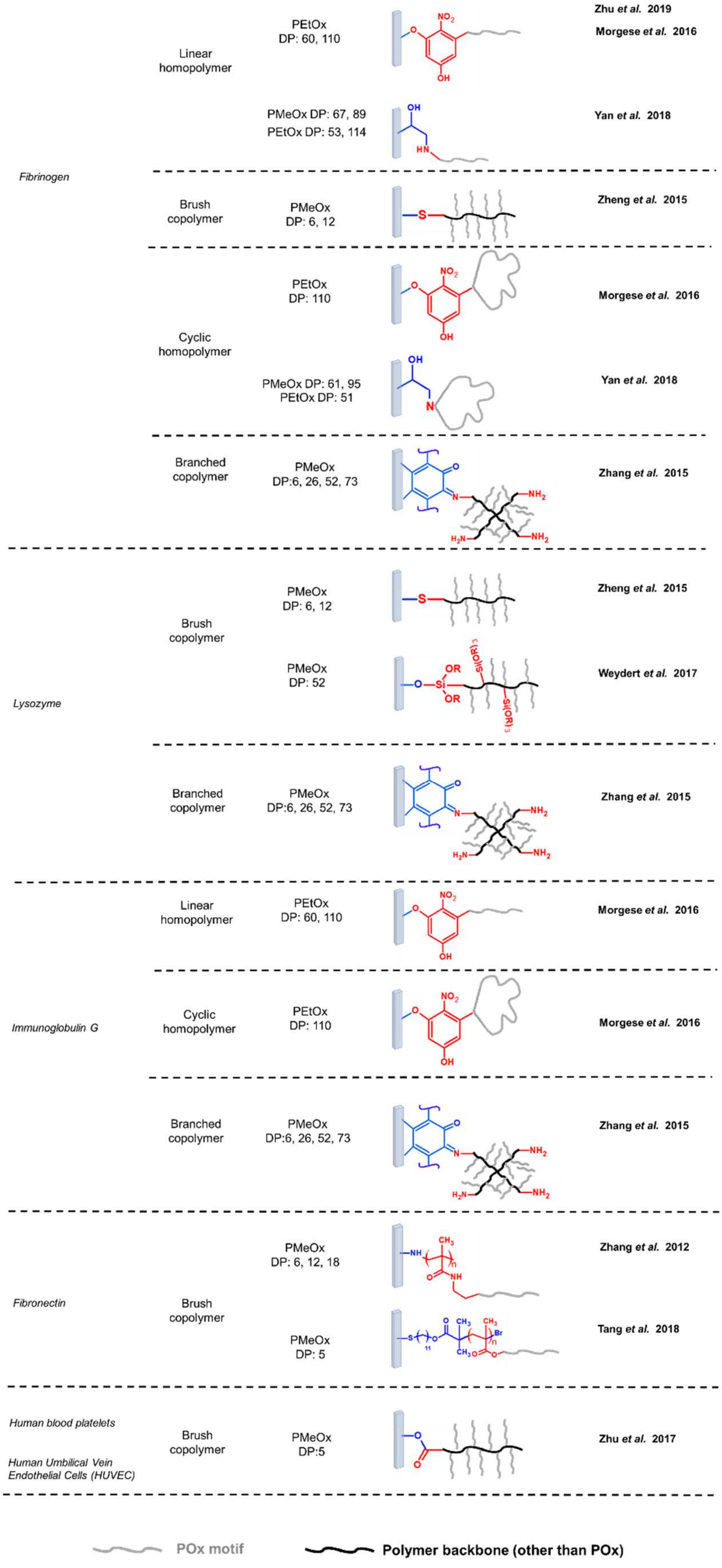


Fig. 13. Proteins and cells tested on POx antifouling coatings.

VI. Conclusion and perspectives

Polyoxazolines are a highly interesting class of polymers endowed with unique structural features which makes them a promising choice for AF coatings in biomedical and marine applications. Only hydrophilic POx (PMeOx and PEtOx) have been studied as alternative to PEG, gold standard for passive AF coatings but other perspectives could be considered with hydrophobic POx to build resistant AF coatings classified in non-erodible materials.[67]

In the biomedical field and more specifically in drug delivery, polymersomes - vesicular structures resulting from the self-assembly of amphiphilic block copolymers - received a high interest. One of the main issues that hampers their clinical translation is the protein fouling (protein corona formation). Recently, Najer *et al.* prepared PMeOx-*b*-PDMS-*b*-PMeOx polymersome derived membranes and investigated their antifouling action against blood proteins.[68] This study could be continued with other flexible hydrophobic partners including hydrophobic POx.

An important result of the literature is the impact of the POx macromolecular architecture and its grafting density on the surface. The most effective antifouling is the densest POx coatings, especially using cyclic polymers. Unfortunately, this kind of architecture requires a complex synthetic route caused by unfavourable thermodynamic cyclic reaction. A breakthrough would be an easier route of access.

Another perspective concerns the development of pH-responsive POx in order to elaborate sensitive AF coatings. These coatings reversibly interact with pathogens and provide a self-cleaning behaviour onto pH changes, which take off the pathogens and regenerate the pristine coating. This proposal is based on previous works of Li *et al.*[65] and He *et al.*[66] who stated the decrease of bacterial adhesion when increasing the thickness of multilayer coated substrates (PEtOx-*stat*-PEI)/PAA, as a result of high hydration of PEtOx and the electrostatic repulsions generated by PAA.

Surprisingly, while various papers attested the high interest of polyoxazolines for AF coatings against proteins, cells and bacteria in biomedical applications, fewer examples were reported in marine antifouling probably due to a low chemical compatibility with the composite surfaces of the ships based on epoxy or unsaturated polyester resins. Some improvements must be investigated to allow the widest use of POx in marine AF coatings. Combining POx additives with the precursors of a matrix is a promising strategy to incorporate POx in AF coatings.

Otherwise, POx would be to make them biodegradable and elaborate biocide release AF coatings using erodible matrix. Despite the hydrophilic character of PMeOx or PEtOx which makes them suitable to create polymers with hydrolytic properties and degradability, the POx are classified as non-degradable polymers even if they can promote the biodegradation of materials.[69] To reach this objective, some chemical modifications of the POx backbone must be operated (**Fig. 14**). The main pathway consists in the introduction of ester bonds (*i.e.*, a rare degradable links) along the POx chains. Wang *et al.* proposed the copolymerization of lactide to synthesize triblock copolymer PLLA-*b*-PEtOx-*b*-PLLA with enzymatic sensitivity.[70] In this case, the proteinase K exhibited remarkable hydrolysis and consequently enzymatic degradation. Another original copolymerization synthetic route was described by Kempe *et al.* who illustrated the zwitterionic copolymerization by redox-initiated RAFT polymerization using acrylic acid or 2-carboxyethyl acrylate with EtOx.[71] However, the degradation of the resulting poly(aminoester) was not studied yet. A complementary approach is the synthesis POx-like structure without the use of oxazoline monomer. For example, Joy *et al.* constructed polyester chains with POx-like units using a diol bearing amide group and a diacid.[72] Hadjichristidis *et al.* investigated another route based on poly(esteramide)s as POx alternative by organocatalytic ROP of oxazepanone monomers.[73] As stated by the authors, a quicker degradability in water compared PCL was observed. The last route towards degradable POx was developed by Goppert *et al.* and consisted in the oxidation of the carbon atom closed to the amino group of main polymer chain acting as preferential anchor point for microorganisms resulting in chain breaks.[74] To this, POx was firstly hydrolyzed into PEI which was then partially oxidized into poly(ethyleneimine-*co*-glycine) in presence of H_2O_2. The last step was the acrylation of residual PEI into POx using an acyl agent. Unfortunately, the enzymatic degradation of these polymers was not still confirmed.

Briefly, the studies recently realized on POx for AF coatings allow to design more efficient AF coatings and other perspectives like erodible surfaces for marine or biomedical applications, as well as self-cleaning surfaces or responsive surfaces.

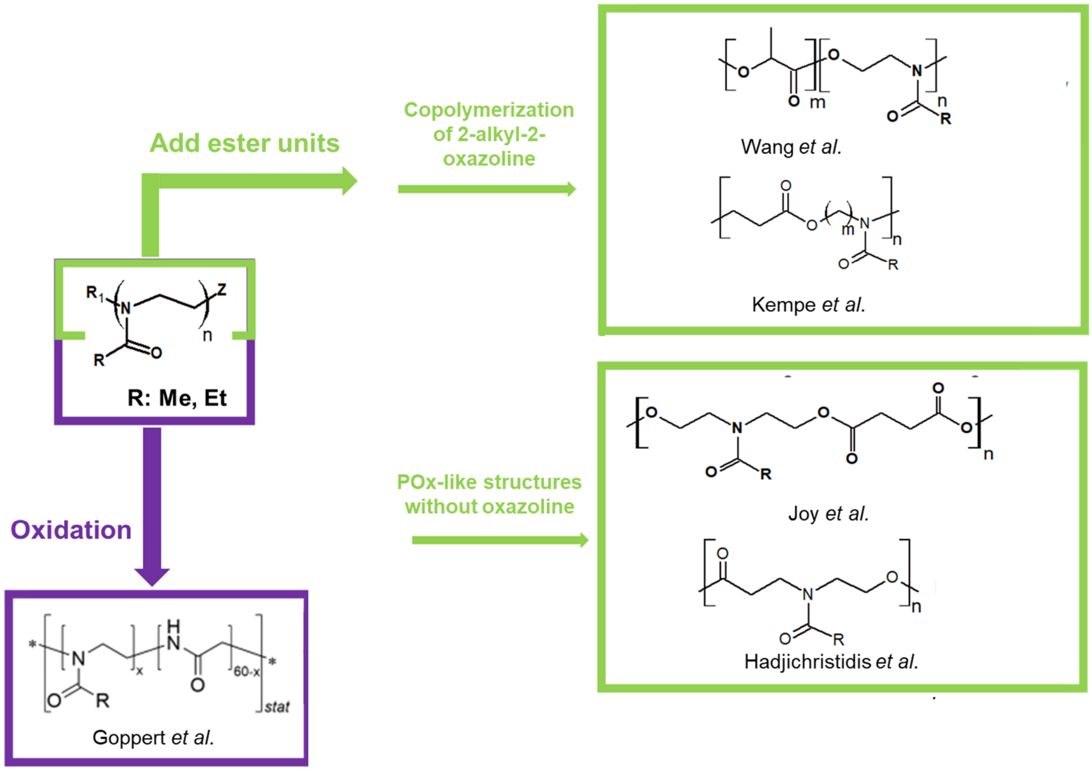


Fig. 14. Synthetic routes towards degradable POx.

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LVA: conceptualisation, writing original draft and reviewing-editing; VL: supervision, funding, conceptualisation, writing original draft and reviewing-editing. The manuscript was written through the contributions of both authors. Both authors have given approval to the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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